Synthesis of Some Substituted Piperidones

By PETER A. RATTO* and ARNOLD A. LIEBMAN‡

5,5-Dimethyl-6-hydroxy-6-phenyl-2-piperidone was obtained from a side reaction of a synthetic sequence aimed at the production of analgesics. A series of these hydroxypiperidones has been prepared and their stability toward dehydration studied.

DURING THE preparation of compounds designed to contain the structural requirements for analgesia (1), a side reaction led to a piperidone structure having possible hypnotic or stimulatory properties. This piperidone was prepared by cyanoethylation of isobutyrophenone (I) according to the procedure of Campbell, *et al.* (2), to give 4-benzoyl-4-methylvaleronitrile (II). Hydrolysis of this ketonitrile to the corresponding acid (III) was effected in the described manner (2), and the acid was then treated with thionyl chloride, followed by cold concentrated ammonia solution. The amide that had formed cyclized into a 6-hydroxypiperidone structure (IV), evidenced by infrared and ultraviolet spectra. In hydroalcoholic solution, the material evidently existed as an equilibrium mixture of the δ-ketoamide and the 6-hydroxypiperidone since a semicarbazone derivative was obtainable.

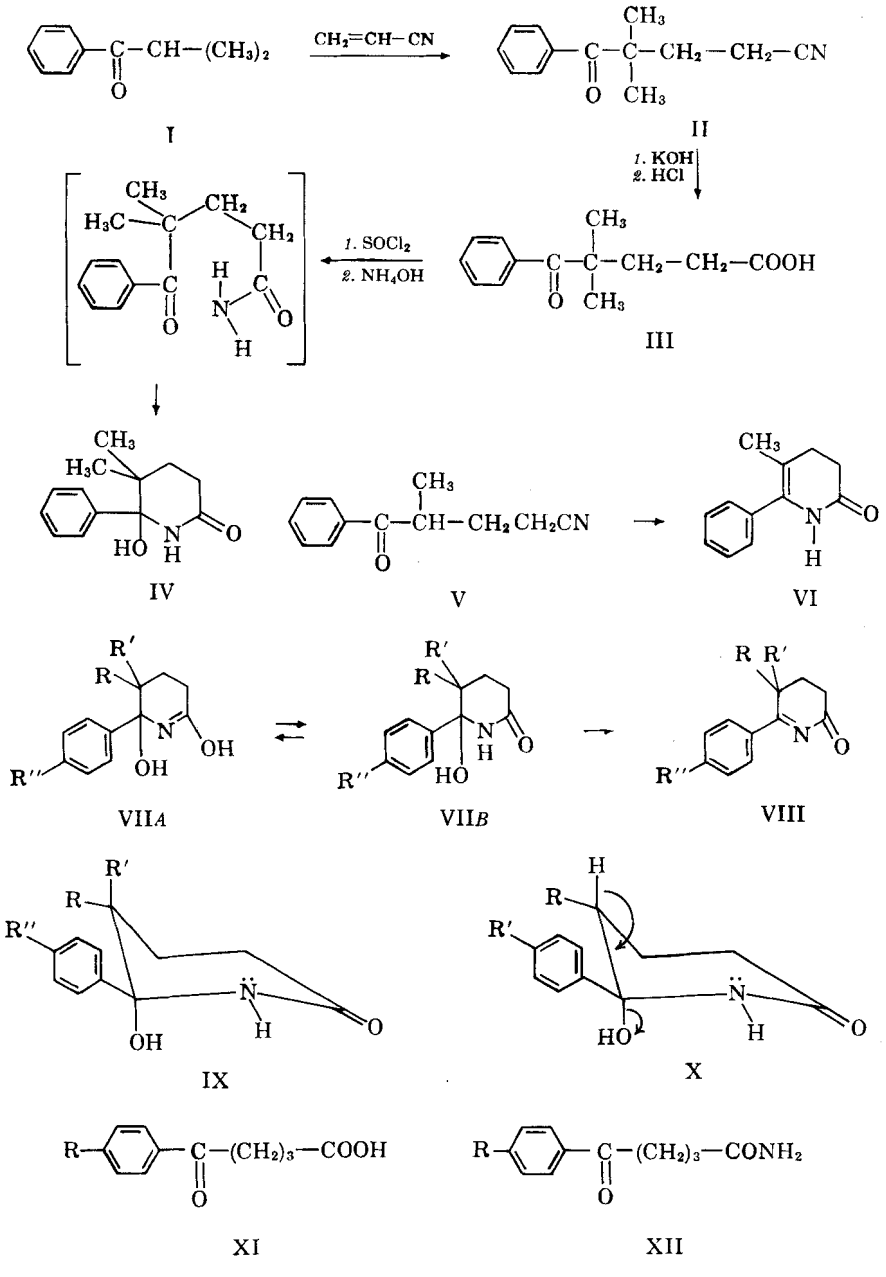
Comparing the structure of the 6-hydroxypiperidone (IV) to phenobarbital or other hypnotics and anticonvulsants, it is noted that the position of the lactam relative to the alkyl substituents suggests possible hypnotic or anticonvulsant activity. On the other hand, the 6-hydroxy-6-phenyl structure, coupled with the hypnotic-producing moiety, could confer convulsive or hypnotic inhibiting activity. In addition to the pharmacological possibilities, the stability of the compound toward dehydration was also of interest.

