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Cyclopropyl and Cyclobutyl Analogs of Phenyl-Substituted Medicinal Agents[1a,b]

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Cyclobutyl analogs of the following phenyl-substituted drugs have been synthesized: phenobarbital, α-phenyl-N-methylsaccinimide, phenylbutazone, cinchophen and 4-amino-2-phenylquinoline. The cyclobutyl group can replace effectively a 1-cyclohexenyl group in hypnotic barbiturates, but produces no sympathomimetic effects in the cyclobutyl analog of amphetamine, nor does it lead to significant metabolite antagonism in β-cyclobutyl-α-alanine for phenylalanine requiring organisms.

In a previous investigation,[1d] the effect of replacing the flat aromatic phenyl group of representative adrenergic structures by smaller flat or near-flat cycloalkyl and cycloalkenyl groups has been evaluated. In such compounds, decreases of planarity of the ring and increases in the angle of substitution paralleled decreases in the intensity of pharmacodynamic activities usually associated with phenylethanolamine and phenethylamine-type agents. The present article concerns the synthesis and preliminary pharmacological study of several small-ring analogs of phenyl-substituted lead structures which are known to exert various pharmacological actions. *A priori*, one may expect such compounds to be less active than their aromatic prototypes, if planarity, resonance energy, ability of Van der Waals binding and lack of bulk are accepted as the basis for the fit of aromatic groups at active sites. But unless an as yet unproven reason exists for a link between activity and a minimum molecular weight of a drug, the gradual physical changes produced by replacing an aromatic group by small, though bulkier, alicyclic moieties should permit "side-effects" to emerge and become predominant. With this in mind we have prepared cyclobutane analogs of aromatic barbiturates, of α-phenyl-N-methylsuccinimide, phenylbutazone, cinchophen and 4-amino-2-phenylquinoline for biological evaluation.

1. Barbiturates.—Because of the relative difficulty of securing large quantities of the starting material, cyclobutanone, exploratory model syntheses were studied using cyclopentanone. Diethyl cyclopentylmalonate, obtained from cyclopentanone as described below, cannot be alkylated,[2] and alkylation of diethyl cyclopropylmalonate remains incomplete,[3] perhaps due to the low acidity of these *sec*-alkylmalonate esters, or because of steric factors.[4] The cyclobutyl derivative could be expected to exhibit reactivity intermediate between that of cyclopropyl and cyclopentyl compounds, and a more profitable route to the necessary three-carbon system of the barbiturate ring had to be sought. Alkylcyanoacetate esters should undergo further alkylation more readily than alkylmalonate esters, presumable because of the higher acidity of the cyano derivatives.[4] Indeed, ethyl cyclopentylcyanoacetate was ethylated readily in the presence of sodium ethoxide, but the resulting disubstituted cyanoacetic ester did not ethanolyze under acidic conditions, and was not hydrolyzed completely upon prolonged refluxing with strong acid or base.[5] Therefore, ethyl α-cyclopentyl-α-ethylcyanoacetate, was condensed directly with urea in a procedure recommended by Conrad.[6] The resulting 5-cyclopentyl-5-ethyl-4-iminobarbituric acid was hydrolyzed easily to the corresponding barbiturate.

The ethyl cyclopentylcyanoacetate needed for this sequence was prepared by reductive alkylation of ethyl cyanoacetate with cyclopentanone patterned on a method of Alexander and Cope[7]; stepwise synthesis involving the isolation of the intermediate ethyl α-cyclopentylidenecyanoacetate[8] was less profitable. The

(1) (a) This research has been supported by a Grant, B-1445, from the Institute of Neurological Diseases and Blindness, National Institutes of Health, U.S. Public Health Service; (b) In honor of Dr. Erich Mosettig, deceased June, 1962; (c) National Science Foundation Predoctoral Fellow, 1961–1962; (d) A. Burger, R. T. Standridge, N. E. Stjernström, and P. Marchini, *J. Med. Pharm. Chem.*, **4**, 517 (1961).

(2) H. A. Shonle, A. K. Kiltch, and E. F. Swanson, *J. Am. Chem. Soc.*, **52**, 2440 (1930).

(3) L. I. Smith and S. McKenzie, Jr., *J. Org. Chem.*, **15**, 74 (1950).

(4) A. C. Cope, H. L. Holmes, and H. O. House, "Organic Reactions," Vol. IX, R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., pp. 120–122, 145–146 (1957).

(5) *Cf.* F. C. B. Marshall, *J. Chem. Soc.*, 2754 (1930).

(6) M. Conrad, *Ann.*, **340**, 310 (1905).

(7) E. R. Alexander and A. C. Cope, *J. Am. Chem. Soc.*, **66**, 886 (1944).

(8) M. Jackman, A. J. Bergman, and S. Archer, *ibid.*, **70**, 497 (1948).

ethyl cyclopentylcyanoacetate could also be ethanolyzed easily to diethyl cyclopentylmalonate.

Following these pilot studies, cyclobutanone was used in the reductive alkylation of ethyl cyanoacetate, the ethyl α-cyano-α-cyclobutylacetate was ethylated, and the ethyl α-cyano-α-ethylcyclobutylacetate condensed with urea to yield 5-cyclobutyl-5-ethylbarbituric acid.

Although ring fission during the reductive alkylation could be discounted on the basis of the analyses of the reaction products, proof for the integrity of the cyclobutane ring was obtained by hydrolysis of ethyl cyclobutylcyanoacetate to cyclobutylmalonic acid. Decarboxylation of this dicarboxylic acid gave cyclobutylacetic acid, the anilide of which was identical with α-cyclobutylacetanilide prepared by the method of Krug[9] from cyclobutylmethylmagnesium bromide and phenyl isocyanate.

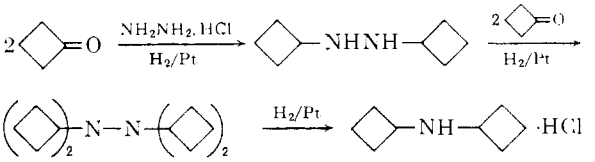
When we first repeated the directions of Krug[9] we obtained an anilide melting 30° higher than reported.[9] Although there was little doubt about the structure of cyclobutylmethyl bromide which served as the starting material in this synthesis,[10] a direct comparison with a sample kindly supplied by Professor Krug showed that the two differently melting materials were isomorphs. Further proof for the inviolateness of the cyclobutane ring in reactions of cyclobutylmethyl bromide was available from the fact that condensation of this halide with diethyl acetamidomalonate followed by hydrolysis had provided 2-amino-3-cyclobutylpropionic acid.[11] We resynthesized this compound, but used cyclobutylmethyl tosylate instead of the bromide. The same β-cyclobutyl-α-alanine was obtained in this sequence.[12] Since primary alkyl tosylates may be expected to undergo nucleophilic substitution in relatively non-polar solvents by an SN2 mechanism, rearrangements using cyclobutylmethyl tosylate can be discounted.[13] The structures of cyclobutylacetic and cyclobutylmalonic acids seem therefore assured.

