Epoxy Ethers. XIX. Reaction of 1,2-Epoxy-1-methoxy-2-methyl-1-phenylpropane with Amines

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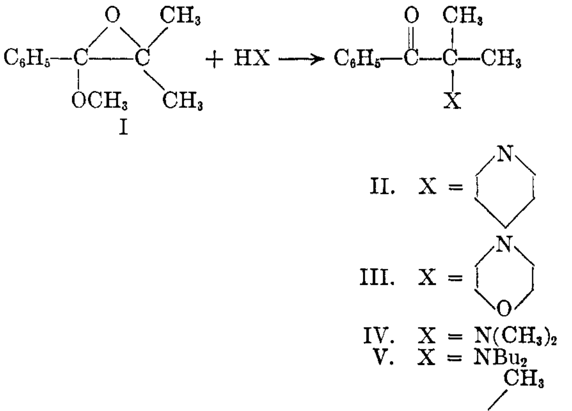
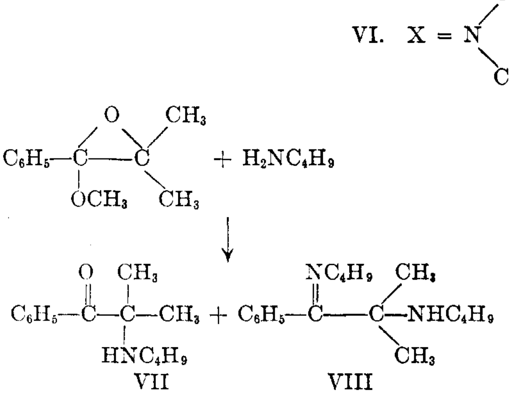
The reaction of epoxy ether I with five secondary amines gave the corresponding α-amino ketones in good yield. The reaction of I with the primary amine, *n*-butylamine, yielded a mixture of VII and a Schiff's base VIII. The amino ketone VII was proven to be the precursor of VIII. The structures of the amino ketones II, III, IV, V, VI, and VII and the Schiff's base, VIII, have been established by chemical and physical data.

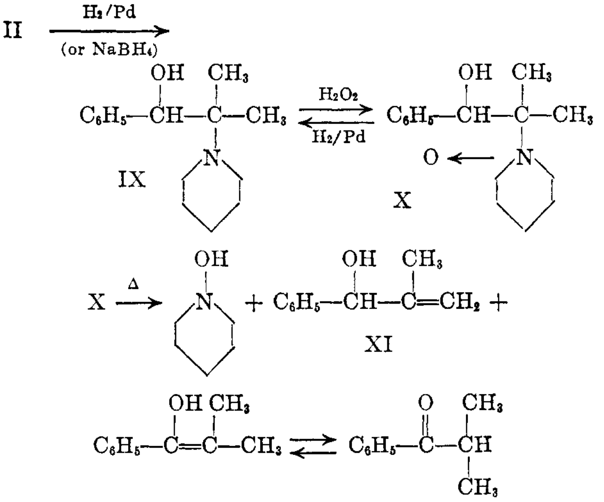
The opening of the epoxide ring of epoxy ethers with amines has not been studied although one example of the reaction has appeared in the chemical literature by Kirrmann and Riehl.[3]

The reaction of 1,2-epoxy-1-methoxy-2-methyl-1-phenylpropane (I) with a number of secondary amines has been shown to give the corresponding α-amino ketones in 38.7 to 92.8% yields. During the reaction of the epoxy ether I with the primary amine, *n*-butylamine, a mixture of the α-amino ketone VII and the corresponding Schiff's base VIII was formed. The latter compound was shown to be formed *via* the reaction of butylamine with the α-amino ketone VII. The reactions are shown in the following equations:





The compounds II–VII inclusive showed conjugated carbonyl groups in the infrared and ultraviolet spectra. The structure of II was further established by degradation and by independent synthesis. Compound II was reduced both catalytically and with sodium borohydride to give the same amino alcohol IX, which was further treated with hydrogen peroxide to give, in quantitative yield, an amine oxide X. Compound X could be catalytically reduced to regenerate the amino alcohol IX or pyrolysed to give isobutyrophenone and N-hydroxypiperidine. No attempt was made to isolate compound XI which should also be formed from the pyrolysis of X.



