[JOINT CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT LABORATORIES, SMITH KLINE AND FRENCH LABORATORIES AND THE RESEARCH INSTITUTE OF TEMPLE UNIVERSITY]

Analogs of Phenothiazines. I. 5H-Dibenz[b,f]azepine and Derivatives. A New Isostere of Phenothiazine[1]

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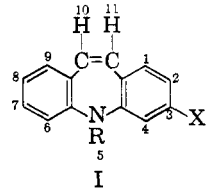
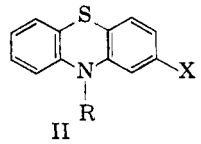
5H-Dibenz[b,f]azepine was prepared by catalytic dehydrogenation of "iminobibenzyl," and also by the ring expansion which accompanies the dehydration of 9-acridanylmethanol. 3-Chloro-5H-dibenz[b,f]azepine was also prepared by the latter route, and was hydrogenated to form 3-chloro-9,10-dihydro-5H-dibenz[b,f]azepine. Several 5-dialkylaminoalkyl derivatives of these new dibenzazepines were prepared and initial pharmacological test results are reported.

In view of renewed interest in 10-aminoalkylphenothiazine derivatives stemming from the discovery of their tranquilizing properties,[3] we prepared derivatives I-c and I-d of 5H-dibenz[b,f]azepines (I-a and I-b) for biological comparison with the isosteric phenothiazine compounds, II-c (promazine) and II-d (chlorpromazine).



I

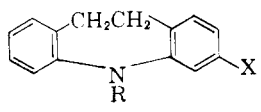


II

a. X = H, R = H
b. X = Cl, R = H
c. X = H, R = $(CH_2)_3N(CH_3)_2$
d. X = Cl, R = $(CH_2)_3N(CH_3)_2$
e. X = H, R = $COCH_3$

According to the concept of isosterism,[4] I-a bears a relationship to phenothiazine analogous to that existing between benzene and thiophene.

Preliminary attempts to dehydrogenate 10,11-dihydro-5H-dibenz[b,f]azepine (III-a "iminodibenzyl"), using sulfur, selenium, or palladium-charcoal under the usual conditions gave poor results. However, sublimation *in vacuo* of III-a

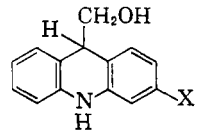


III

a. X = H, R = H
b. X = H, R = $COCH_3$
c. X = Cl, R = H
d. X = Cl, R = $(CH_2)_3N(CH_3)_2$
e. X = H, R = $(CH_2)_3$ N⌒N—CH_3

through a hot glass tube packed with palladium-charcoal sprinkled on glass wool[5] gave 20–50% conversions to I-a, obtained as intensely colored orange-yellow platelets. Acetylation of this compound by acetic anhydride gave the colorless acetyl derivative, I-e, which was also obtained by dehydrogenation of III-b by the method of Baxter, Ramage, and Timson.[5]

A second route to I-a was found in the ring-enlargement of 9-acridane-methanol (IV-a). This reaction is analogous to the rearrangement of 9,10-dihydroanthracene-9-methanol to dibenzocycloheptatriene as reported by Rigaudy and Tardieu.[6] This method was also successfully applied to the preparation of 3-chloro-5H-dibenz-



IV

a. X = H
b. X = Cl

[b,f]azepine (I-b) from 3-chloro-9-acridanemethanol (IV-b). The ring-enlargement of IV was found to be erratic and several methods were studied before those reported in the experimental section were found. The reagents tried included phosphorus oxychloride, 47% hydrobromic acid, thionyl chloride in pyridine, aqueous hydrogen fluoride, zinc chloride, trifluoracetic acid and anhydride, polyphosphoric acid, and phosphorus pentoxide in dimethylformamide or xylene.

Acridinemethanol, IV (X = H), was reported recently.[7] The preparation of 3-chloro-9-acridanemethanol was carried out by the sequence employed for the unsubstituted analog, starting with the known compound, 3,9-dichloroacridine.[8]

(1) Presented in part before the Second Delaware Valley Regional Meeting, ACS, in Philadelphia, February 5, 1958.

(2) Research Institute of Temple University.

(3) J. Delay, P. Deniker, and J. M. Harl, *Annales Medico-Psychologiques*, 110, 112 (1952).

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(5) R. A. Baxter, G. R. Ramage, and J. A. Timson, *J. Chem. Soc.*, 1111 (1950).

