A STUDY OF ALKYLATION OF GUANAZOLE

Jose Juan Fuentes

A Thesis

in

The Department

of

Chemistry

Presented in Partial Fulfillment of the Requirements for
the Degree of Master of Science at
Concordia University
Montreal, Canada

November, 1975

To Maria and Jose Fuentes my beloved parents
and Graziella my patient wife.

"El deber debe cumplirse sencilla y naturalmente"

Jose Marti

TABLE OF CONTENTS

Page

INDEX OF TABLES

ILLUSTRATIONS

ACKNOWLEDGEMENT

The author wishes to express his sincere appreciation for the kind and patient guidance given by Professor Jacques Lenoir during the course of this research project.

ABSTRACT

JOSE JUAN FUENTES

A STUDY OF ALKYLATION OF GUANAZOLE

The alkylation reaction of 3,5-diamino-1,2,4-triazole (guanazole) with a series of alkyl halides in basic media has been studied.

Guanazole was prepared from cyanoguanidine and hydrazine dihydrochloride. Preparative methods involving alternative reaction times, solvents, and starting reagents, produced lower yields and/or poorer quality guanazole.

The alkylated guanazoles were isolated as the picrates and the free bases obtained by removal of the picric acid using an anion exchange resin column. The free bases were recrystallized from the eluates. 1-Methylguanazole was prepared from methylhydrazine dihydrochloride and cyanoguanidine as an extension of the method of preparation of the parent compound guanazole. 1-Phenylguanazole was prepared from phenylhydrazine and cyanoguanidine in a similar manner.

The following 1-alkyl guanazoles obtained in this investigation were new compounds, viz.,

1-n-propyl-3,5-diamino-1,2,4-triazole,

1-benzyl-3,5-diamino-1,2,4-triazole,

methyl (3,5-diamino-1,2,4-triazol-1-yl) acetate,

(3,5-diamino-1,2,4-triazol-1-yl) acetic acid

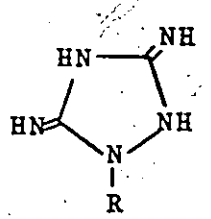
The mono- and di-benzylidene derivatives of the 1-alkyl-

guanazoles mentioned above constitute also new compounds, except the mono-benzylidene derivative of 1-phenyl-guanazole.

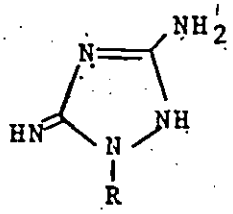
The preparation of the mono- and di-benzylidene derivatives of the alkylated guanazoles, and the analysis of the alkylation products and their benzylidene derivatives by PMR, IR, and UV spectroscopy suggested that alkylation takes place at N-1 of the triazole ring.

INTRODUCTION

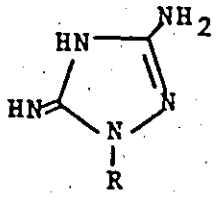
The chemical aspects of guanazole and 1-substituted guanazoles were originally of interest because of the different possible structures that could be ascribed to guanazole (I to V) (1):



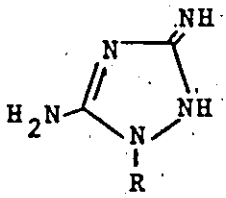
I



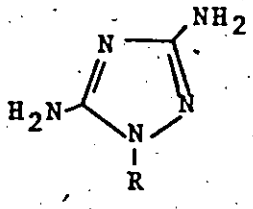
III



II



IV



V

However, alkylation has been limited to 1-phenylguanazole, to produce 1,2-disubstituted guanazoles (2,3). Up to the present time, 1-substituted guanazoles have been obtained from appropriate arylhydrazines as one of the components (4-8).

1. Preparation of guanazole

Pellizzari (4) in 1894 isolated a product from the reaction of hydrazine monohydrochloride and cyanoguanidine in the molten state. He gave the name GUANAZOLE to this product, to which he assigned the structure 3,5-diimino-tetrahydro-1,2,4-triazole (or 3,5-diimino-1,2,4-triazolidine) (I, R = H). The name guanazole was derived

from the then formal relationship of structure I with guanidine.

Various methods have appeared in the literature for the preparation of guanazole. Stolle and Krauch (9) reported the preparation of guanazole from hydrazine hydrate and cyanoguanidine. More recently, Kaiser and Roemer (7) obtained guanazole in 97% yield from hydrazine dihydrochloride and cyanoguanidine. Frankel et al. (10) obtained guanazole in 81% yield from barium cyanamide and hydrazine. An interesting method has been reported by Norris and Henry (11) for the preparation of guanazole in 66% yield from cyanoguanyl azide and hydrazine.

2. Structure of guanazole

The existence of several possible structures for the guanazoles has been mentioned earlier (p. 1). Structure V is the one that presents the greatest degree of conjugation. On the basis of ultraviolet absorption spectra of several 1-arylguanazoles, Steck and Nachod (12), suggested that these compounds should be formulated as 3(5)-amino-1-aryl-5(3)-imino-1,2,4-triazolones (III or IV) rather than 1-aryl-3,5-diimino-1,2,4-triazolidines (I). For the elucidation of the structure of a number of guanazoles, Lopyrev et al. (13) made a comparison of their infra-red spectra before and after deuteration at the N-H bonds. They concluded that for guanazole, 1-methyl, and 1-phenyl,-guanazoles, the diamino structure V is the most likely in the crystalline state.

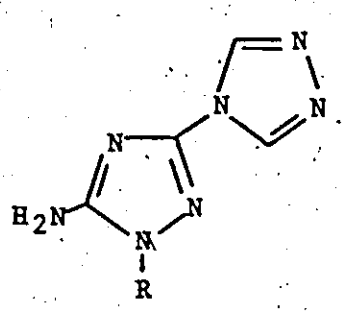
A further argument in favor of structure (V) for guanazole is given by Lopyrev et al. (55). Heat of formation and dipole moments calculated by the MINDO/2 and the CNDO/2 methods respectively gave values agreeing with measured data.

3. Reactions of guanazole

a) Condensation reactions

i) Reaction of guanazole and 1-substituted guanazoles with N,N'-diformylhydrazide.

Products of the reaction of guanazole and 1-substituted guanazoles with N,N'-diformylhydrazide (DFH) have been described in the literature (17). However, different opinion have existed on the structures of the products obtained. Beresneva et al. (17) carried out the condensation of DFH with 1-methyl, and 1-phenyl,- guanazoles. They observed that at a molar ratio of the triazole to DFH of 1:2, only one amino group takes part in the reaction, and the products have the structure of 5-amino-1-methyl- and 5-amino-1-phenyl-3-(1,2,4-triazol-4-yl)-1,2,4-triazoles, VI and VII, respectively.

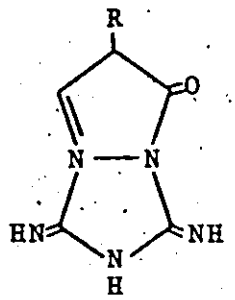


VI, R = CH_3
VII, R = C_6H_5

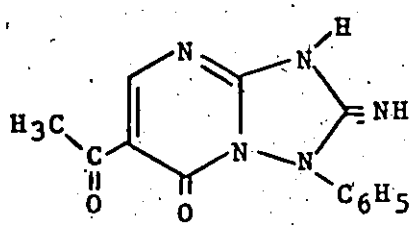
Hauser and Logush (16) have also reported the reaction of only one amino group as a characteristic of many reactions of guanazole.

ii) Reaction of guanazole and 1-substituted guanazoles with esters.

Papini et al. (18,19) studied the reaction of guanazole and 1-substituted guanazoles with ethyl aceto-acetate, derivatives of formic acid and various esters. The products obtained were rationalized as being formed by reaction of the "hydrazine residue" of the triazole ring and the ester. The structures assigned corresponded to polycyclic derivatives of the pyrazole and pyrimidine series, represented below by structures VIII and IX.



VIII

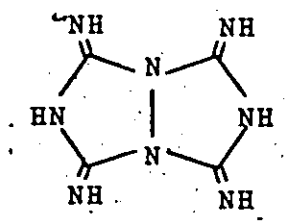


IX

However, a complete proof of these structures was not given and the problem of structure determination in this case is still unsolved.

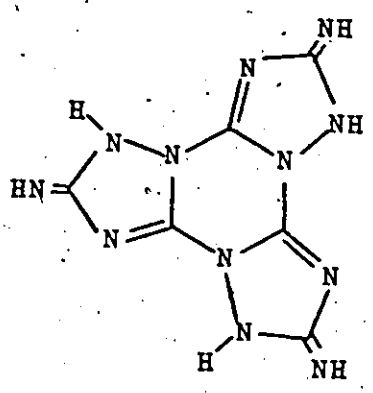
iii) Condensation reactions of guanazole and cyanoguanidine.

Pellizzari and Roncagliolo (3) found that either guanazole hydrochloride with cyanoguanidine, or hydrazine monohydrochloride with two equivalents of cyanoguanidine, yielded an infusible, relatively insoluble compound which they named guanazoguanazole and to which they assigned the structure X.



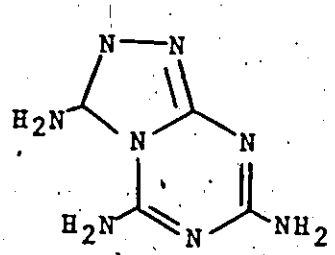
X

Hofmann and Ehrhart found that when cyanoguanidine and either hydrazine monohydrochloride (20), or hydrate (21), were heated to high temperatures, or when the isolated guanazole (21) was heated to a high temperature, a product was formed which these authors first called melamazine (20) and later, pyroguanazole (21). This compound was assigned structure XI (21) and the presence of a s-triazine ring was demonstrated.



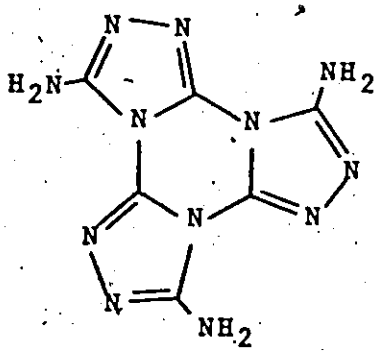
XI

More recently, Kaiser et al. (22) gave evidence for the reassigment of structures to guanazoguanazole and pyroguanazole as XII and XIII respectively.



XII

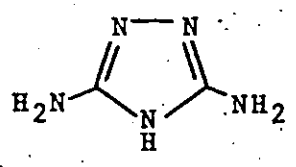
3,5,7-triamino-s-triazolo[4,3-a] s-triazine.



XIII

3,7,11-triamino-tris-s-triazolo[4,3-a, 4,3-c, 4,3-e]s-triazine.

Based on the reassigned structures for guanazoguanazole and pyroguanazole, Kaiser et al. (22) postulated the structure of guanazole as 3,5-diamino-4H-1,2,4-triazole (XIV); a structure proposed much earlier by Stolle and Dietrich (1).



XIV

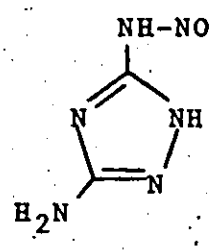
b) Substitution reactions.

i) Acetylation.

Van den Bos (23) studied the acetylation of guanazole. These reactions are summarized in Scheme I.

ii) Diazotization and autocoupling of guanazole.

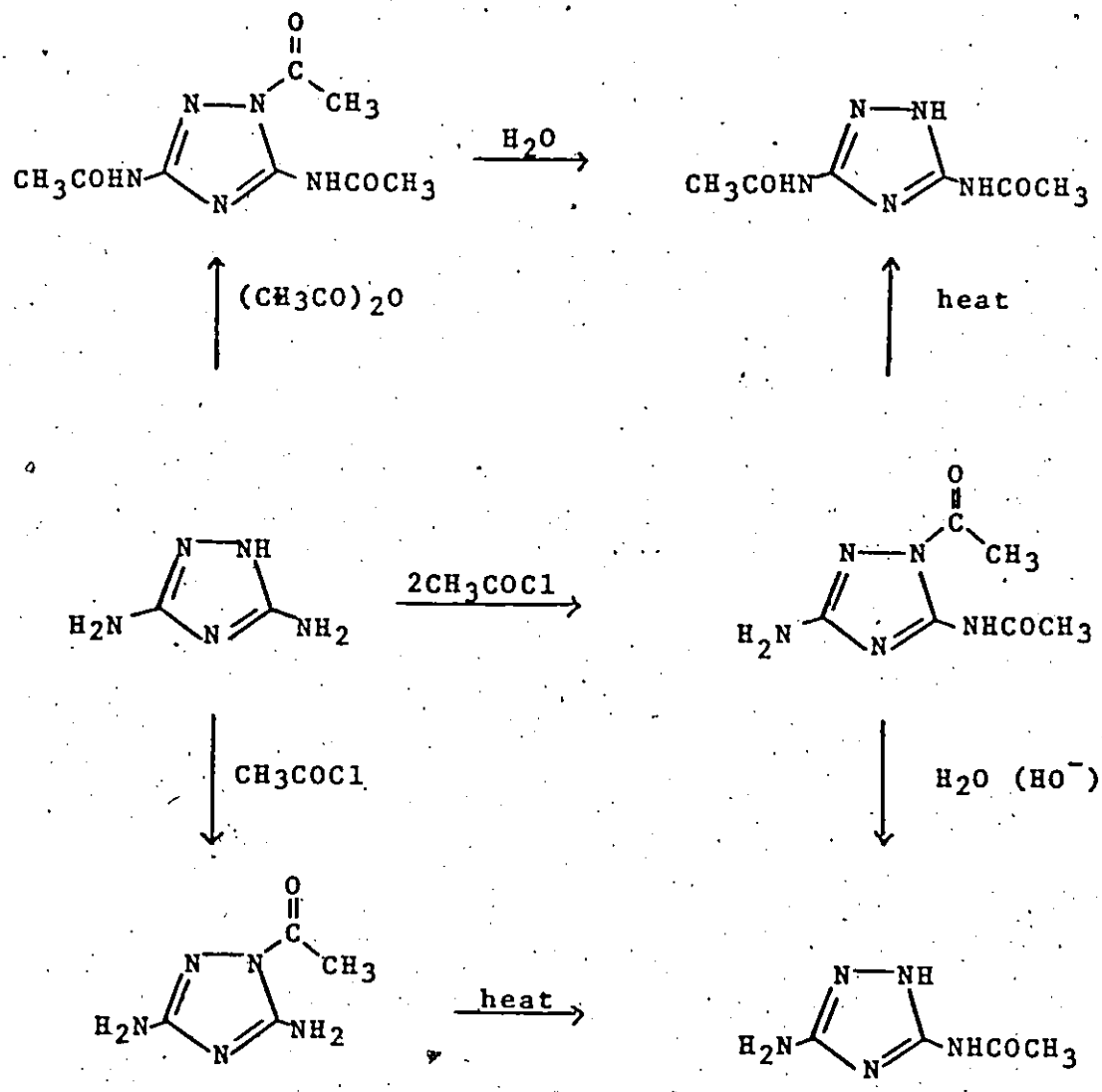
Stolle and Dietrich (1) reported that guanazole could be diazotized or tetrazotized. The diazonium salts are then coupled with a phenol to give the corresponding mono- and bis-azo compounds. These same authors also reported that treatment of 3-amino-5-nitrosoamino-1,2,4-triazole XV



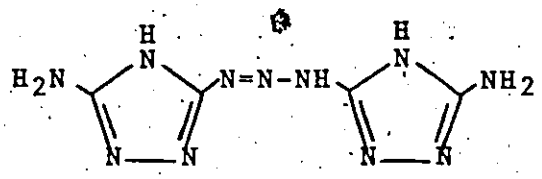
XV

Scheme I

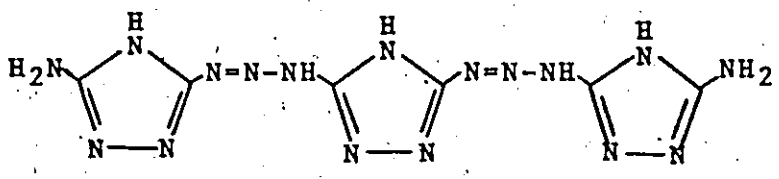
Acetylation of Guanazole



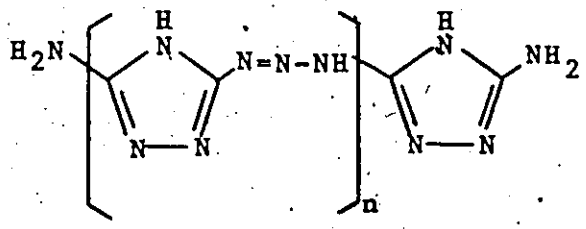
(prepared from guanazole and sodium nitrite in dilute acetic acid (9)) with concentrated hydrochloric acid gave a diazonium salt solution capable of reacting with a coupler. Hauser (24) was able to prepare the dimer 1,3-bis [3-(5-amino-1,2,4-triazolyl)] triazene, the trimer 3,5-bis [3-(5-amino-1,2,4-triazolyl)] triazenyl -1,2,4-triazole, and a polymer, with the structures XVI, XVII and XVIII respectively. When a diazonium salt solution prepared from XV was added to an aqueous solution of an equivalent amount of guanazole, compound XVI was obtained as the dihydrochloride. Dimer XVI was converted to trimer XVII upon diazotization with an equivalent of nitrous acid and coupling with an equivalent of guanazole. The diazonium salt solution from XV self-coupled when the solution was neutralized. The precipitate thus obtained was identified as the polymer XVIII.



XVI $C_4H_7N_{11}$ or $[(C_2H_2N_6)(C_2HN_3)(NH_2)_2]$



XVII $C_6H_9H_{17}$ or $[(C_2H_2N_6)_2(C_2HN_3)(NH_2)_2]$



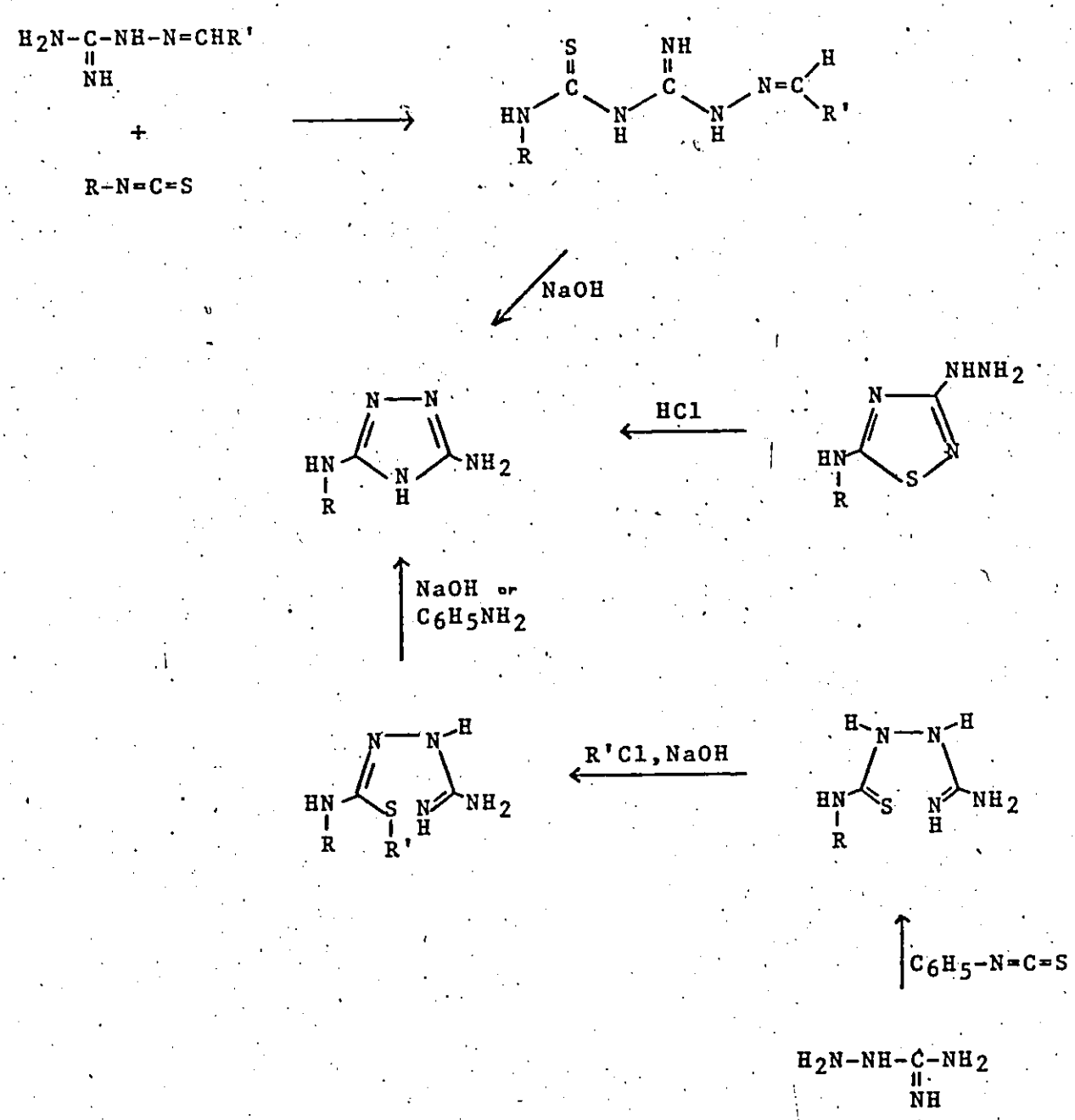
XVIII $[(C_2H_2N_6)_n(C_2HN_3)(NH_2)_2]$

4. Some substituted guanazoles

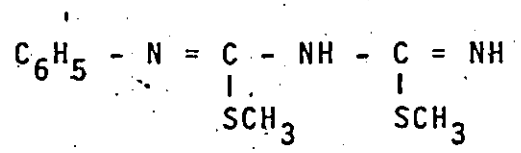
Godfrey and Kurzer (25-28), in a series of publications, have reported the preparation of 3-amino-5-substituted guanazoles. The results are summarized in Scheme II.

