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Amine Derivatives of 1-(1′-Phenyl-2′-bromoethyl)-5-methyltetrazole

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As part of search for a potential new type of antimalarial, several 1-(1′-phenyl-2′-aminoethyl)-5-methyltetrazoles were prepared by the amination of 1-(1′-phenyl-2′-bromoethyl)-5-methyltetrazole using various amines, such as mono- and diamines of aliphatic and alicyclic. The reaction in the presence of a large excess of amine occurred smoothly on heating at 100—130°C, and it gave the title product without any significant by-product such as the bistetrazole compound, even though a primary amine was used.

The addition of halogens to olefins in a nitrile solvent in the presence of silver perchlorate has been shown by Hassner and his co-workers[1] to lead to nitrilium-ion intermediates. The latter reacts with azide ions, thus providing a useful method of synthesizing tetrazoles containing an additional halogen function, which can be converted to other functional groups by nucleophilic substitution. Thus, styrene reacts with bromine and silver perchlorate in acetonitrile in the presence of sodium azide to yield, in one step, 1-(1′-phenyl-2′-bromoethyl)-5-methyltetrazole (I).

A number of tetrazole derivatives have been of interest as synthetic drugs; among them, pentamethylene-tetrazole, 5-(2-dimethylaminoethoxymethyl)-1-phenyltetrazole, 4-phenyl-1-[2-(5-tetrazolyl)ethyl]piperazine, and 1-(*p*-chlorobenzyl)-5-imino-4-octyltetrazoline are especially well known.[2] An examination of the compounds that exhibit a significant therapeutic effect against malaria,[3–6] including quinine, reveals that many of them are structurally composed of a molecule forming a rigid portion, which has a high electron density and which often contains one or more N-atoms, and of a less rigid side chain, which is often an amino alkanol or a dialkylamino alkylamine.

The stability of tetrazole nuclei, the availability of such bifunctional tetrazoles as I, and the interest by one of the present authors[7] in the chemistry of styrene derivatives have led us to study amine and diamine derivatives of I as potential antimalarials. An added advantage of the members of the tetrazole system is their relatively low toxicity, as indicated by an MTD of over 0.20 mg/g in chicks.[4] Although the few tetazoles studied in the past have lacked antimalarial activity, too few were examined and none of them contained aminoalkyl or similar substituents.

The starting material, I, was prepared according to the directions previously reported.[1] Although there was no precipitation when bromine was added to an acetonitrile solution of silver perchlorate, silver bromide precipitation was rapid upon the addition of styrene to this system. This can be attributed to the formation of a three-membered-ring bromonium ion and to the concurrent trapping of the bromide ion by silver perchlorate, thus prohibiting the formation of styrene dibromide and enhancing attack by acetonitrile, all leading to the formation of a nitrilium-ion intermediate. The tetrazole I was obtained in a 48% yield[8] after the extraction of the reaction products with hot petroleum benzine. From the mother liquors of the extraction, styrene dibromide was obtained in an 11% yield. The residue of the above extraction was a crude 2-methyl-4-phenyl-2-oxazoline hydro-

1) A. Hassner, L. A. Levy and R. Gault, *Tetrahedron Letters*, **1966**, 3119.

2) a) G. M. Dyson and P. May, "May's Chemistry of Synthetic Drugs," Longmans, London (1959), p.180. b) E. R. Benson, "The Tetrazoles," in "Heterocyclic Compounds," ed. by R. C. Elderfield, Vol. 8, Wiley, New York (1967), p. 102. c) K. Tsuda and S. Yoshida, "Iyakuhin Goseikagaku (Synthetic Chemistry of Drugs)," Nankodo, Tokyo (1958), p. 317.

3) P. B. Russell in "Medical Chemistry," ed. by A. Burger, 2nd ed., Interscience Publ., New York (1960), pp. 814—845.

4) G. R. Coatney, W. C. Cooper, N. B. Eddy and J. Greenberg, "Survey of Antimalarial Agents," Public Health Monograph, No. 9 (1953), pp. 47—51, 178, 199, 255.

