Anal. Calcd. for $C_{15}H_{17}ON$: C, 79.25; H, 7.54. Found: C, 79.30; H, 7.65.

p-(α-Aminoethyl)-phenyl-2-pyridylmethane.—This compound was prepared by a modification of the procedure described by Ingersoll[6] for the synthesis of α-phenethylamine.

Twenty-one grams (0.1 mole) of p-acetyl-2-benzylpyridine and 25 g. (0.4 mole) of freshly prepared ammonium formate was heated with a free flame in a small round-bottom flask, equipped with a condenser set for distillation and a thermometer extending just above the bottom of the flask. The temperature was raised slowly to 150–155° and after the initial reaction had subsided the temperature was kept at 190–200° for 2 hours. After cooling, the mixture was shaken with water several times to remove the inorganic salts, the water solutions extracted with benzene, and the benzene extracts added to the residue in the flask. The benzene was removed by vacuum concentration on the steam-bath, 150 ml. of concentrated hydrochloric acid added to the residue and the mixture warmed on the steam-bath for two hours. After cooling and basification with concentrated aqueous sodium hydroxide, the organic material was extracted with ether. The ether extracts were combined and washed with water, dried and distilled; yield 11 g. (52.4%), b.p. 154–160° (2 mm.), $n^{28}D$ 1.5762.

Anal. Calcd. for $C_{14}H_{16}N_2$: N, 13.27. Found: N, 13.41.

The p-(α-Dimethylaminoethyl)-phenyl-2-pyridylmethane (VIII).—Ten grams of the amine, described in the preceding paragraph, was dimethylated by the formic acid–formaldehyde procedure. There was obtained 6 g. (55.5%) of a colorless liquid boiling at 157–161° (3 mm.), $n^{27}D$ 1.5592.

Anal. Calcd. for $C_{16}H_{20}N_2$: N, 11.67. Found: N, 12.00.

BLOOMFIELD, NEW JERSEY

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(6) A. W. Ingersoll, "Org. Syntheses," Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 503.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Piperidine Derivatives. XXV. The Reaction of Certain 3-Substituted-1-methyl-4-piperidones with Organometallic Compounds

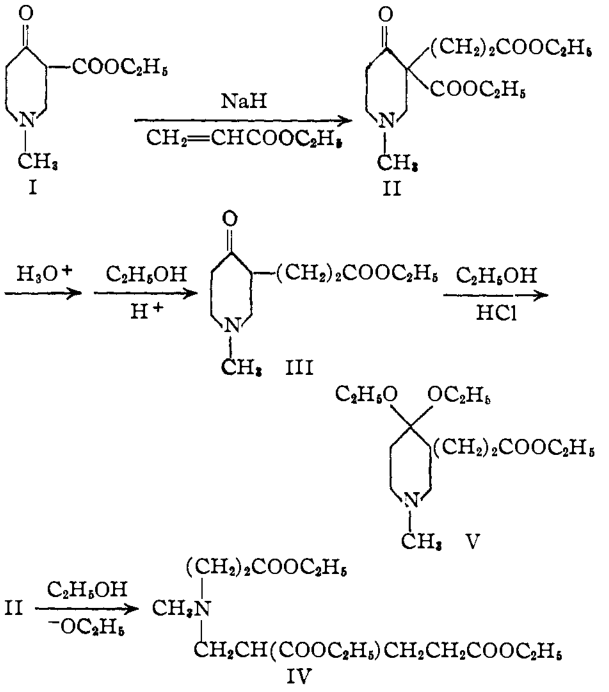
BY S. M. MCELVAIN, WILLIAM B. DICKINSON[1] AND ROBERT J. ATHEY[2]

RECEIVED JULY 15, 1954

1-Methyl-4-piperidones containing the 3-substituents, $-CH_2CH_2R$, in which R is $-COOC_2H_5$ (III), $-CONC_5H_{10}$ (XI), $-CH_2NC_5H_{10}$ (XVII) and $-CH_2OCOC_6H_5$ (XXII), react with phenylmagnesium bromide or phenyllithium to give principally the metal enolate of the ketone; with XVII this is the only reaction. With III the addition of the organometallic compound that does occur takes place on the ester group in preference to or together with addition to the ketone group. With XI and XXII addition of the Grignard reagent occurs only at the ketone group. The 1-methyl-3-substituted-4-phenyl-4-hydroxypiperidines, VIII, XII, XXIII and XXIV, have been isolated and characterized.