Scheme II

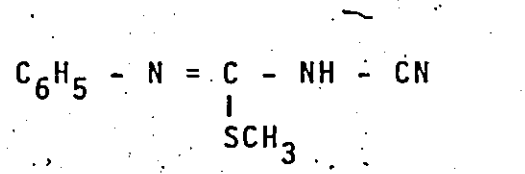
Synthesis of 3-Amino-5-substituted-guanazoles



3-Amino-5-anilinoguanazoles are reported to be formed when the di-isodithiobiuret (29,30),



or the isothiourea (31),



react with hydrazine hydrate.

5. Uses and physiological properties of guanazole and its derivatives.

The guanazoles have often been used in plastics and in color photography (32,34). Kidder et al. (35) found that guanazole administered to rats inhibited tumor growth. Nickell et al. (36) found that guanazole inhibited various tumor growths in *in vitro* experiments. Later, Kirkpatrick and Lindner (37) found that a stone fruit virus (PLMV) inoculated into cucumber plants, or a tobacco mosaic virus (TMV) inoculated into tomato seedlings, were both markedly inhibited by guanazole. More recently, Brockman et al. (38) found that guanazole inhibits the incorporation of adenine, hypoxanthine, and uridine into DNA to a much greater extent than into RNA in L 1210 leukemia cells in vivo.

Hahn and Adamson (39) studied the pharmacology of guanazole. They found that guanazole has antitumor activities against murine leukemias L 1210 and K 1964, mast cell tumor P 815, Walker 256 carcinqsarcoma and reticulum cell sarcoma A-RCS. In the course of their investigation they found that substitution on the 1,2,4-triazole structure, other than an amino group in position 3 and 5, resulted in a loss of cytotoxicity; or else the new compound showed equal cytotoxic activity in vitro, but unacceptable toxicity in vivo.

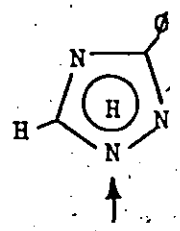
Curd et al. (3) reported that a series of 3-alkylamino-5-p.chloroanilino-1,2,4-triazoles appears to be devoid of antimalarial activity.

Guanazole monohydrochloride has been tested as an inhibitor of the reproduction of house flies. This compound, at a concentration of 1% in either fly food or sugar, compared favorably with the most effective compound (ethylene glycol dimethane sulfonate) at a concentration of 0.25% (40).

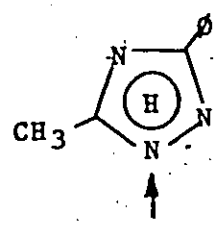
6. <u>The present investigation, and its background</u>

Atkinson and Polya (41,42) found that alkylation of 1,2,4-triazole, and its 3,5-dimethyl and 3,5-diphenyl derivatives, using an alkyl halide in alkaline media introduced an alkyl group onto nitrogen atom 1. In the unsymmetrical compounds 3-phenyl-, and 3-methyl-, 5-phenyl-1,2,4-triazole, substitution occurred on both nitrogen atoms 1 and 2, but preferentially onto the nitrogen atom

adjacent to the carbon atom bearing the hydrogen atom or the methyl group respectively, as indicated with an arrow in the following diagram.



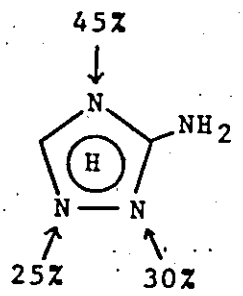
3-phenyl-1,2,4-triazole



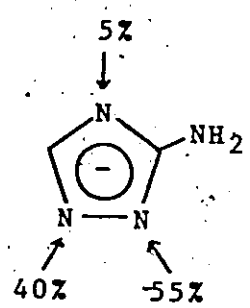
3-methyl-5-phenyl-1,2,4-triazole

The alkylation of several 3(5)-aryl-5(3)-amino-s-triazoles in alkaline media has been reported by Akerblom (43) and Van den Bos (44). The alkylation also took place at the nitrogens 1 and 2 of the triazole ring. Only in the case of the alkylation of 5-furyl-3-amino-1,2,4-triazole (43) with methyl iodide in neutral media did N-4 alkylation occur.

Recently, Barascut et al. (45) reported the methylation of 3(5)-amino-s-triazole. They obtained all three possible substitution products at the nitrogens of the triazole ring. Their results are illustrated in the following diagrams.



Alkylation products, expressed as percentage, in the absence of base.



Alkylation products, expressed as percentage, in the presence of base.

In the present investigation the alkylation of guanazole in basic media was studied.

The three major objectives of this investigation were:

a) To study the alkylation of guanazole using various alkyl halides in basic media.

b) To establish the site of substitution in the molecule of guanazole under the above conditions.

c) To provide a new method for the preparation of 1-substituted guanazoles in cases where the corresponding hydrazines would not be readily available.

Two minor objectives were also present during the progress of this research:

i) To compare the various methods described in the literature for the preparation of guanazole.

ii) To provide novel starting materials for the possible preparation of fused ring systems containing the s-triazole ring.

DATA AND RESULTS

Preparation of guanazole

Guanazole was prepared from cyanoguanidine and hydrazine dihydrochloride according to Kaiser and Roemer (7). A high quality product was obtained in excellent yield (88-91%).

A commercial sample of guanazole (Aldrich Chemical Co.) (85% purity) was compared with the product obtained in this investigation using the procedure of Kaiser and Roemer (7). Both materials had identical infra-red spectra. Thin layer chromatography showed, however, some impurities in the commercial sample that were not present in our product. One of the impurities was identified as guanazoguanazole. Guanazole, as a high quality starting material, was desired for the alkylation reactions in order to avoid misinterpretation of experimental results due to the presence of impurities capable of reacting with the alkylating reagent.

The observation that the yield and quality of guanazole were considerably dependent on the reaction conditions led us to carry out a series of experiments varying the reaction time, the solvent and the materials employed. The results are summarized in Table I.

Pellizzari (46) obtained guanazole in 50% yield from cyanoguanidine and hydrazine monohydrochloride. In this method, the reaction mixture was heated in 95% ethanol at 100°C. for 10 hours in a sealed tube. A similar yield (52.5%) was obtained using the conditions described for

Table I. - Preparation of Guanazole from Cyanoguanidine and Hydrazine Monohydrochloride (A) or Cyanoguanidine and Hydrazine Hydrate (B) using different Solvents, Temperature and Reaction Times.

Expt. No.	Starting Materials (molar ratio)	Solvents	T, °C.	t, hrs	Results
1	A (1 : 1)	Pet. eth.	110-115°	13	52.5% guanazole 7.4% guanazoguanazole[a]
2	A (1 : 1)	n-BuOH	reflux (117-118°)	13	guanazole, guanazo-guanazole, two impurities (by tic)
3	A (1 : 2)	toluene	reflux (110.6°)	2.5	73% guanazole[b]
4	A (1 : 1.1)	Pet. eth.	110-5°	3	65% guanazole[c]
5	A (1 : 2.5)	2-BuOH	reflux (99.5°)	2.5	35% guanazole
6[d]	B (1 : 3.8)	neat	65-67°	1.5	50% guanazole, highly coloured impurity

a) Compared to authentic sample provided by Prof. J.A. Lenoir. (54)
b) Purified by AG-50W, X-8, ion exchange resin in H^+ form. Product eluted with 1.5 N NH_4OH.
c) Purified as indicated in (b).
d) Basically constitutes the method of Stolle and Krauch (9).

experiment 1 (Table I). When n-butanol was used as the solvent (experiment 2, Table I), a complicated mixture of four or more components was detected by thin layer chromatography from which guanazole and guanazoguanazole were identified.

Better yields were obtained when shorter reaction times were used (experiments 3 and 4, Table I). The use of a polar solvent (2-butanol in experiment 5, Table I) afforded a low yield of guanazole.

A lower temperature, and the use of hydrazine hydrate as one of the components, (experiment 6, Table I) gave guanazole in moderate yield. A dark red impurity was present, contaminating the product, formation of the coloration was avoided if the product was kept under a nitrogen atmosphere but appeared when the product was allowed to stand in the air. Attempted purification of the crude coloured product by salt formation with sulfuric acid and recrystallization of the salt, generated a purple colour when the free base was formed and allowed to stand in the air. This behaviour is similar to that of guanylhydrazine as a free base.

The excellent results obtained by the method of Kaiser and Roemer (7) with hydrazine dihydrochloride as one of the components in aqueous medium and under mild temperature conditions is quite remarkable. A possible mechanism is postulated in Scheme III.

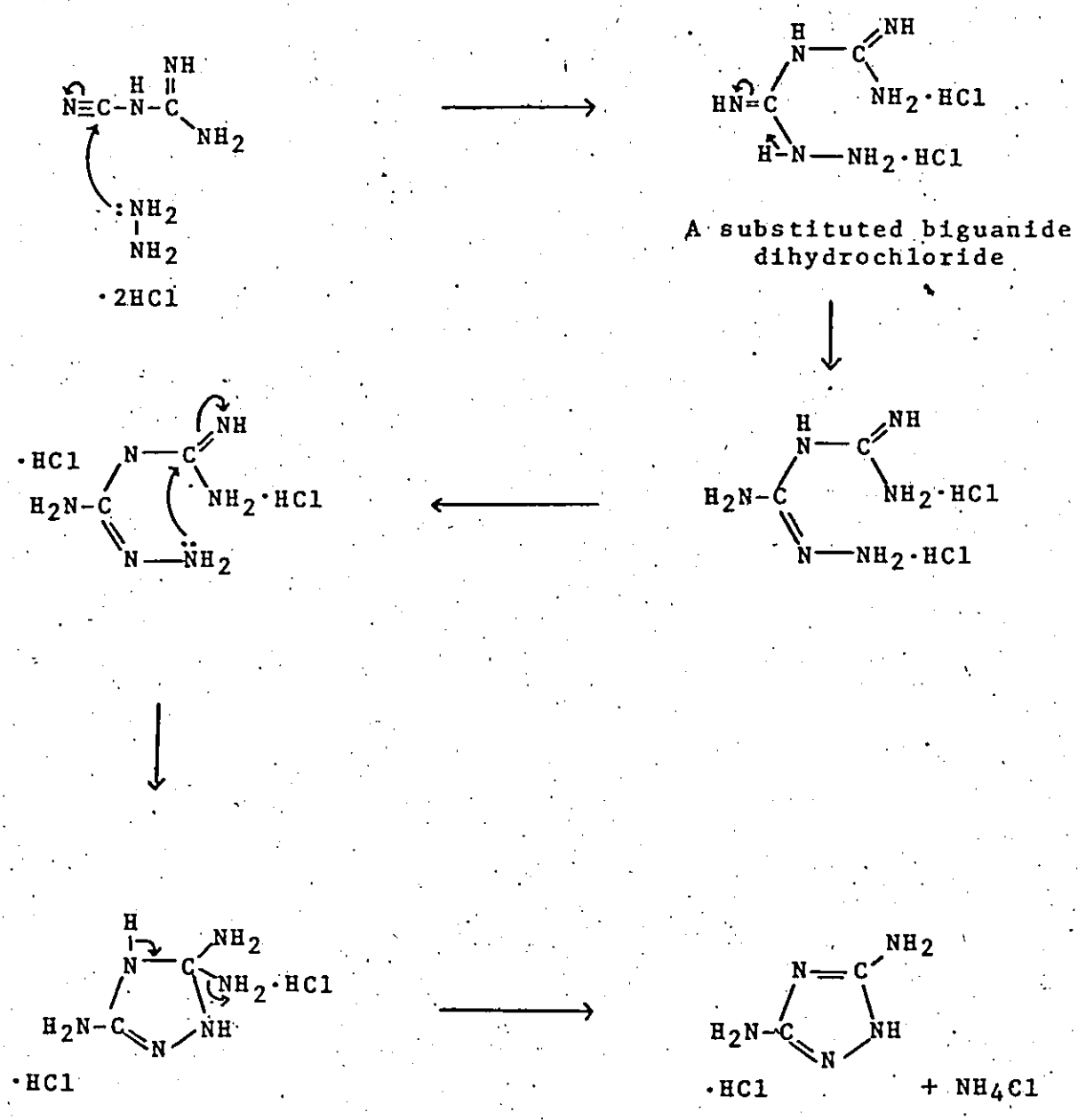
The preparation of 1-methylguanazole and 1-phenyl-

guanazole was carried out under similar conditions as those described by Kaiser and Roemer (7) for the preparation of the parent compound, guanazole.

1-Methylguanazole has been previously prepared from cyanoguanylazide and methylhydrazine (11) and from barium cyanamide and methylhydrazine (10). The extension of the method of Kaiser and Roemer (7) for the preparation of 1-methylguanazole, as reported in the present investigation, may have the advantage of using the more readily available cyanoguanidine as one of the starting materials.

Scheme III

Possible Route to the Formation of Guanazole from Cyanoguanidine and Hydrazine Dihydrochloride:



Alkylation of guanazole

The general method used in this investigation for the alkylation reactions of guanazole consisted of treating guanazole with one or two equivalents of the alkylating reagent in the presence of an equivalent amount of base (sodium methoxide) in methanol.

The mixture was refluxed for several hours and the alkylated product was isolated as the picrate. The picrate was absorbed on an anion exchange resin (Bio-Rad Laboratories, AG-1, x-8, acetate form) the resin column was eluted with water and the free base then crystallized from the eluate. The details of the various alkylating reactions are described in the experimental section. The results for substituted guanazoles are summarized in Tables II-V.

Mono- and dibenzylidene derivatives of the alkylation products were also prepared. The examination of these derivatives by several spectroscopic techniques afforded evidence that strongly indicated alkylation products consisting of 1-substituted guanazoles.

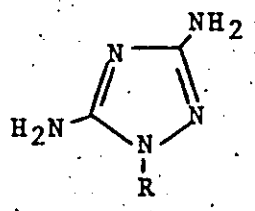
In order to study the possibility of obtaining multiple alkylation products, several experiments were carried out using methyl iodide in different proportions and conditions. The results are summarized in Table VI.

The reaction of guanazole with methyl iodide in the presence of sodium methoxide under various conditions (Table VI) afforded mainly 1-methylguanazole. A less polar spot than the main product was also detected by thin-layer

chromatography. This high R_f compound was isolated by column chromatography on silica gel. A mixture of ethyl acetate-ethanol (1:2 v/v) was used as the eluting solvent. The isolated material had a broad absorption at both 3500 cm^{-1} and 1640 cm^{-1} in the infra-red region. This material softened at 70°C. to an infusible material that darkened during heating up to 360°C. The proton magnetic resonance spectrum showed an exchangeable peak at about 3.46 ppm (DMSO-d_6, TMS internal standard). The addition of acid turned the solution red. Further addition of base regenerated the original yellow solution. This solution contained the same original product as detected by thin-layer chromatography. The material was recovered unchanged after two hours heating at 90°C., under a nitrogen atmosphere (infra-red spectrum, thin-layer chromatography).

No reaction was observed when 1-methylguanazole was refluxed for several hours in methanol in the presence of one equivalent of base (sodium methoxide) and one equivalent of methyl iodide. The recovered starting material was identified by thin-layer chromatography, infra-red and proton magnetic resonance spectroscopy.

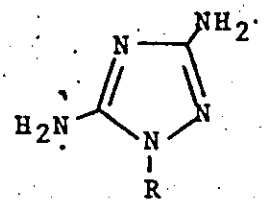
Table II. - Alkylation Reactions of Guanazole. Melting points, R_f values, Yields and Melting points of the corresponding Picrates of Substituted Guanazoles



R	M. pt., °C.	R_f	Yields, %	M. pt. of Picrates, °C.
H	203-204[b]	0.25[a]	88-91	245-248[c]
CH_3	145[d]	0.27[a]	66.5	266-267.5[e]
$CH_2CH_2CH_3$	110-112	0.35[a]	30	194-195
C_6H_5[f]	175-176[g]	0.39[a]	41	230-232[h]
$CH_2C_6H_5$	165	0.43[a]	61	212-215
$CH_2CO_2CH_3$	179-181	0.35[a]	40	235-237
CH_2CO_2H	289	0.21[i]	100[j]	---

a) Solvent A;
b) m.pt. 206°, ref. 46
c) m.pt. 248-249°, ref. 11
d) m.pt. 157-159°, ref. 10
e) m.pt. 273-274°, ref. 11
f) obtained from phenylhydrazine hydrochloride and cyanoguanidine
g) m.pt. 173.7-175°, ref. 8
h) m.pt. 233-235°, ref. 11
i) Solvent B
j) obtained from hydrolysis of the corresponding ester.

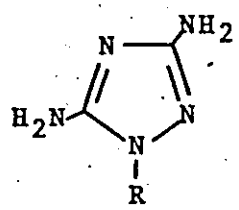
Table III. - Alkylation Reactions of Guanazole. Infra-red Spectra of Substituted Guanazoles (a).



R	Absorption in cm^{-1} ($\pm 5\ cm^{-1}$)
H	3400, 3310, 3130, 1625, 1585, 1560, 1480, 1415, 1340, 1055, 800.
CH_3	3350 (sh), 3310, 3200, 1640, 1590, 1545, 1495, 1430, 1410, 1125, 880, 830, 750, 685, 630.
$CH_2CH_2CH_3$	3395(sh), 3300, 3170, 2960, 2925, 2870, 1635, 1585, 1550, 1480, 1440, 1415, 1380(sh), 1340, 1155(broad), 1100(broad), 1050, 895, 780, 685, 660.
C_6H_5 [b]	3450, 3425, 3300, 3165, 1645(sh), 1620, 1570, 1535, 1500, 1470, 1450, 1390, 1320, 1090, 1065, 1040, 910, 760, 695, 675.
$CH_2C_6H_5$	3310, 3220, 3020, 1625, 1580, 1550, 1490, 1480, 1450, 1435, 1415, 1360, 1255, 1200, 1145, 1095, 1040, 1020, 940, 875, 820, 750, 690, 635.
$CH_2CO_2CH_3$	3420, 3330, 3180, 3000, 2980, 1740, 1630, 1590, 1560, 1550, 1485, 1440, 1420, 1340, 1300, 1255, 1085, 1045, 1010, 955, 880, 850, 755, 685.
CH_2CO_2H	3380, 3280, 2980, 1705, 1665, 1605, 1580, 1525, 1465, 1425, 1395, 1385, 1310, 1080, 1010, 950, 910, 875, 755, 675, 645.

a) KBr disc
b) Obtained from phenylhydrazine hydrochloride and cyanoguanidine.

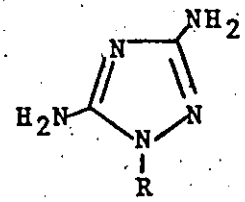
Table IV. - Alkylation Reactions of Guanazole. Proton Nuclear Magnetic Resonance Spectra of Substituted Guanazoles



R	Chemical Shifts (ppm)[a,d]	
H	6.30 (b, exch.)	
CH_3	3.30 (s, 3)	4.75 (s, 2 exch.) 5.85 (s, 2 exch.)
CH_3 (HCl)	3.46 (s, 3)	8.16 (s, 2 exch.) 7.30 (s, 2 exch.)
$CH_2CH_2CH_3$	0.80 (t, 3) 1.56 (sextet, 2) 3.60 (t, 2)	4.66 (b, 2 exch.) 5.86 (s, 2 exch.)
C_6H_5[b]	7.0-8.0 (m, 5)	5.10 (s, 2 exch.) 6.13 (s, 2 exch.)
$CH_2C_6H_5$	4.90 (s, 2) 7.30 (s, 5)	4.76 (b, 2 exch.) 6.08 (s, 2 exch.)
$CH_2CO_2CH_3$	3.71 (s, 3) 4.58 (s, 2)	4.81 (b, 2 exch.) 6.06 (b, 2 exch.)
CH_2CO_2H[c]	4.81 (s, 2)	

a) Solvent: DMSO-d_6, TMS as internal standard.
b) Obtained from phenylhydrazine hydrochloride and cyanoguanidine.
c) Solvent: DMSO-d_6 + DCl/D_2O.
Abbreviations: s = singlet, b = broad, t = triplet, m = multiplet, exch. = exchangeable.
d) Chemical shifts expressed in δ units.

