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Alicyclic Alkylamines and Alkanolamines*

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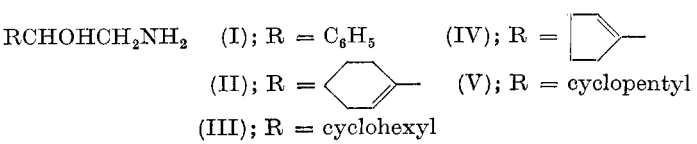
Alicyclic structures carrying alkylamine chains have been the subject of a number of pharmacodynamic studies,[1–3] especially for their effect on blood pressure. By comparison with their aromatic prototypes, such alicyclic compounds show less activity and higher toxicity.[2] Cyclohexenyl, cyclohexyl and cyclopentyl derivatives were of the same general order of lowered activity. Branching of the side chain increased duration of action, in analogy with similar effects of 2-phenylisopropylamines as compared with those of phenethylamines.

These observations acquired renewed significance in the wake of Belleau's proposal[4] of a working model of an adrenergic receptor site which emphasized the importance of van der Waals bonds in reinforcing the ionic linkage between the amino group and an anionic site. Obviously, a flat benzene ring may be expected to furnish a supporting attachment of 2–3 kcal/mole while a puckered, non-aromatic ring will be of much less value as a source of short-range bonds. Three factors should influence the magnitude of these forces: (*a*) the size of the ring; (*b*) the planarity of the ring; and (*c*) the angle between the substituent chain and the ring. In the present work, the amino alcohols II–V were tested and compared with phenylethanolamine (I). The pressor activity of these



compounds increases in the order V < IV ≅ III < II < I.

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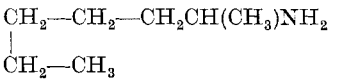
Models show that the order of increasing ring planarity is III < II < V < IV ≅ I, and that of decreasing angle of substitution, III < II < V < IV ≅ I. These comparisons indicate that within a group of analogues having the same number of ring carbon atoms, ring planarity and acuteness of the angle of substitution determine the order of (pressor) activity.

The similarity of the flatness of the cyclopentene and benzene rings had also been noted in a biological comparison of their alanine derivatives.[5]

The literature reports no ethylamine and ethanolamine derivatives containing the cyclobutane ring, and a survey of such compounds appeared as a suitable extension of the above views. To be sure, the cyclobutane ring *per se* is not flat; a non-planar ring with a dihedral angle of 20° (+10°, −20°) has been suggested.[6] The large error in this determination indicates that the true angle is probably much smaller. In addition, the substituent chain lies at a considerable angle to the ring, which must tend to decrease binding to the receptor site. For methylcyclobutane this value is 50° ± 8°.[7] However, too little is known about the geometry of the adrenergic receptor, although Belleau[8] believes that the active group of adrenergic blocking agents of the Dibenamine type lies in the plane of the aromatic ring. A cavity accommodating the basic side chain could well nullify this effect. Of course, the cyclobutane ring contains fewer carbon atoms than its ring homologues to undergo van der Waals bonding. Cyclobutyl analogues of adrenergic structures should therefore be slightly less active as pressors than compounds I–V but more active than the corresponding non-cyclic amines,[9] including some with 7 to 9 carbon atoms in which, for example, four could simulate a cyclobutane ring (tuaminoheptane, VI).[10,11]



(VI)

Pharmacological Results

Preliminary biological studies of the key compounds reported in this article were carried out by members of the Pharmacology Section of Smith Kline and French Laboratories, Philadelphia,

Pa., to whom we are indebted for the following summary data. 2-Amino-1-(1-cyclohexenyl)ethanol hydrochloride elicited about the same pressor action in the anaesthetized cat as phenylethanolamine hydrochloride at low doses (0·05–0·5 mg/kg) but fell behind in this effect at higher doses (1–2·5 mg/kg). 2-Amino-1-(1-cyclopentenyl)ethanol hydrochloride had about one-half the pressor activity of phenylethanolamine hydrochloride over the whole dose range tested. Both compounds were much less potent than norepinephrine. Oral administration of 10–25 mg/kg of 2-amino-1-(1-cyclohexenyl)ethanol hydrochloride to male rats reduced food consumption by 12·4 per cent relative to a control group; for 2-amino-1-(1-cyclopentenyl)ethanol hydrochloride the figure was 6·8 per cent.