Compound II could not be prepared by the reaction of α-bromoisobutyrophenone with piperidine or by the reaction of α-piperidinoisobutyronitrile with phenyl Grignard. However, II could be synthesized in fair yield by the reaction of α-piperidinoisobutyronitrile with phenyllithium.

The structure of compound IV was established by degradation *via* pyrolysis of the amine oxide XIII to give N-hydroxydimethylamine and isobutyrophenone. Further proof of structure for IV was had by sodium periodate cleavage of the

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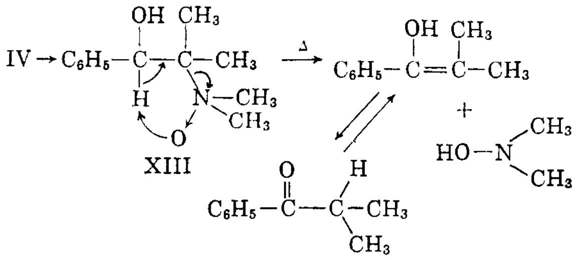
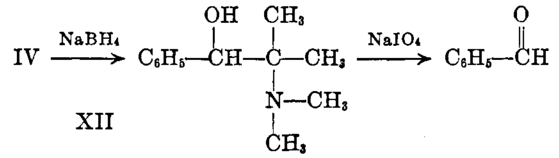
[1] Parke, Davis and Company Research Fellow, September, 1955, to January, 1959.

[2] Abstracted from the dissertation submitted by Charles Hung Chang in partial fulfillment of the requirements for the Degree of Doctor of Philosophy, Wayne State University, January, 1959.

[3] A. Kirrmann and J. J. Riehl, *Compt. rend.*, **243**, 808 (1956). Our first successful reaction of the epoxy ether I with piperidine to give the corresponding α-piperidino ketone, was completed in September, 1955. Prof. Kirrmann reported the use of the reaction to prove the structure of one of his unknown products.

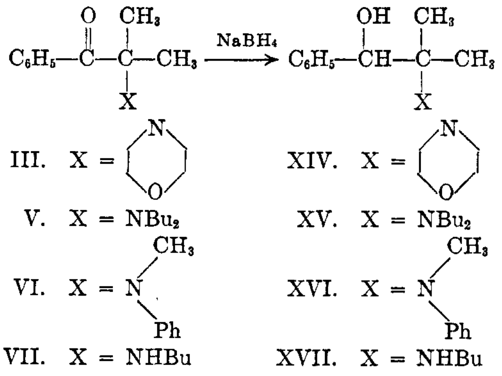


amino alcohol XII resulting from reduction of IV. Benzaldehyde, isolated in 56% yield as its 2,4-dinitrophenylhydrazone derivative, was the only product from the oxidation. The cleavage of compound XII by periodate confirmed the structure as a 1,2-amino alcohol.[4]



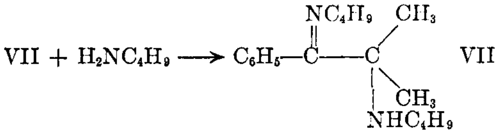
Compound IV has also been prepared by Perrine[5] from the reaction of α-dimethylaminoisobutyronitrile and phenyllithium. Perrine's product and our product had identical physical properties.

Compounds III, V, VI, and VII could be reduced with sodium borohydride to give the corresponding amino alcohols in excellent yields.