Table V. - Alkylation Reactions of Guanazole. U.V. Spectra of Substituted Guanazoles



R	Wavelength (nm)[a]	Molar Extinction Coefficient, E x 10^3	Log ε
H	212	5.0	3.7
CH_3	212	6.0	3.8
$CH_2CH_2CH_3$	213	6.1	3.8
C_6H_5[b]	209	14.0	4.1
	268	7.6	3.9
$CH_2C_6H_5$	210	13.0	4.1
$CH_2CO_2CH_3$	215	6.0	3.8
CH_2CO_2H	215	0.03	1.4

a) Solvent: ethanol.
b) Obtained from phenylhydrazine hydrochloride and cyanoguanidine.

Table VI. - Reaction of Guanazole with Methyl Iodide in Various Conditions

Expt. No.	Starting Materials (Molar Ratio)	Solvent	T, °C	t, hrs	Results
1	Guanazole, MeI, NaOMe (1:1.1:1.1)	Methanol	110-120[a]	1	77% crude 1-methyl-guanazole
2	Guanazole, MeI, NaOMe (1:1.1:1.1)	Methanol	110-120[a]	2	Similar results as in Expt. 1
3	Guanazole, MeI, NaOMe (1:2:2.2)	Methanol	110-120[a]	1	As in Expts. 1 and 2
4	Guanazole, MeI, NaOMe (1:5.5:5.5)	Methanol	120[a]	1	59% 1-methylguanazole isolated as the free base
5	Guanazole, MeI, NaOMe (1:1.1:1.1)	Methanol	120[a]	5	As in Expts. 1, 2 and 3

a) Sealed bomb.
Note: Unless otherwise specified (as in Expt. No. 4) the product was characterized as the picrate (tlc, ir, nmr).

Benzylidene Derivatives

Mono- and dibenzylidene derivatives of substituted guanazoles were prepared according to the general procedure described in the experimental section.

The reaction of guanazole and substituted guanazoles with one equivalent of benzaldehyde at room temperature afforded only one of the two possible isomeric monobenzylidene derivatives.

The use of an excess of benzaldehyde in refluxing ethanol in the presence of a base (sodium acetate or piperidine) yielded the corresponding dibenzylidene derivative.

The dibenzylidene derivatives could also be obtained by refluxing the corresponding monobenzylidene derivatives with one equivalent of benzaldehyde, in the presence of base, in ethanol.

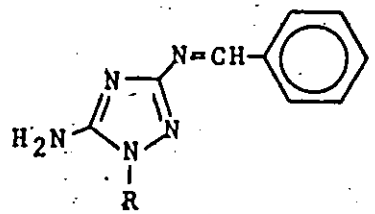
The preparation of the dibenzylidene derivative of 1-n-propylguanazole gave some difficulty. When sodium acetate was used as a base, only a partial conversion to the dibenzylidene derivative was observed. Almost quantitative conversion to the dibenzylidene was obtained when a stronger base, such as piperidine, was added to the reaction mixture and refluxing allowed to continue for 18 hours. The reaction mixture was evaporated to dryness, and the residue then partitioned between chloroform and water. The chloroform layer was rinsed several times with water and dried over sodium sulfate. The dried solution was filtered and

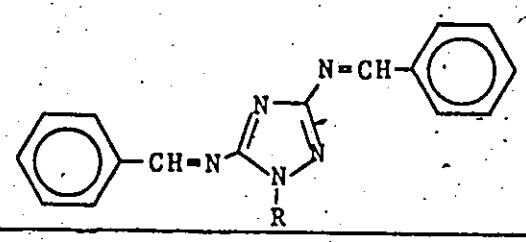
evaporated to dryness on a rotary evaporator to give an oily residue. In order to obtain a crystalline product, it was necessary to eliminate all traces of solvent and any excess reagent using a high vacuum pump and a liquid nitrogen trap. The dibenzylidene derivative slowly crystallized from the oily residue. The product was triturated with cold hexane, filtered and dried under a nitrogen atmosphere to avoid any possible hydrolysis.

During the course of the reaction for the preparation of the dibenzylidene derivatives, a third spot was observed, with an R_f value similar to those obtained from the monobenzylidene derivatives isolated in the experiments at room temperature. This new spot may correspond to the other possible isomeric monobenzylidene derivative (see Discussion section).

The results obtained for the mono- and dibenzylidene derivatives of guanazole and alkylated guanazoles are summarized in Tables VII-XIII. Also included in these Tables are the values for the mono- and dibenzylidene derivatives of 1-phenylguanazole.

Table VII. - Mono- and Di-benzylidene Derivatives of Substituted Guanazoles. Melting Points and R_f Values





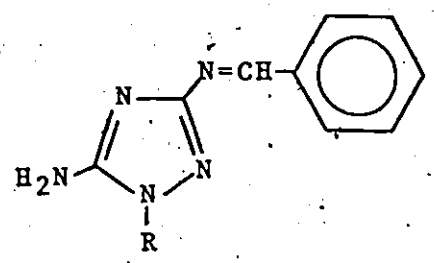
R	M. pt., °C.	R_f[a]	R	M. pt., °C.	R_f[a]
H[b]	235-237[c]	0.21	H[b]	207-210[d]	0.63
CH_3[e]	130-132	0.21	CH_3[f]	145-147	0.75
$CH_2CH_2CH_3$[b]	205-207	0.40	$CH_2CH_2CH_3$[g]	ca. 70	0.73
C_6H_5[b]	230[h]	0.57	C_6H_5[i]	132	0.85
$CH_2C_6H_5$	135-139	0.46	$CH_2C_6H_5$[j]	142-143	0.83
$CH_2CO_2CH_3$[b]	168-169	0.38	$CH_2CO_2CH_3$[k]	83	0.83

a) Silica gel tlc plates, solvent: ethyl acetate.
b) Recrystallized from the reaction mixture.
c) M.pt. 228-233°, ref. 14; m. pt. 234°, ref. 1.
d) M.pt. 206-209°, ref. 14.
e) Recrystallized from ethyl acetate-hexane.
f) Recrystallized from hexane.
g) Oil that crystallized on standing. Rinsed with cold hexane.
h) M.pt. 228°, Ref. 3.
i) Recrystallized from ether-petroleum ether.
j) Purified from the monobenzylidene derivative by silica gel dry column. Solvent: ethyl acetate.

Table VII. - continued

k) Recrystallized from ether-hexane.

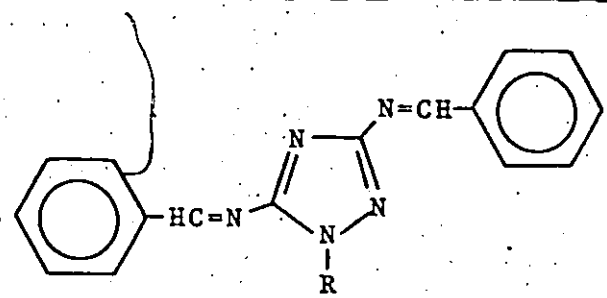
Table VIII. Monobenzylidene Derivatives of Substituted Guanazoles. Infra-red Spectra[a]



R	Absorption in cm^{-1} ($\pm 5\ cm^{-1}$)
H	3260, 3120, 2970, 2850, 2790, 1660, 1600, 1570, 1515, 1490, 1445, 1395, 1355, 1330, 1210, 1120, 1070, 1020, 970, 880, 810, 760, 675.
CH_3	3450, 3310, 3130, 1655, 1615, 1565, 1515, 1445, 1415, 1375, 1350, 1310, 1260, 1220, 1165, 850, 770, 690, 685.
$CH_2CH_2CH_3$	3380, 3300, 3160, 2960, 2920, 2860, 1645, 1615, 1565, 1515, 1450, 1370, 1350, 1305, 1290, 1250, 1210, 1160, 1090, 1070, 1020, 990, 970, 845, 765.
C_6H_5	3370, 3320, 3145, 1650, 1615, 1600, 1575, 1565, 1510, 1490, 1450, 1430, 1370, 1310, 1295, 1165, 1140, 1110, 1070, 1010, 980, 910, 875, 940, 830, 765, 760, 690.
$CH_2C_6H_5$	3220, 3150, 1660, 1600, 1575, 1520, 1495, 1450, 1440, 1375, 1345, 1305, 1290, 1255, 1210, 1175, 1105, 1070, 1020, 995, 970, 850, 765, 720, 695, 685.
$CH_2CO_2CH_3$	3400, 3330, 3120, 2980, 2940, 1730, 1665, 1620, 1575, 1520, 1435, 1400, 1380, 1365, 1345, 1310, 1270, 1225, 1140, 1110, 1000, 960, 765, 685.

a) KBr disc.

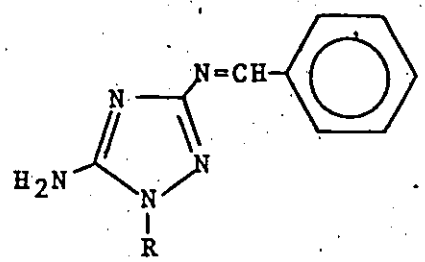
Table IX. Dibenzylidene Derivatives of Substituted Guanazoles. Infra-red Spectra[a].



R	Absorption in cm^{-1} (± 5 cm^{-1})
H	3240, 1575, 1490, 1460, 1385, 1350, 1330, 1310, 1235, 1215, 1200, 1170, 1120, 1070, 1030, 875, 765, 720, 620.
CH_3	2970 (center band), 1610, 1570, 1495, 1485, 1445, 1400, 1360, 1350, 1335, 1310, 1275, 1215, 1210, 1180, 1160, 1150, 1060, 1020, 980, 910, 830, 765, 685, 680, 675.
$CH_2CH_2CH_3$	2960 (center band), 1615, 1580, 1500, 1470, 1450, 1350, 1340, 1305, 1210, 1165, 1070, 990, 840, 800, 770, 740, 690.
C_6H_5	3070 (weak), 1615, 1575, 1550, 1510, 1500, 1405, 1340, 1310, 1215, 1150, 1055, 980, 900, 825, 720, 705, 685.
$CH_2C_6H_5$	3050, 3020, 2890, 1615, 1595, 1575, 1490, 1480, 1450, 1425, 1340, 1305, 1290, 1275, 1220, 1210, 1190, 1160, 1120, 1065, 1015, 970, 840, 765, 730, 715, 695, 680.
$CH_2CO_2CH_2CH_3$	2990 (center band), 1740, 1620, 1570, 1495, 1485, 1455, 1375, 1325, 1310, 1240, 1215, 1200, 1160, 1150, 1140, 1020, 975, 870, 830, 770, 745, 685.

a) KBr disc.

Table X. - Monobenzylidene Derivatives of Substituted Guanazoles. Proton Nuclear Magnetic Resonance Spectra.

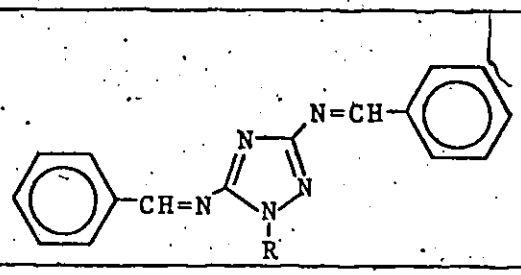


R	Chemical Shifts (ppm)[a,b]	
H	7.20-8.40 (m, 5) 9.20 (s, 1)	6.20 (s, 2 exch.) 12.23 (b, 1 exch.)
CH_3	3.60 (s, 3) 7.30-8.40 (m, 5) 9.13 (s, 1)	6.40 (s, 2 exch.)
$CH_2CH_2CH_3$	0.90 (t, 3) 1.78 (sextet, 2) 3.93 (t, 2) 7.33-8.40 (m, 5) 9.13 (s, 1)	6.43 (s, 2 exch.)
C_6H_5	7.26-8.30 (m, 10) 9.26 (s, 1)	6.70 (s, 2 exch.)
$CH_2C_6H_5$	5.28 (s, 2) 7.50(s)+7.60-8.03(m)(10) 9.20 (s, 1)	6.66 (s, 2 exch.)
$CH_2CO_2CH_3$	3.76 (s, 3) 4.91 (s, 2) 7.35-8.25 (m, 5) 9.13 (s, 1)	6.55 (s, 2 exch.)

a) Solvent: DMSO-d_6, TMS as internal standard.
Abbreviations: s = singlet; b = broad; t = triplet; m = multiplet; exch. = exchangeable.

b) Chemical shifts expressed in δ units.

Table XI. - Dibenzylidene Derivatives of Substituted Guanazoles. Proton Nuclear Magnetic Resonance Spectra.



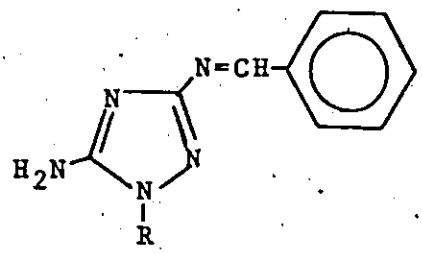
R	Chemical Shifts (ppm)[a,d]	
H	7.25-8.53 (m, 10)	9.50 (s, 2)
CH_3	4.01 (s, 3) 7.40-8.46 (m, 10)	9.34 (d, 2) 9.40
$CH_2CH_2CH_3$	0.93 (t, 3) 1.90 (sextet, 2) 4.40 (t, 2) 7.30-8.35 (m, 10)	9.40 (d, 2) 9.45
$CH_2CH_2CH_3$[b]	1.00 (t, 3) 2.05 (sextet, 2) 4.42 (t, 2) 7.23-8.50 (m, 10)	9.40 (d, 2) 9.46
$CH_2CH_2CH_3$[c]	0.98 (t, 3) 1.98 (sextet, 2) 4.31 (t, 2) 6.98-8.61 (m, 10)	9.26 (d, 2) 9.30
C_6H_5	7.35-8.36 (m, 15)	9.45 (d, 2) 9.52
C_6H_5[d]	7.26-8.36 (m, 15)	9.46 (d, 2) 9.53
$CH_2C_6H_5$	5.66 (s, 2) 7.46(s)+7.60-8.55(m)(15)	9.40 (d, 2) 9.50
$CH_2CO_2CH_2CH_3$	1.26 (t, 3) 4.30 (q, 2) 5.40 (s, 2) 7.32-8.47 (m, 10)	9.42 (d, 2) 9.48

a) Solvent: DMSO-d_6, TMS as internal standard unless otherwise specified.

Table XI. - continued

b) Solvent: $CDCl_3$, TMS as internal standard.
c) Solvent: CD_2Cl_2, TMS as internal standard.
Abbreviations: s = singlet; d = doublet;
t = triplet; q = quartet;
m = multiplet.
d) Chemical shifts expressed in δ units.

Table XII. - Monobenzylidene Derivatives of Substituted Guanazoles. Ultra-violet Spectra

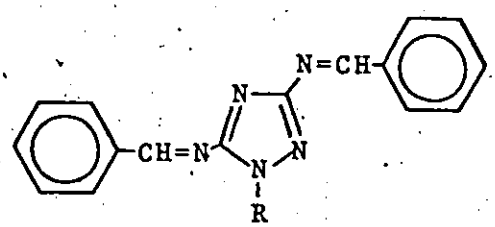


R	Wavelength (nm)[a]	Molar Extinction Coefficient, E x 10^3	Log E
H	211	13.0	4.1
	264	12.7	4.1
	318	9.8	4.0
CH_3	210	14.0	4.1
	218(sh)	11.4	4.0
	264	12.5	4.1
	320	10.6	4.0
$CH_2CH_2CH_3$	207	18.2	4.3
	217	13.3	4.1
	265	13.5	4.1
	323	11.8	4.1
C_6H_5	209	22.2	4.3
	262	17.0	4.2
	322	13.6	4.1
$CH_2C_6H_5$	209	20.0	4.3
	265	13.6	4.1
	321	11.5	4.1
$CH_2CO_2CH_3$	207	18.1	4.2
	265	14.0	4.1
	318	11.0	4.0

a) Solvent: ethanol.

Abbreviation: sh = shoulder.

Table XIII. - Dibenzylidene Derivatives of Substituted Guanazoles. Ultra-violet Spectra.



R	Wavelength (nm)[a]	Molar Extinction Coefficient, E x 10^3	Log E
H	205	4.7	3.7
	274	3.0	3.5
	340	2.4	3.4
CH_3	209	18.2	4.3
	219	19.0	4.3
	273	22.0	4.3
	334	21.5	4.3
$CH_2CH_2CH_3$	205	25.7	4.4
	217	23.5	4.4
	272	23.7	4.4
	335	26.6	4.4
	360(sh)	17.1	4.2
C_6H_5	206	26.0	4.4
	218	19.1	4.3
	290	26.5	4.4
$CH_2C_6H_5$	208	27.0	4.4
	217(sh)	23.2	4.4
	275	23.5	4.4
	336	21.4	4.3
$CH_2CO_2CH_2CH_3$	207	21.3	4.3
	218	19.5	4.3
	274	21.5	4.3
	334	19.8	4.3

a) Solvent: ethanol.
Abbreviation: sh = shoulder.

DISCUSSION

Preparation of guanazole

The improved method of Kaiser and Roemer (7), for the preparation of guanazole, as inferred from the results presented in Table I and previous methods described in the literature (46), most likely involves the participation of the mineral acid (HCl) in the reaction mechanism (54). A possible route to the product (guanazole) was shown in Scheme III (p.21).

Triazoles have been prepared from biguanides as illustrated by the reaction between p-hydroxyphenyl-biguanide and hydrazine (47). Numerous examples on the action of amines on cyanoguanidine to give substituted biguanides of the type shown in Scheme III (p.21) occur throughout the literature (48). The reaction is reported to have been successfully carried out by the conventional fusion techniques (videre Pellizzari's method for the preparation of guanazole (46)). An excess of acid obviates, however, the need for fusion of the reactants and allows aqueous media (videre Kaiser and Roemer's method for guanazole (7)) and other milder conditions (54) to be used. These milder conditions presumably prevent further reaction of guanazole with cyanoguanidine to give guanazoguanazole as observed in the experiments at higher temperature (22) or by the fusion technique (3) as mentioned earlier (p.5).

A highly coloured impurity was observed during the isolation and exposure to the air of the product obtained in

experiment 6, Table I. As tautomerism allows guanazoles to be hydrazo derivatives, the formation of these dark red unstable compounds has been explained (49,50) on the assumption that their corresponding cyclic azo derivatives of unknown structures, are the products formed because of the facile oxidation of the s-triazole ring.

Alkylation of guanazole

Alkylation of 3,5-diamino-1,2,4-triazole (guanazole) with several alkyl halides in the presence of sodium methoxide in refluxing methanol afforded only one alkylated product.

The results reported in this thesis for the benzylidene derivatives of the products, proved that the alkylated products obtained correspond to 1-alkylguanazoles in all cases.

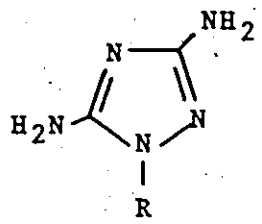
Four isomeric products XIX to XXII (p.45) can be postulated for mono-alkylation, if we consider only the diamino structure for guanazole. Guanazole alkylation could have been tentatively assigned to the number one position by analogy with other 1,2,4-triazoles as indicated in Table XIV. The possibility of tautomerism in the guanazole molecule, however, would lead to ambiguity of prediction as to the site for alkylation. The di-imino structure could conceivably give rise to alkylation products at the exocyclic nitrogen atoms. However neither in the case of 3-amino-s-triazole (45), nor in the present investigation, have products arising from such consideration ever been observed. The characteristic aromaticity of the 1,2,4-triazole in the guanazole molecule (as indicated by diazotization characteristics of aromatic amines) and its possibility of metal salt formation (pK_a = 4.43) (51), both would predict alkylation at the endocyclic nitrogen atoms of the 1,2,4-triazole ring. This consideration, however, would still

lead to ambiguity between N-1 and N-4 alkylation.

Alkylation of guanazole with methyl iodide in a basic medium took place at N-1 position, since the same product was obtained from methylhydrazine and cyanoguanidine (see Tables II-V).

