[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF WASHINGTON]

Cycloöctylalkylamines

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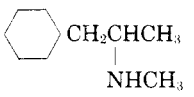
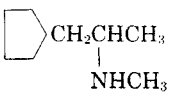
A series of four cycloöctylalkylamines has been prepared from cycloöctanone. These compounds are structurally related to the commercially available sympathomimetic drugs, Benzedrex® and Clopane®. Cycloöctylacetone has been synthesized as an intermediate.

At the present time two cycloalkylalkylamines are commercially available as sympathomimetic drugs, propylhexedrine (Benzedrex®) (I) which contains a six-membered ring, and cyclopentamine (Clopane®) (II) which contains a five-membered ring. In order to obtain more information correlating cycloaliphatic ring size with pharmacological activity, we have undertaken the synthesis of structural analogs which contain larger and smaller

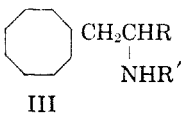


Propylhexedrine (I)



Cyclopentamine (II)

ring systems. The preparation of the cycloheptyl analogs[3] has been reported. In this paper, we report the preparation of the four cycloöctyl analogs that contain the side chains usually associated with greatest activity: the ethylamine (IIIa), N-methylethylamine (IIIb), isopropylamine (IIIc), and N-methylisopropylamine (IIId) groups.



III

a, $R = R' = H$
b, $R = H$, $R' = CH_3$
c, $R = CH_3$, $R' = H$
d, $R = R' = CH_3$

The very convenient ring expansion sequence developed by Dauben and co-workers[4] for the synthesis of cycloheptanone was first tried for the synthesis of the next higher homolog, but none of the desired cycloöctanone was obtained. Blicke and co-workers[5] have reported only a 3% yield of 1-(nitromethyl)cycloheptanol by a similar procedure. In an effort to find the source of difficulty, an attempt was made to isolate the intermediates. After a sample of 1-(nitromethyl)cycloheptanol exploded on attempted distillation at 4 mm. pressure, further study of this method was abandoned in favor of the ring expansion sequence of Tchoubar[6] *via* cycloheptanone cyanohydrin. His method was modified to utilize the convenient reduction of the cyanohydrin by lithium aluminum hydride, as reported by Blicke and co-workers.[5]

Cycloöctanone was condensed with cyanoacetic acid, with ammonium acetate as the catalyst, to produce cycloöctylidenecyanoacetic acid. The double bond apparently rearranged during thermal decarboxylation, to produce cycloöctenylacetonitrile. This shift of the double bond to the β,γ-position has been shown to occur in the analogous compounds with the six-membered ring.[7] The infrared absorption spectrum of our nitrile shows a strong absorption peak at 4.42 microns, which indicates that it is principally the β,γ-unsaturated compound. However, a weak peak at 4.49 microns indicates that there is some of the α,β-unsaturated compound present. It is reported[8,9] that unconjugated nitriles show an absorption peak in the range 4.42–4.46 microns, and that in conjugated nitriles, this peak is shifted to the range 4.48–4.51 microns.

Cycloöctenylacetonitrile was reduced by hydrogen and Raney nickel, in the presence of ammonia, to β-cycloöctylethylamine (IIIa). This amine was converted to the corresponding N-methyl secondary amine (IIIb) by the method of Blicke and Lu,[10] which involves formylation by means of chloral and reduction with lithium aluminum hydride. Cycloöctenylacetonitrile was hydrolyzed to the corresponding acid, and this was catalytically hydrogenated to cycloöctylacetic acid. Both cycloöctenylacetic acid, and cycloöctylacetic acid have been prepared by a different method by Ruzicka and Boekenoogen.[11] The acyl chloride of cycloöctylacetic acid was condensed with the ethoxy-

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(2) Abstracted from the Ph.D. thesis of R. J. Kahl, May 1955.

(3) McCarthy and Brown, *J. Am. Pharm. Assoc.*, **43**, 661 (1954).

(4) Dauben, Ringold, Wade, Pearson, and Anderson, *Org. Syntheses*, **34**, 19 (1954).

(5) Blicke, Azuara, Doorenbos, and Hotelling, *J. Am. Chem. Soc.*, **75**, 5418 (1953).

(6) Tchoubar, *Bull. soc. chim. France*, **216**, 160, 164 (1949).

(7) Kandiah and Linstead, *J. Chem. Soc.*, 2139 (1929).

(8) Miller, in Gilman, *Organic Chemistry*, John Wiley & Sons, Inc., New York, 1953. Vol. 3, page 145.

(9) Kitson and Griffith, *Anal. Chem.*, **24**, 334 (1952).

(10) Blicke and Lu, *J. Am. Chem. Soc.*, **74**, 3933 (1952).

