21 ml (0.15 mole) of triethylamine in 100 ml of acetone or toluene was refluxed several hours. The reaction mixture was filtered and the solvent was removed by distillation. The residue was crystallized from benzene, hexane, or acetone. Methylation was effected with formaldehyde–formic acid in water.[24] The reductions were carried out by refluxing for 24 hr a solution or slurry of 0.016 mole of the 1-alkyl-3-oxo-2-phenylpiperazine and 0.063 mole of lithium aluminum hydride in 250 ml of ether. The products were isolated by standard methods.

4-Alkyl- and 1,4-Dialkyl-2-phenylpiperazines.—The 4-alkyl derivatives were prepared by alkylation of 2-phenylpiperazine, with 1 equiv of alkylating agent by the general procedure given above. The 4-methyl derivative was prepared using methyl iodide since formaldehyde–formic acid gave some disubstitution. The 1,4-dialkyl derivatives were obtained using 3 equiv of alkylating agent. The products were purified by distillation at reduced pressure.

Acknowledgments.—The authors are grateful to Parke, Davis and Co. for financial support of this study, for a fellowship for H. J. P., and for the pharmacological data reported in this paper. We thank Dr. Jack Tadanier of Abbott Laboratories for helpful discussions of the nmr spectra.

(24) H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

Derivatives of 2-Azabicyclo[2.2.2]octane. I

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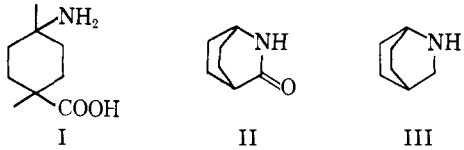
2-Azabicyclo[2.2.2]octan-3-one (isoquinuclidone), prepared by pyrolysis of *cis*-4-aminocyclohexanecarboxylic acid, was reduced in excellent yield to 2-azabicyclo[2.2.2]octane (isoquinuclidine). The isoquinuclidyl ring was substituted for the dimethylamino group in a limited number of clinically effective agents. The following compounds were prepared: N-[3-(*p*-chlorophenyl)-3-(2-pyridyl)propyl]isoquinuclidine (VI), N-[2-(*p*-chlorobenzhydryloxy)ethyl]isoquinuclidine (VII), and 10-[3-(N-isoquinuclidyl)propyl]-2-chlorophenothiazine (VIII). These compounds showed the same type of biological activity as their dimethylamino prototypes but were less active. N-[2-(Guanidino)ethyl]- and N-[3-(guanidino)propyl]isoquinuclidine sulfates were also prepared.

The biological properties of a series of compounds, wherein the bulky bicyclic ring, 2-azabicyclo[2.2.2]-octane, commonly known as isoquinuclidine[1] was substituted for the dimethylamino moiety in a number of clinically active agents, were studied.

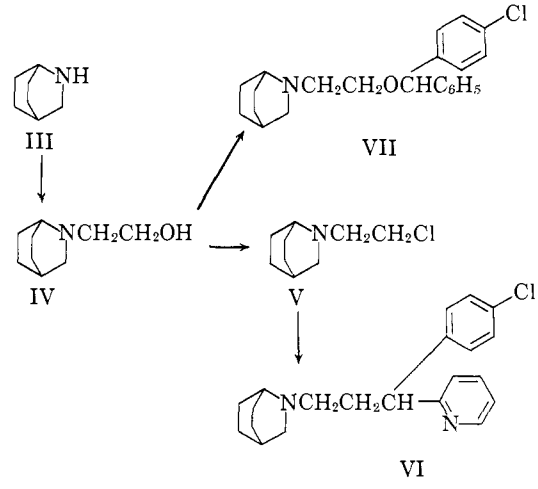
Isoquinuclidine (III) was prepared by pyrolysis of *cis*-4-aminocyclohexanecarboxylic acid (I)[2] to the cyclic lactam, 2-azabicyclo[2.2.2]octan-3-one (II),[3] followed by reduction with lithium aluminum hydride.[4] This series of reactions establishes the conformation of the *cis* acid (I), since the *trans* form cannot be so converted and serves as a convenient method for the preparation of the bicyclic amine (III).