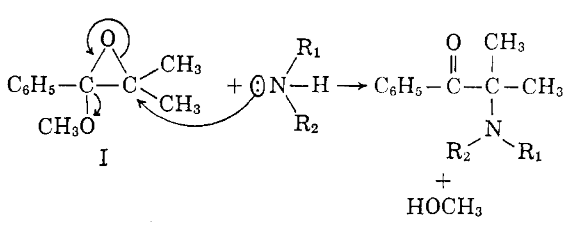


Since the structures of II and IV had been firmly proved by degradation and synthesis, no attempt was made either independently to synthesize or to degrade the other α-amino ketones, III, V, VI, and VII. Rather, assignment of structures to these compounds was made by analogy from the infrared and ultraviolet spectra data shown in Table I.

The structure of VIII was supported by acid hydrolysis which gave the amino ketone VII and butylamine. The amino ketone VII was proved to be the precursor in the formation of VIII by the following reaction. When butylamine and the amino ketone VII were allowed to react, under the identical reaction conditions employed in the reaction of epoxy ether with butylamine, the product was a mixture of VII and VIII in about the same ratio (1:1).



The results obtained from the reaction of the epoxy ether I with various amines allows proposal of the following mechanism:



Experimental

General Procedure for the Reaction of 1,2-Epoxy-1-methoxy-2-methyl-1-phenylpropane (I) with Secondary Amines. Procedure A.—To a flask containing the epoxy ether was added an excess of amine and the reaction mixture was refluxed for 10–20 hr. Distillation through a Vigreux column under reduced pressure gave the corresponding α-amino ketones. Three of the α-amino ketones obtained solidified at room temperature upon scratching and were recrystallized from petroleum ether to give solid products. All of the α-amino ketones obtained showed strong absorption at 5.93 μ in the infrared, except α-morpholinoisobutyrophenone, which showed absorption at 5.96 μ.

Procedure B.—In a glass tube were sealed the epoxy ether I and the lower boiling amine. The sealed tube was heated at the desired temperature for the desired period of time. Distillation through a Vigreux column under reduced pressure gave the α-amino ketones. The results obtained by these general procedures are shown in Table I.

Hydrochloride and Picrate Salts of Some α-Amino Ketones.—The hydrochlorides of some α-amino ketones were made in the usual way by adding isopropyl alcohol saturated with hydrogen chloride to an ether solution of the amino ketone. The precipitate was crystallized from absolute ethanol and ether. The picrates of some α-amino ketones were also prepared in the usual way. Results obtained are shown in Table II.

Reaction of Epoxy Ether I with Monobutylamine.—In a glass tube were sealed 17.8 g. (0.1 mole) of the epoxy ether and 14.6 g. (0.2 mole) of the amine. The sealed tube was heated at 120° for 21 hr. Thereafter, distillation through a glass helices-packed column under reduced pressure gave 10.5 g. (48.9%) of 2-butylamino-2-methylpropiophenone (VII), b.p. 80–85° (0.2 mm.), n^{25}_{D} 1.5022, and 11.0 g. (40%) of N-butyl-β-(butylimino)-α,α-dimethylphenethylamine (VIII), b.p. 85–95° (0.2 mm.), n^{26}_{D} 1.4967. Redistillation of the crude α-amino ketone gave 9.5 g. (44.2%) of pure VII, b.p. 85–87° (0.2 mm.), n^{25}_{D} 1.5052, pK'_a 7.8 (in 50% methanol). The infrared spectrum showed absorption at 3.03 and 5.93 μ. The ultraviolet spectrum showed λ_{max} 241 mμ, ϵ 8190.

Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.66; H, 9.65. Found: C, 76.67; H, 9.44.

Redistillation of the iminoamine through a glass helices-packed column gave 10.5 g. (38.2%) of N-butyl-β-(butylimino-)-α,α-dimethylphenethylamine (VIII), b.p. 94–95° (0.2 mm.), n^{27}_{D} 1.4930, pK'_a 9.3. The infrared spectrum

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[4] B. H. Nicolet and L. A. Shinn, *J. Am. Chem. Soc.*, **61**, 1615 (1939).

[5] T. D. Perrine, *J. Org. Chem.*, **18**, 898 (1953).