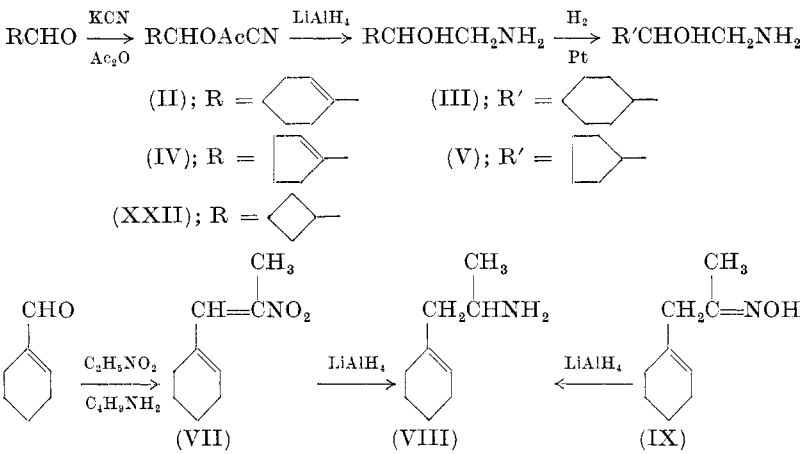
2-Amino-1-(1-cyclopentyl)ethanol hydrochloride, when administered orally to mice, produced no overt activity up to 50 mg/kg. At 100 mg/kg, CNS depression characterized by decreased motor activity and reduced preening was observed; the effects included exophthalmus and piloerection. At higher doses, low posture, hypothermia, analgesia and dyspnea occurred. Asphyxial seizures and death occurred in half of the mice at 2,000 mg/kg, with mydriasis appearing at this dose. No significant inhibition of pernicious preening in mice was noted after an oral dose of 50 mg/kg. At 100 mg/kg orally no alteration in the maximal electroshock pattern occurred in mice, and no potentiation of the subconvulsant dose of tryptamine hydrochloride in rats. In one cat under pentobarbital anaesthesia the compound elicited a slight transient pressor response at 1·0 mg/kg i.v., and moderate responses at 5 and 10 mg/kg. The 10 mg/kg dose was accompanied by an increase in respiratory depth.

In rats, oral doses of 300 mg/kg of 2-cyclobutylethylamine hydrogen succinate, 1-cyclobutyl-2-piperidinoethanol hydrobromide, and 1-cyclobutyl-2-(4-methyl-1-piperazyl)ethanol dihydrobromide failed to produce any overt activity.

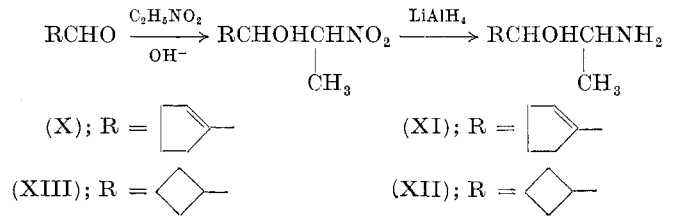
Chemistry

2-Amino-1-(1-cyclohexenyl)ethanol (II) was synthesized from 1-cyclohexenealdehyde;[12] the cyanohydrin acetate of this aldehyde was reduced with lithium aluminium hydride. The double bond

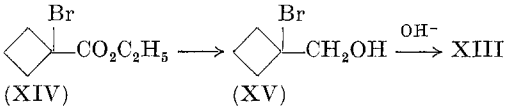
of II could be saturated by hydrogenation (III). In a similar manner, 1-cyclopentenealdehyde[13] was converted to 2-amino-1-(1-cyclopentenyl)ethanol (IV) and hence to 2-amino-1-cyclopentylethanol (V). 1-Cyclohexenealdehyde was also condensed with nitroethane to the unstable 1-(1-cyclohexenyl)-2-nitropropene (VII) which could be reduced to 2-amino-1-(1-cyclohexenyl)-propane (VIII). This amine was identical with a product obtained by Ullyot from cyclohexenylacetone by a Leuckart reaction,[14] and has now also been prepared by reduction of cyclohexenylacetoxime (IX).



When 1-cyclopentenecarboxaldehyde (X) was condensed with nitroethane in sodium hydroxide solution, 1-(1-cyclopentenyl)-2-nitropropanol was obtained, and this was reduced to 2-amino-1-(1-cyclopentenyl)propanol (XI). By an analogous route, 2-amino-1-cyclobutylpropanol (XII) was synthesized from cyclobutanecarboxaldehyde (XIII). Catalytic hydrogenation could also be substituted for lithium aluminium hydride reduction in this case.

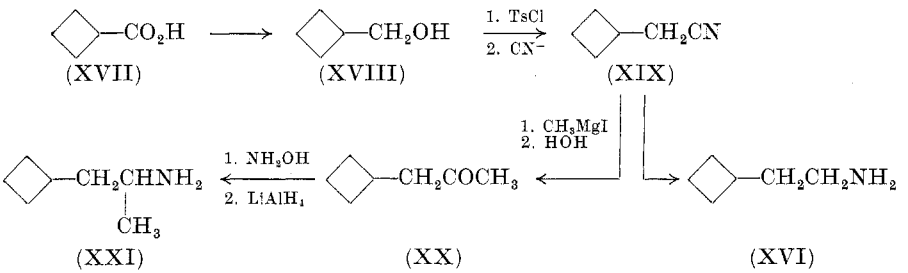


Cyclobutanecarboxaldehyde (XIII) had been obtained by various methods.[15] We found it convenient to reduce the ester group of ethyl 1-bromocyclobutanecarboxylate (XIV)[16] and to dehydrobrominate the resulting (1-bromocyclobutyl)methanol (XV). Lithium aluminium hydride proved a good reducing agent



in the reduction of methyl cyclobutenecarboxylate[16] to 1-cyclobutenylmethanol.

2-Cyclobutylethylamine (XVI) was synthesized in five steps from cyclobutanecarboxylic acid (XVII) which was reduced to cyclobutylmethanol (XVIII) with lithium aluminium hydride. The tosylate of this alcohol was converted to cyclobutylacetonitrile (XIX) which was reduced to XVI.