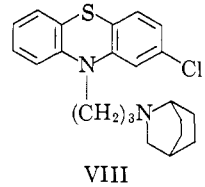
I II III

The preparation of the isoquinuclidyl analogs of the propylamine and aminoalkyl ether types of antihistaminic agents of which chlorpheniramine[5a] and chlordiphenhydramine[5b] are the prototypes is shown in Chart I. Isoquinuclidine (III) was converted into N-(2-hydroxyethyl)isoquinuclidine (IV) by reaction with ethylene oxide. Reaction of IV with thionyl chloride gave the chloride V. Alkylation of 2-(*p*-chlorobenzyl)-pyridine with V in the presence of potassium amide gave the desired N-[3-(*p*-chlorophenyl)-3-(2-pyridyl)-propyl]isoquinuclidine (VI). Compound VII was prepared by heating a dilute xylene solution of IV with *p*-chlorobenzhydryl bromide in the presence of potassium carbonate.

CHART I



The preparation of the isoquinuclidyl analog VIII of the central nervous system depressant, chlorproma-



VIII

(1) Throughout this manuscript, the common name isoquinuclidine is used instead of the more cumbersome chemical name.

(2) F. J. Villani and C. A. Ellis, *J. Org. Chem.*, **29**, 2585 (1964).

(3) E. Ferber and H. Bruckner, *Ber.*, **76**, 1019 (1943).

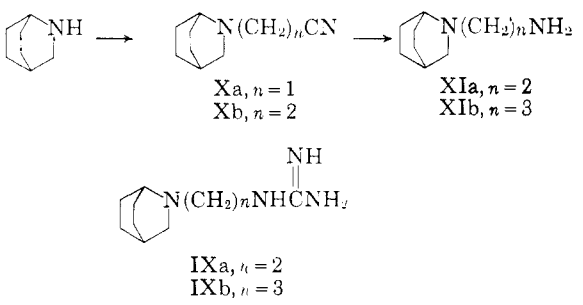
(4) (a) L. H. Werner and S. Ricca, *J. Am. Chem. Soc.*, **80**, 2733 (1958), were unable to effect this reduction. (b) W. Schneider and R. Dillmann, *Chem. Ber.*, **96**, 2377 (1963), prepared this compound in 40% yield using $LiAlH_4$ in tetrahydrofuran. (c) Compound III is unstable and a sample of analytical purity could not be obtained. The compound sublimes quite readily and absorbs CO_2 from the air. See ref 4a and 4b.

(5) (a) 1-(*p*-Chlorophenyl)-1-(2-pyridyl)-3-dimethylaminopropane, Chlor-Trimeton®, Schering Corporation; (b) 2-(*p*-chlorobenzhydryloxy)-N-dimethylethylamine; (c) 10-(3-dimethylaminopropyl)-2-chlorophenothiazine; (d)]2-(octahydro-1-azocinyl)ethyl]guanidine.

zine,[5c] was achieved by the reaction of 10-(3-chloropropyl)-2-chlorophenothiazine with isoquinuclidine (III) in the presence of sodamide.

In addition, compounds IXa and IXb were prepared by the reactions shown in Chart II. N-Cyanomethylisoquinuclidine (Xa) and the cyanoethyl compound Xb were reduced with lithium aluminum hydride to the ethyl- and propylamines (XIa and XIb). The latter, upon reaction with S-methylisothiourea sulfate, were converted into the guanidinoalkyl derivatives IXa and IXb.[6]

CHART II



Pharmacology.[7]—Compounds VI and VII were screened for their *in vitro* antihistaminic activity by the classical guinea pig ileum preparation. These compounds exhibited a slight activity at a concentration of 40 μg/l., whereas the standard agent[5a] is effective at a concentration of 1.8 μg/l. In the mouse activity screen,[8] VI showed slight sedative and moderate anticholinergic effects at 30 mg/kg when administered intraperitoneally. In the cat, an oral dose of 16 mg/kg of VI produced definite sedative effects. Compound VII showed only slight sedative effects in the mouse on intraperitoneal administration of 10 mg/kg. The compound was lethal in this species at a dose of 100 mg/kg ip.

At an intraperitoneal dose of 3 mg/kg in the mouse, VIII showed moderate chlorpromazine like activity but produced marked muscle weakness. This compound showed potent adrenergic blocking activity at a dose of 4 mg/kg in the anesthetized dog.

The intravenous administration of 10 mg/kg of IXa in the anesthetized dog produced a fall in blood pressure comparable to that produced by 5 mg/kg of guanethidine.[5d] However, this compound, at a dose of 3 mg/kg ip in the mouse, caused severe diarrhea. Compound IXb at an intravenous dose of 10 mg/kg in the dog caused cardiac arrest in approximately 10 min. At a dose of 5 mg/kg this compound produced a slight but prolonged hypotensive effect which was accompanied by marked mydriasis.