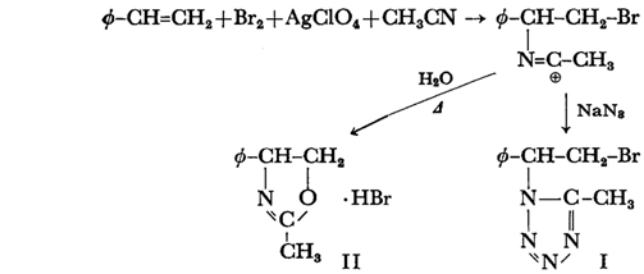
5) I. M. Rollo in "Pharmacological Basis of Therapeutics," ed. by C. S. Goodman and A. Gilman, 3rd ed., MacMillan Co., New York (1965), pp. 1093, 1097.

6) J. H. Williams, "Chemotherapy of Malaria," Lederle Laboratories, New York (1941—1942).

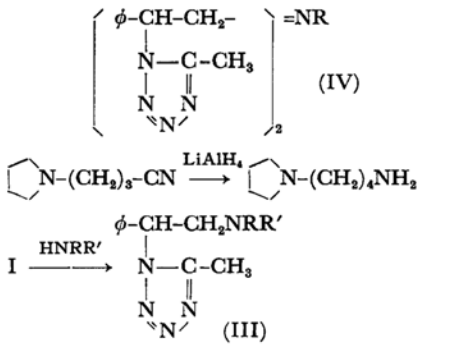
7) For the preceding paper, see A. Terada, This Bulletin, **39**, 2520 (1966).

8) Ref. 1 had reported a 35% yield.

bromide (II).[9] This oxazoline salt is formed even after the reaction products have been washed with a small amount of 20% sodium hydroxide; it must, therefore, result from the cyclization of 1-acetoamido-2-bromoethylbenzene. The latter presumably results from the reaction of some remaining nitrilium ion with water during the work-up. The instability of *N*-(2-haloethyl)-amides and the facility with which they cyclize to oxazoline salts has been recognized by Lusskin and Ritter.[10] It may, therefore, be concluded that heating during the petroleum benzine extraction results in the formation of the oxazoline salt.



The formation of 1-(1′-phenyl-2′-aminoethyl)-5-methyltetrazoles (III) was accomplished smoothly by heating I with a large excess of amine or diamine at 100—130°C for 24 hr.



where

NRR′: -N(CH3)2 (IIIa)

: -N O (IIIb)

: -N (IIIc)

: -NH(CH2)3OH (IIId)

: -NH(CH2)4-N (IIIe)

: -N (IIIf)

: -NHCH2CH2N(C2H5)2 (IIIg)

: -NH-CH(CH2)3N(C2H5)2 (IIIh)
CH3

: -NHCH2CHCH2N(C2H5)2 (IIIi)
OH

No bistetrazole formation of the type IV was observed when the amine was primary, because at least a ten-fold excess of amine was employed. The amines used in this study were dimethylamine, morpholine, piperidine, pyrrolidine, γ-acetoxypropylamine, δ-(pyrrolidino)butylamine, 2-diethylaminoethylamine, 2-amino-5-diethylaminopentane, and 1-amino-3-diethylamino-2-propanol. The δ-(pyrrolidino)butylamine was prepared by the lithium aluminum hydride reduction of γ-(pyrrolidino)-butyronitrile. The tetrazole derivatives obtained (IIIa—i) are shown above. No significant antimalarial activity was found for these compounds in screening tests on mosquitoes A. Aegypti.[11]

Experimental

Materials. All the amines, γ-acetoxypropylamine, dimethylamine, morpholine, piperidine, and pyrrolidine were available commercially as reagent-grade substances and were used without exceptional purification. The γ-(pyrrolidino) butyronitrile was also obtained commercialy. The 2-amino-5-diethylaminopentane (bp 74°C/20 mmHg), 2-diethylaminoethylamine (bp 55—56° C/30 mmHg), and 1-amino-3-diethylamino-2-propanol were furnished by the U.S. Army, Water Reed Medical Center, and were purified by vacuum distillation.