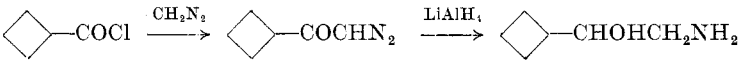


The possibility that ring enlargement might have occurred during the reaction of cyclobutylmethyl tosylate with cyanide could not be excluded because rearrangements under potentially ionizing conditions have been observed in this series.[17] On the other hand, nucleophilic replacement without rearrangement has been reported for cyclopropylmethyl tosylate,[18] and *cis*-[1,2-di-(tosyloxymethyl)] cyclopropane has been converted, via the diiodide, to *cis*-1,2-cyclopropanediacetonitrile.[19] As conclusive proof of the structure of 2-cyclobutylethylamine, salts of cyclopentylmethylamine[20] were compared with those of our amine and found to differ from them in their physical properties.

For the preparation of a methyl-branched homologue of XVI, cyclobutylacetonitrile (XIX) was treated with methylmagnesium

iodide to give cyclobutylacetone (XX). The oxime of this ketone was reduced to 2-amino-1-cyclobutylpropane (XXI).

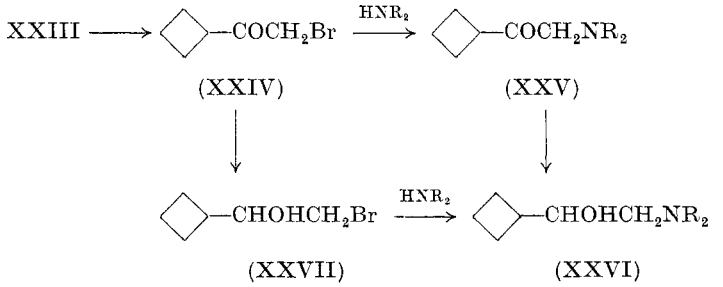
2-Amino-1-cyclobutylethanol (XXII) was synthesized by two routes. Conversion of cyclobutanecarboxaldehyde to 2-acetoxy-2-cyclobutylacetonitrile followed by reduction with lithium aluminium hydride gave XXII in relatively low yield. The idea that a rearrangement of the aldehyde (XIII) to cyclopentanone[21] could have interfered with this sequence could be discounted when the amine XXII was obtained, albeit in very low yields, by lithium aluminium hydride reduction of cyclobutyl diazomethyl ketone (XXIII). The products obtained by the two routes were



(XXIII) (XXII)

identical. Several experiments to prepare cyclobutanecarbonyl cyanide for reduction to XXII remained inconclusive.

Reaction of cyclobutyl diazomethyl ketone (XXIII) with hydrogen bromide furnished the unstable bromomethyl cyclobutyl ketone (XXIV) which could be condensed with secondary amines to yield *t*-aminomethyl cyclobutyl ketones (XXV). These were reduced with aluminium isopropoxide[22] or better still with lithium aluminium hydride in ether or tetrahydrofuran to the corresponding amino alcohols (XXVI). The same product was obtained in one test case (NR_2 = piperidino) by reducing the bromo ketone (XXIV) to 2-bromo-1-cyclobutylethanol (XXVII) with lithium aluminium hydride and treating the bromo alcohol with piperidine. The piperidino alcohol (XXVI, $NR_2 = NC_5H_{10}$) was essentially the only reaction product, and no isomer was found.



Experimental*

α-Acetoxy-1-cyclohexeneacetonitrile. 1-Cyclohexenealdehyde was prepared in high yields according to Heilbron *et al.*[12] A more complicated procedure recommended more recently[23] which disregarded Heilbron's method did not work in our hands, nor did the physical data given[23] agree with ours or other literature data (b.p. 61°/1 mm,[23] 61–63°/10 mm;[24] for the dinitrophenylhydrazone, m.p. 212°,[23] 219–220°[12]).

A solution of potassium cyanide (19·5 g, 0·3 mole) in water (40 ml) was dropped with stirring into an ice-cold solution of 1-cyclohexenealdehyde (16·5 g, 0·15 mole) in acetic anhydride (28 ml, 0·3 mole). Stirring was continued at 28° for 15 h, and the mixture was poured into a saturated solution of sodium bicarbonate and extracted with ether. The residual oil from the ether extract was dissolved in 80 ml of acetic anhydride which contained 4 ml of acetyl chloride, and the solution allowed to stand at 28° for 12 h. The cyanohydrin acetate was isolated by careful neutralization with an ice-cold saturated solution of sodium bicarbonate, extraction into ether, and distillation. The yield of colourless, fruity liquid was 20·6 g (77 per cent), b.p. 141–143°/18 mm, 102–103°/1·2 mm, n_D^{25} 1·4171.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67·02; H, 7·31; N, 7·82. Found: C, 67·04; H, 7·38; N, 7·81.

2-Amino-1-(1-cyclohexenyl)ethanol. A solution of α-acetoxy-1-cyclohexeneacetonitrile (6·63 g, 37 mmoles) in dry ether (30 ml) was dropped into a stirred slurry of lithium aluminium hydride (3·5 g, 92 mmoles) in anhydrous ether (200 ml) under an atmosphere of nitrogen. Stirring was continued overnight, the complex was decomposed with water and worked up as usual. A colourless *hydrochloride,* prepared in absolute ether and recrystallized from absolute ethanol, melted at 137–138°. The yield was 6·0 g (91 per cent).