Experimental Section[9]

Isoquinuclidone (II).—*cis*-4-Aminocyclohexanecarboxylic acid (144 g, 1.0 mole) was heated; water was eliminated and the product distilled at 293–295°. The product solidified immediately and was recrystallized from a mixture of benzene–petroleum ether (bp 30–60°); yield 87 g (70%), mp 194–196°, lit.[3] mp 191–192°.

Isoquinuclidine (III).—A suspension of 72 g (0.57 mole) of II in 500 ml of anhydrous ether was added portionwise to 60 g (1.6 moles) of $LiAlH_4$ in 3 l. of ether. Stirring under reflux was continued for 20 hr. The cooled suspension was decomposed by the dropwise addition of 54 ml of water, 54 ml of 15% NaOH, and 162 ml of water. The inorganic salts were filtered and washed with ether. The ether solution was concentrated on the steam bath. A sample for analysis was recrystallized from hexane[10]; yield 64 g (90%), mp 168–170°.

The **maleate** salt was prepared in ethyl acetate. The analytical sample, mp 112–114°, was recrystallized from a mixture of absolute ethanol–absolute ether.

Anal. Calcd for $C_7H_{13}N \cdot C_4H_4O_4$: C, 58.13; H, 7.54. Found: C, 58.30; H, 7.24.

The **picrate** after recrystallization from ethanol had mp 242–243°, lit. mp 244–247°,[4a] 218°.[3]

The **hydrochloride** salt was recrystallized from ethanol–ether; mp 303–306°.

Anal. Calcd for $C_7H_{13}N \cdot HCl$: C, 57.33; H, 8.93. Found: C, 57.49; H, 8.60.

N-(2-Hydroxyethyl)isoquinuclidine (IV).—A solution of 30 g (0.27 mole) of III in 50 ml of methanol was treated with a solution of 17.5 g (0.44 mole) of ethylene oxide in 100 ml of anhydrous ether. The solution was heated with stirring on the steam bath for 15 hr. The solvents were removed by distillation *in vacuo* and the product was distilled; yield 17 g (58%), bp 105–110° (5 mm), $n^{25}D$ 1.5041.

Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.35; H, 10.86; N, 9.54.

The **picrate** was recrystallized from ethanol; mp 177–179°.

Anal. Calcd for $C_9H_{17}NO \cdot C_6H_3N_3O_7$: N, 14.58. Found: N, 14.90.

The **methyl bromide salt**, after recrystallization from ethanol, had mp 285–287°.

Anal. Calcd for $C_9H_{17}NO \cdot CH_3Br$: C, 50.82; H, 8.54. Found: C, 50.53; H, 8.24.

N-(2-Chloroethyl)isoquinuclidine Hydrochloride (V).—To a solution of 46.5 g (0.3 mole) of IV in 500 ml of dry benzene was added cautiously with vigorous stirring 53 g (0.45 mole) of $SOCl_2$ and the mixture was refluxed with stirring for 6 hr. The cooled reaction mixture was diluted with 2–3 times its volume with anhydrous ether and the crystalline hydrochloride was filtered and washed with ether; yield 53 g (84%). A small sample was recrystallized from ethanol–ether; mp 218–221°.

Anal. Calcd for $C_9H_{16}ClN \cdot HCl$: C, 51.43; H, 8.15. Found: C, 51.72; H, 8.28.

N-[3-(*p*-Chlorophenyl)-3-(2-pyridyl)propyl]isoquinuclidine (VI).—To a solution of KNH_2 prepared from 4.3 g (0.11 mole) of K in about 1 l. of anhydrous NH_3 was added 20 g (0.1 mole) of 2-(*p*-chlorobenzyl)pyridine and the mixture was stirred for 20 min. A solution of the chloramine V (21 g) in ether was added dropwise and stirring was continued for 6 hr. Water was added and the organic material was extracted with ether, dried, and distilled; yield 19.5 g, bp 203–205° (1 mm), $n^{25}D$ 1.5756. The product was crystallized from petroleum ether; yield 18.5 g (54%), mp 67–68.5°.

Anal. Calcd for $C_{20}H_{25}ClN_2$: C, 73.99; H, 7.39. Found: C, 73.89; H, 7.24.

N-[2-(*p*-Chlorobenzhydryloxy)ethyl]isoquinuclidine (VII).—A mixture of 27.5 g (0.1 mole) of *p*-chlorobenzhydryl bromide, 15 g (0.1 mole) of N-(2-hydroxyethyl)isoquinuclidine, 27.5 g (0.2 mole) of anhydrous K_2CO_3, and 1 l. of xylene was refluxed for 24 hr with stirring. Water was added and the layers were separated. The xylene solution was extracted several times with 10% HCl. The acid solution was neutralized with NH_4OH and extracted with $CHCl_3$. The solvent was removed and the residue was distilled to yield 25 g (63%) of a yellow oil, bp 205–210° (1 mm), $n^{25}D$ 1.5723.