Several additional ketones were used as starting materials including *p* substituted propiophenones, *p*-substituted isobutyrophenones, α-methylbutyrophenone, and hexahydrobenzophenone. These substances readily underwent cyanoethylation (2, 3) (Table I).

Received May 16, 1963, from the College of Pharmacy, Loyola University, New Orleans, La.
Accepted for publication August 15, 1963.
Supported in part by a grant from the Greater New Orleans Cancer Association.
Presented to the Scientific Section, A.PH.A., Miami Beach meeting, May 1963.
* Present address: Department of Product Development, Bristol Laboratories, Syracuse, N. Y.
‡ Present address: Department of Chemistry, University of California, Berkeley.

To obtain the desired piperidones from the δ-ketonitriles, several approaches were available. Where applicable, treatment of the nitrile with alkaline peroxide represents a quick method (4, 5). Using this procedure, the expected hydroxylactam (IV) was obtained only with 4-benzoyl-4-methylvaleronitrile (No. 4, Table I); the others in this series exhibiting an inertness toward this reagent. However, sulfuric acid hydrolysis of these δ-ketonitriles yielded the expected hydroxylactams as did complete hydrolysis to the acid, followed by acid chloride formation and treatment with aqueous ammonia. Finally, lactams of this type have been realized directly from the ketone by replacing acrylonitrile with acrylamide (6); however, this procedure was not applied to these compounds.

When propiophenone was used as the starting ketone, cyanoethylation yielded the expected product (V). Either by alkaline hydrolysis of the nitrile followed by amidation or direct sulfuric acid hydrolysis, a cyclic dehydro product resulted (VI). The nitriles prepared from *p*-substituted propiophenones (Table I, nos. 2, 3) gave analogous results when converted to their corresponding amides (Table III). In the case of each δ-ketonitrile containing two alkyl groups in the position α to the aroyl substituent, no dehydration occurred with the cyclization. It is conceivable, but improbable, that inhibition of dehydration of these 5,5-dialkylpiperidones could be attributed solely to tautomerization of the lactam. Since the tautomeric structures must include some *VIIB*, dehydration could occur and result in the formation of the highly conjugated system (VIII). In the case of those compounds that underwent dehydration with the cyclization, infrared spectra showed the presence of NH stretching bands, thereby confirming the formation of a carbon-carbon rather than a carbon-nitrogen double bond (VI). Dehydration of those compounds containing two alkyl groups in the 5 position (IX) could not result in the formation of



