[CONTRIBUTION FROM STERLING-WINTHROP RESEARCH INSTITUTE]

The Preparation of N-γ-Δ¹-Cyclohexenyl-γ-phenylpropylpiperidine Hydrochloride and Related Compounds

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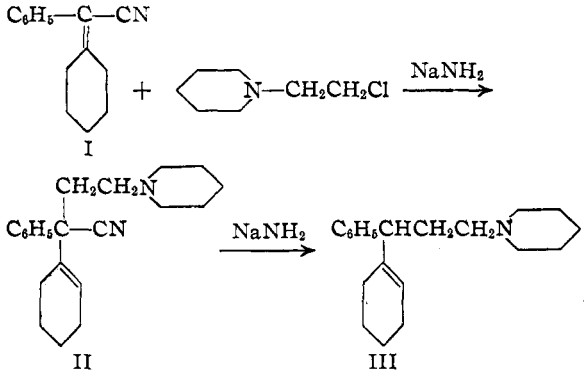
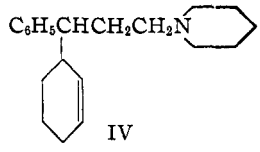
In the course of a program on the synthesis of antispasmodic agents it became desirable to prepare the base III and some related compounds. The method of synthesis is shown in the equations



When cyclohexylidenephenylacetonitrile (I) was alkylated with β-piperidylethyl chloride the basic nitrile II was obtained and isolated as the hydrochloride. The ultraviolet absorption spectrum revealed the disappearance of conjugation, in accord with our expectations. When the basic nitrile II was heated with sodium amide under reflux in xylene,[1] the base III was formed.[2] The ultraviolet absorption spectrum (Fig. 1) did not exhibit any maxima and oxidation of III with potassium permanganate gave no cyclohexanone. It was shown previously that dimethyl-γ-cyclopentylidene-γ-phenylpropylamine exhibited a peak at 246 mμ and on oxidation gave cyclopentanone.[3] When the same reactions were performed with other chloroamines, products analogous to III were obtained (Table I).

The possibility remained that III was actually a Δ²- rather than a Δ¹-cyclohexenyl derivative. The substituted piperidine IV was prepared by a similar series of reactions.



Cyclohexene was brominated by the method of Ziegler and the Δ²-cyclohexenyl bromide[4] then condensed with phenylacetonitrile. Removal of the cyano group gave a base, IV, whose hydrochloride differed markedly from that of III. Thus, the most reasonable structure for the product obtained by the action of sodium amide on the nitrile II is III.

When *m*-methoxyphenylacetonitrile was condensed with cyclohexanone an unsaturated nitrile

TABLE I

HYDROCHLORIDES OF SUBSTITUTED CYCLOHEXENYLALKYLAMINES

Hydrochloride of	Solvent[a]	M. p., °C. (cor.)	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found
α-Δ¹-Cyclohexenyl-α-phenyl-γ-N-piperidyl-butyronitrile	H_2O–HCl	206–207.8					10.28	10.19
γ-Δ¹-Cyclohexenyl-γ-phenylpropylpiperidine	H_2O–HCl	243.8–245.8					11.08	10.85
Diethyl-γ-Δ¹-cyclohexenyl-γ-phenylpropylamine	E–E	127.2–128.8	74.11	73.89	9.82	9.81	11.52	11.50
Dimethyl-γ-Δ¹-cyclohexenyl-γ-phenylpropyl-amine	EtAc	141.6–143.8	72.96	73.20	9.37	9.35	12.67	12.68
Δ-Δ¹-Cyclohexenyl-Δ-phenylbutylpiperidine	EtAc	162.3–164.1	75.53	75.33	9.66	9.84	10.62	10.62
Dimethyl-γ-Δ¹-cyclohexenyl-γ-(*m*-methoxy-phenyl)-propylamine	EtAc	126–128	69.77	69.55	9.11	9.24	11.44	11.33
γ-Δ¹-Cyclohexenyl-γ-(*m*-methoxyphenyl)-propylpiperidine	E–E	192.5–193	72.07	72.06	9.22	9.43	10.13	10.01
α-Δ²-Cyclohexenyl-α-phenyl-γ-N-piperidyl-butyronitrile	E–E	222–225	73.12	73.40	8.47	8.42	10.28	10.04
γ-Δ²-Cyclohexenyl-γ-phenylpropylpiperidine	EtAc	188.4–189.8	75.09	75.35	9.45	9.21	11.08	11.01
γ-Δ²-Cyclohexenyl-γ-phenylpropylpiperidine methiodide	E–E	158.2–160.2	59.29	58.97	7.58	7.01		