The high analgesic activity of certain 4-phenylpiperidines, particularly 1,3-dimethyl-4-phenyl-4-propionyloxypiperidine,[3] indicated that the preparation and pharmacological evaluation of a wider variety of 3-substituted-1-methyl-4-phenyl-4-acyloxypiperidines would be desirable. The present paper reports some work in this direction, in which certain of these types have been prepared in low yields *via* the addition of phenyllithium or phenylmagnesium bromide to the ketonic groups of 1,3-disubstituted-4-piperidones. The main products formed from these reactants, however, were the result of attacks of the organometallic compounds at other more reactive centers of these 4-piperidones.

The keto ester III, which was the principal intermediate in this work, was prepared from the carbethoxypiperidone I by the sequence of reactions shown. The latter keto ester could be used directly as it was obtained from the Dieckmann cyclization of methyldi-(β-carbethoxyethyl)-amine[8] if the precaution was taken to remove the alcohol produced in the cyclization by azeotropic distillation with benzene after neutralization of the reaction mixture with acetic acid. If this precaution was not taken, the reaction product was the triester IV, resulting from the ethanolysis of II in the presence of the base required for its formation. The keto ester III was converted readily to the ketal V; indeed this could be done simply by recrystallization of the hydrochloride of III from ethanol.



The reaction of the keto ester III with phenylmagnesium bromide, either by direct or inverse mixing of the reactants, produced approximately 50% of a magnesium enolate of III as determined by the isolation of both benzene before the enolate was decomposed and of unchanged III after hydrolysis of the initial reaction product. The only other

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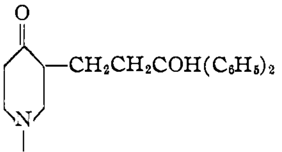
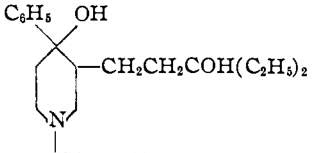
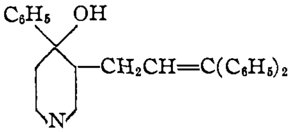
[3] A. Ziering and J. Lee, *J. Org. Chem.*, **12**, 911 (1947).

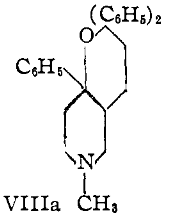
product isolated from this reaction was the diphenylcarbinol VI resulting from the reaction of the Grignard reagent with the ester group of III or its enolate.

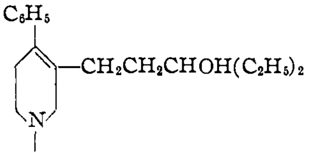
The addition of a solution of phenyllithium to III produced less of the enolization reaction (*ca.* 33% as measured by isolated benzene), and from the work-up of the reaction mixture, after removal of recovered III, an amorphous product believed to have the structure VII was separated in about 45% yield. This product was difficult to purify and did not give satisfactory analyses, but when heated in refluxing 20% hydrochloric acid it was converted in good yield to a crystalline hydrochloride, whose analyses indicate it to be a dehydration product of the amorphous precursor VII. The structure VIII, rather than VIIIa or b, is assigned to this crystalline product on the basis of its infrared and ultraviolet spectra and its ozonolysis to benzophenone in 43% yield.