Anal. Calcd for $C_{22}H_{28}ClNO$: C, 74.24; H, 7.36. Found: C, 73.96; H, 7.26.

10-[3-(N-isoquinuclidyl)propyl]-2-chlorophenothiazine (VIII).—To a solution of 38.7 g (0.14 mole) of 10-(3-chloropropyl)-2-chlorophenothiazine[10] and 15.5 g (0.14 mole) of isoquinuclidine in 1 l. of anhydrous toluene was added at reflux with stirring a

(6) H. Najer, R. Giudicelli, and J. Sette, *Bull. Soc. Chim. France*, 1593 (1962), report a similar preparation of IXa.

(7) The biological data herein reported was obtained by Drs. F. Roth and S. Irwin and their associates of the Biological Research Division of the Schering Corporation, to whom we express our gratitude.

(8) S. Irwin in "Clinical Pharmacology: Animal and Human Techniques in Drug Evaluation," J. Nodine and P. Siegler, Ed., Year Book Medical Publishers, Chicago, Ill., 1964, Chapter 4, p 36.

(9) All melting points are corrected. Microanalyses were performed by Mr. Edwin Conner of these laboratories.

(10) M. Sherlock and N. Sperber, U. S. Patent 2,860,138 (1958); *Chem. Abstr.*, **53**, 7212 (1959).

suspension of 6 g (0.15 mole) of commercial $NaNH_2$. The mixture was refluxed for 7 hr and allowed to cool overnight. After addition of water, the organic layer was separated and extracted with dilute HCl. The acid solution was made basic with NH_4OH and extracted with $CHCl_3$. After removal of the chloroform, the residue soon crystallized. The product was recrystallized from ethyl acetate; mp 90–91°.

Anal. Calcd for $C_{22}H_{33}ClN_2S$: C, 68.12; H, 6.55. Found: C, 67.87; H, 6.31.

N-Cyanomethylisoquinuclidine (Xa).—A mixture of 16.6 g (0.15 mole) of isoquinuclidine, 11.3 g (0.15 mole) of chloroacetonitrile, 41.4 g of anhydrous K_2CO_3, and 500 ml of toluene was refluxed with stirring for 20 hr. The inorganic salt was filtered off, and the filtrate was extracted with dilute HCl. The acid extracts were neutralized with NH_4OH and extracted ($CHCl_3$). The product was distilled; yield 12 g (53%), bp 90–92° (2 mm), $n^{24}D$ 1.4955.

Anal. Calcd for $C_9H_{14}N_2$: C, 71.95; H, 9.39; N, 18.65. Found: C, 72.20; H, 9.52; N, 18.83.

N-(2-Cyanoethyl)isoquinuclidine (Xb).—From 20 g (0.18 mole) of isoquinuclidine, 22.5 g (0.15 mole) of 3-bromopropionitrile, and 41.4 g of K_2CO_3 in 500 ml of toluene, by the above procedure, was obtained 21.5 g (87.5%) of product having bp 95–105° (1 mm), $n^{25}D$ 1.4953.

Anal. Calcd for $C_{10}H_{16}N_2$: C, 73.12; H, 9.82. Found: C, 72.97; H, 9.69.

The **hydrochloride** after recrystallization from ethanol–ether had mp 240–242° dec.

Anal. Calcd for $C_{10}H_{16}N_2 \cdot HCl$: C, 59.84; H, 8.54; N, 13.96. Found: C, 59.77; H, 8.32; N, 14.00.

N-(2-Aminoethyl)isoquinuclidine (XIa).—A solution of 10 g (0.067 mole) of Xa in 50 ml of anhydrous ether was added dropwise with stirring to a refluxing solution of 3 g of $LiAlH_4$ in 600 ml of ether. The mixture was stirred under reflux for 20 hr. After the usual decomposition, the product was isolated as a colorless oil; yield 85 g (82%), bp 90–92° (6 mm), $n^{24}D$ 1.5005.

Anal. Calcd for $C_9H_{18}N_2$: C, 70.07; H, 11.76. Found: C, 70.55; H, 11.88.

The **dihydrochloride** had mp 201–203°.

Anal. Calcd for $C_9H_{18}N_2 \cdot 2HCl$: C, 47.58; H, 8.87. Found: C, 48.09; H, 8.85.

