[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Some Guanazole Derivatives

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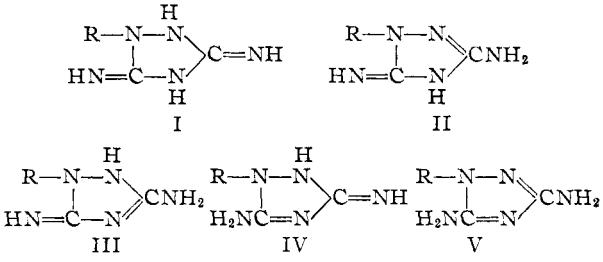
A number of 1-arylguanazoles have been prepared from arylhydrazines and dicyandiamide; certain of these products have been subjected to other reactions. The range of structures of the guanazoles has been indicated in light of earlier work. A series of trials failed to indicate any appreciable biological activity in the guanazoles studied.

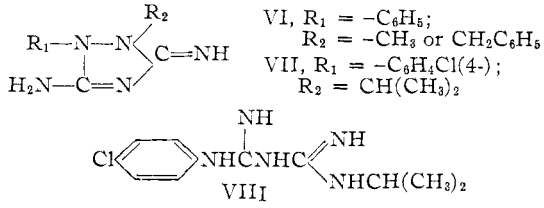
The 1-substituted guanazoles were originally of interest because the range of structures possible (I-V) (*cf.* ref. 2) included several types of potential interest as pharmaceuticals. In the range of these structures there may be seen the relationships present in guanidine and biguanide types, such as are important in certain pharmacologic and chemotherapeutic agents. The guanazoles have been the subject of little investigation from this standpoint,[3] but have been used often in plastics or color photography (*e.g.*, refs. 4–6). This program was concerned primarily with the preparation of 1-arylguanazoles and certain derived compounds.



I II III IV V

Pellizzari[7-9] was responsible for the first preparation of 1-arylguanazoles. The name guanazole was derived from the formal relationship of the structure (I), which was then preferred (being 1-aryl-3,5-diimino-1,2,4-triazolidine), with guanidine. Since that time, we[10] have indicated the structure to be probably III or IV. Pellizzari[7-9] obtained compounds of this class by heating mixtures of the requisite arylhydrazine hydrochloride with dicyandiamide. The method of Cohen,[11] which involved the refluxing of aqueous solutions of the reagents, was here preferred while an atmosphere of nitrogen was maintained. It was highly desirable to use small amounts of sodium dithionite to prevent oxidation during the crystallization of the series of 1-arylguanazoles prepared (Table I). The colored impurities, which were encountered (*cf.* ref. 12) when no reducing agent was added, were removed only with great losses.

Certain reactions of the 1-arylguanazole type were of interest. Alkylation has been stated[8,9] to produce 1,2-disubstituted guanazoles, as 2-methyl-1-phenylguanazole (VI). This type is derivable from structures I, II or IV. On the basis of the considerations given in our contribution[10] on the spectra, the preferred structure, VI, is based on IV; however, one based on III would likewise be satisfactory. It was possible to obtain alkylation of 1-phenylguanazole with methyl iodide and benzyl chloride, but neither it nor 1-(4-chlorophenyl)-guanazole gave any discrete product in a series of trials with isopropyl halides. In the last mentioned case, 1-(4-chlorophenyl)-2-isopropylguanazole would have resulted: on the basis of the old formula (I) for the guanazole moiety, this compound would be VII. Such a structure as VII might be considered as obtainable by the formal abstraction of two hydrogens from chloroguanide (VIII). These compounds have been named as derivatives of the structure IV for guanazole.



VI, R_1 = $-C_6H_5$; R_2 = $-CH_3$ or $CH_2C_6H_5$

VII, R_1 = $-C_6H_4Cl(4-)$; R_2 = $CH(CH_3)_2$

VIII

Fromm and Kapeller-Adler[13] have expressed the opinion that the action of alkyl or aryl isothiocyanates upon 1-phenylguanazole may lead to compounds of either type IX or X. It is to be noted that these two structures are based on V for the parent compound. The preference was for X as the more stable form, and that structure assigned to products isolated from reactions at high temperatures. We have used boiling xylene in the preparation of several compounds from 1-phenylguanazole and from 1-(4-chlorophenyl)-guanazole by reaction with aryl isothiocyanates. It was not possible[14] to distinguish between the structures derivable from V (*i. e.*, IX and X) or those obtainable from III or IV, but we have the view that the latter is the more probable. Thus, the preferred structure here is XI rather than X. Products here prepared included XII-XV, with XII a known compound.[13] The compound obtained by the reaction of 1-phenylguanazole with 1-naphthyl isocyanate was XIV. These guanazoles have been placed in Table II.