a similar carbon-carbon double bond without migration of an alkyl group. Therefore, the only hydrogen atom available for direct participation in dehydration of these latter compounds is the lactam hydrogen. Conformationally, the aromatic substituent, by virtue of its greater size, should be predominantly in an equitorial position, placing the hydroxyl group in the axial position. The lactam hydrogen atom may be considered as existing in an equatorial position relative to the unshared pair of electrons about the nitrogen. The combination of this hydrogen's *cis* relationship to the hydroxyl group and the resonance of the lactam carbonyl precludes dehydration under these reaction conditions. On the other hand, with those compounds containing one alkyl substituent in the 5 position of the piperidone ring (X), an axial hydrogen *trans* to the 6-axial hydroxyl group is available, and cyclization also results in dehydration.

Several δ-ketoacids were prepared which contained no alkyl substituents (XI). Subsequent treatment of these compounds with thionyl chloride or ethyl chloroformate, followed by concentrated ammonia solution, yielded the open chain δ-ketoamides (XII) (Table IV). Failure

TABLE I.—δ-KETONITRILES

No.	R	R′	R″	Formula	B.p., °C.[a]	Yield, %	Semicarbazone Formula	M.p., °C.[a]	Carbon, % Calcd.	Carbon, % Found[b]	Hydrogen, % Calcd.	Hydrogen, % Found
1	CH_3	H	H	$C_{12}H_{13}NO$	163–164/10 mm.	60	...	...	77.00	77.27	7.00	6.96
2	CH_3	H	Cl	$C_{12}H_{12}ClNO$	145–147/0.5 mm.	25	$C_{13}H_{15}ClN_4O$	167–168	56.02	56.22	5.43	5.58
3	CH_3	H	CH_3	$C_{13}H_{15}NO$	132–135/0.4 mm.	37	$C_{14}H_{18}N_4O$	134–135	65.10	64.96	7.06	7.18
4	CH_3	CH_3	H	$C_{13}H_{15}NO$	194–200/23 mm.[c]	...	...	...	...	...	7.4[d]	7.0
5	CH_3	CH_3	Cl	$C_{13}H_{14}ClNO$	174–179/2.6 mm.	66	$C_{14}H_{17}ClN_4O$	179–180	57.43	57.57	5.85	6.01
6	CH_3	CH_3	CH_3	$C_{14}H_{17}NO$	147–150/0.8 mm.	54	$C_{15}H_{20}N_4O$	160–161	66.15	66.12	7.40	7.19
7	CH_3	CH_3CH_2	H	$C_{14}H_{17}NO$	148–160/1.2 mm.	62	$C_{20}H_{21}N_5O_4$[e]	130–131	60.75	60.61	5.35	5.41
8	CH_3	CH_3	CH_3O	$C_{14}H_{17}NO_2$	179–186/3.8 mm.	53	$C_{15}H_{20}N_4O_2$	183–185	62.48	62.45	6.99	6.73
9	—$(CH_2)_5$—		H	$C_{16}H_{19}NO$	190–195/2 mm.	39	...	...	79.63	79.64	7.93	7.98

[a] Boiling points and melting points are uncorrected. Melting points were determined with a Thomas Hoover capillary tube melting point apparatus. [b] Microanalyses were performed by the Microanalytical Laboratories, Department of Chemistry, University of California, Berkeley, and by Weiler and Strauss Microanalytical Laboratory, Oxford, England. [c] This is the reported boiling point (2). [d] Reported (2) values for nitrogen. [e] Characterized as the 2,4-dinitrophenylhydrazone derivative.

of these compounds to cyclize may be explained by their lack of alkyl substituents which in turn facilitate ring formation (7).