TABLE I

REACTION OF 1,2-EPOXY-1-METHOXY-2-METHYL-1-PHENYLPROPANE (I) WITH SOME SECONDARY AMINES

			Product (α-aminoketone)						
Epoxy ether used	Amine used	Procedure and reaction time	Yield, %	Formula	B.p., °C. and n^{25}D	M.p., °C.	Ultraviolet λ_{max}^{EtOH}	Calcd.	Found
10 g. (0.056 mole)	Piperidine 8.59 g. (0.10 mole)	A 17 hr.	91.5	II	95–97 (0.2 mm.) 1.5340	37–38	243 ε 10,900	C 77.87 H 9.15	78.03 9.23
10 g. (0.056 mole)	Morpholine 12.0 g. (0.14 mole)	A 10 hr.	91.5	III	125–127 (0.3 mm.) ...	82.5–84	243 ε 10,700	C 72.07 H 8.21 N 6.00 O 13.71	72.27 8.03 6.29 13.96
9 g. (0.0505 mole)	Dimethylamine 10 g. (0.15 mole)	B 120° 22 hr.	92.8	IV	107–108 (4.5 mm.) 1.5195	...	242 ε 10,300	C 75.35 H 8.95 N 7.32 O 8.36	75.23 8.61 7.50 8.61
10 g. (0.056 mole)	Dibutylamine 9.2 g. (0.07 mole)	A 20 hr.	43.8	V	113–114 (0.2 mm.) 1.5030	...	242 ε 10,300	C 78.49 H 10.16	78.63 10.64
10 g. (0.056 mole)	N-Methyl-aniline 0.2 g. (0.07 mole)	A 20 hr.	38.7	VI	118–122 (0.1 mm.) 1.5857	52–53.4	248 ε 17,700	C 80.59 H 7.56	80.85 7.74

TABLE II

HYDROCHLORIDE AND PICRATE SALTS OF SOME α-AMINO KETONES

	Hydrochloride			Picrate				
		Chloride			Calcd.		Found	
α-Amino ketone	M.p., °C.	Calcd.	Found	M.p., °C.	C	H	C	H
II	...	...	...	166–168	54.77	5.25	54.81	5.52
III	170–172	13.14	13.10	176–177	51.94	4.79	51.85	4.78
IV	190–191	...	...	188–189	...	...	...	...
V	156–157	11.37	11.41	...	...	...	...	...

showed an absorption at 6.03 μ but no absorption in the 5–6-μ region.

Anal. Calcd. for $C_{18}H_{30}N_2$: C, 78.77; H, 11.12; N, 10.21. Found: C, 78.68; H, 11.12; N, 10.38.

Acid Hydrolysis of N-Butyl-β-(butylimino)-α,α-dimethylphenethylamine (VIII).—To a flask containing 5 ml. of 6 *N* hydrochloric acid was added 1.0 g. (0.00364 mole) of the Schiff's base. The reaction solution was heated on a steam bath for 2 hr., then cooled to −76° and a small excess of solid sodium hydroxide added to liberate basic material. The volatile portion, butylamine, was evaporated under reduced pressure and collected in a Dry Ice trap. To the residue left in the flask was added water and the mixture was extracted with two 20-ml. portions of ether. After the ether was evaporated, the remaining brown oil was dissolved in 95% ethanol and reduced with 0.5 g. (0.0132 mole) of sodium borohydride to give 0.76 g. (94.5%) of α-(1-butylamino-1-methylethyl)benzyl alcohol, m.p. 84–85° after crystallization from an alcohol–water mixture. A mixture melting point with the product obtained from the sodium borohydride reduction of VII was undepressed. The infrared spectra were identical, both having an absorption band at 3.0 μ.

The volatile portion which had been collected in the Dry Ice trap, was made acidic with hydrochloric acid and the water was evaporated to give a crystalline residue. The residue was dried twice by the addition of absolute alcohol followed by reconcentration of the solution under reduced pressure in a vacuum desiccator over phosphorus pentoxide. The dried hydrochloride was crystallized from absolute ethanol and ether to yield 0.25 g. (62.8%) of butylamine hydrochloride, m.p. 205–206°. A mixture melting point with an authentic sample of butylamine hydrochloride was undepressed.