The interesting chemical aspects of the guanazoles were not reflected in the results of biological testing. None of the compounds exhibited sufficiently high levels of activity in pharmacologic or

(1) Research Center, Johnson & Johnson, New Brunswick, N. J.

(2) R. Stollé and W. Dietrich, *J. prakt. Chem.*, [2] **139**, 193 (1934).

(3) G. B. Zanda, *Arch. Farmacol. Sperim.*, **18**, 118 (1914); *Chem. Zentr.*, **86**, I, 323 (1915).

(4) (a) W. Zerweck and K. Keller, U. S. Patent 2,218,077; (b) G. D. D'Alelio and J. W. Underwood, U. S. Patent 2,295,566; 2,312,320; 2,389,896.

(5) A. Bavley, U. S. Patent 2,395,776; 2,406,654.

(6) J. K. Simons, U. S. Patent 2,456,090.

(7) G. Pellizzari, *Gazz. chim. ital.*, **21**, II, 14 (1891).

(8) G. Pellizzari, *ibid.*, **24**, I, 481 (1894).

(9) G. Pellizzari and C. Roncagliolo, *ibid.*, **31**, I, 477 (1901).

(10) E. A. Steck and F. C. Nachod, THIS JOURNAL, **79**, 4911 (1957).

(11) G. Cohen, *J. prakt. Chem.*, [2] **84**, 409 (1911).

(12) F. Arndt and F. Tschenscher, *Ber.*, **56B**, 1984 (1923).

(13) E. Fromm and R. Kapeller-Adler, *Ann.*, **467**, 248, 267 (1928).

TABLE I

1-ARYLGUANAZOLE TYPES

1-Substituent	Yield, %	Appearance	Solvent[a]	M.p., °C.[b]	Analyses, % Calcd. C	Calcd. H	Calcd. N[c]	Found C	Found H	Found N
Phenyl[d,e]	56	Creamy white needles	w	173.7–175			39.98			39.90
Picrate[d,e]		Golden needles	wE	226–227 d.			10.39			10.28
Hydrochloride[d]		White cubes	E–EO	235–235.5	16.75[f]		33.09	16.60[f]		33.32
4-Fluorophenyl	62	White prismatic ndls.	E	174–174.5	49.73	4.17	36.25	49.53	4.17	36.21
Picrate		Golden blades	w	233–233.5 d.			9.95			9.75
3-Chlorophenyl	68	Pale pinkish-white ndls.	w	147.5–148	45.82	3.82	33.42	45.85	3.83	33.65
Picrate		Bright yellow ndls.	wE	226–227 d.			9.58			9.70
4-Chlorophenyl	70	Orange parallelepipeds	E	199.5–200	45.82	3.82	33.42	45.94	3.88	33.57
Picrate		Golden prisms	E	234–234.5			9.58			9.80
Hydrochloride		White needles	E	230–231 d.	14.42[f]		28.48	14.56[f]		28.08
4-Bromophenyl	52	Pale orange prisms	w	211.5–212	37.81	3.17	27.56	37.75	3.19	27.58
Picrate		Lemon-yellow needles	wE	222–223			8.70			8.57
Hydrochloride		White needles	E–EO	244.5–245	12.20[f]		24.10	12.14[f]		24.17
4-Iodophenyl	46	Pale tan leaflets	E	232–233	31.91	2.68	23.26	32.04	2.66	23.23
Picrate		Golden prismatic ndls.	wA	245–245.5 d.			7.93			7.92
4-Methylphenyl[d]	58	Pale yellow cubes	w	175–175.5	57.12	5.86	37.02	57.22	6.03	37.12
Picrate[d]		Golden needles	wE	216–217			10.05			10.02
3-Chloro-4-methylphenyl	64	Creamy white needles	w	176.5–177	48.32	4.50	31.60	48.35	4.42	31.58
Picrate		Lemon yellow needles	wE	232–233 d.			9.28			9.15
4-(4′-Methylphenoxy)-phenyl	71	Creamy white needles	B	163.5–164	64.04	5.38	24.90	64.13	5.51	24.90
Picrate		Fine yellow needles	wE	188–189			8.23			8.55
4-(4′-Methylphenylthio)-phenyl	68	Pale orangish ndls.	wE	184–184.5	60.58	5.08	23.56	60.88	5.09	23.28
Picrate		Golden needles	E	199–200			7.98			8.06
4-(4′-Chlorophenylthio)-phenyl	19	Shimmering white platelets	wE	183–184	10.09[g]		22.04	9.84[g]		22.24
4-Xenyl	43	Creamy white needles	w	226.5–227	66.92	5.21	27.87	66.93	5.23	28.04
Picrate		Dull yellow platelets	wC	245–246			8.75			8.94
2-Naphthyl[d]	65	Creamy white platelets	w	196–196.5	63.98	4.92	31.10	64.28	5.02	31.33
Picrate[d]		Lemon-yellow needles	wA	238–239 d.			9.25			9.37

