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Bisethylenebiguanide

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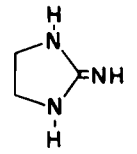
Although large numbers of biguanides have been synthesized as potential antimalarial drugs (1) and as hypoglycemic agents (2), the kinds of substituents on the biguanide skeleton have been restricted mainly to simple alkyl, aryl, and aralkyl groups (3). In this communication, we present the synthesis of the novel bisethylenebiguanide III and its mono- and dibenzene fused analogs VI and IX, which were prepared for evaluation as hypoglycemic agents.

The reaction of 2-iminoimidazolidine (I) and 2-nitriminoimidazolidine (II) yielded the desired 2,2'-iminodi-2-imidazoline (III, bisethylenebiguanide). The structure of III was established by its typical biguanide ultraviolet spectrum, λ max (CH_3OH), 234 mμ (ε, 24,000) which decreased in intensity upon addition of acid or base (5), and its n.m.r. spectrum, which in D_2O displayed a singlet at 6.40 τ (8 methylene protons) and a singlet at 5.14 τ (3 NH protons, expressed as HOD) (6).

The reaction of 2-aminobenzimidazole (IV) and 2-(methylthio)-2-imidazoline hydroiodide (V) yielded 2-(2-imidazolidinylideneamino)benzimidazole hydroiodide (VI). Confirmation of the structure of VI was found in its ultraviolet spectrum, which was strikingly similar to that of 2-guanidinobenzimidazole (7).

The fusion of 2-benzimidazolecarbamonitrile (VII) and *o*-phenylenediamine (VIII) provided 2,2'-iminobisbenzimidazole, isolated as the hydrochloride IX.

Compounds III, VI, and IX failed to display hypoglycemic activity when tested in the chick and the rat (8).



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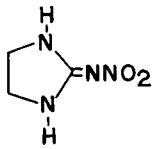

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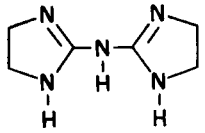

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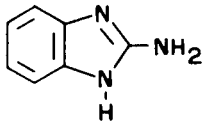

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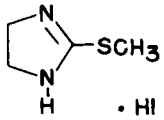

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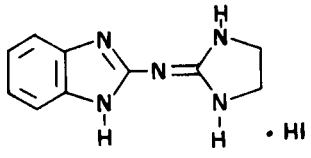

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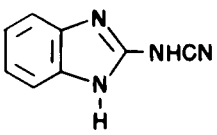

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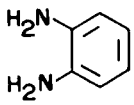
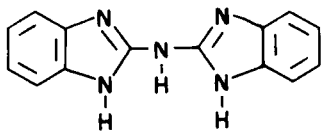


VIII



IX

EXPERIMENTAL (8)

2,2'-Iminodi-2-imidazoline (III).

To a solution of 3.32 g. (0.144 g. atom) of sodium in 100 ml. of anhydrous ethanol was added 17.40 g. (0.144 mole) of 2-iminoimidazolidine hydrochloride (9). The mixture was stirred at room temperature for 10 min. and filtered. The filtrate was concentrated under reduced pressure to an oil.

A mixture of the oil, 18.75 g. (0.144 mole) of 2-nitriminoimidazolidine (10), and 150 ml. of dry diglyme was heated in a 155° oil bath with stirring under nitrogen for 2 hours. The mixture was cooled to 80° and ethanol was added until a clear solution was obtained. Upon cooling, 6.30 g. of colorless needles, m.p. 209-212°, was isolated. Three recrystallizations from ethanol afforded the analytical sample, m.p. 215-217°.

Anal. Calcd. for $C_6H_{11}N_5$: C, 47.04; H, 7.24; N, 45.72. Found: C, 47.34; H, 7.06; N, 45.54.

2-(2-Imidazolidinylideneamino)benzimidazole Hydroiodide (VI).