Reaction of 2-Methyl-2-butylaminopropiophenone (VII) with Monobutylamine.—In a glass tube were sealed 5.5 g. (0.025 mole) of the amino ketone and 1.82 g. (0.025 mole) of the amine. The reaction solution was heated at 120° for 21 hr. Distillation through a glass helices-packed column gave 1.18 g. (21.4%) of the starting amino ketone, collected at 85–87° (0.2 mm.), n^{25}D 1.5050. The infrared spectrum was identical with that of the starting amino ketone. The second fraction amounted to 1.1 g. of a mixture of 2-methyl-2-butylaminopropiophenone (VII) and N-butyl-β-(butylamino)-α,α-dimethylphenethylamine, (VIII), collected at 87–95° (0.2 mm.), n^{25}D 1.4995; infrared spectrum, 3.02, 5.93, and 6.03 μ. The third fraction amounted to 3.2 g. (47%) of VIII, b.p. 95–96° (0.2 mm.), n^{25}D 1.4938; infrared spectrum, 6.03 μ, which spectrum was identical with that obtained for the higher boiling compound from reaction of 1,2-epoxy-1-methoxy-2-methyl-1-phenylpropane and butylamine.

α-[(1-Substituted Amino-1-methyl)ethyl]benzyl Alcohols; IX, XII, XIV, XV, XVI, and XVII.—A. To an Erlenmeyer flask containing the α-amino ketone in methyl alcohol or ethyl alcohol (95%) was added, portionwise, an excess amount of sodium borohydride. The reaction mixture was allowed to stand at room temperature for the desired period of time. The solvent was then removed under reduced pressure. The residue was decomposed by adding small amounts of water, and the aqueous mixture was extracted several times with ether. The combined extracts were washed with water, dried over sodium sulfate, and filtered. After evaporation of the solvent the solid residue was crystallized from petroleum ether and the liquid residue was distilled under reduced pressure to give the corresponding amino alcohols in excellent yields. The infrared spectrum of the pure products showed absorption in the hydroxyl region but no absorption in the carbonyl region. The results obtained from this reduction are shown in Table III.

B. Hydrochlorides of the amino alcohols IX and XII were prepared in the usual way. Their melting points and analyses are listed below:

		Chloride analysis	
	M.p., °C.	Calcd.	Found
IX·HCl	260–261	13.14	13.17
XII·HCl	222–223	15.43	15.67

TABLE III

REDUCTION OF SOME α-AMINO KETONES WITH SODIUM BOROHYDRIDE

α-Amino ketone				Reaction	Product (α-amino alcohol)					
Formula	Amount	Solvent	$NaBH_4$	time, hr.	Yield, %	Formula	M.p. or b.p., °C.	Infrared μ	Calcd.	Found
II	2 g. (0.00864 mole)	Methanol (15 ml.)	0.65 g. (0.0171 mole)	0.5	99.7	IX	105–106	3.08	C 77.20 H 9.94 N 6.00 O 6.85	77.33 10.01 6.20 7.06
III	2 g. (0.0086 mole)	Methanol (15 ml.)	0.65 g. (0.0171 mole)	.5	99.0	XIV	129–130	3.02	C 71.45 H 8.99 N 5.95	71.29 8.97 5.96
IV	5 g. (0.0261 mole)	Ethanol (100 ml.)	2 g. (0.0528 mole)	.5	100	XII	54–55	3.03	C 74.56 H 9.90 N 7.24 O 8.27	74.58 9.97 7.05 8.25
V	4 g. (0.0145 mole)	Ethanol (30 ml.)	1.3 g. (0.0343 mole)	12	90	XV	b. 130–131 (0.1 mm.) $n^{25}D$ 1.5028	3.06	C 77.92 H 11.12	77.55 11.00
VI	0.5 g. (0.002 mole)	Ethanol (10 ml.)	0.2 g. (0.0053 mole)	24	99.3	XVI	64–65	...	C 79.96 H 8.29	80.03 8.45
VII	0.5 g. (0.0023 mole)	Ethanol (10 ml.)	0.2 g. (0.0053 mole)	24	99.2	XVII	84–85	3.00	C 75.97 H 10.47	76.13 10.49