(11) Ruzicka and Boekenoogen, *Helv. Chim. Acta*, **14**, 1319 (1931).

magnesium derivative of malonic ester to produce the corresponding keto-ester which, on acid hydrolysis, smoothly decarboxylated to cycloöctylacetone.[11a] Reductive amination of this ketone in the presence of methylamine, hydrogen, and Raney nickel gave N-methyl-β-cycloöctylisopropylamine[11a] (IIId). The corresponding reduction with ammonia did not give a satisfactory yield of the primary amine[11a] (IIIc), but this compound was obtained by conversion of cycloöctylacetone to its oxime, followed by reduction with lithium aluminum hydride.

The pharmacological testing will be done in the laboratories of the University of Wyoming College of Pharmacy and will be reported elsewhere. Preliminary results indicate that β-cycloöctylisopropylamine (IIIc) has pressor activity in dogs of a magnitude similar to that of Clopane®.

EXPERIMENTAL[12,13]

Cycloöctenylacetonitrile. The method used was similar to that of Cope and co-workers[14] for the corresponding compound with the six-membered ring. From 50.4 g. (0.4 mole) of cycloöctanone[5,6] and 30.4 g. (0.36 mole) of cyanoacetic acid with 0.5 g. of ammonium acetate catalyst, there was obtained 39 g. (63%) of product collected at 135–145° (20 mm.). The analytical sample distilled at 140.5–141.5° (20 mm.); n_D^{25} 1.4864.

Anal. Calc'd for $C_{10}H_{15}N$: N, 9.39. Found: N, 9.01.

β-Cycloöctylethylamine (IIIa). A solution of 6.5 g. of cycloöctenylacetonitrile in 200 ml. of absolute ethanol was saturated with dry ammonia. One teaspoonful of Raney nickel catalyst[15] was added and the hydrogenation was carried out at room temperature at 50 p.s.i. of hydrogen for 22 hours. There was obtained 4.1 g. (67%) of amine, b.p. 115–124° (23 mm.). The analytical sample was collected at 116–117° (23 mm.), n_D^{23} 1.4884.

Anal. Calc'd for $C_{10}H_{21}N$: N, 9.02. Found: N, 8.76.

The *phenylthiourea derivative* was recrystallized from 95% alcohol, m.p. 83–84°.

Anal. Calc'd for $C_{17}H_{28}N_2S$: N, 9.65. Found: N, 9.81.

N-Formyl-β-cycloöctylethylamine. From 9.5 g. (0.062 mole) of β-cycloöctylamine and 9 g. (0.066 mole) of chloral, according to the general method of Blicke and Lu,[10] there was obtained 9.1 g. (81%) of product collected at 150–156° (2 mm.); n_D^{26} 1.5043.

Anal. Calc'd for $C_{11}H_{21}NO$: N, 7.64. Found: N, 7.99.

N-Methyl-β-cycloöctylethylamine (IIIb). N-Formyl-β-cycloöctylethylamine (9 g., 0.05 mole) was reduced with 3.7 g. (0.15 mole) of lithium aluminum hydride[16] in ether. The reaction mixture was worked up in the usual way,[10] and there was collected a yield of 6.8 g. (82%) of amine which distilled at 115–125° (23 mm.). The analytical sample boiled at 121–122° (23 mm.); n_D^{26} 1.4821.

Anal. Calc'd for $C_{11}H_{23}N$: N, 8.27. Found: N, 7.87.

The *phenylthiourea derivative* was recrystallized from dilute alcohol, m.p. 106–107°.

Anal. Calc'd for $C_{18}H_{28}N_2S$: N, 9.20. Found: N, 9.35.

Cycloöctenylacetic acid. A mixture of 38 g. (0.256 mole) of cycloöctenylacetonitrile, 29.1 g. (0.738 mole) of sodium hydroxide, 11 ml. of ethanol, and 145 ml. of water was refluxed in a metal flask for seven days. There was isolated[3] 30 g. (73%) of acid in the fraction collected at 135–140° (2 mm.). Upon redistillation, the analytical sample was obtained at 137–138° (2 mm.); $n_D^{18.5}$ 1.4939.

Anal. Calc'd for $C_{10}H_{16}O_2$; C, 71.39; H, 9.59. Found: C, 70.80; H, 9.53.

The *anilide derivative* was recrystallized from dilute alcohol, m.p. 84–85°.

Anal. Calc'd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70. Found: C, 79.44; H, 8.70.

Cycloöctylacetic acid. One teaspoonful of Raney nickel[15] was added to a solution of 17 g. (0.1 mole) of cycloöctenylacetic acid in 200 ml. of absolute ethanol, and the mixture was shaken at 40° at 50 p.s.i. hydrogen pressure for 21 hours, at which time the theoretical amount of hydrogen had been taken up. A yield of 16 g. (93%) of acid was obtained in the fraction that boiled at 145–152° (2 mm.). A second distillation gave a product that distilled at 149–150° (2 mm.); $n_D^{26.5}$ 1.4800.