2. Succinimide Derivatives.—α-Cyclobutylsuccinic acid was synthesized by the Stobbe condensation of cyclobutanone and diethyl succinate, followed by catalytic hydrogenation of the intermediate 1-ethyl 4-hydrogen 2-cyclobutylidenesuccinate and alkaline hydrolysis of the resulting saturated half ester. The use of sodium hydride as recommended by Daub and Johnson,[11] and strict control of the reaction temperature to prevent excessive foaming, improved the reaction conditions. Methylammonium α-cyclobutylsuccinate was pyrolyzed readily to α-cyclobutyl-N-methylsuccinimide.

3. Hydrazine Derivatives.—4-*n*-Butyl-1-cyclopentyl-2-phenyl-, 4-*n*-butyl-1-cyclobutyl-2-phenyl-, 4-*n*-butyl-1,2-dicyclopentyl- and 4-*n*-butyl-1,2-dicyclobutyl-3,5-pyrazolidinedione were prepared by condensation of the relevant substituted hydrazine with *n*-butylmalonyl chloride in the presence of triethylamine or a threefold excess of the hydrazine. Since *n*-butylmalonyl chloride is known[15] the synthetic problems in this series concerned the preparation of the substituted hydrazines.

Hydrazine underwent facile reductive alkylation[16] with cyclopentanone; the N,N-dicyclopentylhydrazine was isolated as the stable hydrochloride, whereas the free base readily oxidized in the air. Distillation of a week-old sample of the crude base furnished only a non-basic substance, perhaps an azo compound, because this distillate absorbed hydrogen to re-form the hydrazine derivative.[16] Storage of the *sym*-dicyclopentyl- as well as *sym*-dicyclobutylhydrazines as their salts and liberation of the bases immediately prior to their use is therefore recommended.

Reductive alkylation of hydrazine with cyclobutanone under analogous conditions[16] took quite a different course. The only reaction products isolated were a large amount of ammonium chloride, apparently formed by hydrogenolysis of hydrazine dihydrochloride, and a smaller amount of dicyclobutylamine hydrochloride. The path by which this compound may have been formed is outlined in the accompanying scheme.



An explanation of this reaction path with cyclobutanone, as compared with the ("normal") one of cyclopentanone (see above), may be sought in two properties of the carbon atoms of small alicyclic compounds. First, such ring carbons are more electronegative than those constituting larger rings[17,18]; this property will tend to increase the positivity of the carbonyl carbon in small-ring cycloalkanones, and the receptivity of these carbonyl carbons to nucleophilic reagents. Second, the existing steric strain of small-ring carbons will be increased by the presence of a trigonal carbonyl carbon and thus render the ketone more reactive.[19] This is expressed in the relative stability of cyclopentanone and cyclohexanone whereas cyclobutanone undergoes polymerization at 25°, and cyclopropanone is known only in the hydrate and hemiketal forms. Therefore, it may be assumed that N,N′-dicyclobutylhydrazine, produced by catalytic hydrogenation of cyclobutanone and hydrazine in aqueous acidic solution, attacks the reactive cyclobutanone as it is formed. N,N,N′,N′-Tetracyclobutylhydrazine should be the product of this reaction. Hydrogenolysis of this intermediate would give dicyclobutylamine, that is, the observed reaction product. Cyclopentanone, less reactive than cyclobutanone, apparently fails to react with

(9) R. C. Krug, L. W. Smith, and C. W. Fry, *J. Am. Chem. Soc.*, **76**, 3222 (1954).

(10) J. G. Traynham and O. S. Pascual, *J. Org. Chem.*, **21**, 1362 (1956).

(11) K. Heyns, K. Molge, and W. Walter, *Chem. Ber.*, **94**, 1015 (1961).

(12) A sample for comparison was kindly supplied by Dr. W. Walter.

(13) H. Hart and J. A. Wrede, *J. Org. Chem.*, **25**, 1811 (1960).

(14) C. H. Daub and W. S. Johnson, *J. Am. Chem. Soc.*, **70**, 418 (1948); **72**, 501 (1950).

(15) W. H. Puterbaugh, F. W. Swamer, and C. R. Hauser, *ibid.*, **74**, 3438 (1952).

(16) H. L. Locke, J. R. Bailey, and W. L. Noyes, *ibid.*, **43**, 2597 (1921).

(17) Sj. Kaarsemaker and J. Coops, *Rec. Trav. Chim. Pays-Bas*, **70**, 1033 (1951).

(18) A. D. Walsh, *Trans. Faraday Soc.*, **45**, 179 (1949).

(19) The angle between the ring orbitals in cyclopropane is 106°. The two endo bonds of >C=O should lie, ideally, at a 120° angle; addition to the carbonyl carbon will relieve this strain since the C—C bond angle will revert to normal; *cf.* L. L. Ingraham, in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 518–520.

TABLE I

ONSET OF ANESTHESIA AND SLEEPING TIME IN MICE

Hexobarbital			Cyclobarbital			5-Cyclobutyl-5-ethylbarbituric Acid		
Dose, mg./kg., i.v.	Onset of anesthesia, min.	Sleeping time, min.	Dose, mg./kg., i.v.	Onset of anesthesia, min.	Sleeping time, min.	Dose, mg./kg., i.v.	Onset of anesthesia, min.	Sleeping time, min.
50	0	6	135	4	68.5	65	0	0
	0	11.5		15	22		12	63
	0	11		9	39		5	74
	0	28		5	21		11	91
	0	17		21	39		1	77
	0	17		8	83		13	78
	0	23		12	32		19	85
	0	9		15	28		17	76
	0	6		10	58		15	147
	0	15		15	32		15	136
		Mean value, 14.3			Mean value, 42.75			Mean value, 92.0
70	0	29.5	175	1	59	80	4	107
	0	22		3	176		11	53
	0	35.5		2	66		11	101
	0	32		10	74		11	94
	0	27		8	60		15	103
	0	25		12	53		12	96
	0	18		8	83		7	86
	0	28		12	39		11	139
	0	29		10	30		11	141
	0	17		7	131		10	115
		Mean value, 26.3			Mean value, 77.1			Mean value, 103.5

N,N′-dicyclopentylhydrazine under the reaction conditions employed.