Anal. Calcd. for $C_8H_{16}ClNO$: C, 54·07; H, 9·08; N, 7·88. Found: C, 54·05; H, 8·98; N, 7·72.

2-Amino-1-cyclohexylethanol. An absolute ethanolic solution of 2-amino-1-(1-cyclohexenyl) ethanol hydrochloride absorbed the calculated amount of hydrogen rapidly in the presence of Adams'

* All melting points are corrected. Microanalyses by Mrs. Margaret Logan, Mrs. Dolores Ellis, and Miss Winkie Sheffield.

platinum catalyst. Filtration of the solution, concentration and precipitation with ether gave almost quantitatively a hydrochloride which, after recrystallization from ethanol–ether, melted at 210–211°.

Anal. Calcd. for $C_8H_{18}ClNO$: C, 53·47; H, 10·10; N, 7·80. Found: C, 53·58; H, 10·09; N, 7·70.

α-Acetoxy-1-cyclopenteneacetonitrile. 1-Cyclopentenealdehyde was prepared by oxidative fission of cyclohexene and cyclization of the resulting adipaldehyde.[13] To a solution of 1-cyclopentenealdehyde (5·5 g, 33 mmoles) in acetic anhydride (11 ml, *ca.* 120 mmoles) was added dropwise with stirring and cooling in ice a solution of potassium cyanide (7·5 g, 0·11 mole) in water (15 ml). After stirring for another 15 h, the mixture was worked up as described for the cyclohexene homologue above. The yield of clear fruity oil was 6·0 g, (63 per cent), b.p. 123–124°/16 mm, n_D^{25} 1·4613.

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65·43; H, 6·71; N, 8·48. Found: C, 65·42; H, 7·03; N, 8·69.

2-Amino-1-(1-cyclopentenyl)ethanol. A solution of α-acetoxy-1-cyclopenteneacetonitrile (1·65 g, 10 mmoles) was reduced with lithium aluminium hydride (1 g, 26 mmoles) in a total of 70 ml of dry ether, and the mixture was worked up as described for the cyclohexenyl homologue. Recrystallization of the hydrochloride from absolute ethanol yielded 1·5 g (93 per cent) of colourless crystals, m.p. 159·5–160·5°.

Anal. Calcd. for $C_7H_{14}ClNO$: C, 51·37; H, 8·62; N, 8·56. Found: C, 51·64; H, 8·70; N, 8·91.

2-Amino-1-cyclopentylethanol. Hydrogenation of 2-amino-1-(1-cyclopentenyl)ethanol in the presence of platinum oxide gave a near quantitative yield of the saturated hydrochloride, which was recrystallized from ethanol–ether, m.p. 135–136°.

Anal. Calcd. for $C_7H_{16}ClNO$: C, 50·75; H, 9·74; N, 8·46. Found: C, 50·93; H, 9·73; N, 8·46.

2-Amino-1-(1-cyclohexenyl)propane hydrochloride. (*a*) A solution of 1-cyclohexenylacetoxime (8·6 g, 56 mmoles) in dry ether (50 ml) was reduced with lithium aluminium hydride (3·8 g, 0·1 mole) in dry ether (200 ml) for 36 h at 25° and for 30 min under reflux, and worked up. The hydrochloride crystallized from ethyl acetate, m.p. 182–184°; yield 2·8 g (29 per cent).

Anal. Calcd. for $C_9H_{18}ClN$: C, 61·52; H, 10·32; N, 7·97. Found: C, 61·42; H, 10·39; N, 8·28.

(*b*) A solution of 1-cyclohexenealdehyde (10·2 g, 94 mmoles), freshly distilled nitroethane (7 g, 94 mmoles), and 30 drops of *n*-butylamine was heated under nitrogen on a steam bath for 3 h. The cooled mixture was poured into dilute hydrochloric acid, extracted with ether, the ether extract was washed thoroughly with water and dried ($MgSO_4$ anhyd.). From the brown oily residue, a fraction boiling at 107–110°/1 mm was collected in a yield of 3·5 g (21 per cent). The unstable yellow distillate darkened rapidly even at −17°. It was reduced with an excess of $LiAlH_4$ in dry ether as described for other cases above. The amine was distilled, b.p. 84–85°/20 mm. Ullyot[14] reported b.p. 109–114°/55 mm. The hydrochloride (0·85 g), prepared in dry ether solution and recrystallized from ethyl acetate, had m.p. 180–182°. A mixture melting point with a sample obtained by method (*a*) showed no depression, and the infrared spectra of the two salts were identical.

2-Amino-1-(1-cyclopentenyl)propanol. (*a*) To a stirred solution of redistilled nitroethane (6·48 g, 86 mmoles) and 10N sodium hydroxide solution (0·2 ml) in 95 per cent ethanol (5 ml) was added slowly, at 30–35°, 1-cyclopentenecarboxaldehyde (8·3 g, 84·6 mmoles) in ethanol (5 ml). After about two-thirds of the addition was completed, another 0·2 ml of 10N sodium hydroxide solution was added. The solution stood at 25° for 65 h, then it was carefully neutralized with 0·68 ml of 6N hydrochloric acid and evaporated under reduced pressure. Water (30 ml) and ether (50 ml) were added to the residue, and the aqueous layer was extracted with two 30-ml portions of ether. The ether extracts were washed with sodium bicarbonate solution, dried, and evaporated under vacuum. The yield of crude 1-(1-cyclopentenyl)-2-nitropropanol was 13·3 g (89·5 per cent).