(6) J. Rigaudy and P. Tardieu, *Compt. rend.*, 240, 1347 (1955). The authors are indebted to Dr. Joseph Weinstock for suggesting this method.

(7) A. Campbell and E. Morgan, *J. Chem. Soc.*, 1712 (1958).

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Alkylation of I-a and I-b with 3-dimethylaminopropyl chloride in toluene in the presence of sodamide gave the aminopropyl derivatives I-c and I-d.

Although dialkylaminoalkyl derivatives of "iminodibenzyl" (III-a) and symmetrically disubstituted analogs thereof have been prepared[9,10] no compounds monosubstituted in the benzenoid ring have been reported. In the course of this work we prepared 3-chloro-10,11-dihydro-5H-dibenz[b,f]azepine (III-c) and its dimethylaminopropyl derivative III-d.

Catalytic hydrogenation of I-b gave the corresponding dihydro compound III-c in 68% yield, as well as a small amount of III-a, resulting from reductive dechlorination of either I-b or III-c. Alkylation of III-c with β-dimethylaminopropylchloride gave 3-chloro-10,11-dihydro-5-(3-dimethylaminopropyl)-5H-dibenz[b,f]azepine (III-d).

Also prepared was the 5-[3-(4-methylpiperazinylpropyl)] derivative III-e, obtained from the reaction of "iminodibenzyl" (III-a) with 4-(3-chloropropyl)-1-methylpiperazine.

Spectral data for several of these compounds are listed in Tables I & II.

TABLE I

ULTRAVIOLET SPECTRAL DATA

Compound	Wave Length, mμ	Molecular Ext. Coeff.
III-a	290	1.15×10^4
III-b	270	7.5×10^3
	233 (shoulder)	9.3×10^3
I-a	292	3.5×10^3
	258	4.4×10^4
I-e	285	1.1×10^4
I-c (maleate)	284	4.4×10^3
	255	3.1×10^4
I-b	295	2.9×10^3
	262	5.0×10^4

Compound Ic was found to be one seventh as active as IId (chlorpromazine) as an antiemetic agent in dogs,[11] and was essentially inactive in the rat conditioned escape response test.[12] The authors are indebted to Drs. C. A. Leonard and D. H. Tedeschi for this preliminary information.

(9) W. Schindler and F. Hafliger, *Helv. Chim. Acta*, **37**, 472 (1954). Compound 5 (*loc. cit.*) is marketed as "Tofranil"[R] by J. R. Geigy, Inc.

(10) For benzenoid-ring disubstituted derivatives see W. Schindler and F. Hafliger, U. S. Patent 2,813,857, Nov. 19, 1957; also, R. Domenjoz and W. Theobald, *Arch. Intern. pharmacodynamie*, **120**, 450 (1959).

(11) E. M. Boyd, W. A. Cassell, C. E. Boyd, and J. K. Miller, *J. Pharmacol. Exptl. Therap.*, **113**, 299 (1955).

(12) L. Cook, E. Weidley, R. Morris, and P. Mattis, *J. Pharmacol. Exptl. Therap.*, **113**, 11 (1955).

TABLE II

INFRARED SPECTRAL DATA

Compound	Peaks, μ[a]
I-a	2.98 (m), 3.30 (w), 6.20 (m), 6.32 (m), 6.65 (w), 6.80 (vs), 6.95 (s), 7.65 (m), 7.75 (m), 7.93 (m), 8.23 (m), 8.67 (m), 9.00 (s), 9.56 (w), 10.73 (s), 10.94 (m), 11.64 (m), 12.46 (vs), 13.07 (w), 13.26 (s), 13.70 (s)
I-b	3.00 (m), 6.20 (m), 6.33 (s), 6.65 (w), 6.80 (vs), 6.94 (w), 7.04 (m), 7.28 (m), 7.67 (w), 7.78 (w), 7.96 (w), 8.06 (m), 8.27 (m), 8.71 (w), 8.99 (m), 9.16 (m), 9.55 (w), 10.67 (s), 11.47 (w), 11.65 (m), 11.97 (m), 12.20 (vs), 12.70 (s), 13.39 (vs)
III-a	2.96 (m), 3.32 (w), 3.40 (w), 3.47 (w), 3.53 (w), 5.20 (w), 5.28 (m), 5.62 (m), 5.92 (w), 6.20 (m), 6.30 (vs), 6.57 (m), 6.73 (vs), 6.90 (m), 7.35 (w), 7.53 (vs), 7.72 (m), 7.83 (m), 8.00 (m), 8.15 (w), 8.29 (m), 8.45 (w), 8.62 (m), 9.00 (s), 9.50 (w), 10.35 (w), 10.50 (w), 10.68 (s), 11.54 (w), 11.65 (m), 11.86 (m), 13.10 (w), 13.37 (vs), 14.20 (w)
III-c	3.00 (w), 3.33 (w), 3.45 (w), 3.48 (w), 3.55 (w), 5.22 (w), 5.54 (w), 5.90 (w), 6.20 (m), 6.32 (vs), 6.57 (s), 6.76 (vs), 6.95 (vs), 7.20 (m), 7.42 (w), 7.52 (m), 7.83 (w), 7.90 (w), 8.08 (m), 8.30 (m), 8.42 (w), 8.53 (w), 8.70 (w), 8.98 (m), 9.02 (m), 9.17 (s), 9.50 (w), 9.58 (m), 10.53 (vs), 10.60 (vs), 10.69 (s), 11.30 (w), 11.85 (vs), 12.50 (vs), 12.64 (vs), 13.45 (vs), 13.66 (m), 13.95 (w), 14.20 (w)