By avoiding the establishment of an equilibrium between cyclobutanone azine, cyclobutanone, and hydrazine in aqueous acid, N,N′-dicyclobutylhydrazine was finally obtained. Cyclobutanone azine was prepared, isolated and then hydrogenated in glacial acetic acid. This precluded the presence of the ketone during the hydrogenation. The infrared spectrum of the *sym*-hydrazine derivative was similar to that of N,N′-dicyclopentylhydrazine.

N-Cyclopentyl- and N-cyclobutylphenylhydrazine were prepared by catalytic hydrogenation of the corresponding phenylhydrazones in acetic acid, and purified as the bases. Extensive decomposition and loss of material occurred when their hydrochlorides were made.

4. Quinoline Derivatives.—2-Cyclopropylcinchoninic acid has been described.[20] In a similar manner, 2-cyclobutylcinchoninic acid was prepared from isatin and cyclobutyl methyl ketone.[21] Both acids were degraded to the corresponding amines by a modified[22] Curtius reaction. Direct acid hydrolysis of the intermediate isocyanates provided a small amount of amine only, while the major product was the 1,3-disubstituted urea, formed by reaction of the amine with unreacted isocyanate. To bypass this difficulty, the isocyanates were first converted to benzyl urethans; the hydrochlorides of these derivatives were purified and decomposed to virtually pure amine salts by steam distillation in acid medium.

(20) Ng. Ph. Buu-Hoï, R. Royer, Ng. D. Xuong, and P. Jacquignon, *J. Org. Chem.*, **18**, 1209 (1953).

(21) W. Pfitzinger, *J. Prakt. Chem.*, **56**, 283 (1897).

(22) J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961).

Biological Results.—2-Amino-1-cyclobutylpropane hydrogen succinate[1d] was compared with amphetamine sulfate and cyclopentamine hydrochloride (1-cyclopentyl-2-methylaminopropane·HCl) for motor activity effects in mice as measured by a light box technique.[23] It was practically inactive in doses up to 800 μmoles/kg., even after previous administration of iproniazid which potentiates the action of centrally stimulating drugs of the amphetamine type. By contrast, cyclopentamine had clear-cut stimulatory activity at 10 μmoles/kg. with convulsions in a number of the animals at this dose. The standard drug, amphetamine, causes a strong increase in motor activity at 10 μmoles/kg. under the same experimental conditions.

5-Cyclobutyl-5-ethylbarbituric acid was compared with cyclobarbital [5-(1-cyclohexenyl)-5-ethylbarbituric acid] and hexobarbital [5-(1-cyclohexenyl)-1,5-dimethylbarbituric acid] for anesthetic potency. Doses necessary to induce anesthesia and the time lags between intravenous injection and onset and termination of anesthesia were determined. Two dosages were administered to 6 groups of 10 mice each divided randomly. The results are summarized in Table I. 5-Cyclobutyl-5-ethylbarbituric acid caused no anesthesia at 60 mg./kg. but anesthetized the mice at 75, 80 and 90 mg./kg. With cyclobarbital (i.v.) no anesthesia occurred at 60, 75, 90 and 120 mg./kg. in an orienting experiment, 150 mg./kg. anesthetizing the animals. The values listed in Table I indicate that 5-cyclobutyl-5-ethylbarbituric acid resembles cyclobarbital more than it does hexobarbital. Doses of 5-cyclobutyl-5-ethylbarbituric acid needed to produce anes-

(23) (a) J. B. van der Schoot, Thesis, University of Nijmegen (1961); (b) J. B. van der Schoot, E. J. Ariens, J. M. van Rossum, and J. A. Th. M. Hurkmans, *Arzneimittel-Forsch.*, **12**, 902 (1962).

thesia and to maintain sleeping time are about 50% of those of cyclobarbital. The sleeping time includes the time lag between injection and onset of anesthesia. These time lags were 0 for both doses of hexobarbital. The mean value was 11.4 and 7.3 min. for cyclobarbital in doses of 135 and 175 mg./kg., respectively, and 12 and 10.3 min., respectively, for 5-cyclobutyl-5-ethylbarbituric acid in doses of 65 and 80 mg./kg.

β-Cyclobutyl-α-alanine was examined for microbiological inhibitory properties by Prof. William Shive of the University of Texas. It inhibited the growth of *Escherichia coli* 9723 at 200 μg./ml. in a medium of glucose and inorganic salts. In the presence of 5 μg./ml. of DL-leucine, the minimal inhibitory concentration was increased to 500 μg./ml., and 10 μg./ml. of leucine raised this concentration to 1 mg./ml. At this concentration of the analog, the inhibition did not appear to be reversed by further increases in leucine concentration, suggesting that effects other than competition with leucine may be involved at this concentration. It is not unusual for analogs to have inhibitory effects upon other systems at concentrations as high as 1 mg./ml.

Leucine is required for the growth of *Leuconostoc dextranicum* 8086, and in an amino acid medium at concentrations of DL-leucine of 5, 10, and 10 μg./ml., cyclobutylalanine inhibited growth at 200, 500, and 1,000 μg./ml., respectively. Again, inhibition by the highest concentration was not reversed by still higher concentrations of leucine. It thus appears that cyclobutylalanine is an antagonist of leucine for *E. coli* and *L. dextranicum*, but not a particularly effective one, over a small range of concentrations. Incorporation of a cyclobutyl group in place of phenyl in certain types of drugs thus barely produced sympathomimetic effects, nor does it lead to significant metabolite antagonism in the microbial system studied. On the other hand, the cyclobutyl group can replace effectively a 1-cyclohexenyl group in hypnotic barbiturates.

Experimental[24]

Cyclobutylacetyl Chloride.—A mixture of 8.65 g. (0.09 mole) of cyclobutylacetonitrile, 10 g. (0.18 mole) of potassium hydroxide, 30 ml. of water and 25 ml. of ethanol was refluxed for 96 hr. The alcohol was distilled off, the aqueous solution was cooled and extracted with ether. It was then acidified with concentrated hydrochloric acid and the separated oil extracted exhaustively into ether. After drying ($MgSO_4$), fractionation yielded 8.6 g. (83%) of colorless, oily, foul-smelling cyclobutylacetic acid, b.p. 109.5–110° (23 mm.), $n^{25}D$ 1.4420. A mixture of this acid with thionyl chloride (11.9 g., 0.1 mole) was allowed to stand at 25° for 20 hr., refluxed for 0.5 hr., and distilled slowly to avoid foaming. The colorless mobile fuming distillate weighed 9.25 g. (93%), b.p. 55–56° (19 mm.).