(*b*) To a stirred solution of lithium aluminium hydride (5·53 g, 146 mmoles) in refluxing absolute ether (200 ml) was added dropwise, under nitrogen, crude 1-(1-cyclopentenyl)-2-nitropropanol (10·0 g, 58·4 mmoles). The mixture was stirred and refluxed for 1 h and decomposed with water followed by 250 ml of saturated sodium potassium tartrate solution. It was then heated until the inorganic salts had gone into solution, cooled, and extracted with

six portions of ether. After drying the combined ether extracts over potassium carbonate, they were fractionated. The yield of straw-coloured oil, b.p. 94–97°/0·35 mm; $n_D^{25.5}$ 1·4838, was 1·66 g (20 per cent based on 1-cyclopentenecarboxaldehyde).

The *dilituratе* was prepared in aqueous solution, m.p. 231·5–232·5°.

Anal. Calcd. for $C_{12}H_{18}N_4O_6 \cdot H_2O$: C, 43·37; H, 6·06; N, 16·86. Found: C, 42·76; H, 6·25; N, 17·22.

2-Amino-1-cyclobutylpropanol. (*a*) 1-Cyclobutyl-2-nitropropanol was prepared in a similar manner as described for 1-(1-cyclopentenyl)-2-nitropropanol, using nitroethane (5·55 g, 74 mmoles), 10N sodium hydroxide solution (0·4 ml), and cyclobutanecarboxaldehyde (6·0 g, 71·5 mmoles). The nitro alcohol boiled at 76–84°/0·35 mm, n_D^{22} 1·4730. Yield, 7·4 g (62·5 per cent).

(*b*) Hydrogenation of 1-cyclobutyl-2-nitropropanol (4·4 g, 27·8 mmoles) in absolute ethanol (30 ml) in the presence of 0·23 g of platinum oxide, followed by the customary work-up gave an oil which was treated with an ethereal solution of *p*-aminobenzoic acid. The *p*-aminobenzoate salt crystallized from ethyl acetate, m.p. 160–162°. The yield was 3·66 g (49 per cent).

Anal. Calcd. for $C_{14}H_{22}N_2O_3$: C, 63·13; H, 8·33; N, 10·52. Found: C, 63·23; H, 8·28; N, 10·58.

The same amino alcohol was obtained by lithium aluminium hydride reduction of the nitro alcohol in ether as described above for the cyclopentenyl analogue. The *p*-aminobenzoate salt, obtained in 25 per cent yield, melted at 158–160° and did not depress the melting point of a sample from the catalytic hydrogenation procedure.

2-Amino-1-cyclobutylethanol. (*a*) A solution of cyclobutanecarbonyl chloride (26·1 g, 0·22 mole) in 60 ml of dry ether was dropped into a stirred solution of diazomethane (21·2 g, 0·505 mole) in ether (1 l.) at 0°. The mixture was stirred for 1 h at 0° after the addition and concentrated to 100 ml under reduced pressure. The remaining solution was added slowly, under nitrogen, to a stirred solution of lithium aluminium hydride (20·8 g, 0·55 mole) in 1 l. of boiling dry ether. After stirring under nitrogen for 15 h, water (200 ml) was added, the ether solution was decanted and the residue heated with saturated aqueous potassium hydroxide until the salts had gone into solution. The cooled

solution was filtered from some red tar, and extracted thoroughly with ether. The amino alcohol was then extracted from the ether with 2 per cent hydrochloric acid, the acid solution was concentrated, made alkaline and extracted with ether. The residue from the ether extracts was fractionated; only very little amine, b.p. 125°/0·5 mm, n_D^{27} 1·4842, distilled from the tarry product. The neutral *succinate* was prepared in ether solution and recrystallized from acetone, m.p. 157·5–160°.

Anal. Calcd. for $C_{16}H_{32}N_2O_6$: C, 55·15; H, 9·26; N, 8·04. Found: C, 55·39; H, 9·23; N, 7·94.

(*b*) To a stirred solution of cyclobutanecarboxaldehyde (6·0 g, 71·4 mmoles) and acetic anhydride (14·6 g, 143 mmoles) was added slowly, with cooling, a solution of potassium cyanide (9·23 g, 143 mmoles) in water (25 ml). After the initial reaction subsided, the mixture was stirred at 25° for 17 h, poured into an excess of cold saturated sodium carbonate solution, and extracted thoroughly with ether. The ether extracts were washed with water and the washings back-extracted with ether. The combined ether extracts were dried, distilled, and the residual oil was allowed to stand with acetic anhydride (40 ml) and acetyl chloride (2 ml) at 25° for 65 h. Ice-cold saturated sodium bicarbonate solution was added cautiously and the alkaline mixture was extracted well with ether. The residual oily acetoxy nitrile from the ether extracts (5·35 g, 49 per cent) boiled at 104–106°/10 mm, n_D^{25} 1·4433. It was reduced with lithium aluminium hydride as described above for α-acetoxy-1-cyclohexeneacetonitrile. The succinate salt of the amino alcohol was obtained in 12·5 per cent yield after recrystallization from acetone–ethyl acetate, m.p. 154·5–157°. It did not depress the melting point of the succinate obtained by method (*a*).