[a] H_2O–HCl = dilute hydrochloric acid, E–E = ethanol–ether, EtAc = ethyl acetate.

(1) Report No. PB-981, Office of the Publication Board, Department of Commerce, Washington, D. C.

(2) Dr. A. W. Ruddy of the Laboratory first obtained this compound by another route. It was not an unequivocal synthesis as the position of the double bond was uncertain, THIS JOURNAL, **72**, 718 (1950).

(3) Jackman, Bolen, Nachod, Tullar and Archer, *ibid.*, **71**, 2301 (1949).

(4) Ziegler, Späth, Schaaf, Schumann and Winkelmann, *Ann.*, **551**, 80 (1942).

was obtained. The ultraviolet absorption spectrum showed an inflection at about 245 mμ (Fig. 1) but no definite maximum, in contrast to the well-defined peak shown by I. Although we favor a Δ¹-cyclohexenyl structure for this compound we are aware that a definite assignment of the position of the double bond cannot be made on the basis of this evidence alone. On alkylation with either β-piperidylethyl chloride or β-dimethylaminoethyl chloride the expected nitriles were obtained (no absorption maxima or inflections) which were cleaved with sodium amide to give bases corresponding to III. The spectra of the salts of these compounds showed no hint of a maximum. We did not encounter any of the isomeric cyclohexylidene compounds, although it is possible that they were found in minor amounts.

Experimental[5]

α-Δ¹-Cyclohexenyl-α-phenyl-γ-piperidylbutyronitrile.—To a suspension of 11.7 g. of pulverized sodium amide in 200 ml. of dry toluene there was added slowly 49.3 g. of cyclohexylidenephenylacetonitrile.[6] The temperature was raised to 60° and a solution of 37 g. of β-piperidylethyl chloride was added over a one-hour period. The mixture was heated at 70° for sixteen hours before being treated with a small amount of alcohol. The mixture was poured into water and after the layers were separated the basic nitrile was removed by washing twice with 5% hydrochloric acid. The acid extracts were made basic and the oil was taken up in ether. The solution was concentrated at the pump and the residue warmed with 4 *N* hydrochloric acid. The solution was filtered and cooled. The hydrochloride of II deposited overnight. There was obtained 79.2 g. of the product.

γ-Δ¹-Cyclohexenyl-γ-phenylpropylpiperidine.—A portion of the above hydrochloride was converted to the free base which was taken up in benzene and dried by azeotropic distillation. It weighed 25.8 g. This nitrile was heated for twelve hours under reflux with 40 g. of sodium amide suspended in 250 ml. of toluene. The mixture was worked up as above but the crude base was not converted to the hydrochloride, but distilled instead. The fraction, b. p. 169–172° (1.5 mm.) weighed 13.5 g. The hydrochloride was prepared in dilute hydrochloric acid from which it crystallized in the form of glistening needles, wt. 11.5 g. It did not depress the m. p. of a sample prepared by Ruddy.[2] Most of the cleavage reactions were carried out on the crude basic nitriles rather than on the hydrochlorides thereof.