N-(3-Aminopropyl)isoquinuclidine (XIb).—From 20 g of Xb and 6 g of $LiAlH_4$ in ether was obtained 15.5 g (77%) of an oil, bp 86–90° (1 mm), $n^{25}D$ 1.4980.

Anal. Calcd for $C_{10}H_{20}N_2$: C, 71.37; H, 11.98. Found: C, 71.71; H, 12.06.

N-(2-Guanidinoethyl)isoquinuclidine Sulfate (IXa).—A mixture of 7.5 g (0.049 mole) of XIIa and 12.2 g of S-methylisothiourea sulfate in 50 ml of ethanol was heated under reflux with stirring for 6 hr. The white solid was filtered and washed with cold ethanol. The product (9 g, 63%) was purified by dissolving it in water and adding ethanol until turbid; mp 300–303°, lit.[6] mp 310–315°.

Anal. Calcd for $C_{10}H_{20}N_4 \cdot H_2SO_4$: C, 40.80; H, 7.53; N, 19.03. Found: C, 40.30; H, 7.62; N, 19.13.

N-(3-Guanidinopropyl)isoquinuclidine Sulfate (IXb).—By a similar procedure this compound was obtained in 52% yield, mp 310–312°.

Anal. Calcd for $C_{11}H_{22}N_4 \cdot H_2SO_4$: C, 42.84; H, 7.84; N, 18.17. Found: C, 42.52; H, 8.27; N, 18.37.

Analgetic Activity of Some δ-Amino Ketones And Their Derivatives

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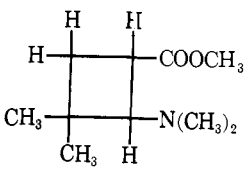
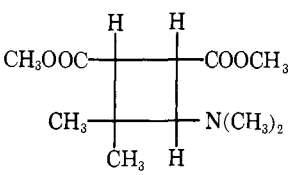
The β-aminocyclobutane, methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate (I), exhibits aspirin-like analgetic activity. Treatment of I with Grignard reagents offers a convenient route to substituted δ-amino ketones. Some of these δ-amino ketones have proved to be more potent analgetics than the parent cyclobutane, I. The completely aliphatic compound, 1,5-dicyclohexyl-2,2-dimethyl-1-dimethylamino-5-pentanone citrate (**10**), is presumed to be a morphine-like analgetic because of its antagonism by nalorphine hydrochloride. Manipulation of the carbonyl group of 1,5-diphenyl-2,2-dimethyl-1-dimethylamino-5-pentanone (1) by reduction or addition has indicated that the degree of analgesia is diminished.

A series of substituted β-aminocyclobutanes, which were received from Tennessee Eastman Co., displayed some analgetic activity in our pharmacological screening program. Both methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate (I)[1] and dimethyl 3,3-dimethyl-4-dimethylaminocyclobutane-1,2-dicarboxylate (II) showed slight analgetic activity as determined by the tail-flick method in the rat.[2] Compound I appears to be nonnarcotic since it is not antagonized by nalorphine hydrochloride. This is the first instance of analgetic activity reported for structures containing a nonaromatic cyclobutane ring.[3] Clinical studies indicate that the degree of analgesia produced by the citrate salt of I is equivalent to that of aspirin. This salt also elicits side effects similar to aspirin.



I



II

Accordingly, we decided to make modifications of I with the hope of improving its analgetic potency. While attempting to convert the ester portion of I into a tertiary alcohol with phenylmagnesium bromide, an unexpected ring-cleavage reaction occurred. The chemistry of this ring opening of I with Grignard reagents has recently been reported.[4] Cleavage of the cyclobutane ring results in the formation of two types of δ-amino ketones. The amount of each type of product depends on the nature of the Grignard reagent. (see Scheme I).

Some of the δ-amino ketones have shown greater analgetic activity than their parent ring compound, I. One of the most interesting observations of this study is that the analgetic activity of a wholly ali-

(1) K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, **26**, 625 (1961).

(2) F. R. D'Amour and D. L. Smith, *J. Pharmacol. Exptl. Therap.*, **72**, 74 (1948).

(3) 1-Aminomethylbenzocyclobutene is reported to have a potency equivalent to morphine with a more rapid onset of action and much shorter duration: J. A. Skorcz and J. E. Robertson, *J. Med. Chem.*, **8**, 255 (1965).

(4) L. Weintraub, A. Wilson, D. L. Goldhamer, and D. P. Hollis, *J. Am. Chem. Soc.*, **86**, 4880 (1964).