[a] Legend: A, acetone; B, benzene; C, 2-ethoxyethanol; D, dioxane; E, ethanol; EO, ethyl ether; P, pyridine; w, aqueous. [b] d. = decomposes. [c] The Dumas method was unsatisfactory for picrates; for these compounds, nitro nitrogen was determined by titanium(II) chloride method. [d] Previously prepared by Pellizzari.[7] [e] Prepared by Cohen.[11] [f] Ionic chlorine. [g] Sulfur analysis. Carbon and hydrogen analyses were not concordant (three trials).

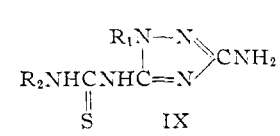
TABLE II

1,5-DISUBSTITUTED GUANAZOLES[a]

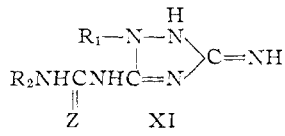
R_1	R_5	Yield, %	Appearance	Solvent[b]	M.p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
C_6H_5	$NHCSNHC_6H_5$[c]	90	White needles	wD	247–248	58.04	4.54	27.08	58.31	4.76	27.08
	$NHCSNHC_{10}H_7(1\text{-})$	86	White cubes	wP	257–258	63.31	4.48	23.32	63.49	4.50	23.40
	$NHCONHC_{10}H_7(1\text{-})$[d]	88	Fluffy white ndls.	wP	236–238	64.57	4.85	23.78	64.66	4.50	23.99
$C_6H_4Cl(4\text{-})$	$NHCSNHC_6H_5$	90	Chalky white ndls.	wD	220–221	52.20	3.72	24.35	52.41	3.93	24.37

[a] Structures as indicated in XII–XV. [b] Legend as in Table I. [c] Previously reported by Fromm and Kapeller-Adler.[12] [d] Hemihydrate. *Anal.* Calcd. for $C_{19}H_{16}N_6O\cdot{}^1/_2H_2O$: H_2O, 2.55. Found: H_2O, 2.40.

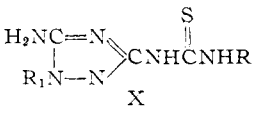
chemotherapeutic trials to justify continuation of the work.



IX



XI



X

XII, $R_1 = R_2 = -C_6H_5$; Z = S
XIII, $R_1 = -C_6H_5$; $R_2 = -C_{10}H_7(1\text{-})$; Z = S
XIV, $R_1 = -C_6H_5$; $R_2 = -C_{10}H_7(1\text{-})$; Z = O
XV, $R_1 = -C_6H_4Cl(4)$; $R_2 = C_6H_5$; Z = S

Experimental[14]

A. Arylhydrazines.—The greater number of requisite arylhydrazines were prepared by reduction of the aryldiazonium salts with sodium sulfite.[15,16] The following known hydrazine derivatives were made: 4-fluorophenyl-,[17] 3-chlorophenyl-,[18,19] 4-chlorophenyl-,[18,20] 4-iodophenyl-,[21] 4-methylphenyl-,[22] 4-xenyl-[23] and 2-naphthylhydrazine.[24] These compounds were isolated as the hydrochlorides in yields of 54–89%.

3-Chloro-4-methylphenylhydrazine hydrochloride was prepared from 3-chloro-4-methylaniline in 93% yield by the usual method. It separated from water as creamy needles, m.p. 230.5–231° dec.