TABLE IV

AMINE OXIDES X AND XIII AND THEIR PICRATES

Amine oxide					Amine oxide picrate		
Formula	Yield, %	M.p., °C.	Calcd.	Found	M.p., °C.	Calcd.	Found
X	98.2	125–126	C 72.25 H 9.29 N 5.61 O 12.83	72.00 9.25 5.65 12.89	141–142	C 52.71 H 5.47 N 11.71 O 30.09	52.45 5.33 11.84 30.32
XIII	97.0	109–110	N 6.69	6.57	128–129	C 49.31 H 5.06 N 12.78 O 32.84	49.26 5.15 12.98 32.74

C. Catalytic reduction of the α-amino ketone II. To 15 ml. of glacial acetic acid was added 0.4 g. of 5% palladium on barium sulfate and the solution hydrogenated for 1 hr. One gram (0.00432 mole) of II dissolved in 5 ml. of acetic acid was then added to the hydrogenation flask followed by 2 ml. of 72% perchloric acid. The mixture was hydrogenated at atmospheric pressure at 70° for 20 hr., during which time only one equivalent of hydrogen was absorbed. To the reaction mixture was added 2.0 g. of potassium acetate to remove the perchloric acid. The precipitate was separated from acetic acid solution by centrifugation. Part of the acetic acid was removed under reduced pressure at a temperature of 50–60°. The concentrated solution was dissolved in water and made basic with sodium hydroxide solution. The alkaline solution was extracted several times with ether, the combined ether extracts were dried over anhydrous magnesium sulfate, and filtered. After evaporation of the solvent, the residue was crystallized from 95% ethanol to give 0.9 g. (90%) of α-(1-piperidino-1-methylethyl)benzyl alcohol, IX, m.p. 103.5–104.5°. A mixture melting point with the compound obtained from sodium borohydride reduction of II was undepressed. The infrared spectrum of the hydrogenated compound showed absorption at 3.08 μ.

α-[(1-Piperidino-1-methyl)ethyl]benzyl Alcohol N-Oxide (X) and α-[(1-Dimethylamino-1-methyl) ethyl]benzyl Alcohol N-Oxide (XIII).—To a small three-necked flask containing 2.0 g. of the amino alcohol IX or XII in 20 ml. of methanol was added dropwise at room temperature 5.0 g. of 30% hydrogen peroxide. The reaction mixture was stirred at room temperature for 24 hr. and then the excess hydrogen peroxide was decomposed with a few crystals of platinum black. The decomposition was allowed to proceed for 24 hr. at room temperature. The solvent was removed as completely as possible under reduced pressure without external heating. The residue was then dissolved in a small amount of absolute alcohol and the alcohol was removed under reduced pressure to ensure the removal of water. The dried material, soluble in water but insoluble in ether, was crystallized from chloroform and petroleum ether. Picrates of the amine oxides were prepared in quantitative yield from water by adding one equivalent of picric acid. Crystallization from 30% alcohol yielded pure products. The results obtained are listed in Table IV.

Catalytic Reduction of the Amine Oxides X and XIII.—The reduction was carried out in alcohol at room temperature and atmospheric pressure using small amounts of 5% palladium on charcoal as catalyst. The hydrogen absorption was almost quantitative. The products were identical in every respect with authentic amino alcohols IX and XII, respectively. The yield of amino alcohols from this reduction was 81.2% for IX and 85% for XII.