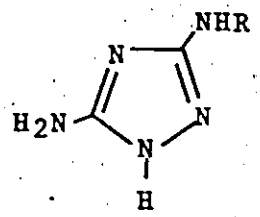
Table XIV. - Alkylation Products for Several 1,2,4-Triazoles

Starting Material	Alkylation Products	Conditions	Ref.
1,2,4-triazole	1-alkyl-1,2,4-triazole	methyl iodide or diazomethane	41
3,5-dimethyl- or 3,5-diphenyl-1,2,4-triazoles	1-alkyl derivatives	Na in methanol plus alkyl halide or diazomethane	42
3-phenyl- and 3-methyl-5-phenyl-1,2,4-triazoles	preferentially to N atom adjacent to C atom bearing the H or CH_3 group, resp.	Na in methanol plus methyl iodide	42
3-phenyl- and 3-methyl-5-phenyl-1,2,4-triazoles	mainly the vicinal N next to the phenyl group	diazomethane	42
3(5)-aryl-5(3)-amino-1,2,4-triazoles	1-alkyl and 2-alkyl derivatives	alkaline media	43
3(5)-amino-1,2,4-triazole	55% at N adjacent to C bearing NH_2 group; 40% at N vicinal to C bearing H atom; 5% at N-4	alkaline media	45
3(5)-amino-1,2,4-triazole	30% at N adjacent to C bearing NH_2 group; 25% at N vicinal to C bearing H atom; 45% at N-4	absence of base	45
5-furyl-3-amino-1,2,4-triazole	N-4 alkylation	neutral media	43



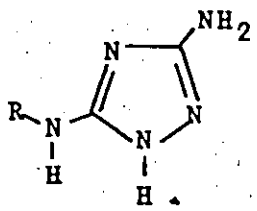
XIX

1-alkyl-3,5-diamino-1H-1,2,4-triazole



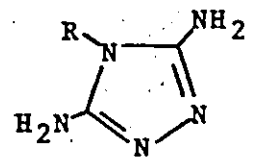
XX

3-alkylamino-5-amino-1H-1,2,4-triazole



XXI

3-amino-5-alkylamino-1H-1,2,4-triazole



XXII

3,5-diamino-4-alkyl-4H-1,2,4-triazole

These results were confirmed when the mono- and di-benzylidene derivatives of the methylated products were analyzed by proton nuclear magnetic resonance (vide infra).

In order to have a second guanazole derivative of known structure for comparison, 1-phenylguanazole was prepared from phenylhydrazine and cyanoguanidine. The preparation of the mono- and dibenzylidene derivatives of this known compound, and the analysis of these derivatives by PMR spectroscopy afforded results leading to the assignment of substitution at position one. This indirect method of structure elucidation was used for all other alkylation products obtained from a sufficient selection of alkyl halides. In the latter case, no published information was available for comparison since these alkylation products constitute new compounds.

This method was chosen in preference to the classical preparation of 1-substituted guanazoles, by the reaction of cyanoguanidine with the corresponding hydrazines, since most of these hydrazines were not easily available and in many cases would lead to undesired products.

Benzylidene derivatives of the alkylation products

Evidence for N-1 substitution

a) Proton nuclear magnetic resonance

The fact that dibenzylidene derivatives were obtained for all the alkylation products of guanazole provided good evidence that alkylation did not take place at the primary amino groups (exocyclic nitrogen atoms). However, these results still leave open the possibility for N-1 substitution and/or N-4 substitution.

If substitution would have taken place at the N-4 position, the symmetry (C_{2v}) of the corresponding dibenzylidene derivatives would have shown equivalence of the benzylidene protons and indistinguishability of these protons by PMR. On the other hand, if substitution had taken place at the N-1 position the loss of symmetry of the dibenzylidene derivatives (C_s) may give rise to different chemical shifts for the benzylidene protons due to non-equivalence. Tables X and XI respectively contain the complete chemical shift values of the mono- and dibenzylidene derivatives of the alkylation products. Differences in the chemical shifts between the two kinds of benzylidene protons are observed in all the dibenzylidene derivatives, except for the dibenzylidene derivative of the parent compound (i.e., guanazole), where the possibility of tautomeric interchange of the ring-nitrogen proton between positions N-1 and N-4 results in equivalence of the benzylidene protons under the experimental conditions used

for the determination of the spectrum. The largest difference in the chemical shift of benzylidene protons was found with the dibenzylidene derivative of 1-benzylguanazole.

Spectra of the monobenzylidene derivatives are characterized by high-field appearance of the benzylidene protons when compared to the values obtained with the dibenzylidene derivatives (see Table XV). These results could be interpreted as being due to the loss of conjugation in the monobenzylidene derivatives.

Two isomeric monobenzylidene derivatives could be postulated. However, only one isomer was isolated, in all cases, under the experimental conditions used. One of the possible reasons for this fact may involve the difference in reactivity of the two amino groups in the original 1-substituted guanazoles. As mentioned earlier (p.3) similar behavior has been observed in the reaction of guanazole and the two amino-1,2,4-triazoles in which only the 3-amino derivative reacted with an excess of diformylhydrazine. The 5-amino-1,2,4-triazole failed to give the reaction under the same conditions. Table XVI, column 4 shows differences of the same order of magnitude for the chemical shifts of similar N-alkyl groups of the free base and the monobenzylidene derivatives. These results may indicate that the same monobenzylidene derivative has been obtained in all cases.

Table XVI, column 5, shows differences of the same order of magnitude for the chemical shifts of similar

Table XV. - Comparison of chemical shift values of the vinyl protons in the mono- and dibenzylidene derivatives of substituted guanazoles[a]

R	Column 1 Monobenzylidene (ppm)	Column 2 Dibenzylidene (ppm)	Diff. in ppm in Column 2
H	9.20	9.50	-
CH_3	9.13	9.36 9.40	0.04
$CH_2CH_2CH_3$	9.13	9.40 9.45	0.05
C_6H_5	9.26	9.45 9.52	0.07
$CH_2C_6H_5$	9.20	9.40 9.50	0.10
CH_2CO_2R' (b)	9.13	9.42 9.48	0.06

a) Solvent: DMSO-d_6, TMS as internal standard.
b) R' = CH_3 in column 1 and R' = CH_2CH_3 in column 2.

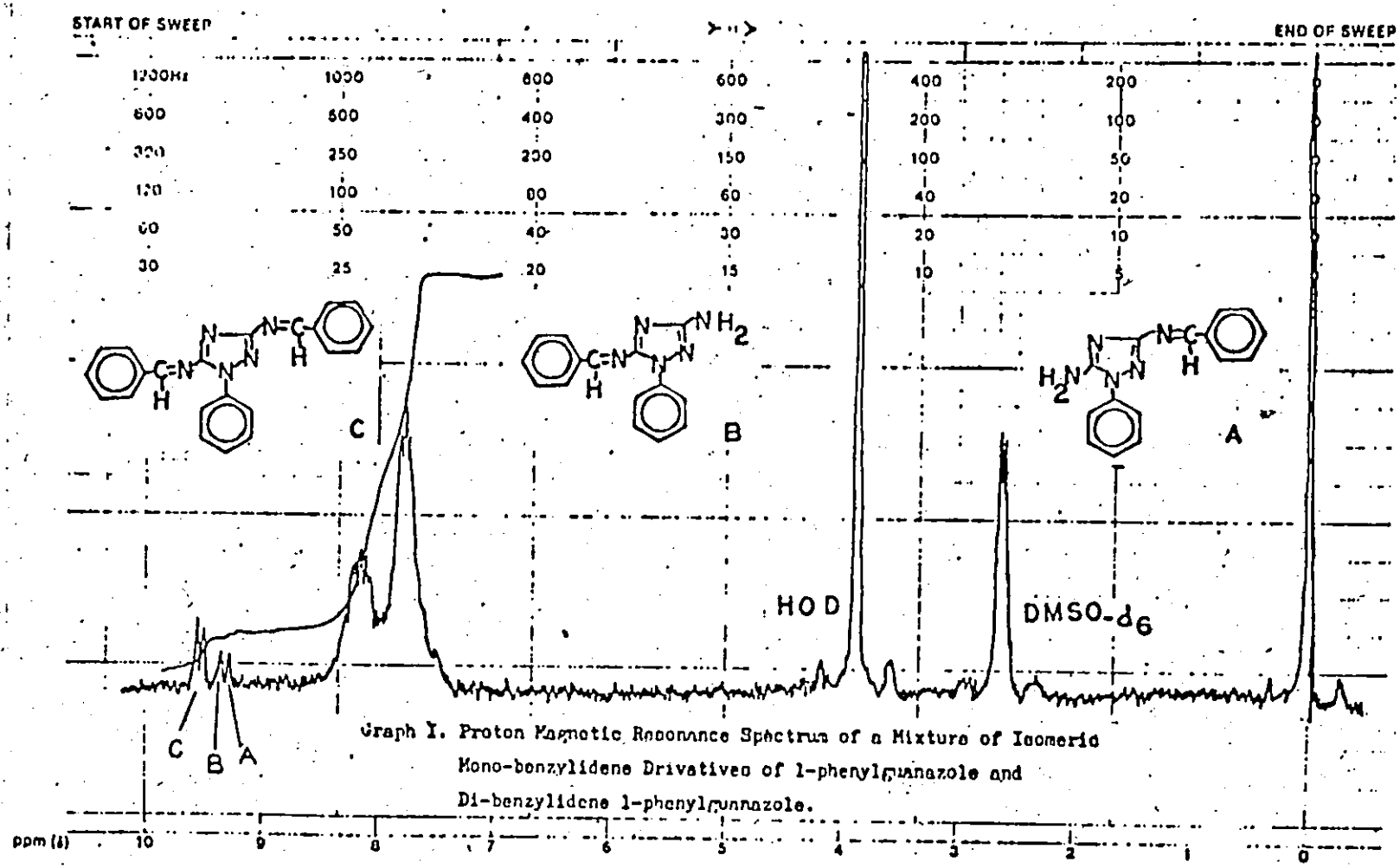
Table XVI. - Comparison of chemical shifts of the N-R groups in similar substituted guanazoles, and its mono- and dibenzylidene derivatives[a]

R	1 δ_1 Subst. guanazole	2 δ_2 Mono-benz.	3 δ_3 Di-benz.	4 $\Delta\delta_{2,1}$	5 $\Delta\delta_{3,1}$
$\underline{C}H_3$	3.30	3.60	4.01	0.30	0.71
$\underline{C}H_2CH_2CH_3$	3.60	3.93	4.40	0.33	0.80
$\underline{C}H_2C_6H_5$	4.90	5.28	5.66	0.38	0.76
$\underline{C}H_2CO_2R'$ (b)	4.58	4.91	5.40	0.33	0.82

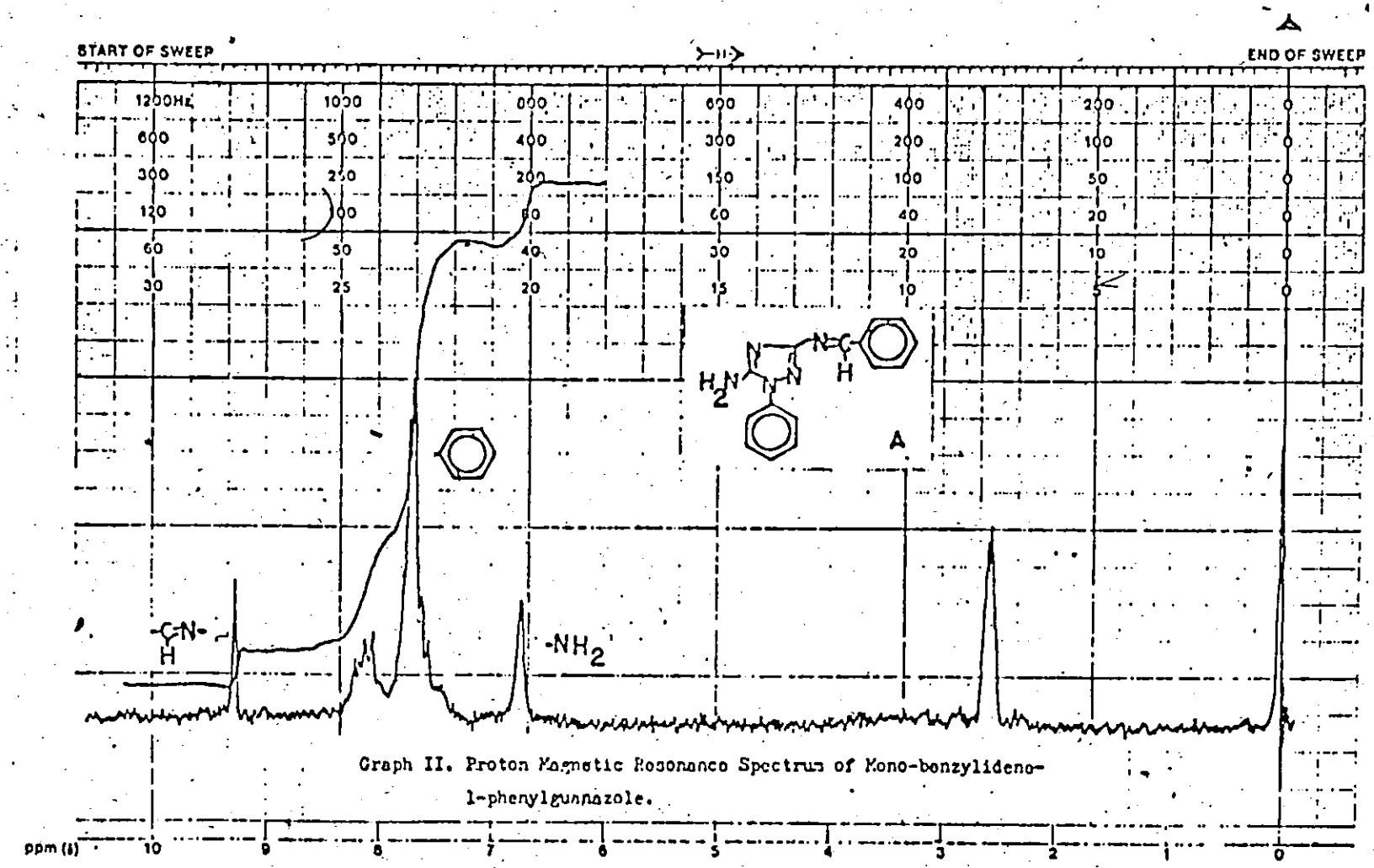
a) Solvent: DMSO-d_6, TMS as internal standard.
b) R' = CH_3 in columns 1 and 2; R' = CH_2CH_3 in column 3.

N-alkyl groups of the free base and the dibenzylidene derivatives. These differences, in all the examples of Table XVI, column 5, correspond to at least twice the values in column 4. These results may indicate that the presence of the second benzylidene group at the position 5 which is closer to the N-alkyl group and therefore should be expected to affect more the chemical shift of the vicinal group.

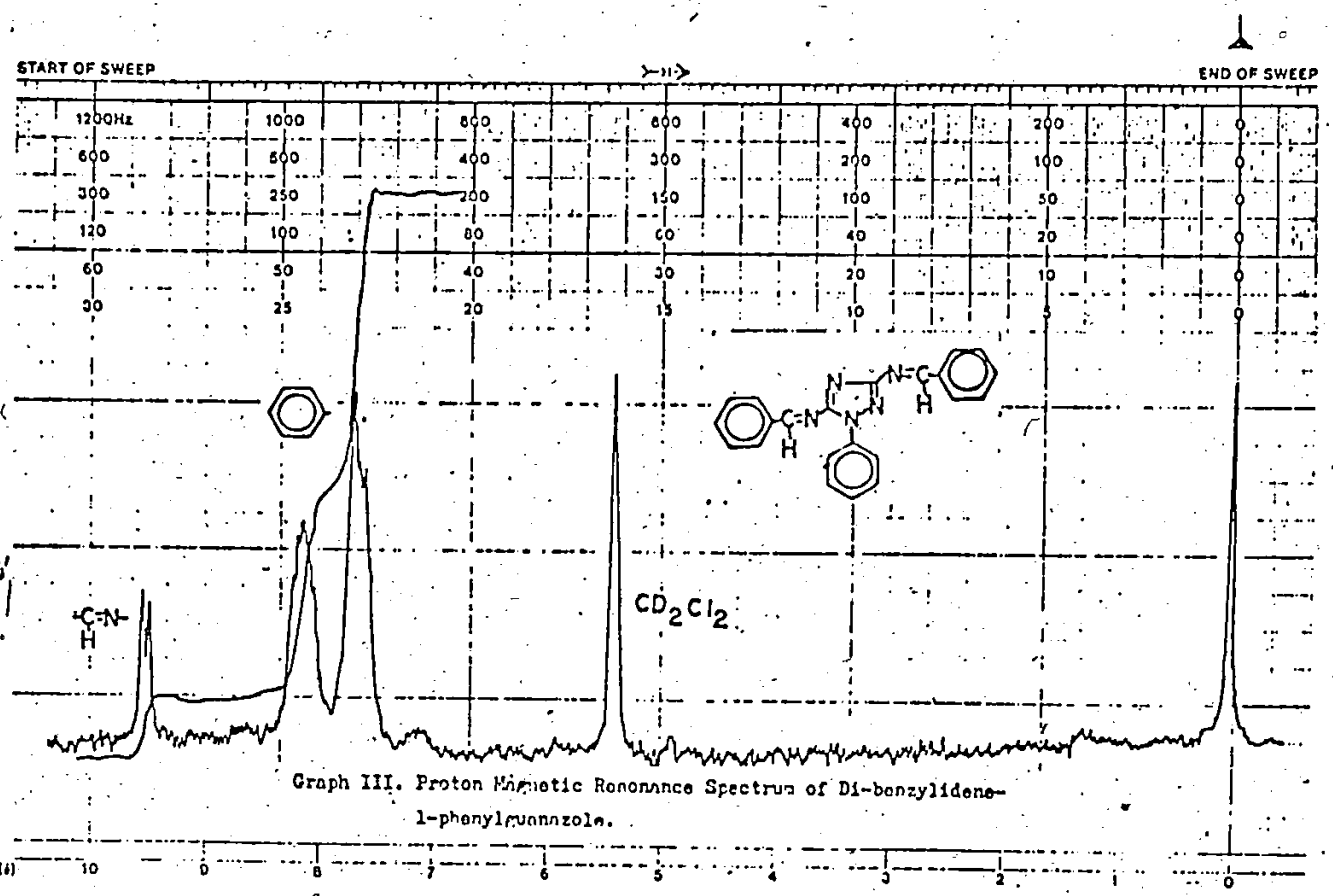
During the preparation of all the dibenzylidene derivatives, somewhat weak evidence for the presence of the other possible isomeric monobenzylidene derivative was obtained. For instance, an experiment was carried out in which a reaction mixture containing the dibenzylidene derivative and both (as detected by TLC but unsuccessfully separated) monobenzylidene derivatives of 1-phenylguanazole was stopped before complete conversion to the dibenzylidene derivative. The mixture was purified in the usual manner to obtain pure benzylidene mixtures and the proton magnetic resonance spectrum was obtained for this mixture. This spectrum was compared with the spectrum corresponding to the monobenzylidene derivative of 1-phenylguanazole obtained in the experiments at room temperature, and with the spectrum of the dibenzylidene derivative of 1-phenylguanazole obtained in an independent experiment. These spectra are shown in Graphs I-III: peaks A and C have the same chemical shifts as compared to the shifts observed with the <u>isolated</u> monobenzylidene derivative



Graph I. Proton Magnetic Resonance Spectrum of a Mixture of Isomeric Mono-benzylidene Drivatives of 1-phenylguanazole and Di-benzylidene 1-phenylguanazole.



Graph II. Proton Magnetic Resonance Spectrum of Mono-benzylideno-1-phenylguanazole.



Graph III. Proton Magnetic Resonance Spectrum of Di-benzylidene-1-phenylguanazole.