[a] (w) = weak, (m) = medium, (s) = strong, (vs) = very strong.

EXPERIMENTAL[13]

Preparation of 5H-dibenz[b,f]azepine (I-a). *Method A.* An upright 35 mm. dia. glass column 14½ inches long, heated by an asbestos-covered electric tape, was packed tightly with glass wool upon which was sprinkled 2 g. of 30% palladium-on-charcoal. The colorless solid, 10,11-dihydro-5H-dibenz[b,f]azepine (2.5 g.), was placed in a flask mounted below the column and a slow stream of nitrogen was passed through the system, which was evacuated and kept between 0.3–0.5 mm. during the distillation. The column was heated first to about 160–170° and the distilling flask was heated between 120–130°. The material was distilled slowly so that a run of 2.5 g. of 10,11-dihydro-5H-dibenz[b,f]azepine required about 2 hr. to be distilled. The products condensed at the top of the column above the heated zone, and were easily removed by scraping.

The crude orange material was dissolved in benzene and chromatographed through a 25 mm. dia. column packed to a depth of about 25 cm. with activated alumina. The products were separated into fractions melting at 195–198°, 155–190°, and 101–154°. The material melting above 155° was twice recrystallized from ethanol and then was essentially pure. The predominantly unchanged material (melting below 155°) was redistilled through palladium-on-charcoal and then rechromatographed. This procedure was repeated until all of the material melted above 150°.

In this manner 13.0 g. of 10,11-dihydro-5H-dibenz[b,f]-azepine was converted to 6.4 g. of 5H-dibenz[b,f]azepine; m.p. 195–198° (I-a). The purest sample of 5H-dibenz[b,f]-azepine obtained had a melting point of 196.5–198°. The overall yield was 50%; the other 50% was lost in the repeated handling required by this procedure.

(13) Melting points uncorrected.

Anal. Calcd. for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 86.75; H, 5.94; N, 7.35.

Refluxing I-a with excess acetic anhydride in benzene for 0.5 hr. afforded the colorless *N*-acetyl derivative, I-e; m.p. 99–101°.

Anal. Calcd. for $C_{16}H_{13}NO$: C, 81.68; H, 5.57. Found: C, 81.33; H, 5.53.

This same derivative was prepared from III (R = CH_3CO, X = H) by the experimental method A above.

Hydrolysis of the *N*-acetyl derivative by refluxing in a mixture of ethanol and 10% hydrochloric acid for 2 hr. gave back I (R = X = H).

Method B. A stirred mixture of phosphorus pentoxide (5 g.), 125 ml. of xylene, and glass beads under nitrogen was heated to reflux. To this mixture was added 2 g. of 9-acridanemethanol[7] *via* the Soxhlet extractor method. After 2 hr. the extraction was completed and the reaction was cooled and quenched with water. The aqueous layer was shaken with hot xylene, and the combined xylene layers were dried and concentrated by distillation. The residue was recrystallized from carbon tetrachloride, using decolorizing charcoal, to give 1.1 g. (58%) of 5H-dibenz[b,f]-azepine (I, R = X = H); m.p. 192–194°. One recrystallization from benzene–petroleum ether (b.p. 30–60°) raised the m.p. to 195.5–196.5°; no depression was observed on mixing with compound prepared by route A. Infrared spectral curves for samples prepared by both routes A and B were identical.

