[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA

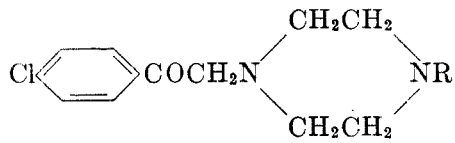
ANTIMALARIALS.[1] SOME PIPERAZINE DERIVATIVES

ROBERT E. LUTZ AND NEWTON H. SHEARER[2]

Received January 6, 1947

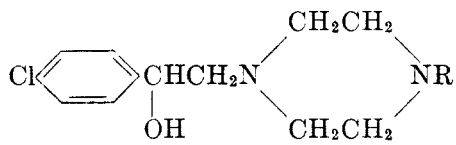
In varying the *tert.*-amino group of the α-aryl-β-aminoethanols which were being made for screening tests against avian malaria (1, 2), it seemed of interest to evaluate the piperazyl group and to compare it on the one hand with the piperidyl group and on the other with dialkylaminoalkylamino groups. Three types of compounds have been prepared, namely: (a) two mono-N-alkylpiperazylmethyl ketones and the two corresponding alcohols (I–IV), (b) several bis-compounds which are di-(amino ketones) and di-(amino alcohols) (V–X), and (c) a few N,N′-dialkyl piperazines (XI–XII), made because at the time (1943) slight antimalarial activity had been reported in the case of a few high molecular weight secondary and tertiary amines (1).

The mono-N-alkylated β-piperazylethanols were prepared by condensing 4-chlorophenacyl bromide with mono-N-amyl and mono-N-benzylpiperazines to produce respectively the amino ketones I and II, and by reducing these compounds by means of aluminum isopropoxide to the amino alcohols, III and IV.



I R = *n*-amyl SN[3]-8415 Q[4] = <0.3

II R = benzyl SN-8121 Q = 0.15



III R = *n*-amyl SN-8782 Q = <0.15

IV R = benzyl SN-8348 Q = <0.1

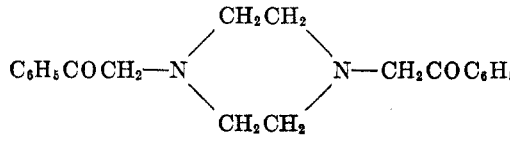
Two piperazyl diketones (V and VI) were made by condensing phenacyl and *p*-chlorophenacyl bromides directly with piperazine, and one typical piperazyl-dialcohol was made by reduction of VI with aluminum isopropoxide.

[1] A portion of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia.

[2] Present address, Eastman Kodak Co., Rochester, N. Y.

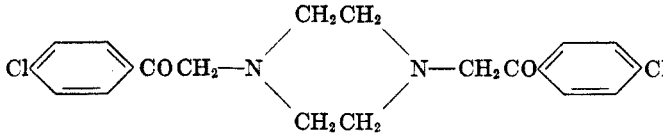
[3] The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned have been tabulated in the monograph (1).

[4] Q = quinine equivalents against *gallinaceum* in the chick, as listed in the Survey Monograph (1) and designated as the A-1 test. These results were obtained at the National Institute of Health under the direction of Dr. G. Robert Coatney.



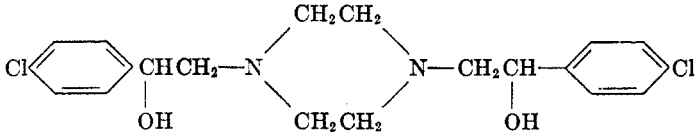
SN-12707 Q = <0.3

V



SN-13028 Q = 0.1

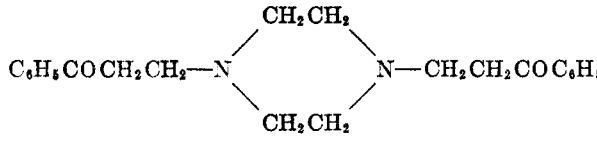
VI



SN-8478 Q = <0.1

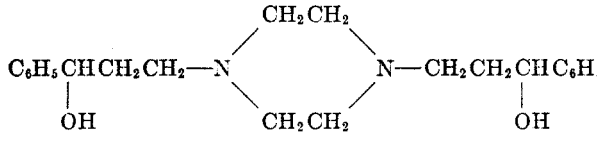
VII

Typical homologs of the piperazyl diketones and dialcohols also were made. These included the two diketones, VIII (3) and X, made by the Mannich reaction on acetophenone and *p*-chloroacetophenone. The first of these two (VIII) was reduced successfully without fission to the piperazyl dialcohol (IX).