Anal. Calc'd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.72; H, 10.64.

The *acid chloride* was obtained by reaction of 13 g. (0.076 mole) of cycloöctylacetic acid with 18 g. (0.15 mole) of thionyl chloride at room temperature for one hour. In order to prevent tar formation, it was found necessary to remove the last traces of excess thionyl chloride by codistillation with benzene under reduced pressure before distillation of the acid chloride was begun. A yield of 13.1 g. (92%) was collected at 123–127° (18 mm.).

The *anilide derivative* was recrystallized from dilute alcohol, m.p. 130–131°.

Anal. Calc'd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45. Found: C, 78.28; H, 9.33.

Cycloöctylacetone. The general method of Walker and Hauser[17] for the synthesis of methyl ketones was used. From 3.8 g. (0.158 g.-atom) of magnesium turnings, 25.3 g. (0.158 mole) of diethyl malonate, and 26 g. (0.138 mole) of cycloöctylacetyl chloride, there was obtained 20 g. (81%) of cycloöctylacetone in the fraction boiling at 120–128° (15 mm.). Upon redistillation, the analytical sample was collected at 124–125° (15 mm.); $n_D^{25.5}$ 1.4663.

Anal. Calc'd for $C_{11}H_{20}O$: C, 78.41; H, 11.98. Found: C, 78.76; H, 11.50.

The *2,4-dinitrophenylhydrazone derivative* was recrystallized from 95% ethanol, m.p. 126–127°.

Anal. Calc'd for $C_{17}H_{24}N_4O_4$: C, 58.60; H, 6.96; N, 16.09. Found: C, 58.71; H, 7.40; N, 15.90.

β-Cycloöctylisopropylamine (IIIc). A mixture of 5 g. (0.033 mole) of cycloöctylacetone, 5 g. (0.09 mole) of hydroxylamine hydrochloride, and 20 g. (0.34 mole) of potassium hydroxide in alcohol was refluxed for two hours, diluted with water, and acidified. The *oxime* separated as an oil and resisted all attempts at crystallization.[18] The oil (6.5 g.) was collected by ether extraction. A solution of 5.5 g. of this oil in absolute ether was reduced with 1.6 g. (0.042 mole) of lithium aluminum hydride and worked up by the usual method. A yield of 3 g. (71%) of amine was collected at 126–131° (20 mm.). A sample further purified for analysis boiled at 126–127° (20 mm.); n_D^{23} 1.4795.

Anal. Calc'd for $C_{11}H_{23}N$: N, 8.27. Found: N, 7.96.

(11a) *Note added in proof.* Since this article was submitted for publication, the preparation of several of these compounds by other methods has been reported by Blicke and Johnson, *J. Am. Pharm. Assoc.*, **45**, 443 (1956).

(12) Melting points are uncorrected.

(13) Cost of chemical analyses has been paid by a grant from the Medical and Biological Research Fund of the State of Washington.

(14) Cope, D'Addieco, Whyte, and Heckert, *Org. Syntheses*, **31**, 25 (1951).

(15) Pavlic and Adkins, *J. Am. Chem. Soc.*, **68**, 1471 (1946).

(16) Nystrom and Brown, *J. Am. Chem. Soc.*, **70**, 3738 (1948).

(17) Walker and Hauser, *J. Am. Chem. Soc.*, **68**, 1386 (1946).

(18) The oxime was also prepared by several other methods, but no crystalline product could be obtained.

The *phenylthiourea derivative* was recrystallized from alcohol, m.p. 67.5–68.5°.

Anal. Calc'd for $C_{18}H_{28}N_2S$: N, 9.20. Found: N, 9.35.

N-Methyl-β-cycloöctylisopropylamine. One teaspoonful of Raney nickel[15] was added to a solution of 10 g. (0.06 mole) of cycloöctylacetone and 6 g. (0.193 mole) of dry methylamine in 100 ml. of absolute ethanol. The mixture was shaken at 50 p.s.i. of hydrogen pressure at room temperature for 36 hours, during which time about two-thirds of the theoretical amount of hydrogen was taken up. The amine was isolated by the usual procedure, and upon distillation, there was collected 6.3 g. (58%) of product at 129–134° (20 mm.). The analytical sample boiled at 131–132° (20 mm.); n_D^{23} 1.4743.

Anal. Calc'd for $C_{12}H_{25}N$: N, 7.62. Found: N, 7.75.

The *phenylthiourea derivative* was recrystallized from alcohol, m.p. 90.5–91.5°.

Anal. Calc'd for $C_{19}H_{30}N_2S$: N, 8.80. Found: N, 8.60.

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