EXPERIMENTAL[1]

Cyanoethylation.—The appropriate ketone (0.1 mole), potassium hydroxide, 300 mg. (50% aqueous solution), and 75 ml. of *tert*-butanol were treated with 7 Gm. (0.13 mole) of freshly distilled acrylonitrile according to the procedure of Cason and Chang (3). Distillation yielded up to 66% of the δ-ketonitriles (Table I, Nos. 4–9). With propiophenone and *p*-substituted propiophenones, the same procedure was followed; however, a 2:1 *M* ratio of the ketone to acrylonitrile was employed. The yields of cyanoethylated product from these ketones were slightly less (Table I, Nos. 1–3).

Semicarbazone derivatives were prepared in the usual manner (Table I).

Alkaline Hydrolysis.—The appropriate δ-ketonitrile, 0.05 mole, was heated under reflux with 200 ml. of 20% aqueous potassium hydroxide solution until the evolution of ammonia ceased (16–20 hours). The solution was cooled and extracted with 25 ml. of chloroform. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with three 50-ml. portions of chloroform which were then combined and dried with anhydrous calcium chloride. The chloroform was evaporated under reduced pressure leaving 85–90% of the crude acid which was not further purified.

The acid was treated with 11.9 Gm. (0.1 mole) of thionyl chloride dissolved in 50 ml. of anhydrous benzene. The solution was heated under reflux for 1 to 2 hours and the benzene and excess thionyl chloride then removed by distillation under reduced pressure. The residue was cooled and poured slowly with stirring into 25 ml. of cold ammonia solution (28%). The product (60–70%) was filtered, washed with water, and recrystallized from methanol or methanol-water. (Tables II, III.) Infrared spectra of these compounds showed the following peaks. In the case of 5,5-dimethyl-6-hydroxy-6-(*p*-methoxyphenyl)-2-piperidone (No. 5, Table II), 2.8μ (hydroxyl), 3μ (lactam NH), and 6.09μ (lactam carbonyl). Similar spectra were obtained from those compounds in this series containing two alkyl substituents in the 5 position of the piperidone ring. For those compounds containing one alkyl substituent in the 5 position of the piperidone ring, *i.e.*, 5-methyl-6-(*p*-tolyl)-Δ5-tetrahydro-2-pyridone (No. 3, Table III), 2.99μ (lactam NH), and 6.05μ (lactam carbonyl).

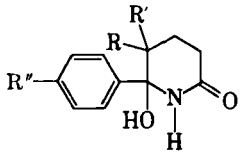
5,5-Dimethyl-6-hydroxy-6-phenyl-2-piperidone Semicarbazone.—The first member of this series (No. 1, Table II) readily formed a semicarbazone derivative in the usual manner. After recrystallization from ethanol, the derivative melted at 219–220°.

Anal.—Calcd. for $C_{14}H_{20}N_4O_2$: N, 20.29. Found: N, 20.33.

Sulfuric Acid Hydrolysis.—One gram of the appropriate δ-ketonitrile was treated with 5 Gm. of concentrated sulfuric acid. The solution was allowed to stand at room temperature for 15 minutes, then poured with stirring into 150 ml. of ice water.

[1] The procedures listed are typical of those used for the preparation of compounds listed in Tables I–IV.

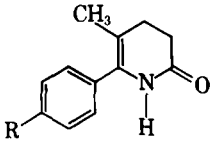
TABLE II.—6-ARYL-5,5-DIALKYL-6-HYDROXY-2-PIPERIDONES



No.	R	R′	R″	Formula	Yield,[a] %	Recrystallizing Solvent	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	CH_3	CH_3	H	$C_{13}H_{17}NO_2$	60.5	Methanol	175–176	71.20	71.45	7.81	7.90
2	CH_3	CH_3	Cl	$C_{13}H_{16}ClNO_2$	64	Methanol	175–176	61.53	61.60	6.36	6.43
3	CH_3	CH_3CH_2	H	$C_{14}H_{19}NO_2$	72	60% Methanol	160–161	72.07	72.44	8.21	8.42
4	CH_3	CH_3	CH_3	$C_{14}H_{19}NO_2$	72	Methanol	172–174	72.07	71.89	8.21	8.13
5	CH_3	CH_3	CH_3O	$C_{14}H_{19}NO_3$	63	60% Methanol	188–190	67.44	67.25	7.69	7.71
6	—$(CH_2)_4$—		H	$C_{16}H_{21}NO_2$	67	Methanol	185–186	74.11	74.39	8.16	8.31

[a] Yields calculated from the nitriles.