VI

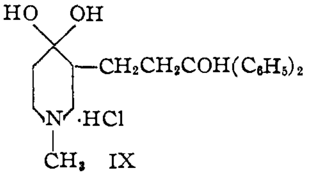

VII

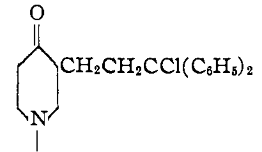

VIII


VIIIa


VIIIb

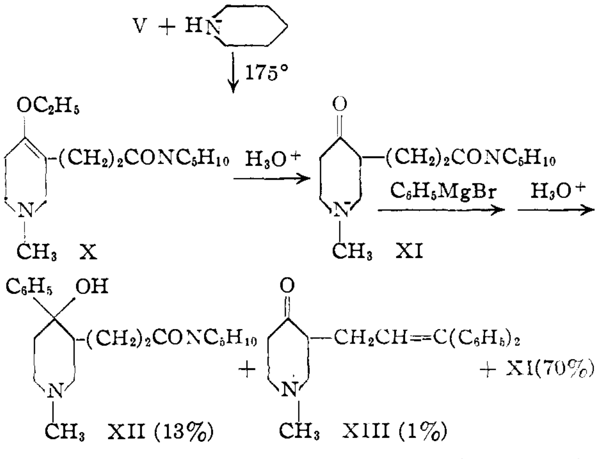
The reaction of phenyllithium with the ketal V in ether solution produced no precipitate such as was obtained immediately when this organometallic compound is mixed with the keto ester III; this behavior indicates that the enolization reaction in the latter case involves the ketone rather than the ester group. Replacement of the ether solvent with petroleum ether left a precipitate of lithium ethoxide. The residual gum remaining after evaporation of the separated petroleum ether solution was completely soluble in 15% hydrochloric acid. Neutralization of this acid solution with potassium carbonate gave a water-insoluble oil which readily dissolved in benzene. However, this benzene solution rapidly became cloudy and within a few minutes contained a crystalline precipitate. This product, which separated in 36% yield, proved to be the *hydrochloride* IX of the hydrate of VI and was apparently formed from the hydrolysis of a water-insoluble, benzene-soluble chloro *free base*, probably the diphenylcarbinyl chloride IXa, which could have formed from the reaction of the hydrochloric acid with the carbinol. The benzene solution from which IX was separated contained 22% of VI, which was identical with the product isolated from the reaction of III with phenylmagnesium bromide, and 40% of III resulting from the hydrolysis of the unreacted ketal V.


IX


IXa

The compounds VI and IX were readily interconvertible: a solution of VI (m.p. 126.5–127.5°) in 20% hydrochloric acid after a few minutes began to deposit crystals of IX; when IX (m.p. 150.5–151.5°) was dissolved in water and this solution neutralized with a small amount of potassium carbonate, pure VI was obtained by recrystallization of the precipitate formed.

The competitive reactivity of the ester function of III with organometallic reagents indicated modification of this group in the hope that its reactivity would be reduced sufficiently for the ketone function to be the only center of reaction. The ketal V was converted to the keto amide XI *via* the enol ether X. The amide XI reacted with phenylmagnesium bromide primarily at the ketone group, but the main reaction (70%) was enolization; only 13% of the phenylcarbinol XII was isolated. The small yield of XIII that was isolated doubtless resulted from the reaction of the Grignard reagent with the enolate[4] of XI rather than by a preferential reaction of the amide group of XI. The ratio of the amounts of XII and XI isolated from this reaction were not significantly changed by an inverse order of mixing the reactants or at temperatures ranging from −50 to 80°. The use of phenyllithium instead of phenylmagnesium bromide did not change the yield of XII.



The carbinol-amide XII is quite stable and could be distilled (b.p. 225° (0.1 mm.)) without decomposition. It was evidently a mixture of isomers as

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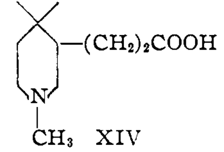
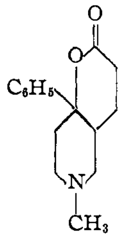
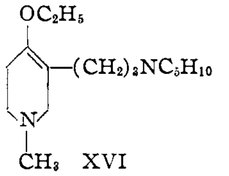
(4) That the enolate of XI was formed rather than a coördination complex of XI with the Grignard reagent was shown by separation of the supernatant ether from the precipitate produced by mixing equivalent amounts of XI and the Grignard reagent and the isolation of 60% of the theoretical amount of benzene from this ether solution. Also XI gave a 58% yield of methane when treated with methylmagnesium iodide.

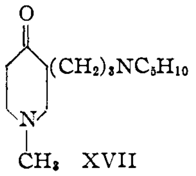
only a 40–45% yield of crystalline hydrochloride or methiodide could be obtained from it; the infrared spectrum of the free base from the crystalline hydrochloride was identical with that of the free base from the non-crystallizable material. The crystalline hydrochloride yielded a crystalline acetyl derivative, which could not be obtained from crude XII.

The amide XII was quite resistant to alkaline hydrolysis but was readily hydrolyzed under acidic conditions. Both the crystalline and the non-crystalline hydrochlorides of XII gave the same amphoteric hydroxy acid XIV, indicating that the 4-hydroxyl group of one of these isomers was epimerized under the acidic conditions of hydrolysis. However, when the crystalline salt of XII was hydrolyzed in 60% sulfuric acid, a 31% yield of a base-insoluble product, whose analyses corresponded to the lactone XV, was isolated.