Preparation of 3-chloro-5H-dibenz[b,f]azepine. (Ib) *9-Cyano-3-chloroacridane.* Into a stainless steel pressure reactor was placed a mixture of 3,9-dichloroacridane (53.5 g., 0.216 mole), sodium cyanide (12 g., 0.24 mole), and anhydrous methanol (375 ml.). Pre-purified nitrogen was introduced (1 atm.) and the reactor was heated at 130–140° for 4.5 hr. with continuous rocking. The reactor was cooled, vented, and the product was removed with acetone. The insoluble yellow needles were filtered and washed well with water. There was obtained 9-cyano-3-chloroacridine as yellow needles (42 g., 84%); m.p. 197–199.5°. After several recrystallizations from methanol the compound melted at 202.5°.

Anal. Calcd. for $C_{14}H_7ClN_2$: C, 70.45; H, 2.96. Found: C, 70.60; H, 3.15.

Ethyl 3-chloro-9-acridinecarboxylate. A mixture of 3-chloro-9-cyanoacridine (135 g., 0.565 mole) and 90% sulfuric acid (700 ml.) was heated in a 4-l. beaker in a boiling water bath for 3 hr. with mechanical stirring. The reaction mixture was cooled to 0° and sodium nitrite (210 g.) was added in small portions. The yellow suspension was allowed to remain 1 hr. at 0–5° and 1 hr. at room temperature. The reaction beaker was gradually heated by a water bath to 55–60°, when a vigorous evolution of gas occurred. When the latter subsided, the reaction was heated 2 hr. on a boiling water bath, cooled to 0° and was diluted with ice water, dissolved in dilute sodium hydroxide, and the solution was treated with decolorizing charcoal. Acidification of the filtrate gave 3-chloro-9-acridinecarboxylic acid as a yellow solid (135 g., 86%); m.p. 268° dec.

A mixture of the above acid (128 g., 0.5 mole) and thionyl chloride (405 g.) was refluxed with stirring until all the acid dissolved (usually 3 to 4 hr.). The dark red solution was cooled and diluted with dry benzene. The yellow solid that precipitated upon scratching was collected and washed well with benzene. It was then added in portions to 800 ml. of ethanol. The mixture was gradually heated and refluxed for 2 hr. The cold dark brown solution was diluted with water and made alkaline with a cold solution of sodium carbonate. The product that formed was washed with water in a Waring Blendor. Recrystallization from hexane, with treatment by decolorizing charcoal, gave the ester as pale yellow needles, m.p. 96–96.5°. Evaporation of the mother liquors, with a subsequent recrystallization of the residue from hexane, gave a second crop of same melting point; total yield 140 g. (73%).

Anal. Calcd. for $C_{16}H_{12}ClNO_2$: C, 67.25· H, 4.23. Found: C, 67.25· H, 4.31.

3-Chloro-9-acridanemethanol. (IVb) This reaction was conducted in a carefully dried system under an atmosphere of purified nitrogen. To 300 ml. of anhydrous ether was added in portions 28 g. (0.7 mole) of lithium aluminum hydride, and the mixture was refluxed for 30 min. To this stirred suspension at room temperature was added dropwise a solution of 100 g. (0.35 mole) of ethyl 3-chloro-9-acridinecarboxylate in 1500 ml. of anhydrous ether at a rate which produced moderate refluxing of the ether. After two thirds of the addition was completed, an additional 10 g. of lithium aluminum hydride was added to the reaction to ensure its completion. Refluxing was then continued for 3 hr. The dark brown mixture was cooled to 0° in an ice-salt bath and was decomposed slowly with wet ether, followed by an excess of water. The ether layer was decanted; the milky-white aqueous layer was acidified with dilute hydrochloric acid, and was extracted with ether. The combined ether portions were dried over Drierite and the solvent was removed either *in vacuo* or in an atmosphere of pre-purified nitrogen. The brown residue, after a recrystallization from benzene–petroleum ether (b.p. 30–60°) with decolorizing charcoal, gave 3-chloro-9-acridanemethanol as white needles (65 g., 75%); m.p. 139–140°.

Anal. Calcd. for $C_{14}H_{12}ClNO$: C, 68.22; H, 4.63; N, 5.72. Found: C, 68.17; H, 4.52; N, 5.73.