2-Cyclobutylethylamine. (*a*) Cyclobutanecarboxylic acid was reduced to cyclobutylmethanol with lithium aluminium hydride,[25] b.p. 65–66°/20 mm, 48°/16 mm; n_D^{26} 1·4440.[26] The yield was 83 per cent. *p*-Toluenesulphonyl chloride (30 g, 0·156 mole) was dissolved gradually in 50 ml of ice-cold dry pyridine, and a solution of cyclobutylmethanol (13·2 g, 0·154 mole) in dry pyridine (25 ml) was added. A precipitate of pyridinium chloride soon appeared. The mixture was allowed to warm to 25° overnight and then poured into a mixture of ice (200 g) and conc. hydrochloric acid

(95 ml). The precipitated oil was extracted with ether, the extracts were washed with bicarbonate solution and water, dried ($MgSO_4$ anhyd.), and evaporated. The residual colourless oily cyclobutylmethyl *p*-toluenesulphonate weighed 29·6 g (80 per cent), n_D^{28} 1·5190, and was used directly in the next step.

(*b*) To a stirred refluxing solution of sodium cyanide (9·18 g, 0·188 mole) in absolute methanol (150 ml) was added dropwise a solution of cyclobutylmethyl *p*-toluenesulphonate (15 g, 0·0625 mole) in dry methanol (25 ml). After refluxing for 2·5 h, the mixture was concentrated to 40 ml, water (100 ml) was added, the mixture was extracted with ether and worked up as usual. The residual amber oil boiled at 78–79°/25 mm, 81–82°/24 mm, $n_D^{27.5}$ 1·4321. Yield, 3·58 g (60 per cent). The material turned yellow on standing and was reduced directly.

(*c*) To a stirred solution of lithium aluminium hydride (2 g, 0·06 mole) in tetrahydrofuran (100 ml) was added dropwise a solution of cyclobutylacetonitrile (4 g, 0·04 mole) in the same solvent (15 ml). After refluxing for 1 h under an atmosphere of nitrogen, the mixture was decomposed as described by Amundsen and Nelson,[27] and the oily residue from the ether solution was treated with an ether solution of succinic acid. The yield of colourless crystals of the hydrogen succinate was 3·6 g (39 per cent). Recrystallization from ethanol–ether or acetone gave material, m.p. 113–115°.

Anal. Calcd. for $C_{10}H_{19}NO_4$: C, 55·31; H, 8·75; N, 6·45. Found: C, 55·02; H, 8·72; N, 6·41.

On one occasion, a succinate salt melting at 134–139° was observed, but the melting point changed on recrystallization from acetone to 113–116°.

A mixture melting point with cyclopentylmethylamine hydrogen succinate was 109–114°.

Cyclopentylmethylamine[20] *hydrogen succinate* crystallized from ethanol–ether or acetone, m.p. 126–127°.

Anal. Calcd. for $C_{10}H_{19}NO_4$: C, 55·28; H, 8·81. Found: C, 55·76; H, 8·85.

Cyclobutylacetone. To a stirred ethereal solution of methylmagnesium iodide (15·0 g, 81·6 mmoles) was added dropwise a solution of cyclobutylacetonitrile (2·58 g, 27·2 mmoles) at such a rate as to maintain reflux. After 4 h boiling, the mixture was

poured into ice (100 g) and 5 per cent hydrochloric acid (35 ml) and worked up. The amber oily ketone gave a *2,4-dinitrophenylhydrazone*, orange plates, m.p. 131–133°.

Anal. Calcd. for $C_{13}H_{16}N_4O_4$: C, 53·41; H, 5·52. Found: C, 53·50; H, 5·51.

2-Amino-1-cyclobutylpropane. A mixture of cyclobutylacetone (1·5 g), hydroxylamine hydrochloride (2·85 g), sodium acetate trihydrate (4·44 g) and water (10 ml) was heated at 60° with vigorous shaking. The oily oxime was extracted with ether, the solution was dried ($MgSO_4$ anhyd.), reduced with a 50 per cent excess of lithium aluminium hydride for 4 h, and worked up as usual. The oily amine was converted to the *p*-aminobenzoate salt, m.p. 185–188° (d.) but this salt was unstable. Therefore, the *succinate* was prepared in ether solution. The colourless powder crystallized from acetone–ethyl acetate, m.p. 117·5–119°.

Anal. Calcd. for $C_{11}H_{21}NO_4$: C, 57·12; H, 9·15. Found: C, 56·82; H, 8·95.