Pyrolysis of the Amine Oxide X.—A round-bottom flask was fitted with a capillary nitrogen inlet through which nitrogen was passed into the flask and then 0.15 g. (0.0006 mole) of the amine oxide was added. The reaction flask was connected with a glass tube to two receivers in series cooled with Dry Ice. The system was evacuated to 5 mm., and the flask was immersed in an oil bath at 100°. The bath temperature was gradually raised to 160° during 10 min. and further raised to 190° for 20 min. to complete the pyrolysis. The collected condensates were dissolved in ether and to the ether solution was added 15 ml. of a saturated solution of anhydrous oxalic acid in ether. Filtration gave

0.11 g. (95.6%) of the oxalate of N-hydroxypiperidine, m.p. 104–110°. Crystallization from absolute ethanol and ether gave 0.1 g. (87%) of pure material, m.p. 109–110°. Rogers[6] reported the melting point of the oxalate to be 104–106°. To the ether filtrate was added 5 ml. of a solution of 2,4-dinitrophenylhydrazine dissolved in hydrochloric acid and methanol. Evaporation of the solution gave 0.02 g. (10.1%) of the 2,4-dinitrophenylhydrazone of isobutyrophenone, m.p. 160–161°. A mixture melting point with an authentic sample was undepressed.

Pyrolysis of the Amine Oxide XIII.—The apparatus set-up and the pyrolysis procedure were the same as those for the pyrolysis of the amine oxide X. After decomposition of the amine oxide the receivers and the pyrolysis flask were washed with pentane. The pentane solution was washed with three 5-ml. portions of 3 *N* hydrochloric acid. The acid solution was extracted with pentane, and the pentane solution was washed with water until neutral. The combined aqueous layers containing hydrochloric acid were concentrated under reduced pressure until a crystalline residue remained. This was dried by the addition of absolute alcohol followed by reconcentration of the solution under reduced pressure in a vacuum desiccator over phosphorus pentoxide. The yield of N-hydroxydimethylamine hydrochloride was 0.05 g. (42.8%), m.p. 101–104° which is in agreement with Cope's results.[7] To the pentane layer was added 5 ml. of 2,4-dinitrophenylhydrazine reagent which was prepared according to the procedure described by Shriner and Fuson.[8] Evaporation of the pentane on a steam bath and filtration gave 0.04 g. (12.7%) of the 2,4-dinitrophenylhydrazone of isobutyrophenone, m.p. 159–161°. A mixture melting point with an authentic sample was undepressed.

Sodium Periodate Cleavage of the Amino Alcohol XII.—To a 50-ml. Claisen distilling flask containing 15 ml. of 0.1 *N* sodium metaperiodate solution was added 0.2 g. (0.001 mole) of the amino alcohol XII. The outlet of the distilling flask was immersed in 5 ml. of 2,4-dinitrophenylhydrazine reagent which was prepared according to Shriner and Fuson's procedure.[8] The solution was allowed to stand at room temperature for 48 hr., after which time a benzaldehyde odor appeared. The reaction solution was then distilled for 2 hr. maintaining the vapor of the reaction mixture below 60° so that acetone but not benzaldehyde would distil. However, some benzaldehyde 2,4-dinitrophenylhydrazone was formed in the hydrazine reagent, and melted at 228–236° without crystallization. The distilled mixture was then extracted with ether and to the ether extract was added 5 ml. of the hydrazine reagent to produce an additional portion of the 2,4-dinitrophenylhydrazone of benzaldehyde, m.p. 230–236° without crystallization. Crystallization of the combined hydrazone derivative gave 0.177 g. (56%) of pure product, m.p. 237–238°. A mixture melting point with an authentic sample of benzaldehyde 2,4-dinitrophenylhydrazone was undepressed. No acetone derivative was observed.

After evaporation of the ether, 0.5 g. of solid sodium hydroxide was added to the extracted solution. The mixture was immediately connected to a Dry Ice trap and lyophylized. To the trap was added 3 ml. of concentrated hydrochloric acid. The acid solution was then evaporated to dryness at room temperature under reduced pressure. A small amount of an unidentified solid, m.p. 218–220°, was obtained after crystallization from alcohol–ether. No dimethylamine hydrochloride was observed.