3-Chloro-5H-dibenz[b,f]azepine. (Ib) A mixture of 3-chloro-9-acridanemethanol (1 g., 0.004 mole) and 10 g. of reagent sea sand was stirred in 30 ml. of refluxing pre-dried xylene under purified nitrogen. To this was added in four portions over a 2-hr. period 4 g. (0.028 mole) of phosphorus pentoxide. The yellowish-orange reaction mixture was refluxed for an additional 90 min. It was then cooled and cautiously treated with a large excess of water. The sand was removed by filtration and the two layers separated. The aqueous layer and sand were separately extracted with hot benzene. The benzene extracts and xylene layers were combined, dried, and the solvents were removed *in vacuo*. The solid orange residue (m.p. 180–186°) was recrystallized twice from benzene with decolorizing charcoal to give 3-chloro-5H-dibenz-[b,f]azepine (0.45 g., 49%) as yellow-orange platelets, m.p. 208–209°.

Anal. Calcd. for $C_{14}H_{10}ClN$: C, 73.85; H, 4.43; N, 6.15. Found: C, 73.85; H, 4.62; N, 6.10.

5-[3-Dimethylaminopropyl]-5H-dibenz[b,f]azepine (I-c). A solution of 5.5 g. (0.029 mole) of 5H-dibenz[b,f]azepine in 200 ml. of hot toluene was added to a suspension of freshly prepared sodamide (0.047 mole) in 100 ml. of dry toluene. After refluxing the stirred mixture 2 hr., a solution of 5.5 g. of 3-dimethylaminopropyl chloride in 50 ml. of dry toluene was added, and the mixture was refluxed and stirred for 17 hr. After cooling the mixture, 125 ml. of water was added and stirring continued for 20 min. The layers were separated and the toluene layer was extracted seven times with a 1:1 hydrochloric acid–water solution. The combined acid extracts were treated with 40% sodium hydroxide solution and the alkaline solution was extracted four times with benzene. The benzene was evaporated, leaving 8.5 g. of a dark brown oil. This oil was dissolved in benzene and chromatographed through a 25 cm. dia. column packed to a depth of 20 cm. with activated alumina. The 6.0 g. of orange-red oil obtained from the chromatogram (representing a 75% yield of free base) was dissolved in 40 ml. of ethyl acetate and added to a solution of 2.55 g. of maleic acid in 50 ml. of ethyl acetate. The maleate salt was twice recrystallized from alcohol-ether with Darco to give 7.0 g., m.p. 148–149.5° (62% overall).

Anal. Calcd. for $C_{23}H_{25}N_3O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 69.88; H, 6.62; N, 7.11.

3-Chloro-10,11-dihydro-5H-dibenz[b,f]azepine. (Ib) A mixture of 2.28 g. (0.01 mole) of 3-chloro-5H-dibenz[b,f]azepine, (IIIc) 100 mg. of platinum oxide, and 100 ml. of ethanol was hydrogenated at atmospheric pressure and room temperature.

Hydrogenation was continued until the originally dark orange mixture became a pale yellow solution. At this point 120–130% of the calculated amount of hydrogen had been absorbed. The catalyst was filtered and the ethanolic filtrate was evaporated *in vacuo*. The yellow residual solid was dissolved in 10 ml. of benzene and the solution was placed on a ¾″ × 18″ alumina column. The column was eluted with petroleum ether (b.p. 30–60°) (100 ml.), 100 ml. of 20% benzene in petroleum ether (b.p. 30–60°), and finally with 100 ml. of 50% benzene in petroleum ether (b.p. 30–60°). The first fraction was cut at the first sign of yellow coloration in the eluate. A strongly yellow colored second fraction was obtained by further elution with benzene. The second fraction was concentrated *in vacuo* to give a yellow solid, which was recrystallized from ethanol to give 0.3 g. of yellow plates; m.p. 186–195°. An infrared spectrum indicated this material was mostly recovered I-b.

The first fraction was concentrated *in vacuo* to give 1.7 g. of an almost colorless residue, m.p. 80–83° after recrystallization from aqueous ethanol. The colorless crystals were sublimed at 78° and 0.3 mm. to give a small amount of sublimate, m.p. 97–100°. The melting point of this sample was not depressed by mixture with 10,11-dihydro-5H-dibenz[b,f]azepine. The material which did not sublime was recrystallized from aqueous ethanol to give 1.55 g. of colorless crystals, m.p. 84.5–86°. (III-c.)