1-Cyclobutyl-1-oxo-2-piperidinoethane. To cyclobutyl diazomethyl ketone, prepared from cyclobutanecarbonyl chloride (0·19 mole) and diazomethane (0·505 mole) in ether as described above [*see* 2-amino-1-cyclobutylethanol, (*a*)] was added 48 per cent hydrobromic acid (64·5 g, 0·38 mole) with stirring at 0°. After 10 min, saturated sodium bicarbonate solution was added to alkaline reaction, and the organic layer was separated and combined with ether extracts of the aqueous phase. The ether extracts were washed with sodium bicarbonate solution and water, dried (Na_2SO_4 anhyd.) and fractionated. The oily *cyclobutyl bromomethyl ketone* boiled at 83–87°/10 mm, $n_D^{25·5}$ 1·4945. It could be stored over magnesium oxide. Its 2,4-dinitrophenylhydrazone decomposed on heating.

A solution of piperidine (17·0 g, 0·2 mole) in dry benzene (50 ml) was dropped into a stirred solution of cyclobutyl bromomethyl ketone (8·8 g, 0·047 mole) in refluxing dry benzene (50 ml). After stirring for an additional 4 h under reflux, the solution was concentrated under reduced pressure and treated with 20 per cent potassium hydroxide solution (50 ml). The product was extracted into ether, dried, and fractionated. The piperidino ketone (7·3 g, 81·5 per cent) boiled at 91–93°/1·4 mm, n_D^{28} 1·4774.

The *picrate* (from ethanol) had m.p. 126·5–128·5°.

Anal. Calcd. for $C_{11}H_{19}NO \cdot C_6H_3N_3O_7$: C, 49·75; H, 5·40. Found: C, 49·55; H, 5·24.

1-Cyclobutyl-2-diethylamino-1-oxoethane was prepared in a similar manner from bromoacetyl cyclobutane (8·8 g, 0·047 mole) and diethylamine (13·75 g, 0·188 mole) in ether. Distillation gave 5·80 g (73 per cent) of product, b.p. 63–65°/0·55 mm, n_D^{28} 1·4520. The *picrate* melted at 55–57°.

Anal. Calcd. for $C_{10}H_{19}NO \cdot C_6H_3N_3O_7$: C, 48·24; H, 5·57. Found: C, 47·75; H, 5·53.

1-Cyclobutyl-2-(4-methyl-1-piperazyl)-1-oxoethane was prepared similarly from the bromo ketone and *N*-methylpiperazine in benzene solution. The yield was 36 per cent, b.p. 115–119°/1·2 mm, $n_D^{25·5}$ 1·4802.

The *dihydrobromide* crystallized from absolute ethanol, m.p. 230–232° (d.).

Anal. Calcd. for $C_{11}H_{20}N_2O \cdot 2HBr$: C, 36·88; H, 6·19; N, 7·82. Found: C, 36·50; H, 6·07; N, 7·79.

1-Cyclobutyl-2-piperidinoethanol. (*a*) To a stirred solution of lithium aluminium hydride (1·52 g, 0·04 mole) in refluxing absolute ether (150 ml) was added dropwise, under nitrogen, 1-cyclobutyl-1-oxo-2-piperidinoethane (7·3 g, 0·04 mole) in absolute ether (50 ml). After addition was complete, the mixture was refluxed for 2·5 h and stirred under nitrogen overnight. It was decomposed with water (20 ml), followed by hot 50 per cent potassium hydroxide solution (50 ml), extracted with ether, and the residue from the dried ether extract was distilled. The yield of colourless oil was 6·1 g (83·5 per cent), b.p. 80°/0·5 mm, $n_D^{25·5}$ 1·4812.

The *hydrobromide* was prepared in ethereal solution, m.p. 222–224·5°, after recrystallization from acetone.

Anal. Calcd. for $C_{11}H_{21}NO \cdot HBr$: C, 50·00; H, 8·39; N, 5·30. Found: C, 49·87; H, 8·10; N, 5·54.

(*b*) Reduction of 1-cyclobutyl-1-oxo-2-piperidinoethane with aluminium isopropoxide following a general procedure[22] gave a 56·5 per cent yield of the same product.

(*c*) Reduction of bromoacetyl cyclobutane (13·0 g, 73·5 mmoles) with lithium aluminium hydride (0·80 g, 21 mmoles) at 0° gave a brown oil which upon distillation yielded 4·55 g (31 per cent) of 2-bromo-1-cyclobutylethanol, b.p. 94–99°/10 mm; $n_D^{27·5}$

1·4948. Reaction of this compound (4·55 g, 25·4 mmoles) with 8·65 g (10·2 mmoles) of redistilled piperidine under the usual conditions gave 2·56 g (56·5 per cent) of 1-cyclobutyl-2-piperidinoethanol, b.p. 79–83°/0·5 mm, $n_D^{26.5}$ 1·4800.

The *hydrobromide* after recrystallization from acetone, had m.p. 221–224°. The melting point was not depressed by mixture with the compound previously obtained by method (*a*), and the infrared spectra of the two samples were identical.

1-Cyclobutyl-2-(4-methyl-1-piperazyl)ethanol was obtained by reduction of 1-cyclobutyl-2-(4-methyl-1-piperazyl)-1-oxoethane (5·0 g, 0·0256 mole) with lithium aluminium hydride (0·970 g, 0·0256 mole) in tetrahydrofuran. Yield, 3·3 g (66 per cent), b.p. 96–99°/0·5 mm, n_D^{28} 1·4850.