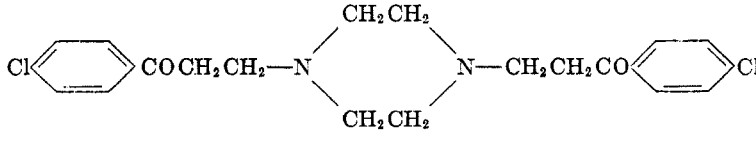
SN-3689 Q = <0.08

VIII



SN-8119 Q = <0.1

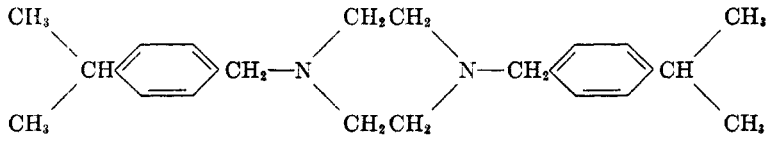
IX



SN-7388 Q = <0.08

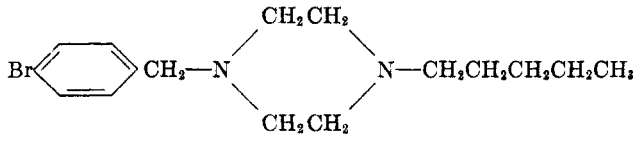
X

The following two new N,N′-dialkylpiperazines were made and tested:



SN-8120 Q = <0.6

XI



SN-9587 Q = <0.15

XII

EXPERIMENTAL[5, 6]

The preparation of 1-benzylpiperazine differed slightly in detail from the directions of Baltzly *et al.* (4). To a solution of 144 g. (1.8 moles) of anhydrous piperazine in 500 ml. of absolute ethanol was added over twelve minutes with stirring, 76 g. (0.6 mole) of benzyl chloride. After standing overnight, and filtering off the precipitate, the ethanol was evaporated under reduced pressure and the residual oil was partitioned between equal volumes of ether and 3 *N* sodium hydroxide. The aqueous layer was extracted twice with ether and the ether solution evaporated. The oil thus obtained was fractionated; yield 47 g. (45%); b.p. 128–135° (6 mm.).

1-(n-Amyl)piperazine. To 431 g. (5 moles) of anhydrous piperazine in 1.2 l. of methanol was added 396 g. (2 moles) of amyl iodide over ten minutes, with stirring and cooling to take care of the considerable heat of reaction. After standing for four days and filtering from precipitated salts, the methanol was distilled and the product dissolved in ether and washed three times with 3 *N* sodium hydroxide to remove excess piperazine. Evaporation of the ether gave 343 g. of oil which was fractionated; yield 161 g. (52%) of hygroscopic oil; b.p 105–110° (9 mm.); n_D^{20} 1.4650–1.4659.

The *dihydrochloride* was obtained from ether by addition of ethereal hydrogen chloride; two recrystallizations from isopropanol gave colorless rods of m.p. 267–269°.

Anal. Calc'd for $C_9H_{20}N_2 \cdot 2HCl$: Cl^-, 30.94. Found: Cl^-, 30.90.

1,4-Di-(4-isopropylbenzyl)piperazine (XI). A mixture of 13.2 g. (0.15 mole) of piperazine, 100 ml. of methanol, and 42.2 g. (0.25 mole) of *p*-isopropylbenzyl chloride was heated almost to boiling and allowed to stand at room temperature overnight. The tan precipitate, after cooling in ice, was filtered and washed with water to remove piperazine hydrochloride, and was treated with 2.5 *N* sodium hydroxide and extracted with ether. Evaporation under reduced pressure gave 14.6 g. of solid which was recrystallized from ethanol; 9.3 g. (18% from piperazine); hexagonal rods; m.p. 83–84°. After repeated recrystallizations from ethanol it melted at 84–85.°

Anal. Calc'd for $C_{24}H_{34}N_2$: N, 7.99. Found: N, 8.03.

The *dihydrochloride* was prepared from ether with ethereal hydrogen chloride and was recrystallized from ethanol; rectangular plates; m.p. 274–275° (*in vacuo*).

Anal. Calc'd for $C_{24}H_{34}N_2 \cdot 2HCl$: N, 6.62. Found: N, 6.83.

1-(n-Amyl)-4-(4-bromobenzyl)piperazine dihydrochloride (XII). A mixture of equimolar amounts of *p*-bromobenzyl bromide and 1-*n*-amylpiperazine in ether was refluxed for five

---

[5] All melting points are "corrected".

[6] Microanalyses were by Miss Geraldine Alley, Mrs. Joyce Blume Caliga, R. J. Rowlett, Jr., J. W. Wilson, III, and C. S. Floyd.

minutes (with formation of a crystalline precipitate). After treatment of the ether solution with aqueous sodium carbonate, separation, washing, and drying over sodium sulfate, the product was precipitated as the dihydrochloride with ethereal hydrogen chloride. Recrystallization from ethanol gave a 56% yield; m.p. 275–277° (*in vacuo*).