Treatment of a small amount of cyclobutylacetyl chloride with excess aniline in benzene gave shining platelets of **α-cyclobutylacetanilide,** m.p. 110–112.5° after recrystallization from petroleum ether (b.p. 65–110°).

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 75.85; H, 8.02; N, 6.98.

A sample of this compound did not depress the melting point of the anilide of the acid prepared by decarboxylation of cyclobutylmalonic acid. A sample of α-cyclobutylacetanilide prepared from cyclobutylmethylmagnesium bromide and phenyl isocyanate,[9] kindly supplied by Professor R. C. Krug of Virginia Polytechnic Institute, consisted of colorless needles, m.p. 83–85°. When dissolved in petroleum ether (b.p. 30–60°) and seeded with our anilide, the melting point rose through 97–102° to 105–108°. A mixture melting point of this material and our anilide (m.p. 110–112.5°) remained undepressed, and the infrared spectra of the two substances were identical.

DL-β-Cyclobutyl-α-alanine.[10]—To a stirred suspension of 2.08 g. (0.045 mole) of sodium hydride (52.6%, in mineral oil) in 25 ml. of dimethylformamide freshly distilled from calcium hydride, was added portionwise 8.25 g. (0.038 mole) of diethyl acetamidomalonate. Foaming of the mixture was allowed to subside between successive portions. After stirring for 1 hr. at 26° and rapid filtration, the greenish solution was mixed with 9.6 g. (0.04 mole) of crude cyclobutylmethyl *p*-toluenesulfonate[24] and heated at 130–135° for 1.25 hr. The dark semisolid mass was evaporated to dryness at 100° (1 mm.), 90 ml. of water was added to the residue, and the mixture was extracted with ether. The combined ethereal extracts were washed with saturated sodium bicarbonate solution and then with water and dried over magnesium sulfate. Evaporation of the ether gave 7.4 g. of a brownish residue; this was refluxed with 70 ml. of 18% hydrochloric acid for 2 hr., the solution was cooled, extracted with ether, and the aqueous hydrochloric acid was removed at 1 mm. The crude hydrochloride was washed with ether, treated with charcoal in 30 ml. of water, and neutralized with concentrated ammonium hydroxide. A tan precipitate formed slowly, and was augmented by concentration of the solution. Recrystallization from aqueous ethanol gave 0.9 g. (17%) of product, m.p. 298–300° dec., the bath being preheated to 290° and the temperature being raised 10°/min.

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.92; H, 9.07; N, 9.84.

The phenylhydantoic acid derivative was prepared as described by Walter,[25] m.p. 157–158.5° dec.

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.30; H, 7.02; N, 10.64.

Mixture melting points of our amino acid with a sample kindly furnished by Dr. W. Walter, and of our phenylhydantoic acid derivative with that of a sample prepared from Dr. Walter's amino acid, respectively, were undepressed. The infrared spectra of the respective compounds were also identical.

5-Cyclopentyl-5-ethylbarbituric Acid. (a) **Diethyl Cyclopentylmalonate.**—This was prepared by heating diethyl malonate (0.5 mole), acetic anhydride (0.625 mole) and cyclopentanone (0.6 mole) and zinc chloride (9.6 g.) according to the method of Cope and Hancock,[26] followed by work-up to diethyl cyclopentylidenemalonate[26] [b.p. 83–89° (0.25 mm.); $n^{22}D$ 1.4685; yield (pure) 15%] and hydrogenation in ethanol in the presence of 0.2 g. of platinum oxide catalyst at atmospheric pressure. The saturated ester [yield, 13.25 g. (79%)] had b.p. 84–87° (0.35 mm.), $n^{24.5}D$ 1.4470; reported,[2] b.p. 114° (4 mm.), $n^{20}D$ 1.4434. Basic hydrolysis of the ester gave cyclopentylmalonic acid, m.p. 163–166° dec. (from chloroform). Reported,[27] m.p. 165° dec.

Ethyl cyclopentylmalonate was also obtained by slowly treating a stirred solution of 21.7 g. (0.12 mole) of ethyl cyclopentylcyanoacetate (see below) in 23.2 g. (0.48 mole) of 95% ethanol at 0°, with 23.5 g. (0.24 mole) of concd. sulfuric acid, refluxing the mixture for 5 hr., allowing to stand at 26° for 10 hr., pouring into 200 ml. of water, and extracting the oil into ether. The yield of ester, b.p. 93–106° (0.8–1.6 mm.), was 17.2 g. (64%).

Attempts to ethylate diethyl cyclopentylmalonate with ethyl iodide in ethanolic sodium ethoxide solution, or using sodium hydride in dry benzene, failed as shown by the condensation of the reaction products with urea which yielded only 5-cyclopentylbarbituric acid,[2] m.p. 222–224°.

(b) **Ethyl Cyclopentylcyanoacetate.**[5]—This was obtained best by condensation of cyclopentanone with ethyl acetate followed by hydrogenation according to the literature;[8] yield, 75%; b.p. 80–82° (0.3 mm.), 104–112° (1.5–1.7 mm.); $n^{25}D$ 1.4527, $n^{26.5}D$ 1.4530. A small portion was hydrolyzed under basic conditions. The resulting cyclopentylmalonic acid[27] melted at 164–166° dec.

(c) **Ethyl Cyclopentylethylcyanoacetate.**—To a stirred solution of 11.4 g. (0.063 mole) of ethyl cyclopentylcyanoacetate and 4.75 g. (0.07 mole) of sodium ethoxide in 75 ml. of absolute ethanol was added 11 g. (0.07 mole) of ethyl iodide. The dark solution was heated at 50–55° for 3 hr., allowed to stand at 26° for 48 hr., and poured into 1 l. of water. The oil and ethereal extracts of

(24) Melting points are corrected, boiling points uncorrected. Microanalyses by Miss Winkie Sheffield, Mrs. Dolores Ellis (University of Virginia), and Alfred Bernhardt, Mühlheim, Germany. Infrared spectra were taken on a Perkin–Elmer Infracord, ultraviolet spectra on a Beckman DK-2 recording spectrophotometer.

(25) A. C. Cope and E. M. Hancock, *J. Am. Chem. Soc.*, **60**, 2901 (1938).