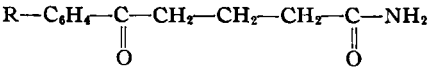
TABLE III.—6-ARYL-5-METHYL-Δ5-TETRAHYDRO-2-PYRIDONES



No.	R	Formula	Yield, %	Recrystallizing Solvent	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	H	$C_{12}H_{13}NO$	72[a]	Methanol	136–136.5	77.00	77.00	7.00	6.96
2	Cl	$C_{12}H_{12}ClNO$	60[b]	Methanol	159–160	65.03	65.09	5.46	5.22
3	CH_3	$C_{13}H_{15}NO$	60[b]	Methanol	146–147	77.60	77.54	7.52	7.60

[a] Yield calculated from the acid. [b] Yields calculated from the nitriles.

TABLE IV.—4-AROYL-BUTYRAMIDES



No.	R	Formula	Yield,[a] %	Recrystallizing Solvent	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	H	$C_{11}H_{13}NO_2$	65	Water	156–157	69.10	69.40	6.85	6.81
2	CH_3	$C_{12}H_{15}NO_2$	90	Water	170–171	70.21	69.96	7.37	7.55
3	CH_3O	$C_{12}H_{15}NO_3$	90	Water	145–146	65.14	65.24	6.83	6.96

[a] Yields calculated from the 4-aroyl-butyric acids.

The crude product (50–60%) was filtered and washed with 5% sodium hydroxide solution. Recrystallization was effected from methanol or methanol-water. Since the yield of product from this reaction was less than that obtained from the two-step procedure previously described, only compounds 2 and 3 of Table III were prepared by this latter procedure.

4-Aroyl-butyric Acids.—The appropriate aromatic hydrocarbon was condensed with glutaric anhydride in the presence of anhydrous aluminum chloride as described by Berliner (8).

4-Aroyl-butyramides.—The appropriate acid (0.005 mole), prepared in the above experiment, was dissolved in 10 ml. of chloroform and the solution neutralized with 0.005 mole of triethylamine. The resulting mixture was chilled to 0°. A solution of 0.005 mole of ethyl chloroformate dissolved in 5 ml. of chloroform was added slowly so that the temperature of the mixture did not rise above 10° (9). The reaction mixture was kept in an ice bath for 30 minutes, after which time 3 ml. of cold concentrated ammonium hydroxide solution was added. A gas evolved followed by the formation of a precipitate. The precipitate was collected and recrystallized from water (Table IV).

REFERENCES

(1) Ratto, P. A., and Oneto, J. F., to be published.
(2) Campbell, A. D., Carter, C. L., and Slater, S. N., *J. Chem. Soc.*, **1948**, 1743.
(3) Cason, J., and Chang, M. P., *J. Org. Chem.*, **21**, 449 (1956).
(4) Snyder, H. R., Buck, J. S., and Ide, W. S., "Organic Syntheses," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 333.
(5) Noller, C. R., *ibid.*, p. 586.
(6) Elad, D., and Ginsberg, D., *J. Chem. Soc.*, **1953**, 4137.
(7) Eliel, E. L., "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 191.
(8) Berliner, E., "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 263.
(9) Barnden, R. C., Evans, R. M., Hamlet, J. C., Hems, B. A., Jansen, A. B. A., Trevet, M. E., and Webb, G. B., *J. Chem. Soc.*, **1953**, 3733.