Anal. Calc'd for $C_{16}H_{25}BrN_2 \cdot 2HCl$: Cl^-, 17.81. Found: Cl^-, 17.85.

1-n-Amyl-4-(p-chlorophenacyl)piperazine dihydrochloride (I). A suspension of 70 g. (0.3 mole) of *p*-chlorophenacyl bromide in 450 ml. of ether was treated over three minutes with 46.9 g. (0.3 mole) of 1-*n*-amylpiperazine; a precipitate began to form almost immediately; 450 ml. of 1 *N* sodium carbonate was added and the mixture was shaken for 24 hrs. The ether layer was separated, dried over sodium sulfate, and treated with ethereal hydrogen chloride. The largely crystallized product was digested with isopropanol, filtered, and washed with ether; 85 g. (79%). A portion of this was reduced (see below). Recrystallization from ethanol gave rhombic prisms of m.p. 235° decomp.

Anal. Calc'd for $C_{17}H_{25}ClN_2O \cdot 2HCl$: N, 7.34. Found: N, 7.61.

α-4-Chlorophenyl-β-(1-n-amyl-4-piperazyl)ethanol dihydrochloride (III). Reduction was carried out in the usual way with aluminum isopropoxide (see VII), under refluxing for eight hours, with hydrolysis in 10 *N* sodium hydroxide and extraction of the product by ether. Since the product did not crystallize upon evaporation of the solvent, it was converted into the hydrochloride by ethereal hydrogen chloride. The yield after two recrystallizations from ethanol (one with Darco treatment) was 31%; white rhombic crystals; m.p. 241–242° (*in vacuo*).

Anal. Calc'd for $C_{17}H_{27}ClN_2O \cdot 2HCl$: N, 7.30. Found: N, 7.43.

1-Benzyl-4-(4-chlorophenacyl)piperazine dihydrochloride (II). To 46.8 g. (0.2 mole) of *p*-chlorophenacyl bromide in 300 ml. of ether was added slowly 35.2 g. (0.2 mole) of 1-benzylpiperazine. When the precipitation had apparently ceased, 42 g. of sodium carbonate in 300 ml. of water was added and the mixture was shaken for 24 hours. The ether layer was separated, dried over sodium sulfate, and acidified (to Congo) with ethereal hydrogen chloride; the product, washed repeatedly with ether (69.7 g.; 87%), melted at 236–240° (sintering). Recrystallization from ethanol gave cubic prisms; sintered at 237–239° *in vacuo*.

Anal. Calc'd for $C_{19}H_{21}ClN_2O \cdot 2HCl$: Cl^-, 17.65. Found: Cl^-, 17.62.

α-4-Chlorophenyl-β-(1-benzyl-4-piperazyl)ethanol (IV) was prepared from the piperazine diketone dihydrochloride (II) in the usual way by aluminum isopropoxide reduction (under reflux for 13 hrs.). The crude product, as the base, was crystallized from ethanol as fluffy crystals (rods) of m.p. 152° in a yield of 59%. Recrystallization from ethanol did not raise the melting point.

Anal. Calc'd for $C_{19}H_{23}ClN_2O$: N, 8.47. Found: N, 8.59.

1,4-Diphenacylpiperazine (V). A suspension of 39.8 g. (0.2 mole) of phenacyl bromide in 170 ml. of 95% ethanol was treated by slow addition of 8.6 g. (0.1 mole) of piperazine under stirring; heat was evolved and a copious precipitate formed. Sodium carbonate (21 g.; 0.2 mole) was added slowly and stirring continued for 30 min. After cooling and filtering, addition of 150 ml. of hot water, and again filtering, the solid was slurried with 200 ml. of hot water, filtered, and washed with three 50-ml. portions of hot water; cubic prisms; 25 g.; m.p. 139–142°. Recrystallization from 300 ml. of 25% ethanol and 100 ml. of ethyl acetate gave 23 g. (71.5%); m.p. 141–142°. The melting point was not raised upon repeated recrystallizations.

Anal. Calc'd for $C_{20}H_{22}N_2O_2$: N, 8.69. Found: N, 8.90.

It was soluble in ethyl acetate, slightly soluble in ethanol and insoluble in ether and water.