(26) G. A. R. Kon and E. A. Speight, *J. Chem. Soc.*, 2727 (1926).

(27) I. Vogel, *ibid.*, 2021 (1928).

the water layer were combined, dried and fractionated, b.p. 104–111° (1.4–2.0 mm.), $n^{23}D$ 1.4522; yield, 10.1 g. (77%). The product could not be hydrolyzed completely upon boiling for 18 hr. with either 50% sulfuric acid or 40% aqueous–ethanolic potassium hydroxide.

(d) **5-Cyclopentyl-5-ethylbarbituric Acid.**—Condensation of ethyl cyclopentylethylcyanoacetate with urea in ethanol solution under standard conditions yielded a small amount of 5-cyclopentyl-5-ethylbarbituric acid, m.p. 184–185°. Reported,[2] m.p. 182–183°.

Cyclobutylmalonic Acid.—To a solution of 15 g. (0.214 mole) of cyclobutanone, 24.2 g. (0.214 mole) of ethyl cyanoacetate, 2.6 g. (0.043 mole) of glacial acetic acid and 1.7 g. (0.0214 mole) of ammonium acetate in 50 ml. of 95% ethanol, was added 0.5 g. of 10% Pd/C catalyst, and hydrogenation begun immediately at 2.8 kg./cm.² pressure. The required amount of hydrogen was absorbed in 21 hr., the catalyst was filtered and the solution poured into 1 l. of water. The mixture was extracted exhaustively with ether, the ether extract was dried ($MgSO_4$) and fractionated. The yield of colorless ethyl cyclobutylcyanoacetate was 21.8 g. (61%), b.p. 61.5–65.5° (0.3–0.4 mm.); $n^{26}D$ 1.4435. A sample of this ester (1.67 g.) was refluxed in a solution of 3.5 g. of potassium hydroxide in 15 ml. of 40% aqueous ethanol for 3 hr. Ethanol was distilled off under vacuum, the aqueous solution was acidified, saturated with salt and extracted exhaustively with ether. The semisolid residue from the ether was recrystallized from chloroform (with charcoal), m.p. 146–147.5° dec.

Anal. Calcd. for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.56; H, 6.18.

Upon heating cyclobutylmalonic acid at 155–165° for 3 hr., a foul-smelling liquid was obtained which was converted to the anilide, m.p. 110–112.5°. A mixture melting point with α-cyclobutylacetanilide described above was undepressed, and the infrared spectra of the two materials were superimposable.

5-Cyclobutyl-5-ethylbarbituric Acid.—To a stirred solution of sodium ethoxide [from 1.6 g. (0.07 mole) of sodium] and 10.9 g. (0.065 mole) of ethyl cyclobutylethylcyanoacetate in 50 ml. of absolute ethanol was added 12.5 g. (0.08 mole) of ethyl iodide in 2 portions. The solution turned dark brown. The temperature was maintained at 50°, first with cooling, then with heating, for 2 hr. The cooled solution was poured into 500 ml. of water, the opalescent mixture was extracted with ether, the ether extracts were dried and fractionated. The straw-colored distillate (9.8 g., 77%) boiled at 64–66° (0.35 mm.); $n^{25}D$ 1.4430.

Neither ethanolysis nor hydrolysis of this cyano ester could be effected unambiguously.

To a stirred refluxing solution of 0.9 g. (0.039 mole) of sodium in 100 ml. of dry *t*-butyl alcohol (distilled from Drierite) was added 1.17 g. (0.0195 mole) of dried urea and 3.8 g. (0.0195 mole) of ethyl cyclobutylethylcyanoacetate. A white precipitate separated after several hours. Stirring and refluxing was continued for 24 hr., the mixture was cooled, 2.35 g. (0.039 mole) of glacial acetic acid was added, and the mixture was evaporated to dryness under vacuum. The white gummy residue was dissolved in excess 5% hydrochloric acid, and the solution was scrubbed with ether. Addition of ammonia to a sample gave colorless 5-cyclobutyl-5-ethyl-4-iminobarbituric acid, m.p. 277–279° dec., which was not purified further. Instead, it was hydrolyzed by heating its acid solution at 95° for 2.5 hr. A colorless precipitate appeared soon, and was collected by filtering the cooled mixture. A small additional amount was obtained by evaporating the acid filtrate to dryness, dissolving the residue in a minimum of boiling water, and cooling. The total yield was 1.8 g. (44%), m.p. 167–169.5°. Recrystallization from water gave a microcrystalline powder, m.p. 162–163°.

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.27; H, 6.35; N, 12.75.

5-(2-Butyl)-5-cyclobutylbarbituric Acid.—Sodium (1.52 g., 0.066 mole) was dissolved with stirring in 100 ml. of refluxing anhydrous *t*-butyl alcohol over a period of 6 hr. To this solution, 10.9 g. (0.065 mole) of ethyl cyclobutylcyanoacetate and then 11 g. (0.08 mole) of 2-bromobutane were added rapidly, the latter dropwise. After stirring and refluxing for an additional 13 hr. and standing at room temperature for 24 hr., the mixture was separated from precipitated sodium bromide and worked up as usual. Distillation of the crude product yielded 7.65 g. (53%) of colorless oil, b.p. 78–85° (0.4 mm.), $n^{24}D$ 1.4512. Using 2.32 g. (0.1 mole) of sodium dissolved in 175 ml. of *t*-butyl alcohol, this ester (7.5 g., 0.0336 mole) was condensed with 2.85 g. (0.0475 mole) of dry urea as described for the cyclobutylethyl homolog. The barbituric acid derivative crystallized from water (charcoal) as colorless needles, m.p. 167–168.5°. The yield was 2.1 g. (26%).

Anal. Calcd. for $C_{12}H_{18}N_2O_3$: C, 60.48; H, 7.61; N, 11.76. Found: C, 60.83; H, 7.72; N, 11.95.