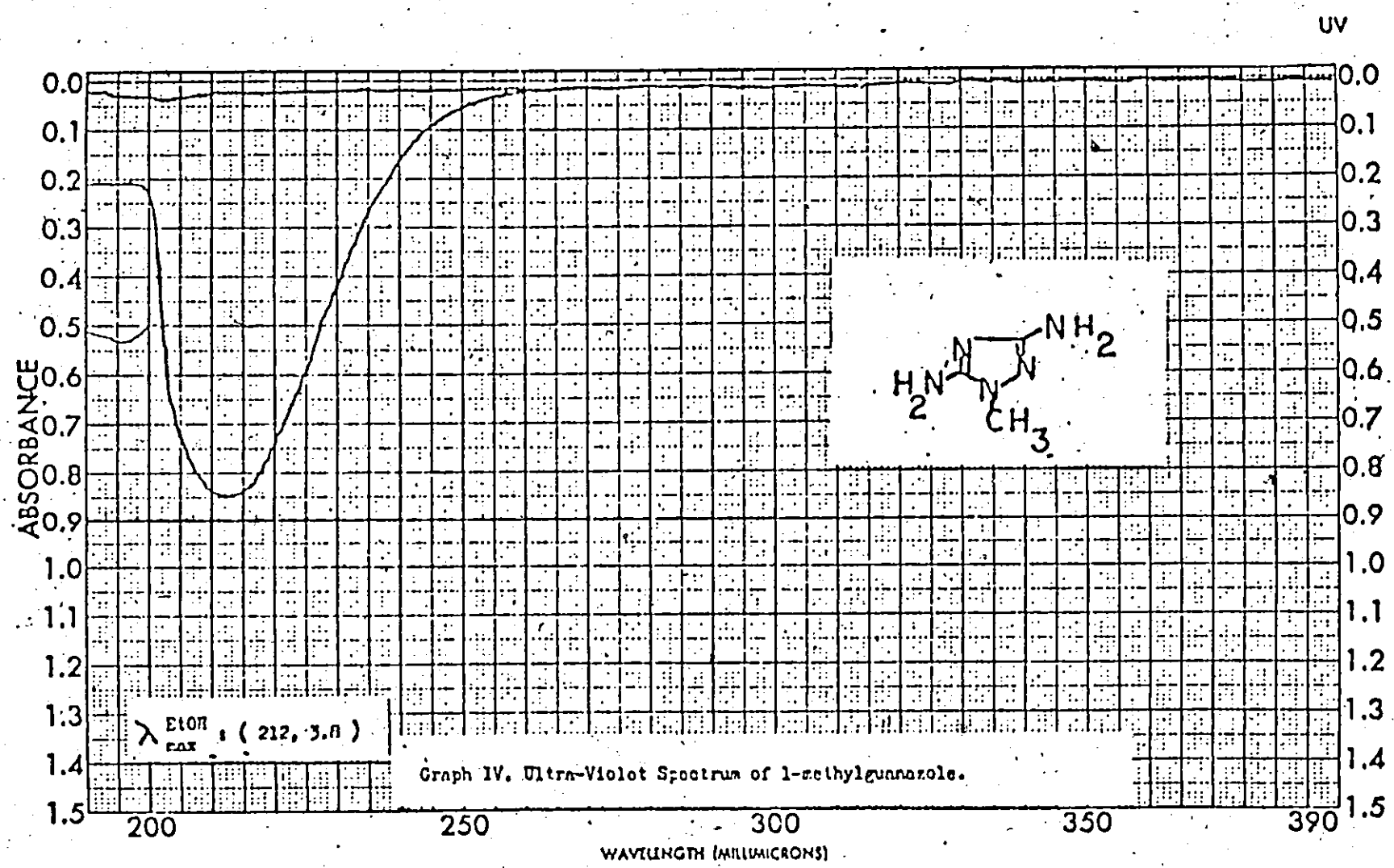
and dibenzylidene derivative, respectively. Peak B should correspond to the benzylidene proton of the other isomeric non-isolated monobenzylidene derivative. The intermediate value observed for the benzylidene proton in the isomeric non-isolated monobenzylidene derivative B (named after peak B), might be expected from the consideration that in this case a deshielding effect due to the proximity of the N-1 phenyl group should be more pronounced than in the isomeric isolated derivative A (named after peak A) where the N-1 phenyl group is much more distal.

The method of analysis used above has been successfully applied to the structure determination of the mono- and dibenzylidene derivatives of 3,4,5-triamino-4H-1,2,4-triazole (guanazine) (52).

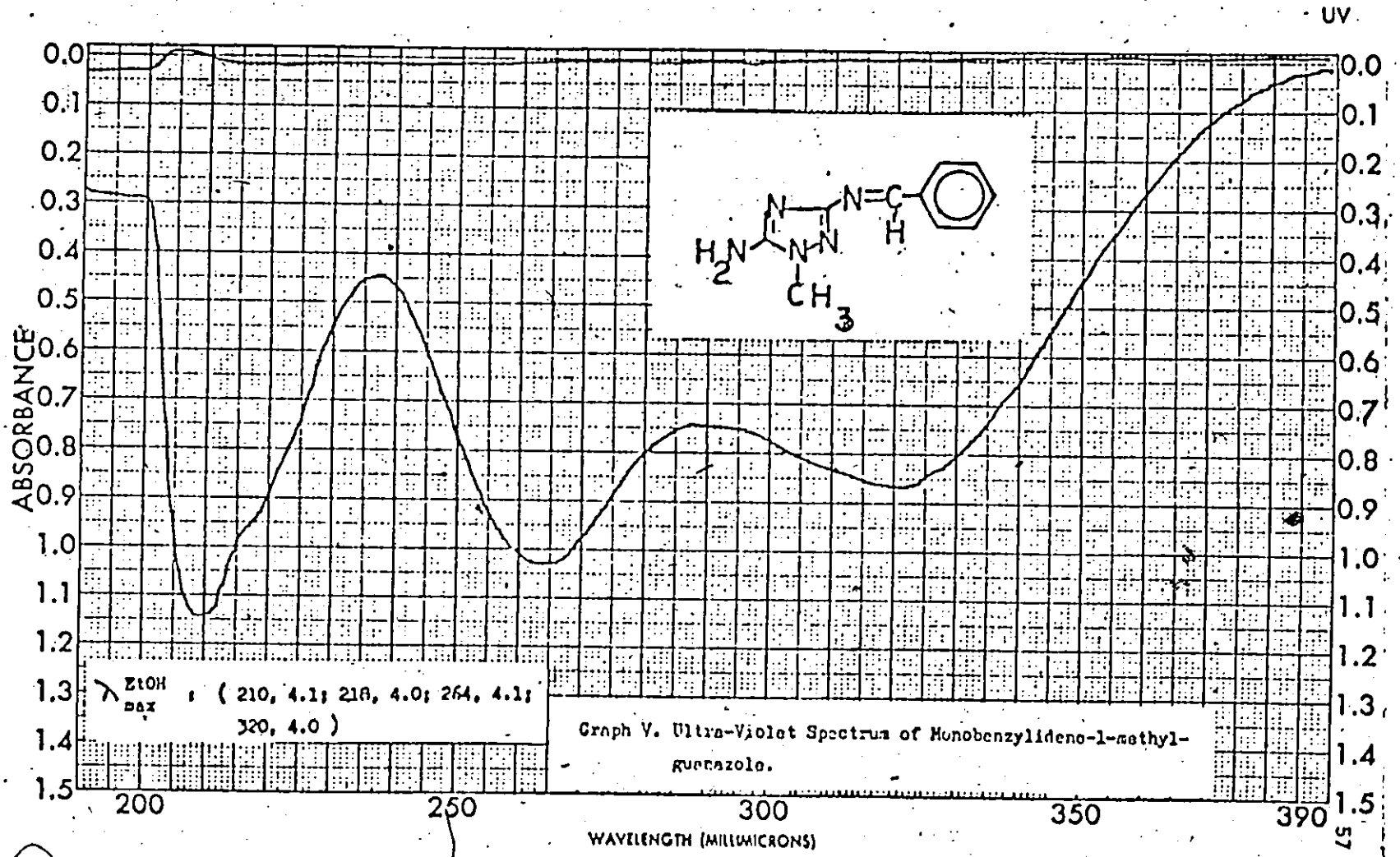
b) The ultra-violet spectra

3,5-Diamino-1,2,4-triazole (guanazole) and its alkyl derivatives prepared for this investigation (Table V) have no absorption bands above 215 nm. The effect of substitution by alkyl groups do not alter considerably the overall spectrum. Also included in Table V are the absorption values obtained for 1-phenylguanazole. The band at longer wavelengths may be due to the presence of the phenyl group known to cause serious changes in the spectra consequent with increased conjugation path.

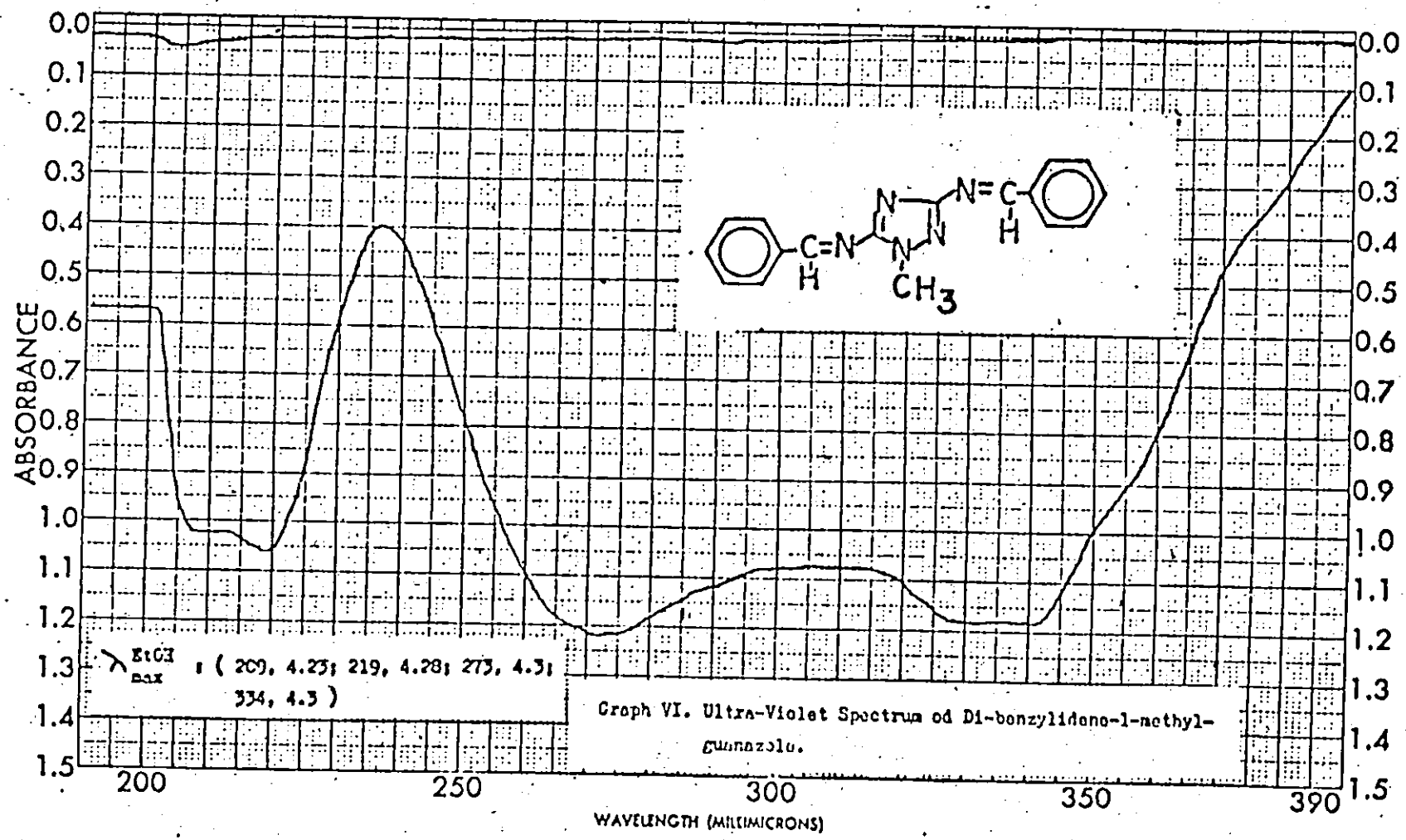
The U.V. absorption values for the mono- and dibenzylidene derivatives of alkylated guanazoles are presented in Tables XII-XIII. The values for the mono- and di-



Graph IV. Ultra-Violet Spectrum of 1-methylguanazole.



Graph V. Ultra-Violet Spectrum of Monobenzylideno-1-methyl-guanazole.



Graph VI. Ultra-Violet Spectrum od Di-benzylidene-1-methyl-guanazole.

benzylidene derivatives of 1-phenylguanazole are also included in Tables XII-XIII.

Similarities are observed among each type of derivatives as well as among both groups.

The bands at longer wavelengths obtained for the dibenzylidene derivatives show a bathochromic-hyperchromic shifts. These results could be considered as the direct resultant of the extended conjugation present in the dibenzylidene derivatives.

c) The infra-red spectra

The spectra of guanazole and the alkylation products from guanazole have strong absorption bands in the region 3400-3100 cm^{-1}. These absorptions are probably caused by the symmetrical and antisymmetrical stretching vibrations of the $-NH_2$ groups and also, in guanazole, by the ring N-H vibrations.

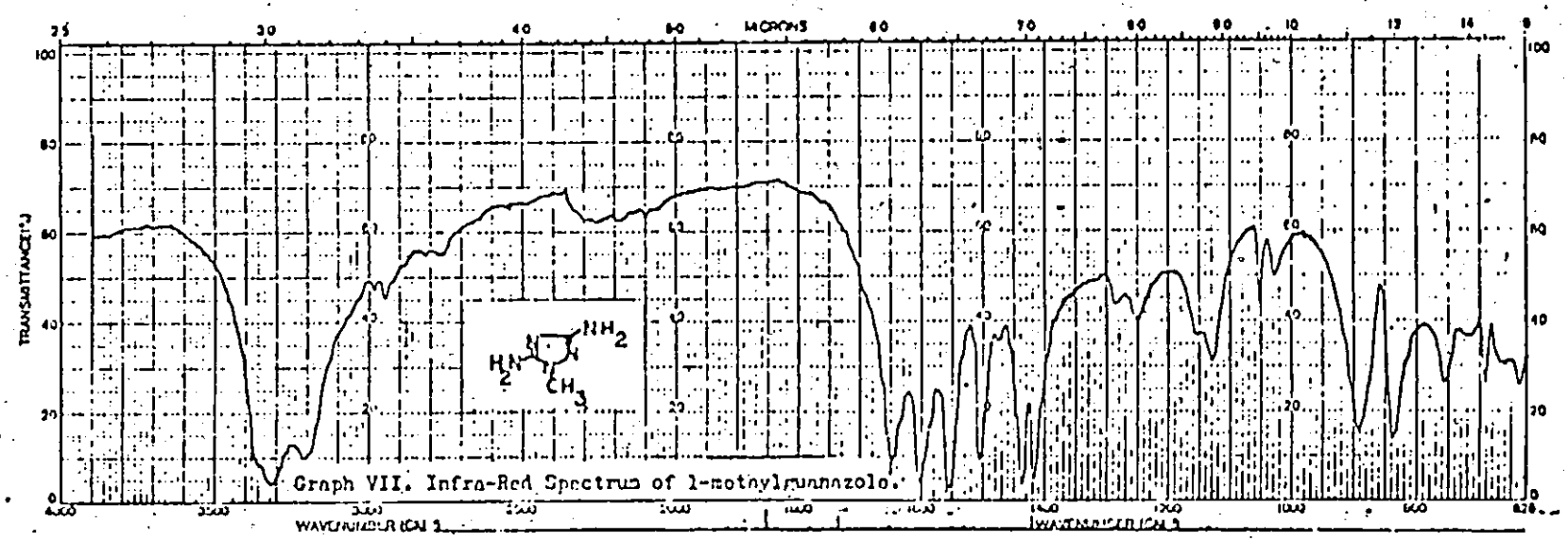
Strong absorption bands in this region are also present in the spectra of the monobenzylidene derivatives of guanazole and of the monobenzylidene derivatives of 1-substituted guanazoles. These absorptions are probably caused by the remaining $-NH_2$ group and also, in guanazole, by the ring N-H absorptions.

No absorption appeared in this region for the corresponding dibenzylidene derivatives, which indicates that both amino groups have reacted with benzaldehyde to give the corresponding double Schiff's bases. The infra-red spectrum of the dibenzylidene derivative of guanazole

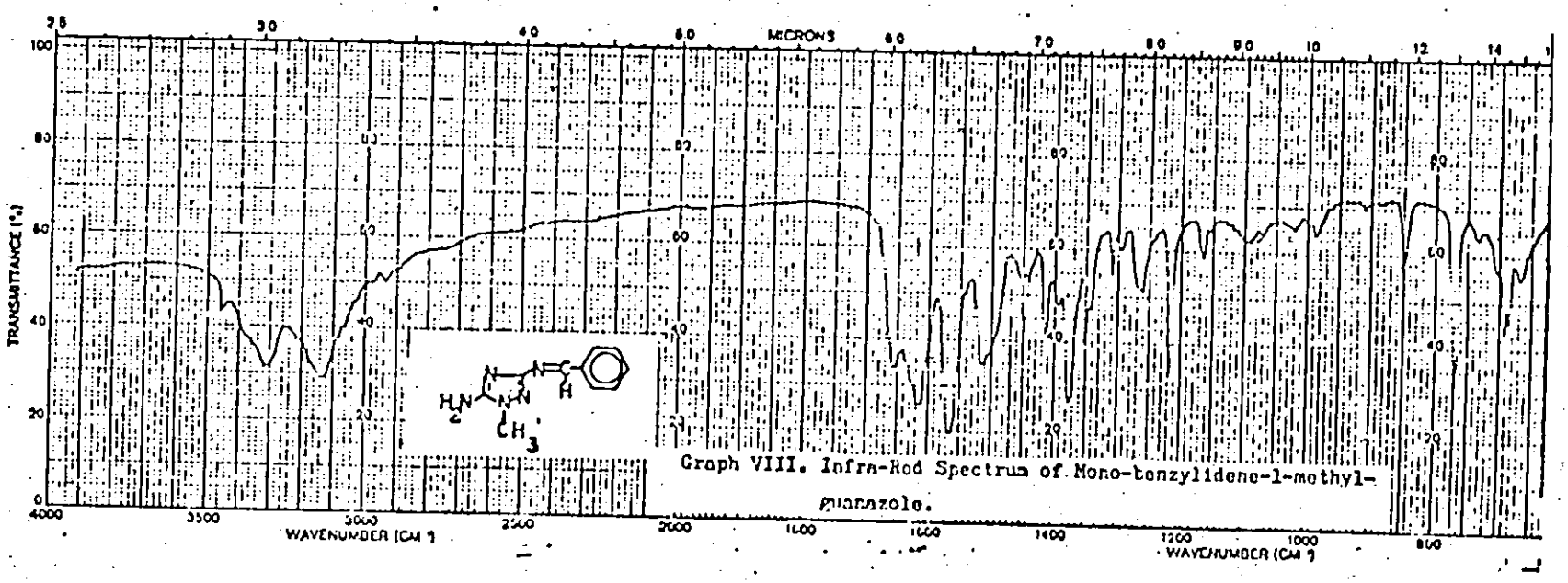
presented an absorption band at 3240 cm^{-1} which can be attributed to the ring N-H vibrations.

The absorption bands for the region 1650-1590 cm^{-1} corresponding to the N-H deformation vibrations is simplified in the order: alkylated guanazole, monobenzylidene derivative and dibenzylidene derivative.

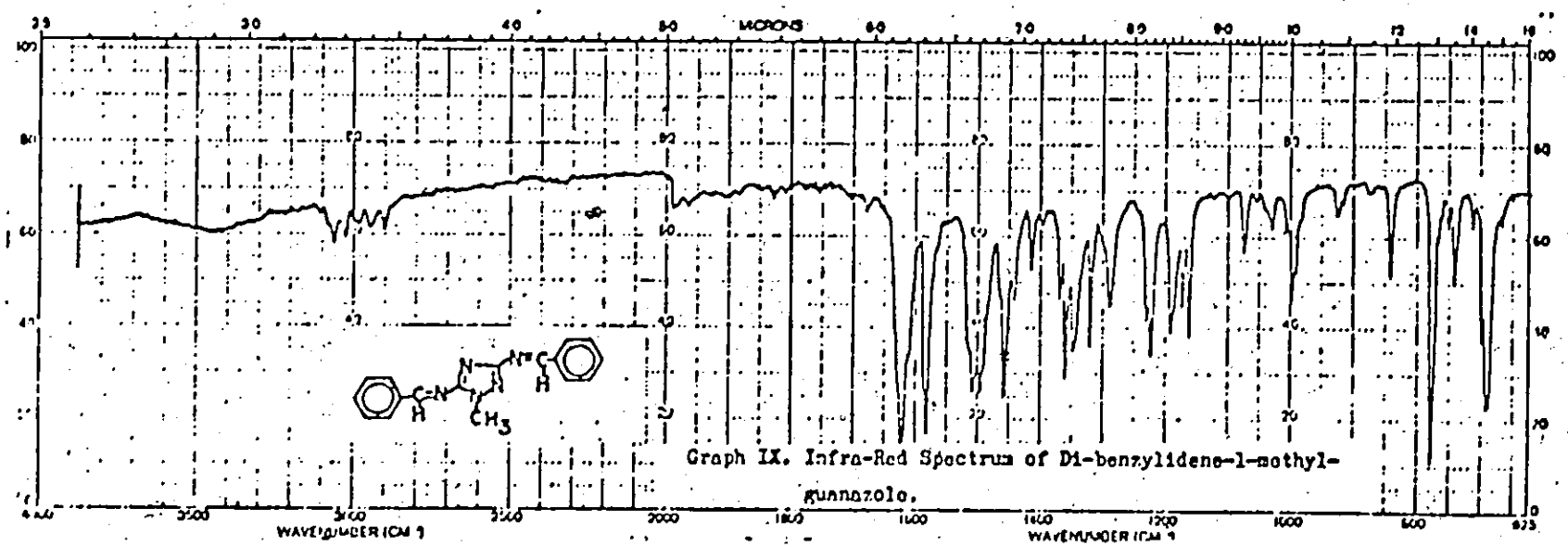
The region near 1630 cm^{-1} has been assigned as a characteristic absorption of the cyclic C=N stretching vibrations (53). See graphs VII, VIII and IX.



Graph VII. Infra-Red Spectrum of 1-methylguanazole.



Graph VIII. Infra-Red Spectrum of Mono-benzylidene-1-methyl-guanazole.