Anal. Calcd. for $C_{14}H_{12}NCl$: C, 73.20; H, 5.27. Found: C, 72.73, 72.62; H, 5.39, 5.28.

3-Chloro-10,11-dihydro-(3-dimethylaminopropyl)-5H-dibenz[b,f]azepine (III-d). Alkylation was accomplished essentially as described above for the preparation of 5-(3-dimethylaminopropyl)dibenz[b,f]azepine. Toluene was used as the solvent, and the crude free base was not chromatographed, but was distilled; b.p. 160–170° at 0.3 mm. The hydrochloride was recrystallized from acetone-ether and then from methanol-ether to give a 75% yield of colorless crystals; m.p. 189–190°.

Anal. Calcd. for $C_{19}H_{22}ClN\cdot HCl$: C, 64.93; H, 6.89. Found: C, 64.66; H, 6.96.

3-Chloro-5-(3-dimethylaminopropyl)-5H-dibenz[b,f]azepine (I-d). Alkylation of 3-chloro-5H-dibenz[b,f]azepine was carried out as described above for the alkylation of 5H-dibenz[b,f]azepine. Toluene was used as the solvent, and instead of chromatography, distillation was used to purify the free base of the product; b.p. 168–176° at 0.4–0.5 mm. The maleate was formed in ethyl acetate and was recrystallized three times from acetone-ether to give a 45% yield of yellow crystals; m.p. 124.5–125.5°.

Anal. Calcd. for $C_{19}H_{22}ClN_2\cdot C_4H_4O_4$: C, 64.40; H, 5.88. Found: C, 64.01; H, 6.01.

10,11-Dihydro-5-[3-(4-methyl-1-piperazinyl)propyl]-5H-dibenz[b,f]azepine (IIIe). The alkylation differed from that described above for the alkylation of 5H-dibenz[b,f]azepine as follows. Toluene was used as the solvent, and the alkylation required 12 hr. The free base was purified by distillation; b.p. 199–212° at 0.2–0.3 mm. The dihydrochloride was recrystallized from methanol-ether three times to give a 63% yield of colorless crystals; m.p. 245–246.5°. The infrared spectrum indicated that a trace of water was present.

Anal. Calcd. for $C_{22}H_{29}N_3\cdot 2HCl$: C, 64.70; H, 7.16. Found: C, 62.90; H, 7.82.

Anal. Calcd. for hemihydrate: C, 63.30; H, 7.73.

Addendum. Subsequent to the original preparation of this paper, two papers have appeared in which the preparation of Ia is reported.[14,15]

PHILADELPHIA, PA.

(14) R. Huisgen, E. Laschtuvka, and F. Bayerlein; *Chem. Ber.*, 93, 392 (1960).

(15) E. D. Bergmann and M. Rabinovitz, *J. Org. Chem.*, 25, 827 (1960).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

Synthesis of Potential Anticancer Agents. V. Azetidines[1,2]

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The problem of azetidine synthesis is reviewed, several unsuccessful approaches are described, and a relatively convenient method for the preparation of certain azetidines is reported. Cyclization to the azetidine system is considered as a conformational problem.

Although azetidine (I) and its derivatives have been known since the latter part of the nineteenth century,[4] comparatively little work has been done on methods of preparation, which in general appears to be inherently difficult, azetidine or an azetidine derivative often being but a minor constituent of the reaction products.

The present work was undertaken because of the potential relationship between azetidine and ethylenimine as regards "alkylating action," which in the latter has generally been credited with its effectiveness in certain anticancer agents.[5] To this end it was proposed to prepare azetidine analogs of various ethylenimine derivatives of known clinical use in the control of neoplastic disease.

It rapidly became apparent that the major barrier to such a program was the lack of convenient syntheses affording a good yield of azetidine itself or of its carbon-substituted derivatives. Potential approaches are from 2-azetidinones (*e. g.*, β-lactams) by reduction or from acyclic 3-functionally substituted (*e. g.*, halogen, *O*-sulfonate) amines.

(1) Previous paper in this series, R. C. Elderfield and R. N. Prasad, *J. Org. Chem.*, 25, 1583 (1960).

(2) This work supported by a Research Grant (CY-2961) from the National Cancer Institute to The University of Michigan.

(3) Abstracted in the main from the Ph.D. Dissertation of Robert Stephen Klonowski, The University of Michigan, 1959.

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