α-Cyclobutylsuccinic Acid.—A mixture of 26.13 g. (0.15 mole) of redistilled diethyl succinate, 3.5 g. (0.05 mole) of cyclobutanone and 25 ml. of dry benzene was added all at once under nitrogen to a stirred suspension of 6.85 g. (0.15 mole) of sodium hydride (52.6% in mineral oil) in 25 ml. of anhydrous benzene, and cooled immediately to 0° to prevent a violent reaction. After about 30 min. a brownish material separated which impeded stirring. After about 1 hr., 10.5 ml. of glacial acetic acid was added dropwise, and then ether and water. The aqueous layer was washed with ether and the combined ether solutions were extracted repeatedly with 25 ml. portions of 5% sodium carbonate solution until a test showed no appreciable cloudiness upon acidification. The combined alkaline extracts were acidified in the cold, and the deep yellow oil was extracted into ether, dried, and the ether distilled. The residue solidified upon standing. It was dissolved in 50 ml. of 95% ethanol, hydrogenated (PtO_2), and the mixture was worked up. The resulting colorless oil (6.6 g.) was refluxed with 30 g. of a 20% potassium hydroxide solution and 5 ml. of ethanol for 24 hr., the mixture was cooled, acidified with 37% hydrochloric acid, and extracted exhaustively with ether. After drying ($MgSO_4$) and evaporation under vacuum, the brownish residue (5.1 g., 59%) slowly crystallized. Recrystallization of the tan solid from ethyl acetate–petroleum ether (b.p. 65–110°) gave, after some manipulation, colorless crystals, m.p. 109–111° (after softening at *ca.* 100°).

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 56.17; H, 7.19.

α-Cyclobutyl-N-methylsuccinimide.—An amber solution of crude α-cyclobutylsuccinic acid (4.1 g., 0.024 mole) in 3.9 g. (0.05 mole) of 40% aqueous methylamine was distilled until the temperature of the mixture reached 220°. The dark brown residue failed to crystallize but distilled as a colorless oil, b.p. 93–96° (0.5 mm.), $n^{21}D$ 1.4860. The yield was 1.2 g. (30%).

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.83. Found: C, 64.30; H, 8.06.

N,N'-Dicyclopentylhydrazine.—(a) Hydrazine dihydrochloride (21.0 g., 0.2 mole) and 33.6 g. (0.4 mole) of cyclopentanone were dissolved in 100 ml. of water; the solution became hot and was immediately subjected to hydrogenation (2.8 kg./cm.²) in the presence of 0.3 g. of Adams' platinum catalyst. Hydrogenation was complete within 4 hr., the catalyst was filtered off, and the colorless aqueous solution evaporated to dryness under vacuum at 100°. The residue was dissolved in a minimum of hot absolute ethanol and 5 volumes of absolute ether was added. The **hydrochloride** (30.4 g., 74%) separated slowly as colorless prisms which could be crystallized further from acetone–ethanol, m.p. 235–237°.

Anal. Calcd. for $C_{10}H_{20}N_2 \cdot HCl$: C, 58.66, H, 10.34; N, 13.69. Found: C, 58.72; H, 9.97; N, 13.32.

(b) A mixture of 10.5 g. (0.1 mole) of hydrazine dihydrochloride and 16.8 g. (0.2 mole) of cyclopentanone was treated dropwise and with stirring with a 20% solution of sodium hydroxide until just basic. A reddish oil separated. The hot mixture was cooled, the azine extracted into ether, dried ($MgSO_4$), and the solvent was evaporated at 40° under vacuum. The residue was hydrogenated (PtO_2) in 50 ml. of acetic acid. After 3 hr. it was diluted with 50 ml. of water, the catalyst was filtered off, and the cooled filtrate made strongly alkaline. The hydrazine derivative was extracted into ether and converted to the hydrochloride as described above; m.p. 235–239°, yield, 15.7 g. (77%).

The azine formed also when an aqueous solution of N,N'-dicyclopentylhydrazine hydrochloride was made alkaline, the oil was extracted into ether, dried, and fractionated under nitrogen. The yellowish distillate (11.5 g.) had b.p. 92–106° (19 mm.), $n^{24}D$ 1.4790. Its infrared spectrum contained no NH band, and the compound failed to give a hydrochloride in acetone. It could be hydrogenated in 10% aqueous ethanolic hydrochloric acid (PtO_2) within 1.25 hr. and reconverted to N,N'-dicyclopentylhydrazine, m.p. 235–237°, on work-up as above.

N,N'-Dicyclobutylhydrazine.—To a stirred mixture of 5.25 g. (0.05 mole) of hydrazine dihydrochloride and 7.0 g. (0.1 mole) of cyclobutanone was added rapidly and dropwise 20 g. (0.1 mole) of 20% sodium hydroxide solution, and the mixture was made just basic. A straw-colored oil separated which crystallized

as the mixture cooled. The solid was dissolved in 70 ml. of ether, the layers were separated, and the basic solution was extracted with ether. The solvent was stripped from the combined and dried ether extracts at 40° (15 mm.). The azine was hydrogenated and the mixture worked up as described for the dicyclopentyl homolog. **N,N'-Dicyclobutylhydrazine hydrochloride** formed colorless crystals (4.0 g., 45%), which were recrystallized from acetone, m. p. 187–190°.

Anal. Calcd. for $C_8H_{16}N_2$·HCl: C, 54.37; H, 9.70; N, 15.86. Found: C, 54.36; H, 9.66; N, 15.78.

Hydrogenation of a mixture of 71.5 mmoles of cyclobutanone and 30 mmoles of hydrazine dihydrochloride in 40 ml. of water in the presence of 0.2 g. of PtO_2 gave, on work-up, a white solid, consisting mainly of ammonium chloride. Hot acetone (200 ml.) extracted a colorless material which crystallized on cooling of the filtrate, m.p. 241–243°. Its infrared spectrum contained no NH band; yield, 40%.

Anal. Calcd. for $C_4H_{10}N$·HCl: C, 59.43; H, 9.98; N, 8.67. Found: C, 59.19; H, 9.87; N, 8.84.

To confirm that this substance was **dicyclobutylamine hydrochloride,** two additional derivatives were prepared *via* the free base.

Dicyclobutylamine oxalate, formed in ether solution, crystallized from acetone, m.p. 158–161°.

Anal. Calcd. for $C_9H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 56.27; H, 7.95; N, 6.55.

N,N'-Dicyclobutyl-3,5-dinitrobenzamide, m.p. 103–105° (from dilute ethanol) was prepared with 3,5-dinitrobenzoyl chloride in pyridine–benzene solution.[28]

Anal. Calcd. for $C_{15}H_{17}N_3O_5$: C, 56.42; H, 5.37. Found: C, 56.43; H, 5.09.

N-Cycloalkyl-N'-phenylhydrazines.—Cycloalkanone (0.1 mole) was added rapidly to a stirred solution of 14.5 g. (0.1 mole) of phenylhydrazine hydrochloride in 300 ml. of water. A 20% sodium hydroxide solution was added dropwise. The oily precipitate crystallized as the solution was cooled, and was extracted with three 100 ml. portions of ether. The residue from the dried ether extracts was hydrogenated in 60 ml. of acetic acid (50 mg. of PtO_2, 2.8 kg./cm.^{2}). After 0.1 mole of hydrogen had been absorbed (1–3 hr.) the reduction was interrupted to avoid hydrogenolysis of the hydrazine. The mixture was worked up as usual, liberating the base and fractionating.