Graph IX. Infra-Red Spectrum of Di-benzylidene-1-methyl-guanazole.

Acid and base stabilities of benzylidene derivatives of guanazole and of alkylated guanazoles

The mono- and dibenzylidene derivatives of guanazole and alkylated guanazoles have shown instability to mineral acids even at room temperature. This evidence has been obtained from proton magnetic resonance and ultra-violet spectroscopies before and after addition of acid to a solution of the derivatives.

The proton magnetic resonance spectra of these derivatives in DMSO-d_6 gave the results shown in Table IX. When mineral acid (DCl/D_2O) was added to the n.m.r. tubes, and the spectra re-run immediately after the addition of acid, the characteristic =C-H absorption peaks for the mono- and dibenzylidene derivatives disappeared and absorptions at 10.15 ppm due to the presence of free benzaldehyde (i.e., its O=C-H) was observed instead.

The ultra-violet spectrum of the dibenzylidene derivative of 1-propylguanazole was obtained in ethanol (Table X). The spectrum was re-run after addition of mineral acid (aq. HCl). The absorption bands at higher wavelengths became weaker and the resultant spectrum resembled that of the corresponding monobenzylidene derivative of 1-n-propylguanazole (Graph XV). Instability of benzylidene derivatives of guanazole to acid hydrolysis has been previously observed (14).

Papini and Checchi (14) have also reported that a series of condensation products obtained from guanazoles

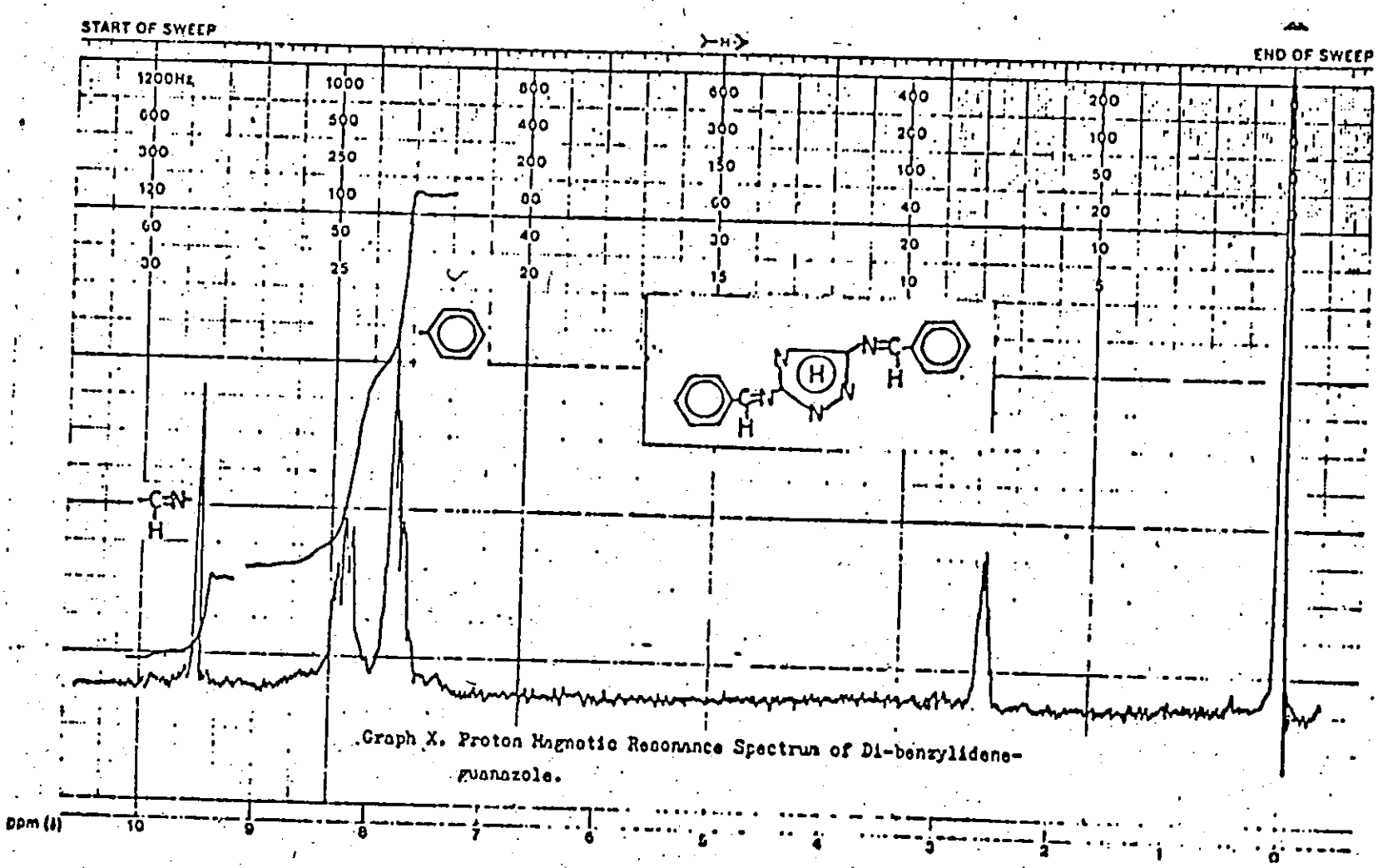
and different aromatic aldehydes were stable to alkalis. However, in this investigation it was observed that upon addition of $NaOD/D_2O$ to a solution of the dibenzylidene derivative of guanazole in DMSO-d_6 no appreciable change was observed in the proton magnetic resonance spectrum of this compound when the spectrum was re-run immediately after the addition of the base. Some decomposition was observed, however, when the proton magnetic resonance of the same sample was re-run after twenty-four hours.

The proton magnetic resonance spectrum of the dibenzylidene derivative of 1-n-propylguanazole was taken in DMSO-d_6. Then $NaOD/D_2O$ was added to the p.m.r. tube and the spectrum re-run immediately after; the results in this case shows the disappearance of the doublet characteristic of the benzylidene protons of the dibenzylidene derivative (9.40 and 9.45 ppm). Peaks at 10.05 ppm and at 9.13 ppm characteristic of the aldehydic protons of benzaldehyde and of the monobenzylidene derivative were observed instead. Upon standing at room temperature for a longer period of time (10 days), the absorption peak for the monobenzylidene derivative also disappeared.

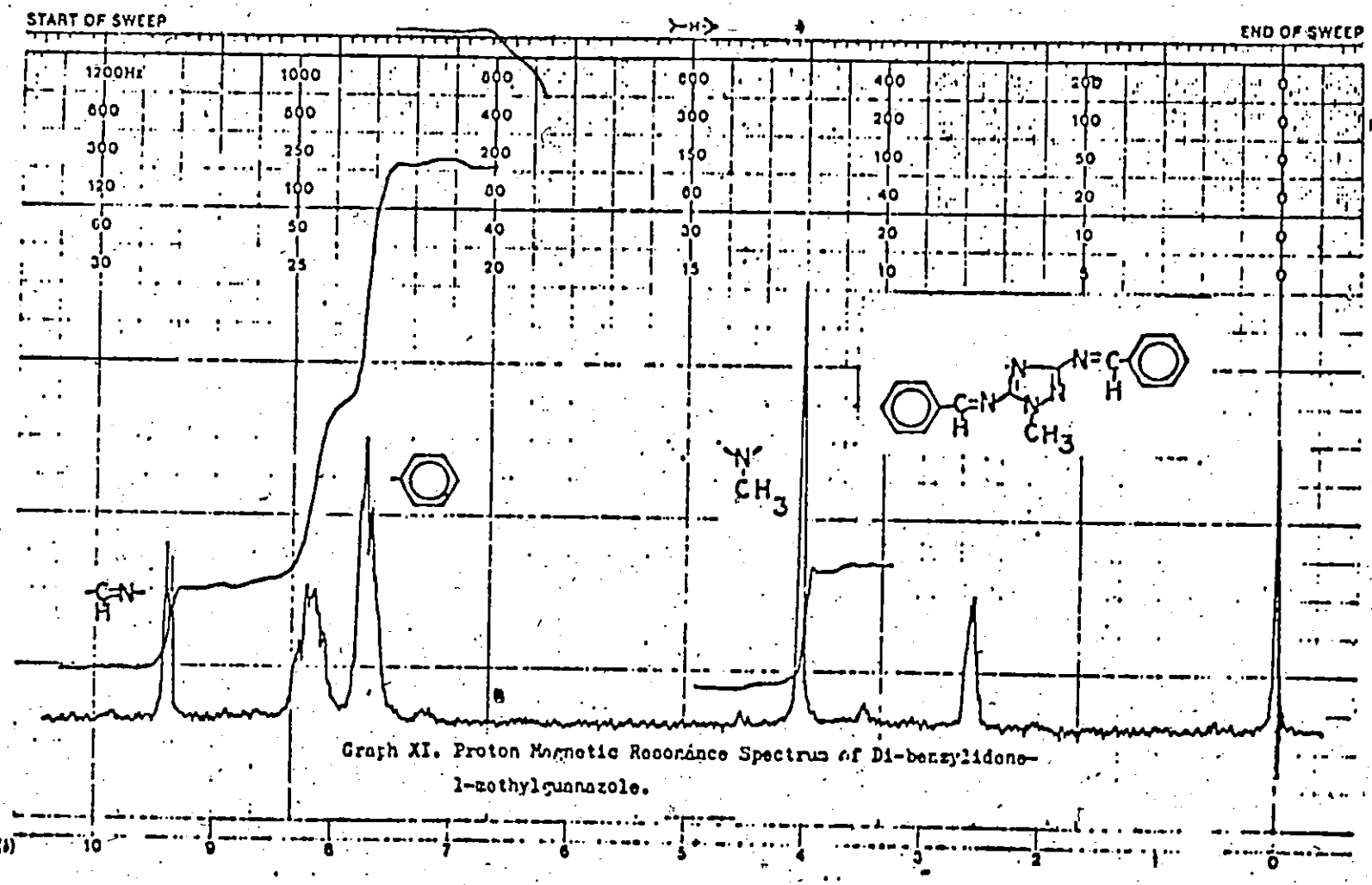
Similar results were obtained for the dibenzylidene derivative of 1-methylguanazole. Absorptions at 10.05 ppm and 9.13 ppm for the aldehydic protons of benzaldehyde and of the monobenzylidene derivative, respectively, were observed. Complete hydrolysis was observed after twenty-four hours at room temperature.

The fact that one benzylidene group cleaved easier than the other might be related to the preferential formation of one isomeric monobenzylidene derivative and to the different reactivities observed in the amino groups of the guanazoles and of the 3-amino- and 5-amino-1,2,4-triazoles.

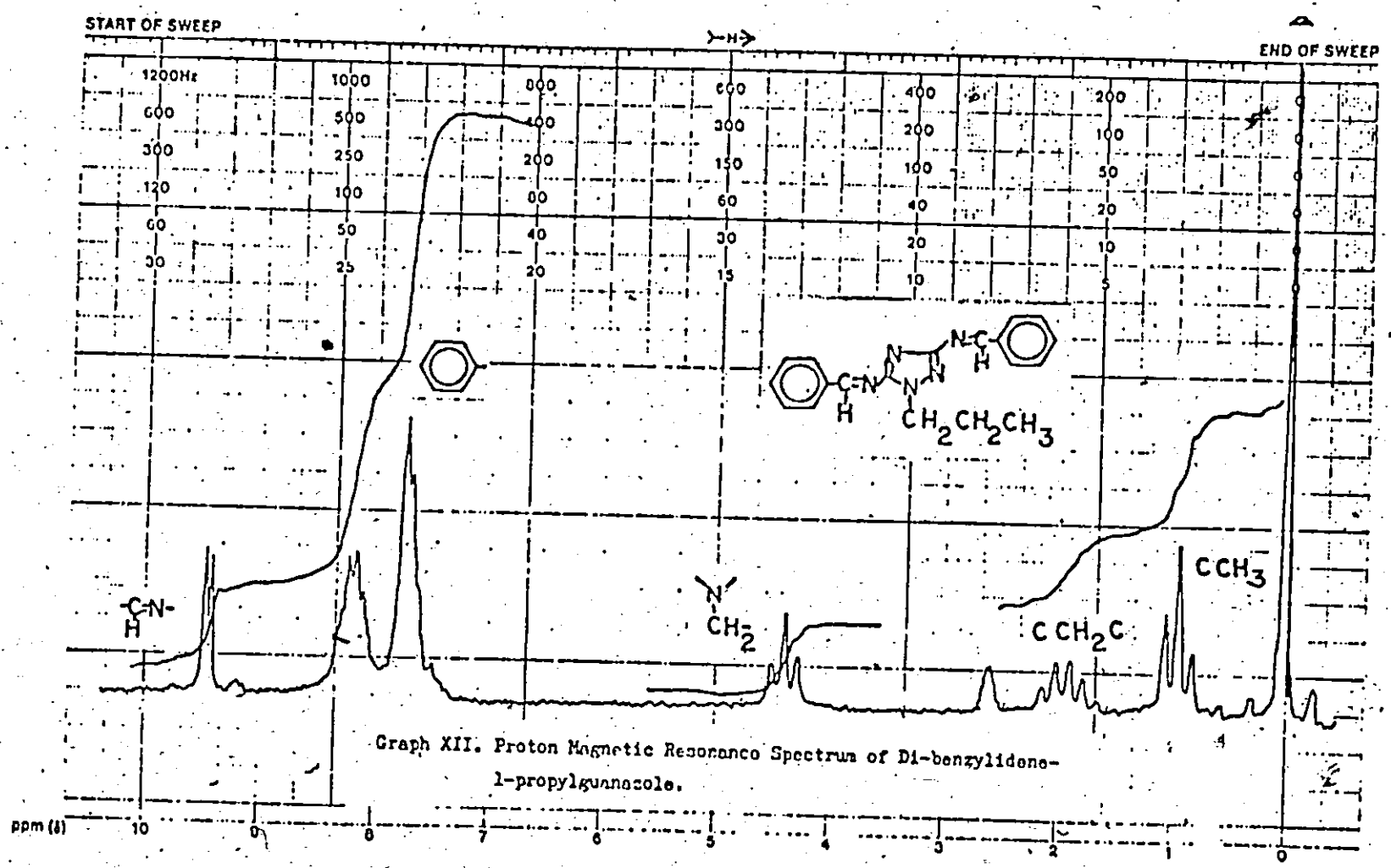
Graphs X to XIV, the proton magnetic resonance spectra give the assignment of the peaks thus indicating that alkylation products consist of 1-substituted guanazoles.



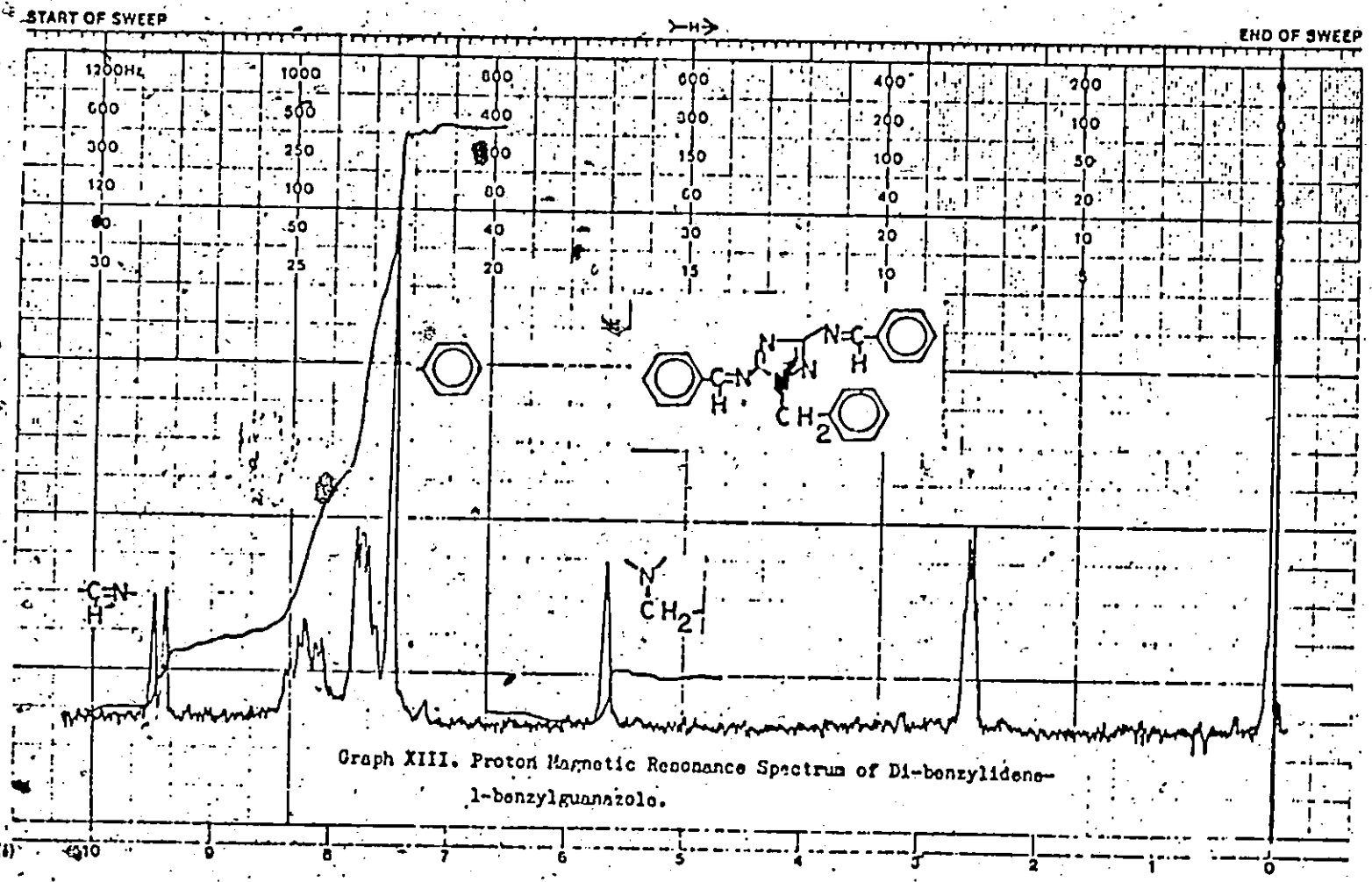
Graph X. Proton Magnetic Resonance Spectrum of Di-benzylidene-guanazole.



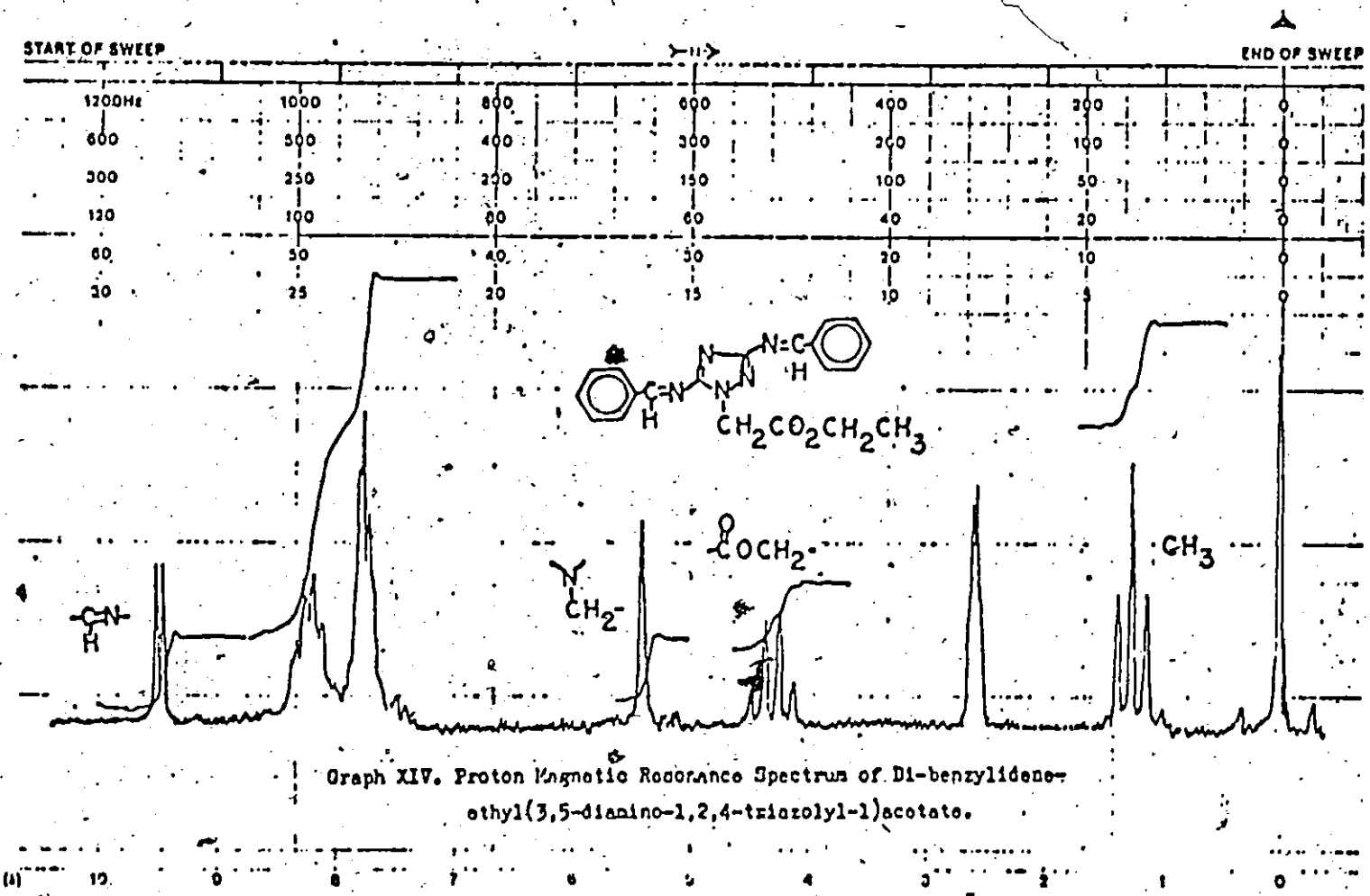
Graph XI. Proton Magnetic Resonance Spectrum of Di-benzylidene-1-methylguanazole.