1-(1′-Phenyl-2′-bromoethyl)-5-methyltetrazole (I). According to the directions of Gault,[9] I was prepared using acetonitrile as the only solvent of the system, while Gault used ether as the solvent in his styrene additions. A brown oil (3.612 g) was obtained from 1.17 g of styrene (0.012 mol) after the usual work-up. The repeated extraction of the oil with boiling petroleum benzine gave 1.444 g (48.3%) of I, mp 109—110°C (lit,[1] mp 109—111°C, 35% yield).

From the mother liquor, 319 mg (10.8%) of styrene dibromide were recovered, mp 69—70.5°C (lit,[12] mp 73°C). Its identity was proved by a mixed-melting-point test with an authentic sample.

The residue of the above hot-petroleum-benzine extraction was 1.758 g, which solidified on standing. Recrystallization from benzene gave white crystals of 2-methyl-4-phenyl-2-oxazoline hydrobromide; mp 163—165°C (lit,[9] 165°C, 169—170°C).

1-(1′-Phenyl-2′-dimethylaminoethyl)-5-methyl tetrazole (IIIa). A mixture of 267 mg (1 mmol) of 1-(1′-phenyl-2′-bromoethyl)-5-methyltetrazole (I) and 10 m*l* of diethylamine (25% aq. solution) was heated in a sealed glass tube in a steam bath for 24 hr. After concentration to dryness under a vacuum, the residue was dissolved in dilute hydrochloric acid and filtered. Concentration and alkalization with potassium hydroxide gave 186 mg (80.5%) of needles; mp 86—87°C. Recrystallization from benzene-petroleum benzine gave an analytical sample. This product was easily soluble in water.

Found: C, 62.41; H, 7.39%. Calcd for $C_{12}H_{17}N_5$:

9) R. Gault, M. S. Thesis, University of Colorado (1966), p. 29.

10) R. M. Lusskin and J. J. Ritter, *J. Am. Chem. Soc.*, **72**, 5577 (1950).

11) E. J. Gerberg, L. T. Richard and J. B. Poole, *Mosquito News*, **26**, 359 (1966).

12) R. H. Baundy and R. F. Boyer, "Styrene, Its Polymers, Copolymers and Derivatives," Reinhold Publ. Corp., New York (1952), p. 89.

C, 62.31; H, 7.41%.

ν_{max}^{KBr}: 3125, 3003 (phenyl); 2959, 2890 (CH_3, CH_2); 2778 (N–CH_3); 1524 (tetrazole ring); 1456, 1404, 1383; 1276, 1263, 1120, 1096, 1062, 1030, 875, 829; 730, 702 cm^{-1} (monosubstituted benzene).

1-(1′-Phenyl-2′-morpholinoethyl)-5-methyltetrazole (IIIb). A mixture of 267 mg (1 mmol) of I in 20 m*l* of mopholine was refluxed for 17 hr. Working-up as usual gave 234 mg (85%) of the product; mp 156—157°C. Recrystallization from ethanol-water raised the melting pount to 158—160°C.

Found: C, 61.34; H, 7.11%. Calcd for $C_{14}H_{19}N_5O$: C, 61.52: H, 7.01%.

ν_{max}^{KBr}: 2967, 2941, 2865 (CH_3, CH_2); 2809, 1114 (morpholino); 1520 (tetrazole ring); 1493, 1460, 1443, 1403, 1379, 1127, 1068, 1033, 1008, 913, 873, 793; 728, 701 cm^{-1} (monosubstituted benzene).

1-(1′-Phenyl-2′-piperidinoethyl)-5-methyltetrazole (IIIc). The usual procedure gave an 86% yield of the product; mp 130—130.5°C. Recrystallization from ethanol-water raised the melting point to 132—133°C.

Found: C, 66.20; H, 7.79%. Calcd for $C_{15}H_{21}N_5$: C, 66.39; H, 7.80%.

ν_{max}^{KBr}: 3049 (phenyl); 2950, 2865 (CH_3, CH_2); 2793, 2770 (piperidino); 1529 (tetrazole ring); 1497; 1453, 1445, 1403, 1381, 1309, 1279, 1167, 1124, 1111, 1098, 1044, 870, 782; 730, 701 cm^{-1} (monosubstituted benzene).