The *dihydrobromide* was prepared in ethereal solution; after recrystallization from acetone–ethanol it melted at 241·5–244°.

Anal. Calcd. for $C_{11}H_{22}N_2O \cdot 2HBr$: C, 36·68; H, 6·72. Found: C, 36·69; H, 6·37.

In an analogous manner, *1-cyclobutyl-2-diethylaminoethanol* was prepared by reduction of 1-cyclobutyl-2-diethylamino-1-oxoethane. Yield, 3·0 g, (55 per cent), b.p. 61°/0·8 mm; n_D^{30} 1·4511.

The *cyclohexylsulphamate* was obtained from equimolar amounts of the amino alcohol and cyclohexylsulphamic acid* in ethyl acetate solution. It crystallized from acetone, m.p. 134–136°.

Anal. Calcd. for $C_{10}H_{21}NO \cdot C_6H_{13}NO_3S$: C, 54·82; H, 9·78. Found: C, 54·52; H, 9·54.

1-Cyclobutenylmethanol. The starting material for the preparation of this alcohol, methyl cyclobutenecarboxylate, was obtained by the method of Campbell and Rydon;[16] instead of being methylated with diazomethane, potassium cyclobutenecarboxylate could also be stirred and refluxed with excess thionyl chloride for 30 min, and the cooled mixture treated with excess methanol. Dilution with water, extraction with ether and fractionation gave the same ester, b.p. 65°/28 mm.

A solution of methyl cyclobutenecarboxylate (7 g) in ether (25 ml) was added dropwise to a solution of lithium aluminium hydride (4 g) in 200 ml of ether at a rate designed to maintain

* We are grateful to Abbott Laboratories, North Chicago, Illinois, for a generous supply of cyclohexylsulphamic (Hexamic ®) acid.

reflux. Refluxing was continued for 1 h, and the mixture was treated with water followed by 15 per cent hydrochloric acid. The ether solution was dried ($MgSO_4$ anhyd.) and fractionated. The yield of colourless liquid, b.p. 67°/34 mm; n_D^{23} 1·4553, was 1·8 g (15 per cent). The infrared spectrum showed OH and C=C bands.

Anal. Calcd. for C_5H_8O: C, 71·44; H, 9·51. Found: C, 70·44; H, 10·50.

Treatment with an equal weight of phenylisocyanate gave a urethane which crystallized from petroleum ether, m.p. 63–64°.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70·94; H, 6·39. Found: C, 70·57; H, 6·35.

(1-Bromocyclobutyl)methanol. A solution of ethyl 1-bromocyclobutanecarboxylate[16] (10 g) in ether (50 ml) was added to a stirred solution of lithium aluminium hydride (0·95 g) in ether (100 ml) at 0° and stirring was continued for 2 h, allowing the mixture to warm slowly to 25°. Decomposition with water was followed by addition of 20 per cent sulphuric acid, the ether solution was dried (Na_2SO_4) and fractionated. The yield of colourless oil was 6 g (75 per cent), b.p. 67–69°/16 mm; 81–83°/29 mm; n_D^{24} 1·5125.

The *phenylurethane derivative* melted at 69–70°.

Anal. Calcd. for $C_{12}H_{14}BrNO_2$: C, 50·73; H, 4·92. Found: C, 50·79; H, 4·76.

The *tetrahydropyranyl ether* was prepared by adding gradually dihydropyran (4·35 g) to (1-bromocyclobutyl)methanol (5·8 g) containing a catalytic amount of dry hydrogen chloride, the temperature being controlled by occasional immersion in ice-water. After 1 h, ether was added, the solution washed carefully with 5 per cent sodium hydroxide solution and with water, and the dried ethereal layer was distilled. The main fraction (6·3 g, 72 per cent) had b.p. 90–93°/1·3 mm; 99°/2·6 mm; n_D^{24} 1·496.

Anal. Calcd. for $C_{10}H_{17}BrO_2$: C, 48·23; H, 6·82. Found: C, 48·22; H, 6·91.

Hydrolysis with dilute sulphuric acid reconverted the tetrahydropyranyl ether to (1-bromocyclobutyl)methanol, identified with an authentic sample.

Cyclobutanecarboxaldehyde. To refluxing 5-ethyl-2-methylpyridine (12·1 g) was added (1-bromocyclobutyl)methanol (14·7 g)

and the mixture was refluxed for 1 h.* Ether was added, the mixture was washed with dilute hydrochloric acid, and then with bicarbonate solution and water. Fractionation of the ether solution yielded 4·3 g (57 per cent) of an oil, b.p. 112–117°, n_D^{23} 1·459.

The *2,4-dinitrophenylhydrazone* melted at 154–156° (lit. m.p.[15] 155–156°).

Anal. Calcd. for $C_{11}H_{12}N_4O_4$: C, 50·01; H, 4·58. Found: C, 50·43; H, 4·64.

Summary. The synthesis of a number of ethylamine and propylamine, as well as ethanolamine and propanolamine, derivatives of cyclohexane, cyclohexene, cyclopentene and cyclobutane is reported. Pharmacological comparison of several of these compounds confirmed the prediction that decreases of planarity of the ring and increases in the angle of substitution are paralleled by decreases in several activities associated with phenethylamine- and phenylethanolamine-type structures.

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