A mixture of 3.40 g. (0.025 mole) of 2-aminobenzimidazole and 12.20 g. (0.050 mole) of 2-(methylthio)-2-imidazoline hydroiodide (11) in 150 ml. of dioxane was heated under reflux with stirring under nitrogen for 1 1/2 hours. The mixture was cooled and filtered, and the filtrate was concentrated under reduced pressure to a white paste. Trituration with 4 ml. of acetonitrile left 1.17 g. of a colorless solid. Recrystallization from acetonitrile yielded 0.81 g. of colorless prisms, m.p. 247-251° (dec.). Another recrystallization gave the analytical sample, m.p. 249-252° (dec.).

Anal. Calcd. for $C_{10}H_{11}N_5 \cdot HI$: C, 36.49; H, 3.68; N, 21.28; I, 38.56. Found: C, 36.62; H, 3.85; N, 21.29; I, 37.95.

The ultraviolet spectrum exhibits λ max, 292 (ε, 27,000) and 244 mμ (ε, 20,600) in 0.1 N methanolic hydrogen chloride, and λ max, 303 (ε, 23,000) and 293 mμ (ε, 24,600) in 0.1 N methanolic potassium hydroxide.

2,2'-Iminobisbenzimidazole Hydrochloride Hemihydrate (IX).

A finely ground mixture of 3.00 g. (0.019 mole) of 2-benzimidazolecarbamonitrile (12) and 2.25 g. (0.021 mole) of *o*-phenylenediamine was heated in a 140° oil bath for 1 1/2 hrs. During this time ammonia was evolved. The dark solid which formed after cooling was taken up in 100 ml. of boiling dilute hydrochloric acid, and the solution treated with charcoal. The solid which separated on cooling amounted to 1.53 g. of fine colorless needles, m.p. 295-305° (dec.). An additional recrystallization from dilute hydrochloric acid did not change the melting point.

Anal. Calcd. for $C_{14}H_{11}N_5 \cdot HCl \cdot {}^1/_2H_2O$: C, 57.05; H, 4.44; N, 23.76; Cl, 12.03. Found: C, 57.03; H, 4.30; N, 23.69; Cl, 12.06.

The ultraviolet spectrum exhibits λ max, 335 (ε, 40,700), and 226 mμ (ε, 30,000) with shoulders at 264 and 214 mμ in 0.1 N methanolic potassium hydroxide; λ max, 319 (ε, 48,900) and 214 mμ (ε, 28,900) with weak maxima at 278, 272, 268, 255 and 248 mμ in 0.1 N methanolic hydrogen chloride.

REFERENCES

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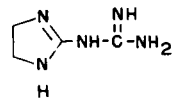
(2) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, 81, 3728 (1959).

(3) Several claims for the synthesis of monoethylenebiguanide (i) have appeared, although these reports have been challenged. A recent article (4) claims to have settled the controversy, but experimental details have not yet appeared.



(i)

(4) S. N. Poddar, *Science and Culture* (Calcutta), 29, 50 (1963).

(5) W. J. Fanshawe, V. J. Bauer, E. F. Ullman, and S. R. Safir, *J. Org. Chem.*, 29, 308 (1964).

(6) In aqueous solution, the strongly basic (*p*H *ca.* 13) biguanide III exists largely as the monocation. In a formal sense, it might be expected that double bond character between the central nitrogen and its neighboring carbons should confer a degree of rigidity to the molecule which would be expressed as non-equivalence of the methylene groups. The appearance of a sharp singlet, however, indicates that rotation about the central C-N bonds must be sufficiently rapid to prevent discrete n.m.r. signals for non-equivalent methylenes.

(7) The ultraviolet spectrum of 2-guanidinobenzimidazole exhibits λ max, 303 (ε, 21,500) and 293 mμ (ε, 22,900) when determined in 0.1 N methanolic potassium hydroxide.

(8) Melting points were determined on a Kofler hot stage. Ultraviolet and n.m.r. spectra were determined by Mr. W. Fulmor and staff. Microanalyses were performed by Mr. L. M. Brancone and staff. Biological testing was conducted by Drs. S. Gordon and E. Tocus.

(9) P. Pierron, *Ann. chim. et phys.*, [9], 11, 361 (1919).

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(12) G. Pellizarri, *Gazz. chim. ital.*, 51, I, 140 (1921).

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