Δ¹-Cyclohexenyl-*m*-methoxyphenylacetonitrile.—To a solution of 11.5 g. of sodium in 300 ml. of absolute ethanol there was added 73.5 g. of *m*-methoxyphenylacetonitrile. The mixture was cooled to room temperature and 50 g. of cyclohexanone was added dropwise. After stirring for two hours at room temperature the mixture was heated to reflux and poured into ice-water. After the mixture was made acid to congo red, the oil was separated with ether. The solution was washed with water, sodium carbonate solution and again with water. After drying over sodium sulfate the solution was distilled. A middle cut of the fraction, b. p. 210–216° (16 mm.) was analyzed. The product weighed 67.4 g. or 60% of the theoretical.

Anal. Calcd. for $C_{15}H_{17}NO$: N, 6.16. Found: N, 5.93.

Δ²-Cyclohexenylphenylacetonitrile.—One hundred grams of phenylacetonitrile was added slowly with stirring to a suspension of 40 g. of sodium amide in 250 ml. of toluene. After one hour 137.1 g. of Δ²-cyclohexenyl bromide[4] was added at such a rate that the temperature never rose above 30°. After all the halide was added the mixture was stirred for twelve hours. The sodium amide was destroyed with alcohol and the mixture poured into ice-water. The organic layer was washed thoroughly with water and then dried and distilled. The fraction boiling at 165–174° (9 mm.) was collected; wt. 88.2 g. (53%). It was suitable for use in the alkylation step. A middle fraction was analyzed.

Anal. Calcd. for $C_{14}H_{15}N$: N, 7.10. Found: N, 7.09.

(5) Analyses were carried out under the supervision of Mr. M. E. Auerbach.

(6) Harding and Haworth, *J. Chem. Soc.*, **97**, 497 (1910).

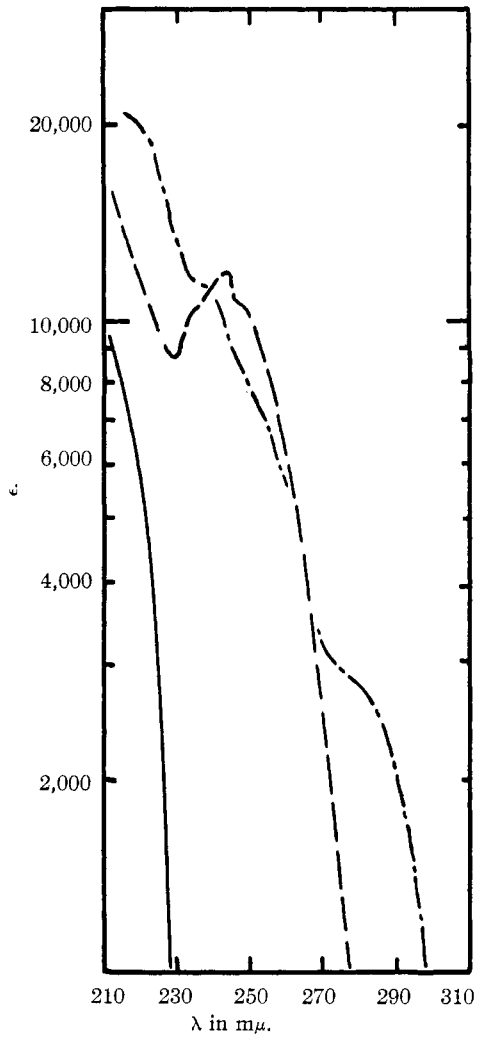


Fig. 1.—Absorption spectra of —·—· Δ¹-cyclohexenyl-*m*-methoxyphenylacetonitrile; — — cyclohexylidenephenylacetonitrile; — N-(γ-Δ¹-cyclohexenyl-γ-phenyl)-propylpiperidine in 95% ethanol.

Summary

γ-Δ¹-Cyclohexenyl-γ-phenylpropylpiperidine and a series of related compounds were prepared by cleavage of the corresponding α-Δ¹-cyclohexenyl-α-aryl-γ-dialkylaminobutyronitriles. The absorption spectrum of cyclohexylidenephenylacetonitrile indicated that the double bond was conjugated with the benzene ring.

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