Anal. Calcd. for $C_7H_9ClN_2\cdot HCl$: N, 14.51. Found: N, 14.73.

Benzaldehyde 3-chloro-4-methylphenylhydrazone crystallized from ethanol as creamy needles, m.p. 119.5–120°.

Anal. Calcd. for $C_{14}H_{13}ClN_2$: N, 11.45. Found: N, 11.43.

4-Hydrazino-4′-methyldiphenyl Ether Hydrochloride.—The required 4′-methyl-4-nitrodiphenyl ether was made by the Ullmann procedure,[25] then reduced (Raney nickel in ethanol at 50°, 25 atm.) to the amine. It was desirable to reduce the diazonium salt from this amine by tin(II) chloride in hydrochloric acid.[26] A 55% yield of 4-hydrazino-

(14) Unless otherwise noted, all melting points are corrected values. Analyses have been done by Mr. M. E. Auerbach and staff in the Analytical Laboratories of this Institute.

(15) E. Fischer, *Ann.*, **190**, 79 (1878).

(16) G. H. Coleman, "Organic Syntheses," Coll. Vol. I, second Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 442.

(17) G. Schiemann and W. Winkelmüller, *Ber.*, **66**, 729 (1933).

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(20) C. Willgerodt and A. Böhm, *ibid.*, [2] **43**, 482 (1891).

(21) A. Neufeld, *Ann.*, **248**, 93 (1888).

(22) E. Fischer, *Ber.*, **9**, 890 (1876).

(23) H. Müller, *ibid.*, **27**, 3106 (1894).

(24) E. Fischer, *Ann.*, **232**, 242 (1886).

(25) A. N. Cook, THIS JOURNAL, **25**, 61 (1903).

(26) V. Meyer and M. T. Lecco, *Ber.*, **16**, 2976 (1883).

4'-methyldiphenyl ether hydrochloride (white platelets from water, m.p. 175° dec.) was obtained, based upon the nitro compound used.

Anal. Calcd. for $C_{13}H_{14}N_2O \cdot HCl$: N, 11.18; Cl^-, 14.14. Found: N, 11.42; Cl^-, 14.04.

The above hydrazine and benzaldehyde gave a product which separated from aqueous ethanol as tan needles, m.p. *ca.* 212–216°.

Anal. Calcd. for $C_{20}H_{18}N_2O$: N, 9.27. Found: N, 8.98.

4-Hydrazino-4'-methyldiphenyl sulfide hydrochloride was made from the aniline type[27] in the manner used above for 4-hydrazino-4'-methyldiphenyl ether hydrochloride. The yield of hydrochloride (from the amine) was 71%; it crystallized from ethanol–ether as creamy platelets, m.p. 188–188.5° dec.

Anal. Calcd. for $C_{13}H_{14}N_2S \cdot HCl$: S, 12.01; Cl^-, 13.29. Found: S, 11.87; Cl^-, 13.23.

The, benzaldehyde hydrazone from this arylhydrazine was obtained as white laminae from ethanol–ether, m.p. 135–136°.

Anal. Calcd. for $C_{20}H_{18}N_2S$: N, 8.80. Found: N, 8.66.

4'-Chloro-4-hydrazinodiphenyl Sulfide Hydrochloride.—The intermediate 4-amino-4'-chlorodiphenyl sulfide hydrochloride was prepared in 79% yield from 4-chlorothiophenol.[28] A solution of 19.4 g. (0.3 mole) of 86% potassium hydroxide in 0.25 l. of water was mixed with a solution of 43.3 g. (0.3 mole) of chlorothiophenol in 0.1 liter of ethanol. The stirred mixture was refluxed during the addition of 47.4 g. (0.3 mole) of 4-chloronitrobenzene, dissolved in 0.2 l. of ethanol and for ten hours thereafter. Prisms of 4'-chloro-4-nitrodiphenyl sulfide (m.p. 88–88.5°) separated, but were neglected. The mixture was diluted with 100 cc. of water and then 100 g. of iron powder and 10 cc. of concd. hydrochloric acid was added during one hour. After four hours of refluxing, with vigorous stirring, the mixture was filtered and the cake washed with hot ethanol. The filtrates were acidified strongly with hydrochloric acid, then concentrated *in vacuo*, and the residues crystallized from ethanol–ether. The 4-amino-4'-chlorodiphenyl sulfide hydrochloride (64.5 g., white needles) melted at 183–185° dec. (uncor.).