1,4-Di-(4-chlorophenacyl)piperazine (VI). Piperazine [8.6 g. (0.1 mole)] was added with stirring to a suspension of 46.4 g. (0.2 mole) of *p*-cholorophenacyl bromide in 200 ml. of ethanol. The mixture became warm and the *p*-chlorophenacyl bromide partially dissolved. Sodium carbonate (21 g., 0.2 mole) was added with stirring and the mixture was refluxed for 1.5 hours and allowed to stand at room temperature for twelve hours. A cream-colored solid precipitated during this time. The mixture was thoroughly chilled in an ice-bath and

the solid was filtered and washed, once with 50% ethanol and seven times with water; 34.3 g. (88%); m.p. 156–158°. Recrystallization was effected by dissolving the solid in a 4:1 mixture of warm dioxane and ethanol and diluting with 100 ml. of water; colorless rhomboids; 21.4 g. (54%); m.p. 156–158°. It was soluble in dioxane but only slightly soluble in ethanol and insoluble in ether.

Anal. Calc'd for $C_{20}H_{20}Cl_2N_2O_2$: N, 7.16. Found: N, 7.21.

1,4-Di-[β-(4-chlorophenyl)-β-hydroxyethyl]piperazine (VII). A mixture of 25.5 g. (0.065 mole) of the piperazine diketone (VI) and 165 ml. of 2.5 *N* aluminum isopropoxide was heated under a fractionating column under partial reflux (4.5 hrs.) until a negative test for acetone was obtained (2,4-dinitrophenylhydrazine). The solvent was distilled under diminished pressure and the product treated with 10 *N* sodium hydroxide and crystallized several times from toluene; m.p. 186–187°. It was difficultly soluble in ethanol, ethyl acetate and dioxane.

Anal. Calc'd for $C_{20}H_{24}Cl_2N_2O_2$: N, 7.09. Found: N, 7.30.

The *preparation of 1,4-bis-(β-benzoylethyl)piperazine dihydrochloride* (VIII) was according to the method of Mannich and Lammering (3); yield 65%; sintered and turned dark at 203°; after one recrystallization from 50% ethanol it melted at 205° (dec.) (M. and L., 190° dec.).

1,4-Bis-(γ-hydroxy-γ-phenylpropyl)piperazine (IX). A mixture of 25 g. (0.06 mole) of the above diketone dihydrochloride (VIII), 150 ml. of dry isopropanol and 65 ml. of 3 *N* aluminum isopropoxide was heated under reflux for seven hours, and three hours more after addition of 70 ml. additional 3 *N* aluminum isopropoxide; only toward the end of the reduction period did the test for acetone become negligible. The isopropanol was distilled under reduced pressure. The residue was shaken with 6 *N* sodium hydroxide for half an hour. The brown precipitate was filtered, washed with water, dried, and then washed with ether, which removed the brown color; white solid; 11.7 g. (46%); m.p 154–157°. Upon treatment with 100 ml. of 6 *N* hydrochloric acid, it momentarily dissolved and the dihydrochloride precipitated. This was filtered, reconverted to the base, and crystallized first from butanone and then from ethanol; m.p. 158–161°. It was soluble in ethanol, butanone, and dilute hydrochloric acid.

Anal. Calc'd for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90.
Found: C, 74.66; H, 8.65; N, 7.89.

1,4-Di-[γ-(4-chlorophenyl)-γ-ketopropyl]piperazine dihydrochloride (X). A mixture of 17.2 g. (0.2 mole) of piperazine, 40 ml. of concentrated hydrochloric acid, 200 ml. of absolute ethanol, 64 g. (0.415 mole) of *p*-chloroacetophenone, and 18 g. (0.6 mole) of paraformaldehyde was refluxed for 3 hrs. and allowed to stand overnight. The white needle crystals were filtered and washed with ether; 75 g. (77%): m.p. 210° decomp. After recrystallization from water it melted at 212° decomp.

Anal. Calc'd for $C_{22}H_{24}Cl_2N_2O_2 \cdot 2HCl$: Cl^-, 14.41. Found: Cl^-, 14.48.

SUMMARY

New derivatives of piperazine made for screening tests against avian malaria, include two N-alkylpiperazyl alcohols and the corresponding ketones, several N,N′-piperazyl-α-bis-acetophenones and β-bis-propiophenones and the corresponding dialcohols, and two N,N′-dialkylpiperazines.

CHARLOTTESVILLE, VIRGINIA

REFERENCES

(1) WISELOGLE, F. Y., "A Survey of Antimalarial Drugs, 1941–1945." J. W. Edwards (1946).
(2) LUTZ *et al.*, *J. Org. Chem.*, **12**, second preceding paper.
(3) MANNICH AND LAMMERING, *Ber.*, **55**, 3510 (1922).
(4) BALTZLY, BUCK, LORZ, AND SCHÖN, *J. Am. Chem. Soc.*, **66**, 263 (1944).