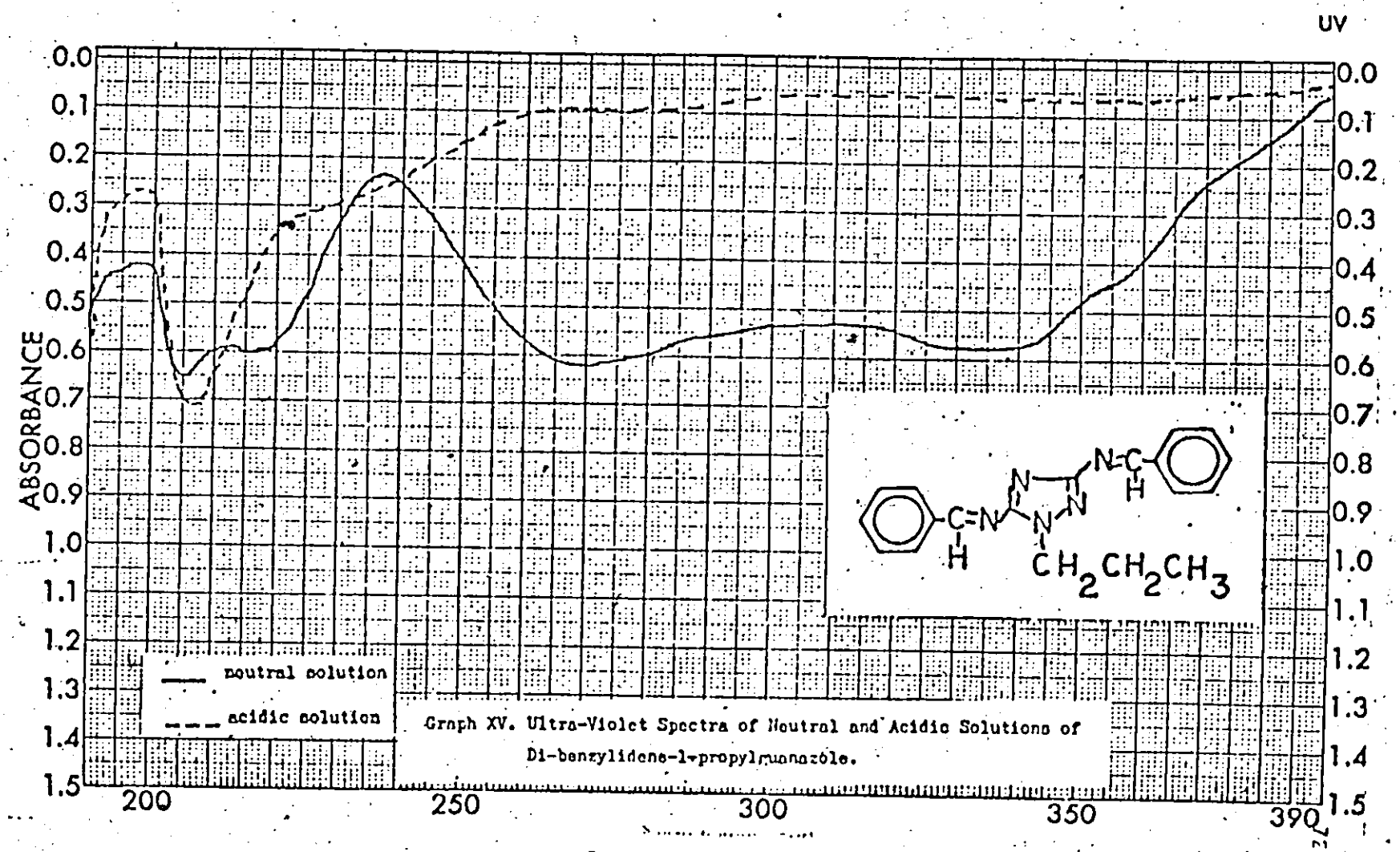
Graph XII. Proton Magnetic Resonance Spectrum of Di-benzylidene-1-propylguanazole.



Graph XIII. Proton Magnetic Resonance Spectrum of Di-benzylidene-1-benzylguanazole.



Graph XIV. Proton Magnetic Resonance Spectrum of Di-benzylidene-ethyl(3,5-diamino-1,2,4-triazolyl-1)acetate.



Graph XV. Ultra-Violet Spectra of Neutral and Acidic Solutions of Di-benzylidene-1-propylguanazole.

SUMMARY

1.- A study has been made on the alkylation of 3,5-diamino-1,2,4-triazole using a series of alkyl halides in basic media. Only the mono-alkylated products were observed and isolated under the above conditions. The examination of the alkylated products and their mono- and dibenzylidene derivatives by spectroscopic techniques (IR, NMR, UV), elemental analysis and TLC gave evidence that alkylation had taken place at N-1 of the triazole ring.

2.- A series of experiments was conducted to study the preparation of guanazole from cyanoguanidine and hydrazine dihydrochloride, hydrazine monohydrochloride or hydrazine hydrate respectively, varying the solvents and the reaction times. It was found that the preparation of guanazole from cyanoguanidine and hydrazine dihydrochloride constituted the most convenient method taken after the patent of Kaiser and Roemer (7).

3.- The alkylation of guanazole in basic media constitutes a valuable alternative for the preparation of 1-alkylguanazoles when the corresponding monoalkylhydrazines are not readily available or when the reaction of the alkylhydrazines with cyanoguanidine may give rise to different types of compounds instead of the desired 1-substituted guanazoles due to the nature of the alkyl group involved in the reaction.

4.- The following 1-substituted guanazoles prepared in this study constitute new compounds, viz.,

1-n-propyl-3,5-diamino-1,2,4-triazole,

1-benzyl-3,5-diamino-1,2,4-triazole,

methyl (3,5-diamino-1,2,4-triazol-1-yl) acetate,

(3,5-diamino-1,2,4-triazol-1-yl) acetic acid.

Also, a series of mono- and dibenzylidene derivatives of the above and of 1-methyl- and 1-phenylguanazoles constitute new compounds.

5.- Cyclization of methyl (3,5-diamino-1,2,4-triazol-1-yl) acetate or of (3,5-diamino-1,2,4-triazol-1-yl) acetic acid to 2-amino-4H-imidazo[1,2-b]-s-triazole-5-one could not be brought about under the various experimental conditions used. This result was attributed to the weak base character of the amino groups in guanazole. The pK_a value for guanazole is 12.12 (51).

EXPERIMENTAL

The infra-red spectra were taken on a Perkin Elmer Model 257 Grating Infrared Spectrophotometer. The samples were prepared in the form of pellets with potassium bromide. Main absorption bands are reported in Tables III, VIII and IX.

The Proton Magnetic Resonance Spectra were obtained on a 60 MHz, E M 360 NMR Spectrometer, Varian Anaspect. The samples were dissolved in DMSO-d_6, unless otherwise specified, using TMS as internal standard. The chemical shift values were expressed in ppm units from the TMS peak.

The ultra-violet spectra were taken on a Perkin Elmer Model 202 Ultraviolet-Visible Spectrophotometer. The samples were dissolved in absolute ethanol.

Thin-Layer Chromatography (TLC):-

T.L.C. were performed on silica-gel plates prepared by Eastman Kodak with fluorescent indicator.

Solvents used:- (A) Ethyl acetate-abs. ethanol (1:2, v/v).

(B) Methanol-chloroform-conc. ammonium hydroxide (4:4:1, v/v/v).

(C) Ethyl acetate.

The plates were developed in the appropriate solvent. The solvent was removed by hot air and the plates were placed in an atmosphere of iodine vapors. Guanazole and the substituted guanazoles gave brown spots. The benzylidene derivatives were visible under the ultra-violet light.

Preparation of 3,5-diamino-1,2,4-triazole (guanazole)

This compound was prepared according to the method of Kaiser and Roemer (7).

Cyanoguanidine (210 g., 2.5 mole) and hydrazine dihydrochloride (260 g., 2.5 mole) were powdered and mixed in a two-liter three-necked flask equipped with a magnetic stirring bar and a thermometer. Water (650 ml.) was added to the mixture. The magnetically stirred suspension was warmed up to 30°C. on a steam bath. An exothermic reaction began, the heating bath was removed and the reaction maintained itself at approximately 50°C. for twenty minutes with intermittent cooling in an ice bath until the exothermic phase subsided. The resulting solution was heated at 50°C. for two hours. The reaction mixture was cooled in an ice bath, and neutralized with a solution of sodium hydroxide (200 g.) in water (400 ml.). The temperature was not allowed to rise over 40°C. during the addition of the base. The solution was evaporated to dryness on a rotatory evaporator at 50°C. The solid residue was dissolved in 3.7 liters of boiling methanol and filtered hot from the salts. The filtrate was concentrated and allowed to crystallize to yield the final product (218 g., 88%), melting point 203-204°C. (m.pt. 201-202°C., ref. 11). The picrate had a melting point of 245-248°C. (m.pt. 248-249°C., ref. 11).

I.r.: - 3400, 3310, 3130, 1625, 1585, 1560, 1480, 1415, 1340, 1055, and 800 cm^{-1}.

U.v.:- (nm, log E) (212, 3.7).

P.m.r.:- 6.30 ppm (b, exch.).

R_f:- 0.25 (solvent A).

Several attempts at the preparation of guanazole in various conditions are summarized in Table I.

Preparation of 1-methyl-3,5-diamino-1,2,4-triazole (1-methylguanazole)

To an ice-cooled solution of methylhydrazine (4.6 g., 0.1 mole) in water (10 ml.), conc. hydrochloric acid (16.5 ml., 0.2 mole) was added (resultant pH slightly acidic). Cyanoguanidine (8.4 g., 0.1 mole) was added to this acidic solution. The suspension was warmed up to 30°C. on a steam bath. The temperature of the exothermic reaction mixture was allowed to rise spontaneously up to 50-55°C. and then cooled. The resultant solution was heated approximately at 80°C. for five hours. The reaction was then cooled to yield, upon crystallization, the monohydrochloride salt of the product (8.33 g., 56%) after drying in a vacuum oven at 50°C. for eighteen hours. The melting point thus obtained was 215°C. (m.pt. 218-220°C., ref. 11).

The free base was obtained from a sample of the monohydrochloride salt dissolved in water. The resultant solution was rendered alkaline with 2 N sodium hydroxide a and absorbed on a AG-50w-8, 100-200 mesh, cation exchange resin column (excess) in the hydrogen ion form. The column was rinsed with water until the effluent was neutral to indicator paper. Elution from the column with 1.5 N ammonium hydroxide followed by evaporation to dryness, dissolution in methanol, drying with anhydrous sodium sulfate and concentration yielded the free base with a melting point of 145°C. (m.pt. 157-159°C., ref. 10).

I.r.:- 3350(sh), 3310, 3200, 1640, 1590, 1545, 1495, 1430, 1410, 1125, 880, 830, 750, 685, and 630 cm^{-1}.

U.v.:- (nm, log E) (212, 3.8)

P.m.r.:- (free base) 3.30(s, 3); 4.75(s, 2 exch.); 5.85(s, 2 exch.).

(monohydrochloride) 3.46(s, 3); 8.16(s, 2 exch.); 7.30(s, 2 exch.).

R_f:- 0.27 (solvent A).

To a saturated solution of picric acid in 95% ethanol, an ethanolic solution of the free base was added. Two recrystallizations of the picrate afforded a material melting at 267° (m.pt. 273-274°C., ref. 11).

The use of methylhydrazine as a free base in ethanol at total reflux with cyanoguanidine for ten hours or the use of methylhydrazine dihydrochloride at lower temperature (50°C.) with cyanoguanidine failed to give the 1-methylguanazole in good yields.

Preparation of 1-phenyl-3,5-diamino-1,2,4-triazole (1-phenylguanazole)

To a suspension of phenylhydrazine monohydrochloride (14.46 g., 0.1 mole) in water (50 ml.), cyanoguanidine (8.4 g., 0.1 mole) was added. The mixture was stirred at approximately 50°C. until complete solution was achieved. The mechanically stirred reaction mixture was heated on a steam bath for three hours. The reddish residue obtained on evaporation to dryness was treated with 40% potassium hydroxide solution and the crude product was filtered and dried under vacuum for eighteen hours. Crystallization of the crude product from ethanol (100 ml.) yielded the expected product (7 g., 41%) melting at 175-176°C. (m.pt. 173.7-175°C., ref. 8). The picrate had a melting point of 230-232°C. (m.pt. 226-227°C., ref. 8; m.pt. 233-234°C., ref. 11).

I.r.:- 3450, 3425, 3300, 3165, 1645(sh), 1620, 1570, 1535, 1500, 1470, 1450, 1390, 1320, 1090, 1065, 1040, 910, 760, 695, and 675 cm^{-1}.

U.v.:- (nm, log E) (209, 4.1; 268, 3.9)

P.m.r.:- 7.0-8.0(m, 5); 5.10(s, 2 exch.); 6.13(s, 2 exch.).

R_f:- 0.39 (solvent A).

Alkylation reactions of guanazole

Reaction of guanazole with methyl iodide

Sodium methoxide (0.6 g., 0.011 mole) was added to a stirred solution of guanazole (1 g., ca. 0.01 mole) in methanol (100 ml.). The solution thus obtained was heated under reflux and a solution of methyl iodide (1.72 g., 0.012 mole) in methanol (15 ml.) was added dropwise over a period of thirty minutes. The reaction mixture was refluxed for an additional ninety minutes. The reaction mixture was then cooled and sodium methoxide (0.6 g., 0.011 mole) was added followed by the addition of a solution of methyl iodide (1.72 g., 0.012 mole) in methanol (15 ml.). This new mixture was then refluxed for three hours and the solution was evaporated to dryness. Ethanol was added to the semi-solid residue then neutralized with 2 N hydrochloric acid.

A solution of picric acid (3.4 g.) in a minimum amount of hot ethanol was added to the neutralized ethanolic solution. Upon cooling, the picrate (2.35 g., 68.7%) of the product, melting at 253-258°C., was obtained. Two recrystallizations of a sample of the crude picrate raised the melting point to 266-267.5°C. (m.pt. 273-274°C., ref. 11). The compound was identified as 1-methylguanazole. The infra-red spectrum was identical to that of the picrate of the product prepared from cyanoguanidine and methylhydrazine.

The proton magnetic resonance spectrum is: 3.43 (s, 3);

7.75 (s, exch.); 8.65 (s, aromatic protons of picric acid).

The picrate was dissolved in hot water and absorbed on AG-1, x-8, 100-200 mesh, (Bio Rad Labs.) anion exchange resin column in the acetate form, which retained the picric acid. The column was rinsed with water and the effluent was evaporated. The oily residue from the evaporation was dissolved in benzene and the resulting solution then evaporated to dryness. This process was repeated three times, with the result that traces of water were eliminated. This final residue was crystallized from methanol-diethyl ether to give the free base corresponding to 1-methyl-guanazole (0.75 g., 66.3%) melting at 145°C. (m.pt. 157-159°C., ref. 11). The infra-red spectrum of this product was identical to an authentic sample of 1-methyl-guanazole prepared from cyanoguanidine and methylhydrazine. Proton magnetic resonance, ultra-violet and infra-red spectroscopies and thin-layer chromatography confirmed the above results.

Alternatively, the picrate of the product and an excess of the anion exchange resin were stirred in ethanol at room temperature for thirty minutes. The resin was filtered and the free base of the product was isolated upon concentration of the colorless filtrate.

Other experiments for the alkylation of guanazole with methyl iodide under different conditions are summarized in Table II.

Reaction of guanazole with n-propyl iodide

To a solution of guanazole (20 g., ca. 0.2 mole) in methanol (500 ml.) was added sodium methoxide (21.6 g., 0.4 mole) and n-propyl iodide (38 g., 0.224 mole). The mixture was refluxed for three hours and a sample was checked by TLC. No further significant change was observed even after forty-eight hours of refluxing as shown by thin-layer chromatography. The reaction mixture was evaporated to dryness. The pH was adjusted to a value of 8 by the addition of 2 N hydrochloric acid to the oily residue. The resulting solution was then evaporated to dryness. This final residue was dissolved in ethanol-methanol (9:1, v/v) and filtered from the salts. The filtrate was added to a saturated solution of picric acid in ethanol. The crude picrate of the product was obtained upon cooling (44 g.). This material was heated under reflux in ethanol-methanol (9:1, v/v) (800 ml.). A solid (13.2 g.) corresponding to the picrate of unreacted guanazole was filtered from the hot solution. The filtrate upon cooling afforded a material (22.3 g., 30%) melting at 190°C.; two recrystallizations yielded the pure picrate (16.6 g.) melting at 194-195°C.

P.M.R.: - 0.9(t, 3); 1.73(sextet, 2); 3.83(t, 2); ca. 8.0(exch.); 8.8(s, aromatic protons of picric acid).

The original filtrate mainly contained some product and unreacted guanazole as indicated by thin-layer chromatography.

The free base was obtained from the pure picrate dissolved in hot water. The hot solution was absorbed on AG-1, x-8, 100-200 mesh, (Bio Rad Labs.) anion exchange resin column, in the acetate form. The column was rinsed with water. The colorless effluent was evaporated. The oily residue was evaporated twice from benzene to remove traces of water. The residue thus obtained was crystallized from ethanol-diethyl ether to yield the free base corresponding to 1-n-propylguanazole melting at 110-112°C.

I.r.: - 3395(sh), 3300, 3170, 2960, 2925, 2870, 1635, 1585, 1550, 1480, 1440, 1415, 1380(sh), 1340, 1155(broad), 1100(broad), 1050, 895, 780, 685, and 660 cm^{-1}.

U.v.: - (nm, log E) (213, 3.8)

P.M.R.: - 0.80(t, 3); 1.56(sextet, 2); 3.60(t, 2); 4.66(b, 2 exch.); 5.86(s, 2 exch.).

R_f: - 0.35 (solvent A)

Analysis: $C_5H_{11}N_5$; % N (calc'd) = 49.65; % N (found) = 49.04.

Reaction of benzyl iodide with guanazole

Benzyl iodide was prepared from benzyl bromide and sodium iodide by the standard procedure of halogen exchange in acetone (the Finkelstein procedure, Ber., 43, 1531 (1910)).

Benzyl bromide (34.2 g., 0.2 mole) was added to a stirred solution of sodium iodide (30 g., 0.2 mole) in acetone (300 ml.). The precipitate of sodium bromide was filtered. The filtrate was divided into two equal volumes and each portion was evaporated. The residues were evaporated from methanol to eliminate the traces of acetone. The residues thus obtained were redissolved in methanol.

Sodium methoxide (6 g., 0.11 mole) was added to a solution of guanazole (10 g., 0.1 mole) in methanol (500 ml.). Benzyl iodide (17.1 g., 0.1 mole) in methanol (as per above) was added to the stirred solution. The resulting mixture was refluxed for twelve hours and a second equivalent of benzyl iodide in methanol was added. The reaction mixture was refluxed for another four hours, then cooled in an ice-bath, followed by the addition of 2 N hydrochloric acid until a pH of 8. Evaporation of the solution gave a solid residue which was dissolved in ethanol-methanol (9:1, v/v) and filtered hot from the salts. A hot solution of picric acid in ethanol-methanol (9:1, v/v) was added to the filtrate. Upon cooling, the picrate of the product was obtained (24 g., 57%), melting at 212-215°C.

The proton magnetic resonance spectrum is: 3.85(broad,

exch.); 5.05(s, 2); ca. 7.4(s, 5); 8.7(s, aromatic protons of picric acid).

The free base was obtained from the above crude picrate by dissolving in hot water. The hot solution was absorbed on a AG-1, x-8, 100-200 mesh, (Bio Rad Labs.) anion exchange resin column in the acetate form, which retained the picric acid. The column was rinsed with hot water and the colorless effluent was evaporated down to give a solid residue (7.64 g., 40%) melting at 165°C. This material upon recrystallization from benzene gave pure 1-benzylguanazole (4.08 g.) melting at 169-170°C.

