New Compounds:

3-[2-(2-Chloro-10-phenothiazinyl)ethyl]-3-azabicyclo[3.2.2]nonane

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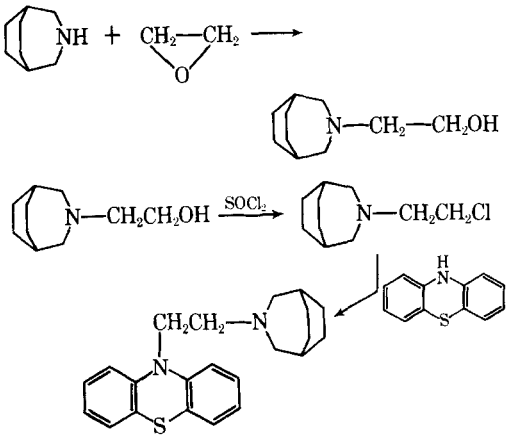
The synthesis of 3-[2-(2-chloro-10-phenothiazinyl)ethyl] - 3 - azabicyclo[3.2.2]nonane is reported; the pharmacological evaluation of this agent, an analog of promethazine, has not yet been reported.

PREVIOUSLY, Anderson and his associates (1) reported the synthesis of 3 [3-(2-chloro-10-phenothiazinyl)propyl] - 9 - methyl - 3,9 - diazabicyclo - [3.3.1]nonane dihydrochloride in the course of preparing synthetic relatives of various 2-substituted phenothiazines and their 10-aminoalkyl derivatives. Almost simultaneously, the authors were experimenting with the use of an analogous heterocyclic amine, 3-azabicyclo[3.2.2]nonane, as a possible intermediate in the synthesis of potential medicinals (2–5). Thus, the present report is to indicate the extension of these studies to the preparation of the 3-azabicyclo[3.2.2]nonane analog of existing phenothiazines which are of significant value as tranquilizers.

This new compound was prepared by means of the outline shown in Scheme I.



Scheme I

The results of the pharmacological testing of this compound will be reported elsewhere.

EXPERIMENTAL

3-Azabicyclo[3.2.2]nonane-3-ethanol.—To 37.5 Gm. (0.3 mole) of 3-azabicyclo[3.2.2]nonane dissolved in 50 ml. of methanol was added 17.8 Gm. (0.4 mole) of ethylene oxide over a 1-hr. period. The temperature of the reaction mixture was maintained below 47° by keeping the mixture in ice water. The reaction mixture was stirred for 1 hr. and 45 min. after the completion of the addition; the methanol was then removed under reduced pressure. Distillation of the product then yielded 32.3 Gm. (60%) of 3-azabicyclo[3.2.2]nonane-3-ethanol, b.p. 94° (1.8 mm.).

Anal.—Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28. Found: C, 70.93; H, 11.06; N, 8.29.

2-(3-Azabicyclo[3.2.2]nonyl)ethyl Chloride Hydrochloride.—A solution of 32.3 Gm. (0.19 mole) of 3-azabicyclo[3.2.2]nonane-3-ethanol in 175 ml. of benzene was placed in a dry, three-necked flask. The solution was stirred while 29.7 Gm. (0.25 mole) of thionyl chloride in dry benzene was added dropwise. The reaction was slightly exothermic. After the addition of the thionyl chloride, the mixture was refluxed for 3 hr. and then cooled. The solid product was collected by filtration and washed with benzene to yield 35.6 Gm. (54%) of the desired product, m.p. 225° (sublimation).

Anal.—Calcd. for $C_{10}H_{18}ClN.HCl$: C, 53.50; H, 8.54; N, 6.24. Found: C, 53.42; H, 8.64; N, 6.18.

3-[2-(2-Chloro-10-phenothiazinyl)ethyl]-3-azabicyclo[3.2.2]nonane.—The hydrochloride salt, indicated above, was converted to the free base by the addition of a saturated solution of sodium carbonate until the solution was slightly basic to litmus. This basic solution was extracted with three 200-ml. portions of ether. The ether layer was dried over anhydrous sodium carbonate for 24 hr. and the free base obtained by distillation after the evaporation of the ether. To 4 Gm. (0.1 mole) of sodamide, dissolved in diethyleneglycol dimethyl ether in an atmosphere of nitrogen, was added 20.3 Gm. (0.11 mole) of 2-(3-azabicyclo[3.2.2]nonyl)ethyl chloride; then 25 Gm. (0.9 mole) of 2-chlorophenothiazine (dissolved in 125 ml. of diethyleneglycol dimethyl ether) was added. After the reaction mixture was stirred and heated for 2 hr. at 135°, it was cooled to room temperature. Filtration produced a muddy semisolid mass which liquefied on exposure to air. Small quantities of this material were dissolved in butanol and precipitated with anhydrous ether. Recrystallization from butanol–hexane yielded a white powder, m.p. 205–206°.

Anal.—Calcd. for $C_{22}H_{25}ClN_2S$: C, 62.69; H, 6.22; N, 6.25. Found: C, 62.29; H, 6.50; N, 6.47.

Received August 15, 1966, from the Department of Pharmaceutical Chemistry, School of Pharmacy, University of Mississippi, University 38677.

Accepted for publication October 27, 1966.

Abstracted in part from an exhibit prepared by William T. King as an entry in the Mississippi Science Fair, Spring 1964.

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