α-Piperidinoisobutyronitrile.—The aminonitrile was prepared in 73% yield from the reaction of acetone cyanohydrin and piperidine at 50–60° for 2 hr. It has b.p. 98–100° (18 mm.), m.p. 42–45°.[9]

Independent Synthesis of the Amino Ketone II. A. Reaction of α-Piperidinoisobutyronitrile with Phenylmagnesium Bromide.—The Grignard reagent was prepared in the usual way from 2.3 g. (0.095 g.-atom) of magnesium and 14.1 g. (0.09 mole) of bromobenzene. The nitrile, 13.0 g. (0.085 mole), dissolved in 60 ml. of dry ether was added dropwise to the Grignard reagent with stirring. During addition of the nitrile some gelatineous material formed in the reaction flask, making stirring very difficult. After the addition of all the nitrile the reaction mixture was refluxed for 6 hr. without stirring. After evaporation of the ether, the complex was decomposed by adding water and enough hydrochloric acid to make the solution acidic. The acid solution was heated on a steam bath for 1 hr. and then made alkaline with sodium hyroxide solution. After the solution was cooled, it was extracted with three 60-ml. portions of ether. The combined extracts were dried over anhydrous sodium sulfate and filtered. Distillation gave 3 g. (17.3%) of 1-(α,α-dimethylbenzyl)piperidine[10a,b] as a colorless liquid, b.p. 88–90° (0.5 mm.), n^{25}_{D} 1.5210. The infrared spectrum showed no absorption in the 4–5- and 5–6-μ regions.

Anal. Calcd. for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.88. Found: C, 82.94; H, 10.59; N, 6.60.

The picrate of 1-(α,α-dimethylbenzyl) piperidine melted at 190–191°.

Anal. Calcd. for $C_{20}H_{24}N_4O_7$: C, 55.55; H, 5.59. Found: C, 55.57; H, 5.72.

B. Reaction of α-Piperidinoisobutyronitrile with Phenyllithium.—A 500-ml. three-necked flask was equipped with a stirrer and a reflux condenser carrying a nitrogen inlet tube. The apparatus was swept with dry nitrogen and then 50 ml. of dry ether was introduced. While the flow of nitrogen was continued, 2.94 g. (0.42 g.-atom) of metallic lithium, which was cut into small pieces, was added to the flask. Thirty drops of a solution of 31.4 g. (0.2 mole) of bromobenzene in 100 ml. of ether were added to the flask to initiate the reaction. After the reaction had been initiated, the rest of the bromobenzene solution was added at a moderate rate until vigorous boiling began. The mixture was further stirred for 2 hr. at room temperature after all the bromobenzene had been added. The unchanged lithium was filtered under a nitrogen atmosphere. The ether was then removed under reduced pressure and replaced with dry benzene. The benzene solution was evaporated under reduced pressure (water pump) at a temperature of 40° to ensure the removal of all the solvent. Thirteen grams (0.085 mole) of α-piperidinoisobutyronitrile dissolved in 80 ml. dry benzene was added dropwise to the flask under a nitrogen atmosphere. The mixture was stirred for 10 min. during the nitrile addition. The reaction mixture was further stirred at reflux temperature for 1 hr. The resulting complex was hydrolyzed with 20 ml. of water and 150 ml. of 6 *N* hydrochloric acid and then heated on a steam bath for 12 hr. to remove all of the benzene and to ensure complete hydrolysis. The acid solution was made basic with sodium hydroxide and extracted several times with ether. The combined ether extracts were dried over anhydrous sodium sulfate and filtered. Two distillations gave 8.5 g. (42%) of a yellowish oil, b.p. 110–112° (0.5 mm.), n^{25}_{D} 1.5338. The oil solidified at room temperature and the solid was then crystallized from petroleum ether to give a yellowish solid, m.p. 38–39°. The infrared spectrum of the compound showed an absorption band at 5.93 μ. A mixture melting point of this compound with 2-methyl-2-piperidinopropiophenone obtained from the reaction of I with piperidine was undepressed.

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