I.r.: - 3310, 3220, 3020, 1625, 1580, 1550, 1490, 1480, 1450, 1435, 1415, 1360, 1255, 1200, 1145, 1095, 1040, 1020, 940, 875, 820, 750, 690, and 635 cm^{-1}.

U.v.: - (nm, log E) (210, 4.1).

P.M.R.: - 4.90(s, 2); 7.30(s, 5); 4.76(broad, 2 exch.); 6.08(s, 2 exch.).

R_f: - 0.43 (solvent A).

Analysis: $C_9H_{11}N_5$; % N (calc'd) = 37.38; % N (found) = 37.38.

The conversion of the picrate of the product to the free base was more efficiently achieved in the following way: - The picrate of the product was dissolved in ethanol at room temperature. An excess of the anion exchange resin was added and the mixture stirred for some thirty minutes.

After the resin was filtered, the free base was isolated from the colorless filtrate upon evaporation to dryness and crystallization of the solid residue from benzene.

Reaction of guanazole with ethyl bromoacetate

Sodium methoxide (1.08 g., 0.02 mole) and ethyl bromoacetate (3.36 g., 0.02 mole) were added to a stirred solution of guanazole (2 g., 0.02 mole) in methanol (50 ml.). The resulting solution was refluxed for eighteen hours. The reaction mixture was then evaporated to dryness and the residue was dissolved in ethanol-water (pH neutral). The solution thus obtained was added to a hot saturated solution of picric acid in ethanol. Upon cooling, the crude picrate of the product was obtained (4.96 g., 62%). Recrystallization from ethanol afforded the pure picrate (3.1 g., 38.7%) melting at 235-237°C. The proton magnetic resonance indicated ester exchange with the solvent used in the substitution reaction. The product obtained is the picrate of methyl (3,5-diamino-1,2,4-triazolyl-1)acetate and the proton magnetic resonance for this methyl ester is: 3.75 (s, 3); 4.8 (s, 2); 8.0 (b, exch.); 8.65 (s, aromatic protons of picric acid).

To obtain the free base, the above methyl ester picrate derivative was dissolved in hot water. The resulting hot solution was absorbed on a AG-1, x-8, 100-200 mesh anion exchange resin column in the acetate form (Bio Rad Labs.). The column was rinsed with water and the colorless eluate was concentrated. Upon cooling, crystals of the product (1.2 g., 35%) melting at 179-181°C. were obtained. These crystals corresponded to methyl (3,5-diamino-1,2,4-triazolyl-1)acetate.

I.r.: - 3420, 3330, 3180, 3000, 2980, 1740, 1630, 1590, 1560, 1550, 1485, 1440, 1420, 1340, 1255, 1085, 1045, 1010, 955, 880, 850, 755, and 685 cm^{-1}.

U.v.: - (nm, log E) (215, 3.8).

P.M.R.: - 3.71 (s, 3); 4.58 (s, 2); 4.81 (broad, 2 exch.); 6.06 (b, 2 exch.).

R_f: - 0.35 (solvent A).

Analysis: $C_5H_9N_5O_2$; % N (calc'd) = 40.92; % N (found) = 40.44.

Preparation of (3,5-diamino-1,2,4-triazolyl-1)acetic acid

Methyl (3,5-diamino-1,2,4-triazolyl-1)acetate (1.71 g., 0.01 mole) was stirred at room temperature for eighteen hours in 2 N sodium hydroxide (30 ml.). The resulting light colored solution was adjusted to pH 7 by the dropwise addition of 6 N hydrochloric acid. A white solid crystallized immediately (1.5 g., 100%) with a melting point of 290°C.

A sample of the hydrolysis product was redissolved in 2 N sodium hydroxide and reprecipitated by acidification with formic acid. This purified product melted at 294°C. This product corresponded to (3,5-diamino-1,2,4-triazolyl-1)-acetic acid, and was soluble in mineral acid; it can be recovered by neutralization with base.

I.r.: - 3380, 3280, 2980, 1705, 1665, 1605, 1580, 1525, 1465, 1425, 1395, 1385, 1310, 1080, 1010, 950, 910, 875, 755, 675, and 645 cm^{-1}.

U.v.: - (nm, log E) (215, 1.4).

P.M.R.: - 4.81 (s, 2) (Solvent, DMSO-d_6 + DCl/D_2O).

R_f: - 0.21 (solvent B).

Analysis: $C_4H_7N_5O_2 \cdot 1/2\ H_2O$

% (calc'd)			% (Found)		
C	H	N	C	H	N
30.57	5.13	42.15	31.07	5.68	42.50

Mass spectrum[a] of (3,5-diamino-1,2,4-triazolyl-1) acetic acid

The mass spectrum of the title compound was very simple. The isotopic analysis was in good agreement with the theoretical value for $C_4H_7N_5O_2$.

m/e	Found	$C_4H_7N_5O_2$ (theoretical)
157	100	100
158	6.29	6.42
159	0.75	0.58

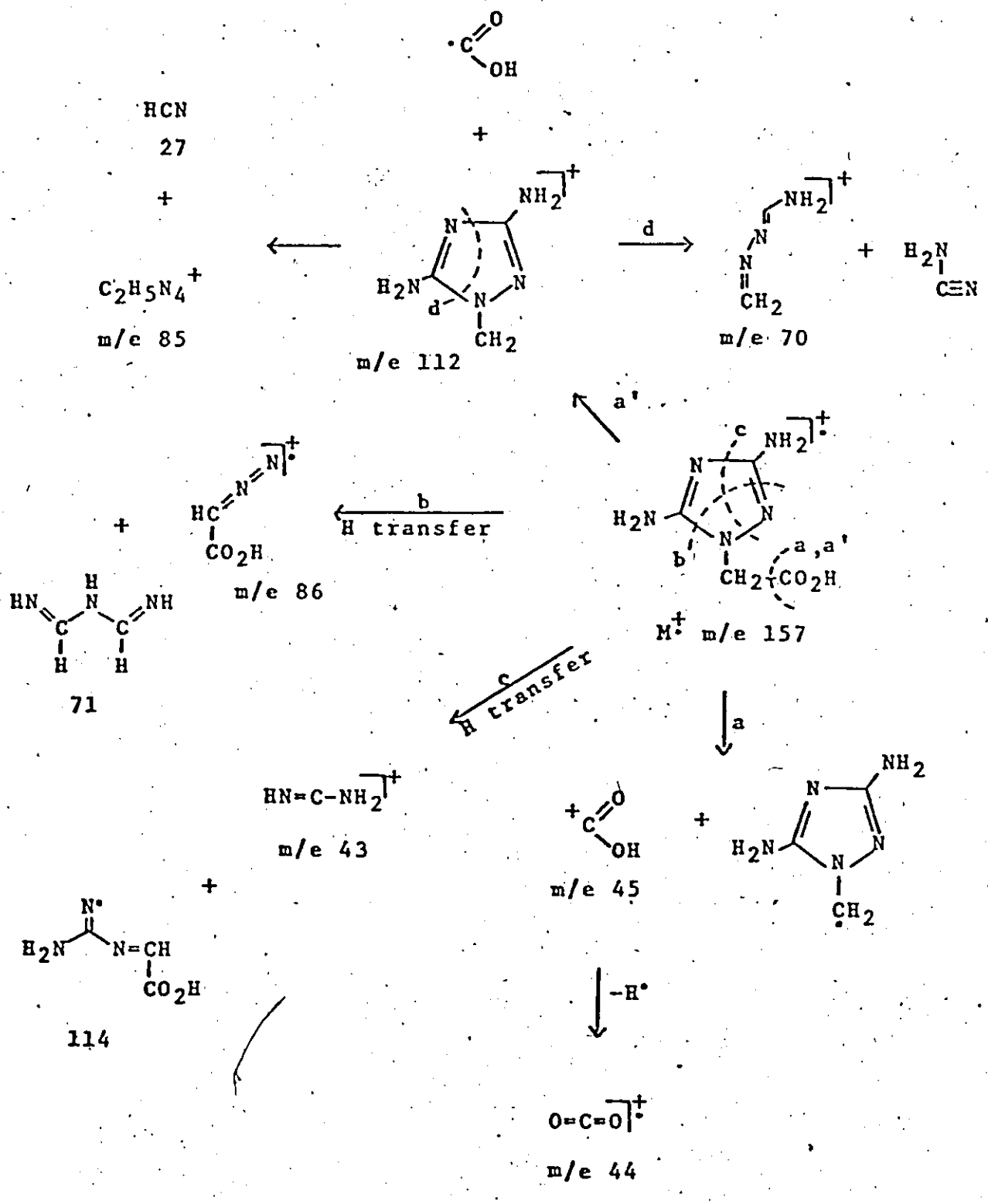
The fragmentation pattern has been rationalized in an analogous manner to previously reported mass spectra of 1,2,4-triazoles (56,57). (Scheme IV).

a) The mass spectrum was performed by Morgan Schaffer Corporation, Montreal, Quebec.

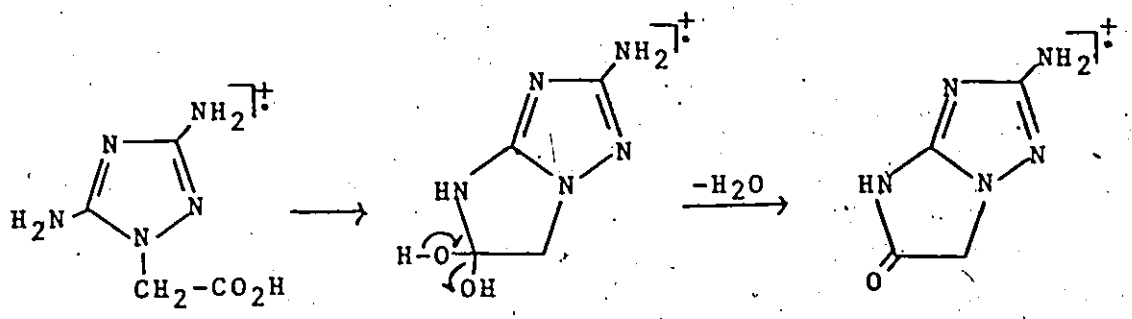
Scheme IV

Possible Fragmentation Pattern for

(3,5-Diamino-1,2,4-triazolyl-1)acetic Acid



Scheme IV (cont'd)



$M^{+\cdot}$ m/e 157 m/e 157 m/e 139

Preparation of the monobenzylidene derivatives of guanazole and 1-substituted guanazoles

General procedure:

Equimolar amounts of guanazoles (position 1 where R = H; CH_3; $CH_2 \cdot CH_2 \cdot CH_3$; C_6H_5; $CH_2 \cdot C_6H_5$; $CH_2 \cdot CO_2 \cdot CH_3$) and benzaldehyde were stirred in ethanol for several hours at room temperature in the presence of sodium acetate. In most cases, the product crystallized from the reaction mixture. Alternatively, the reaction mixture was evaporated. The residue was partitioned between chloroform and water. The organic layer was rinsed with water and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was evaporated to dryness. The crude monobenzylidene derivative was recrystallized from the appropriate solvent (see Table VII).

Preparation of dibenzylidene derivatives of guanazole and 1-substituted guanazoles

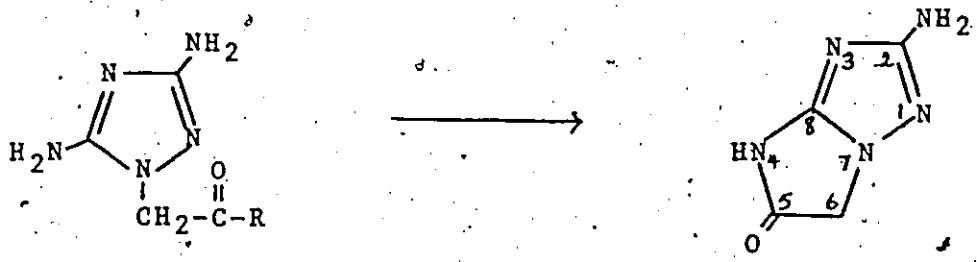
General procedure:

The guanazoles and excess benzaldehyde in absolute ethanol were refluxed for several hours (when R = H, the reaction was completed in one hour as shown by thin-layer chromatography), in the presence of anhydrous sodium acetate, piperidine or both basic catalysts. The resulting yellow solution was evaporated and the residue was partitioned between chloroform and water (in the case of guanazole itself, the dibenzylidene derivative crystallized from the reaction mixture). The chloroform layer was rinsed with water and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was evaporated to dryness. The dibenzylidene derivative was obtained by recrystallization of the residue from the appropriate solvent (see Table VII). The dibenzylidene derivatives of substituted guanazoles were also prepared from the corresponding monobenzylidene derivatives and excess benzaldehyde.

Elemental Analysis

	Monobenzylidene derivative of 1-subst. guanazoles			Dibenzylidene derivative of 1-subst. guanazoles		
		% N			% N	
		calc'd	found		calc'd	found
$-CH_3$	$C_{10}H_{11}N_5$	34.80	34.74	$C_{17}H_{15}N_5$	24.20	24.46
$-CH_2C_6H_5$	$C_{16}H_{15}N_5$	25.25	24.85	$C_{23}H_{19}N_5$	19.16	18.97
$-CH_2CO_2CH_3$	$C_{12}H_{13}N_5O_2$	27.02	26.23	$C_{19}H_{17}N_5O_2$	20.11	18.82
$-CH_2CH_2CH_3$	$C_{12}H_{15}N_5$	30.54	30.46	$C_{19}H_{19}N_5$	22.06	22.55
$-C_6H_5$	$C_{15}H_{13}N_5$	26.14	26.59	$C_{22}H_{17}N_5$	19.92	19.31

ATTEMPTED PREPARATION OF 2-AMINO-4H-IMIDAZO[1,2-b]-s-TRIAZOLE-5-ONE



XXIII

XXIIIa

2-amino-4H-imidazo-[1,2-b]-s-triazole-5-one

Several attempts at the preparation of XXIIIa failed. The experimental conditions used were as follows:

(1)	XXIII, (R = OCH_3)	NaH/DMF[a]/50°-90°	No reaction (ir)
(2)	XXIII, (R = OCH_3)	Xylene/reflux	No reaction (ir)
(3)	XXIII, (R = OH)	CH_2Cl_2/DCC[b]/ room temp.	Addition to DCC with formation of the corresponding urea (nmr)
(4)	XXIII, (R = OH)	DCC/CH_3CN, THF[c] (1:1) reflux, 18 hours	No reaction (ir)
(5)	XXIII, (R = OH)	150°/vacuum/P_2O_5	Recovered starting material (ir)
(6)	XXIII, (R = OCH_3)	150°/vacuum/P_2O_5	Starting material plus some decomposition products (nmr)

(7)	XXIII, (R = OCH_3)	pyridine/reflux 18 hours	No reaction (ir)

(a) dimethylformamide;
(b) dicyclohexylcarbodiimide;
(c) tetrahydrofurane.

REFERENCES

1. R. Stollé and W. Dietrich, J. Prakt. Chem., 139, 193 (1934).
2. G. Pellizzari, Gass. Chim, Ital., 24, I, 481 (1894).
3. G. Pellizzari and C. Roncagliolo, id., 31, I, 477 (1901).
4. G. Pellizzari, id., 24, II, 222 (1894).
5. G. Cohn, J. Prakt. Chem., (2) 84, 109 (1911).
6. J.P. Thurston and J. Walker, J. Chem. Soc., 4542 (1952).
7. D. Kaiser and J. Roemer, U.S. Patents 2,648,670; 2,648,671.
8. E. Steck, R. Brundage, and L. Fletcher, J. Am. Chem. Soc., 80, 3929 (1958).
9. R. Stolle and K. Krauch, J. Prakt. Chem., (2) 88, 306 (1913).
10. M.B. Frankel, E.A. Burns, J.C. Butler, and E.R. Wilson, J. Org. Chem., 28, 2428 (1963).
11. W.P. Norris and R.A. Henry, J. Org. Chem., 29, 650 (1964).
12. E.A. Steck and F.C. Nachod, J. Am. Chem. Soc., 79, 4411 (1957).
13. V.A. Lopyrev, N.K. Beresneva, and B.Kh. Strelets, Khim. Geterotsikl. Soedin., 5, 544 (1969).
14. P. Papini and S. Checchi, Gazz. Chim. Ital., 82, 735 (1952).
15. R.H. Wiley and A.J. Hart, J. Org. Chem., 18, 1368 (1953).
16. M. Hauser and O. Logush, id., 29, 972 (1964).
17. N.K. Beresneva, V.A. Lopyrev, and K.L. Krupin, Khim. Geterotsikl. Soedin., 5, 848 (1969).
18. P. Papini, S. Checchi, and M. Ridi, Gazz. Chim. Ital., 87, 931 (1957).
19. P. Papini, id., 80, 100; 850; 855 (1950).
20. K.A. Hofmann and O. Ehrhart, Ber., 44, 2713 (1911).

21. K.A. Hofmann and O. Ehrhart, id., 45, 2731 (1912).

22. D.W. Kaiser, G.A. Peters, and V.P. Wystrach, J. Org. Chem., 18, 1610 (1959).

23. B.G. Van den Bos, Rec. Trav. Chim. Pays-Bas, 79, 836 (1960).

24. M. Hauser, J. Org. Chem., 29, 3449 (1964).

25. L.E.A. Godfrey and F. Kurzer, J. Chem. Soc., 3437 (1960).

26. L.E.A. Godfrey and F. Kurzer, id., 5137 (1961).

27. L.E.A. Godfrey and F. Kurzer, id., 3561 (1962).

28. L.E.A. Godfrey and F. Kurzer, id., 4558 (1963).

29. H.G. Underwood and F.B. Dains, Univ. Kansas Sci. Bull., 24, 5 (1936).

30. F.H.S. Curd, D.G. Davey, D.N. Richarson, and R.B. Ashworth, J. Chem. Soc., 1739 (1949).

31. J.S. Davidson, id., (C), 2471 (1967).

32. (a) W. Zerweck and K. Keller, U.S. Patent 2,218,077.

(b) G.D. D'Alelio and J.W. Underwood, U.S. Patents 2,295,566; 2,312,320; 2,389,896.

33. A. Bayley, U.S. Patents 2,395,776; 2,406,654.

34. J.K. Simons, U.S. Patent 2,456,090.

35. G.W. Kidder, C. Dewey, R.E. Parks, and G.L. Woodside, Science, 109, 511 (1949).

36. L.G. Nickell, P. Greenfield, and R.P. Burkholder, Bot. Gaz., 112, 42 (1950).

37. H.C. Kirkpatrick and R.C. Lindner, Phytopathology, 44, 529 (1954).

38. R.W. Brockman, S. Shaddix, W.R. Laster, Jr., and F.M. Schabel, Jr., Cancer Research, 30, 2358 (1970).

39. M.A. Hahn and R.H. Adamson, J. National Cancer Inst., 48, 783 (1972).

40. R.L. Fye and G.C. LaBrecque, J. Econ. Entomol., 64, 756 (1971).

41. M.R. Atkinson and J.B. Polya, J. Chem. Soc., 141 (1954).

42. M.R. Atkinson and J.B. Polya, id., 3319 (1954).

43. E. Akerblom; Acta Chim. Scand., 19, 1142 (1965).

44. B.G. Van den Bos, Rec. Trav. Chim. Pays-Bas, 79, 1142 (1960).

45. J.L. Barascut, R.M. Claramunt, and J. Elguero, Bull. Soc. Chim. France II, 1849 (1973).

46. G. Pellizzari, L'Orosi, 17, Fasc. VI, 185 (1894).

47. G.F. D'Alelio, U.S. Patent 2,406,591.

48. F. Kurzer and E.D. Pitchfork, Forschr. Chem. Forsch., 10, No. 3, 375-472 (1968).

49. J. Thiele and O. Stange, Ann., 283, 1 (1894).

50. F. Arndt and F. Tschenscher, Ber., 56, 1984 (1923).

51. C.-F. Kroger and W. Freiberg, Zeit. Chem., 5, 381 (1965).

52. R.G. Child, J. Heterocycl. Chem., 2, 98 (1965).

53. M.B. Frankel, E.A. Burns, J.C. Butler, and E.R. Wilson, J. Org. Chem., 28, 2428 (1963).

54. J.A. Lenoir, L.D. Colebrook, and D.F. Williams, Canadian J. Chem., 50, 2661 (1972).

55. V.A. Lopyrev, V.V. Makarsky, V.A. Zubkov, E.F. Shibanova, and M.G. Voronkov, Fifth International Congress of Heterocyclic Chemistry, p. 375-376, Ljubljana, Yugoslavia, July 13-18, 1975.

56. B.T. Heitke, C.G. McCarty, Can. J. Chem., 52, 2861 (1974).

57. K.T. Potts, R. Armbruster, and E. Houghton, J. Heterocycl. Chem., 8, 773 (1971).