N-Cyclopentyl-N'-phenylhydrazine distilled as a dark yellow oil, b.p. 95–100° (0.2 mm.), $n^{25}D$ 1.5585; yield, 12.0 g. (68%). Dry ethereal hydrogen chloride furnished a mixture of isomeric **hydrochlorides** which crystallized as hexagonal prisms from acetone–ethanol, m.p. 197–207°.

Anal. Calcd. for $C_{11}H_{17}N_2$·HCl: C, 62.10; H, 8.06; N, 13.17. Found: C, 62.37; H, 7.96; N, 13.21.

N-Cyclobutyl-N'-phenylhydrazine, bright yellow oil, b.p. 86–92° (0.2 mm.); yield, 7.4 g. (46%). The compound darkened rapidly and had to be used immediately. A mixture of the isomeric **hydrochlorides** crystallized from ethyl acetate–acetone, m.p. 137–141°, but decomposed too quickly to be analyzed.

4-*n*-Butyl-1,2-dicycloalkyl-3,5-pyrazolidinediones.—The oily N,N'-dicycloalkylhydrazine (0.2 mole) in 150 ml. of dry ether was treated with 0.04 mole (5.5 ml.) of anhydrous triethylamine, and at −5° *n*-butylmalonyl chloride[15] in 50 ml. of anhydrous ether was added dropwise, with rapid stirring, over a period of 2 hr. After stirring an additional 3 hr. at −5° and 2 hr. at 25°, triethylammonium chloride was filtered off, washed well with ether, the ethereal filtrate was washed with water, then with four 25 ml. portions of 1% sodium bicarbonate solution, and was extracted with four 25 ml. portions of *N* sodium hydroxide solution. The ice-cooled alkaline extracts were acidified strongly, the separated oil was extracted into ether, dried, and worked up.

4-*n*-Butyl-1,2-dicyclobutyl-3,5-pyrazolidinedione was obtained in 33–47% yield as a colorless oil, b.p. 140–145° (0.4 mm.).

Anal. Calcd. for $C_{15}H_{24}N_2O_2$: C, 68.14; H, 9.15. Found: C, 68.62; H, 9.31.

4-*n*-Butyl-1,2-dicyclopentyl-3,5-pyrazolidinedione was a colorless oil, b.p. 154–156° (0.35 mm.). The yield was 35–48%.

Anal. Calcd. for $C_{17}H_{28}N_2O_2$: C, 69.82; H, 9.65. Found: C, 69.45; H, 9.35.

The sodium salt formed as a colorless, hygroscopic solid when the oil was triturated with excess 20% sodium hydroxide solution. It melted at *ca.* 120° but was too unstable to be recrystallized. The calcium salt precipitated upon adding the oily compound to a concentrated solution of calcium ethoxide or *n*-butoxide in the appropriate alcohol. It could not be recrystallized and was decomposed by water.

4-*n*-Butyl-1-cycloalkyl-2-phenyl-3,5-pyrazolidinediones were prepared essentially by the same method but using an excess of phenylhydrazine instead of triethylamine to neutralize the hydrogen chloride formed.

4-*n*-Butyl-1-cyclopentyl-2-phenyl-3,5-pyrazolidinedione crystallized slowly from methanol (charcoal) in the cold. The yield was 40%, m.p. 79–81°.

Anal. Calcd. for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.88; H, 8.06; N, 9.49.

4-*n*-Butyl-1-cyclobutyl-2-phenyl-3,5-pyrazolidinedione crystallized in 51% yield from methanol–water, m.p. 43–46°.

Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.75. Found: C, 71.43; H, 7.82.

2-Cyclobutylcinchoninic acid.—Cyclobutyl methyl ketone was prepared from cyclobutanecarbonyl chloride and dimethylcadmium.[29] The yield of product of b.p. 52° (15 mm.), $n^{25}D$ 1.4300, was 36%. A solution of 11.8 g. (0.21 mole) of potassium hydroxide, 10.3 g. (0.07 mole) of isatin, and 8.0 g. (0.082 mole) of cyclobutyl methyl ketone in 50 ml. of 50% ethanol was refluxed for 24 hr., then cooled and extracted well with ether. The ether extracts were washed with water, and the washings added to the aqueous layer. The latter was concentrated to half its volume, cooled to 2°, and acidified slowly with glacial acetic acid. The brownish pasty precipitate was washed with water and recrystallized twice (charcoal) from 50% ethanol. The yield of pale tan powder was 9.5 g. (61%), m.p. 179.5–182°. An analytical sample (from 50% ethanol) melted at 181–182°, λ_{max}^{EtOH} 314 mμ.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.76; N, 6.17. Found: C, 74.25; H, 5.58; N, 6.50.

β-Diethylaminoethyl cyclobutanecarboxylate was prepared from molar quantities of cyclobutanecarboxylic acid and β-diethylaminoethyl chloride in 2-propanol solution by the method of Horenstein and Päblicke.[30] The **hydrochloride** crystallized from anhydrous ethyl acetate as hygroscopic nodules, m.p. 106.5–108.5°. The yield was 21%.

Anal. Calcd. for $C_{13}H_{25}NO_2$·HCl: C, 56.04; H, 9.41; N, 5.94. Found: C, 56.21; H, 9.13; N, 5.89.

β-Diethylaminoethyl 2-cyclopropylcinchoninate was prepared similarly from 2-cyclopropylcinchoninic acid.[20] The **hydrochloride** crystallized from 2-propanol, m.p. 176.5–177° dec.

Anal. Calcd. for $C_{24}H_{29}N_3O_2$·HCl: C, 65.41; H, 7.22. Found: C, 65.64; H, 7.24.