Reaction of I and γ-Acetoxypropylamine. A mixture of 267 mg (1 mmol) of I and 3 m*l* of γ-acetoxypropylamine was heated on a steam bath for 24 hr. Evaporation under reduced pressure, extraction with dil. hydrochloric acid, alkalization of the extract with sodium hydroxide, and extraction again with benzene as usual finally gave 158 mg (60.5%) of the product, a white viscous oil. The infrared spectrum showed no carbonyl peaks of acetoxyl, but there were peaks of hydroxyl; this oil was, therefore, concluded to be 1-[1′-phenyl-2′-(γ-hydroxypropylamino)ethyl]-5-methyltetrazole (IIId).

ν_{max}^{Liquid}: 3367 (NH, OH); 3058 (phenyl); 2985, 2882; 2717; 1531 (tetrazole ring); 1504, 1408, 1383; 1111 (alcohol); 749, 701 cm^{-1} (monosubstituted benzene).

All attempts to form a crystalline salt by the use of hydrobromic, hydrochloric, fumaric, sorbic, and tartaric acids were unsuccessful.

The Picrate. This was obtained as usual. Recrystallization from benzene gave yellow crystals, mp 149.5°C.

Found: C, 48.75; H, 5.66%. Calcd for $C_{19}H_{22}N_8O_8$: C, 48.50; H, 6.43%.

δ-(Pyrrolidino)butylamine. Into a solution of 4.20 g (0.1 mol as 90% purity) of lithium aluminum hydride in 200 m*l* of absolute ether under ice-cooling, 13.8 g (0.1 mol) of γ-(pyrrolidino)butylonitrile in 20 m*l* of absolute ether were stirred over a 40-min period. The reaction system was then allowed to stand overnight at room temperature. Four m*l* of water were vigorously stirred in, drop by drop, under deep cooling, and then 3 m*l* of 20% sodium hydroxide and 14 m*l* of water were added. The ether layer was separated by decantation, and the residue was washed twice with much ether. The combined ether solution was dried over potassium hydroxide pellets. On the removal of the solvent, 13.87 g of a yellow oil were obtained. This was shown to be an almost pure δ-(pyrrolidino)butylamine by the infrared spectrum determination. The yield was almost theoretical.

ν_{max}^{Liquid}: 3413, 3322, 3226, 1639 (NH_2); 2817 (*N*-alkylpyrrolidine); 1149 (tertiary amine); 1099 (primary amine); 880 cm^{-1} (amine., liquid).

Purification by vacuum distillation gave 11.35 g of a water-white liquid, bp 83—85°C/7 mmHg, whose infrared spectrum was completely identical with that of the original sample.

The Dihydrobromide. The usual method of preparation gave crystals. Recrystallization from ethanol gave an analytical sample; mp 126—127°C.

Found: C, 31.58; H, 6.74%. Calcd for $C_8H_{18}N_2 \cdot 2HBr$: C, 31.60; H, 6.63%.

1-[1′-Phenyl-2′-(δ-pyrrolidinobutylamino)ethyl]-5-methyltetrazole (IIIe). One mmol (267 mg) of I in 969 mg of the diamine obtained above was heated on a steam bath for 24 hr. After the excess amine had been removed by vacuum distillation and usual work-up, 228 mg of a yellow oil were obtained. The Beilstein reaction was negative.

ν_{max}^{Liquid}: 3356 (NH); 3058, 1499, 729, 701 (phenyl); 2809 (pyrrolidinoalkyl); 1527 (tetrazole ring); 1143, 1121 cm^{-1} (tertiary amine).

The usual salt formation with hydrochloric acid and crystallization from a solvent, an acetone-benzene-ethanol mixture, gave 318 mg (79%) of the analytical sample, dihydrochloride; mp 193—195°C.

Found: C, 53.73; H, 7.56%. Calcd for $C_{18}H_{28}N_6 \cdot 2HCl$: C, 53.86; H, 7.53%.

1-(1′-Phenyl-2′-pyrrolidinoethyl)-5-methyltetrazole (IIIf). A mixture of 167 mg (0.625 mmol) of I and 2 m*l* of pyrrolidine was refluxed for 24 hr. After work-up as usual, alkalization with conc. ammonia gave 132 mg (82%) of the product; mp 122—123°C.