Anal. Calcd. for $C_{12}H_{10}ClN_2S \cdot HCl$: Cl, 25.9; N, 5.15. Found: Cl, 25.61; N, 5.04.

4'-Chloro-4-hydrazinodiphenyl sulfide hydrochloride was obtained in 42.5% yield from the diazotized amine by tin(II) chloride–hydrochloric acid. The compound separated from ethanol as white leaflets, m.p. 196–197° dec. (uncor.).

Anal. Calcd. for $C_{12}H_{11}ClN_2S \cdot HCl$: N, 9.76; Cl^-, 12.35. Found: N, 9.95; Cl^-, 12.51.

The hydrazone formed by reaction with benzaldehyde separated from ethanol as yellow needles, m.p. 143–144° (uncor.).

Anal. Calcd. for $C_{19}H_{15}ClN_2S$: N, 8.27. Found: N, 8.15.

(27) G. H. Law and T. B. Johnson, THIS JOURNAL **52** 3623 (1930).

(28) A. E. Senear, M. M. Rapport and J. B. Koepfli, *J. Biol. Chem.*, **167**, 232 (1947).

B. 1-Arylguanazoles.—One equivalent of dicyandiamide and 1.1 equivalents of the hydrazine hydrochlorides were interacted in a volume of water equal to twice the weight of the latter reagent. The mixtures were refluxed in an atmosphere of nitrogen for two to four hours, cooled and basified with 35% sodium hydroxide, then the products dried *in vacuo*. Crude yields of 82–93% were obtained by this procedure akin to that of Cohen.[11] The compounds were all purified by crystallization from solvents containing traces of sodium dithionite; in many cases, washing of the 1-arylguanazoles with peroxide-free ether helped in the removal of colored by-products (*cf.* ref. 12). Table I gives data concerning the 1-arylguanazoles here synthesized; the yields listed are for analytically pure samples.

All of these compounds reduced mercury(II) salts to the metal in warm, aqueous solutions. No definite products could be isolated from attempts to oxidize 1-phenylguanazole with copper(II) sulfate or potassium permanganate. All of the guanazoles formed mono-salts.

C. 1,2-Disubstituted Guanazoles.—The alkylations of 1-phenylguanazole with methyl iodide or benzyl chloride were run at 135–140° in a stainless steel autoclave in methanol for ten hours. Considerable tarry material was mixed with the residues obtained after removal of the solvent. The use of sodium dithionite was necessary in the crystallizations. 1-(4-Chlorophenyl)-guanazole and 1-phenylguanazole did not give any isolable alkylation product even after 16 hours at 180–190° in an isopropyl alcohol solution with an excess of isopropyl bromide or iodide. An attempt to alkylate the former with use of isopropyl iodide in the presence of sodamide in xylene also failed.

2-Methyl-1-phenylguanazole was isolated as the **hydriodide** in 48% yield. The cubic crystals which separated from ethanol melted at 236–237°.

Anal. Calcd. for $C_9H_{11}N_5 \cdot HI$: N, 22.08; I, 40.02. Found: N, 22.33; I, 39.85.

2-Benzyl-1-phenylguanazole hydrochloride was obtained in 41% yield. It crystallized from ethanol–ether as white platelets, m.p. 229–231°.

Anal. Calcd. for $C_{15}H_{16}N_5 \cdot HCl$: C, 59.67; H, 5.34; N, 23.20. Found: C, 59.63; H, 5.24; N, 22.91.

D. 1,5-Disubstituted Guanazoles.—The compounds XII–XIV were obtained by refluxing (4 to 5 hours) the appropriate isocyanate or isothiocyanate (in 10% excess) with 1-phenylguanazole, or the related 1-(4-chlorophenyl) compound, in xylene. In each case, the crude products were collected, washed with ether, and crystallized. These 1,5-disubstituted guanazoles have been placed in Table II with appropriate information relating to them.

Acknowledgments.—We are pleased to make recognition of the encouragement and advice which Dr. C. M. Suter and Dr. E. J. Lawson offered during this work. Dr. L. C. Miller and Dr. E. W. Dennis of the Biology Division, together with their associates, have tested the compounds for potential value as pharmacologic and chemotherapeutic agents.

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