4-Amino-2-cyclopropylquinoline.—2-Cyclopropylcinchoninic acid (5 g., 23.4 mmoles) was suspended in 25 ml. of water and 2.5 g. (3.5 ml., 2.5 mmoles) of triethylamine was added with stirring. The clear amber solution was cooled to −5° and a solution of 2.8 g. (2.6 mmoles) of ethyl chlorocarbonate in 15 ml. of acetone was stirred in dropwise, followed by a solution of 2.3 g. (3.5 mmoles) of sodium azide in 25 ml. of water. The azide slowly separated as colorless needles. After stirring at −5° for an additional hour, the azide was extracted into ether, the ether solution was dried ($MgSO_4$) and evaporated under vacuum. The crystalline azide was dissolved in 50 ml. of anhydrous toluene and heated at 95° until nitrogen evolution ceased. The solvent was distilled off under vacuum, leaving a yellowish oil with a typical isocyanate absorption at 4.4 μ. The oil was dissolved in 3.25 g. (3.1 ml., 30 mmoles) of benzyl alcohol and heated at 95° for 30 min. The oily carbamate was mixed with 50 ml. of 10% hydrochloric acid and steam distilled (300 ml.) until the distillate was clear. The residual acidic solution was filtered, the yellowish filtrate was made strongly alkaline, the cream-colored product extracted into ether, dried, and converted to the **hydrochloride** in dry ether solution. Recrystallization from absolute ethanol (charcoal)–ethyl acetate led to a microcrystalline powder, which softened at 125°, resolidified, and melted at 220–221°. The yield was 1.5 g. (27%).

Anal. Calcd. for $C_{23}H_{22}N_2$·HCl·H_2O: C, 60.37; H, 6.33. Found: C, 60.97; H, 6.18.

When the oily isocyanate was hydrolyzed with 90 ml. of 20% hydrochloric acid, a white material precipitated out which did not go into solution during 10 hr. of refluxing. It consisted of **1,3-bis-(2-cyclopropyl-4-quinolyl) urea dihydrochloride.** Recrystalliza-

(28) *Cf.* R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 227.

(29) R. Pinson, Jr., and S. L. Friess, *J. Am. Chem. Soc.*, **72**, 5333 (1950).

(30) H. Horenstein and H. Päblicke, *Chem. Ber.*, **71**, 1044 (1938).

tion from water or ethanol gave a powder which did not melt below 340°.

Anal. Calcd. for $C_{25}H_{22}N_4O\cdot 2HCl$: C, 64.24; H, 5.18; N, 11.99. Found: C, 64.23; H, 5.25; N, 11.65.

From the acidic hydrolysis mixture, only a small amount of the amine (4.5%) was isolated as the hydrochloride.

4-Amino-2-cyclobutylquinoline.—This compound was prepared in a manner similar to that used for the 2-cyclopropyl analog, converting the isocyanate to the benzylcarbamate by heating with excess benzyl alcohol at 95° for 15 min. The carbamate was refluxed with 100 ml. of 1% hydrochloric acid, 50 ml. of 5% hydrochloric acid was added and the solution was distilled (300 ml.). Upon cooling, the carbamate hydrochloride, m.p. 123–125°, crystallized out. The mixture was filtered, the urethan refluxed with 50 ml. of 10% hydrochloric acid for 3 hr., and the acid solution was again steam-distilled and worked up. The colorless microcrystalline powder (yield, 45%) of **4-amino-2-cyclobutylquinoline hydrochloride** melted at 284–284.5° dec. after softening at *ca.* 250°.

Anal. Calcd. for $C_{13}H_{14}N_2\cdot HCl\cdot H_2O$: C, 61.77; H, 6.78. Found: C, 61.90; H, 6.91.

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Synthesis of Phenethylamines Related to Mescaline as Possible Psychotomimetic Agents[1]

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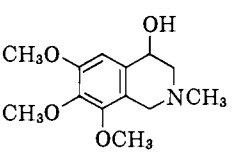
In order to determine the effect of particular structural modifications on the psychopharmacologic properties of mescaline, a series of β-substituted derivatives was synthesized for biologic testing.

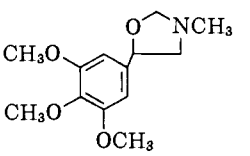
Mescaline, a well-known hallucinogenic agent, produces psychic effects only at very high dosages. Possibly, therefore, a metabolite of mescaline is the active agent. Creveling, *et al.*,[2] have reported that mescaline is converted by dopamine-β-oxidase to β-hydroxymescaline, a compound more closely related to the physiologically very active norepinephrine than is mescaline; and Axelrod[3] has reported that mescaline is N-methylated by an enzyme contained in rabbit lung, a transformation often associated with the formation of psychotomimetic products from naturally occurring compounds. In fact, although mescaline is of plant origin, metabolic products of the type suggested could conceivably be formed by mammals, including man, as abnormal products of tyrosine metabolism. In addition to the two enzymes referred to above, both of which act on a variety of phenethylamines other than mescaline, Axelrod[4] reported that 3,4,5-trihydroxyphenethylamine is transformed by O-methyltransferase to the 3,4-dimethoxy product. There is consequently, biochemical analogy for most of the transformations required.

In order to study their psychopharmacological properties, we have undertaken syntheses of metabolites of this type. We report here the synthesis of β-substituted compounds related to mescaline.

Hydroxymescaline (IV) which had previously been synthesized, was prepared by the reported procedure[5] from trimethoxybenzoic acid (I) through the acid chloride II condensed with cuprous cyanide to give the ketonitrile III which afforded IV on reduction with lithium aluminum hydride. Methylation of the primary amine (IV) with formaldehyde and formic acid by the Leuckart procedure did not give the expected dimethyl compound V.[6] The n.m.r. and infrared spectral data favor 2-methyl-4-hydroxy-6,7,8-trimethoxytetrahydroisoquinoline (XIX) as the structure for the reaction product. The finding of a singlet at 3.25 τ[7] in the aromatic hydrogen region with an intensity exactly one-ninth that of the peak at 6.17 τ produced by the nine methoxyl protons establishes the presence of only one aromatic hydrogen atom in the molecule and supports the assignment of structure XIX. The presence of hydroxyl, indicated by hydroxy proton signals in deuterochloroform which shifted characterically in position from 5.97–6.08–6.53τ with changes in concentration of solution, was confirmed by disappearance of the hydroxy proton signal when the sample was shaken with D_2O and the appearance of a new peak at 5.35τ due to the proton in H–OD formed in the exchange of the benzylic hydroxyl proton. The cyclization of the phenylethanolamine IV to a substituted tetrahydroisoquinoline XIX, postulated here, is analogous to that formulated[8] in the Pictet–Spengler synthesis. These observations rule out the other possible structure for the product, the oxazolidine XX, although cyclization to XX would otherwise seem improbable under these reaction conditions.[9]



XIX



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(9) E. D. Bergmann, *Chem. Rev.*, **53**, 309 (1953). Also, the infrared spectrum of the product did not have the triplet of bands in the 1080–1200 cm.$^{-1}$ region characteristic of the O–C–N system in oxazolidines.