Found: C, 65.44; H, 7.48%. Calcd for $C_{14}H_{19}N_5$: C, 65.34; H, 7.44%.

ν_{max}^{KBr}: 3049 (phenyl); 2994, 2959, 2841; 2778 (pyrrolidinoalkyl); 1520 (tetrazole ring); 731, 703 (monosubstituted benzene); and other spectral peaks, 1495, 1456, 1437, 1404, 1383, 1355, 1325, 1297, 1261, 1236, 1205, 1156, 1147, 1111, 1092, 1053, 1031, 952, 880, 777 cm^{-1}.

1-[1′-Phenyl-2′-(β-diethylaminoethylamino)ethyl]-5-methyltetrazole (IIIg). A sample of 534 mg (2 mmol) of I in 10 m*l* of β-diethylaminoethylamine was heated under reflux for 24 hr. After work-up as usual, 409 mg (45%) of the dihydrobromide were obtained. Recrystallization from an acetone-benzene-*n*-butanol mixture gave an analytical sample; mp 157—159°C (decomp).

Found: C, 41.70; H, 6.21%. Calcd for $C_{16}H_{26}N_6 \cdot 2HBr$: C, 41.39; H, 6.08%.

ν_{max}^{KBr}: 3521, 3436 (NH); 3030 (phenyl); 2778, 2632, 2445 (amine hydrobromide, broad); 1520 (tetrazolering); 1453, 1433, 1403, 1017; 740, 698 cm^{-1} (monosubstituted benzene).

1-[1′-Phenyl-2′-(δ-diethylamino-α-methylbutylamino)ethyl]-5-methyltetrazole (IIIh). A mixture of 534 mg (2 mmol) of I and 10 m*l* of 2-amino-5-diethylaminopentane was heated under reflux for 24 hr. After work-up as usual, the hydrobromide amorphous was obtained. This was very hygroscopic and gave a negative result on attempted crystallization. The dried sample was submitted to elemental analysis and showed the following results:

Found: C ,44.76; H, 7.53; N, 12.21%. Calcd for $C_{19}H_{32}N_6 \cdot 2HBr$: C, 45.08; H, 6.77; N, 16.60%.

ν_{max}^{KBr}: 3413 (NH); 2950, 2874 (CH_3, CH_2); 2688

(amine hydrobromide, broad); 1524 (tetrazole ring); 741 (weak), 701 (monosubstituted benzene), and other peaks, 1453, 1395, 1072, 1042, 1031 cm^{-1}.

1-[1′-Phenyl-2′-(γ-diethylamino-β-hydroxypropylamino)ethyl]-5-methyltetrazole (IIIi). A mixture of 534 mg (2 mmol) of I and 10 m*l* of 1-amino-3-diethylamino-2-propanol was refluxed for 24 hr. After work-up as usual and after the removal of the excess amine by vacuum distillation, 349mg of an oil, a free amino product, was obtained. The usual hydrobromide formation and the trituration of the oily product in acetone gave a brown powder. This decomposed at 160—163°C and was also very hygroscopic.

Found: C, 37.31; H, 6.67; N, 9.38%. Calcd for $C_{17}H_{28}N_6O \cdot 2HBr$: C, 42.69; H, 6.32; N, 17.57%.

Disagreements in these analytical results can be explained to some extent if we assume that some 1-amino-3-diethylamino-2-propanol dihydrobromide(Calcd for $C_8H_{18}N_2O \cdot 2HBr$: C, 27.27; H, 6.54; N, 9.09%) might contaminate the analytical sample. However, the excess amine had been completely removed by vacuum distillation after the reaction. The following infrared spectrum determination shows that the product was mainly an amine derivative of tetrazoe (this sample was submitted to the screening test previously described).

ν_{max}^{KBr}: 3413 (OH, NH); 2778—2353 (amine hydrobromide, broad); 1538 (tetrazole ring); 765, 703 (monosubstituted benzene), and other peaks, 1558, 1453, 1395, 1099, 1028, 826, 800 cm^{-1}.

Attempts to purify the crude products of IIIh and IIIi further by recrystallization were unsuccesful because of their high hygroscopicities and low crystallinities.

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