XIV

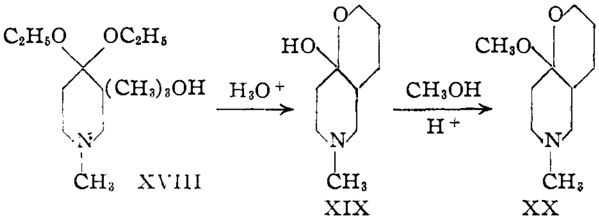

XV

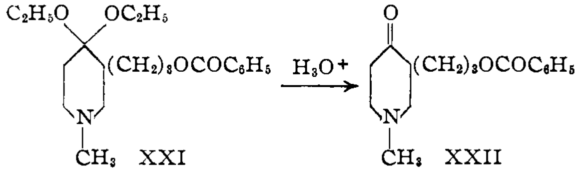

XVI


XVII

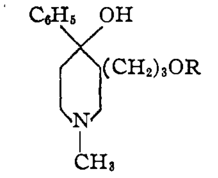
The enol ether X was reduced by lithium aluminum hydride to the corresponding diamine XVI, which was readily hydrolyzed to the keto diamine XVII. This ketone reacted with phenylmagnesium bromide completely by enolization.

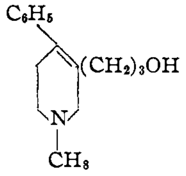
The reduction of the ketal ester V with lithium aluminum hydride gave the hydroxy ketal XVIII, which was readily hydrolyzed in acidic solution. The product was the hemiketal XIX, the structure of which was shown by its infrared spectrum and its conversion to the cyclic ketal XX. The hydroxy ketal XVIII yielded a benzoate XXI, which was hydrolyzed to the ketone XXII.

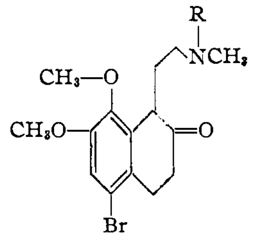




When phenylmagnesium bromide was added to the ketone XXII, the carbinol XXIII was formed in 28% yield; the remainder of the reaction product was unchanged XXII resulting from the enolization reaction. When the order of addition of the reactants was reversed the yield of XXIII was reduced to 10%. When phenyllithium was used instead of the Grignard reagent, only the enolization reaction occurred; none of the carbinol XXIII resulting from the addition reaction could be isolated.


XXIII, R = C_6H_5CO
XXIV, R = H


XXV


XXVIa, R = CH_3
XXVIb, R = tosyl

Only a portion (57%) of the hydrochloride of XXIII could be obtained crystalline; this salt yielded a crystalline acetyl derivative. The hydrolysis of XXIII, as obtained from XXII, in dilute acid gave a quantitative yield of benzoic acid and a 27% yield of the unsaturated amino alcohol XXV. This structure rather than isomeric, bicyclic, tetrahydropyran was indicated by the spectra of the compound. The infrared spectrum of both the free base and the hydrochloride showed a hydroxyl band at 3.00 μ. The ultraviolet spectrum was typical of styrene structures with a single band at 235 mμ, log ϵ_{max} 4.01; the ultraviolet spectrum of the glycol XXIV was typical of benzene derivatives with six distinct peaks in the range of 241 to 267 mμ, the strongest (log ϵ_{max} 2.31) being at 257 mμ.

Saponification of XXIII in 80% ethanol gave the glycol XXIV, a white granular solid, m.p. 161°, in 64% yield (*cf.* 57% of crystalline hydrochloride of XXII). This glycol was recovered unchanged after standing in concentrated hydrochloric acid solution at room temperature for 24 hours. When such an acid solution of XXIV was heated, the glycol was converted to XXV, which was isolated in 50% yield.

It appears from the foregoing results that enolization of the carbonyl group is the principal reaction between a Grignard reagent and the ketones III, XI and XXII and the only reaction with the keto diamine XVII. A similar enolization behavior of the aminoethyltetralone XXVIa with a Grignard reagent was noted by Stork and Conroy[5]; however, the non-basic tosyl derivative XXVIb gave none of the enolization reaction, but instead addition to and reduction of the ketone group. These authors attributed the enolization of XXVIa to the presence of the basic nitrogen in a position to facilitate the removal of a hydrogen in the α-position to the carbonyl group. A similar suggestion has been made to explain the complete enolization of a 4-

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[5] G. Stork and H. Conroy, THIS JOURNAL, 73, 4748 (1951).

piperidylidene cyanoacetic ester by Grignard reagents.[6] The results reported in the present work with the various amino ketones, and particularly with the diamino ketone XVII lend some support to this theory. It seems likely, however, that the basicity of the ketone is not the only factor involved, as 1-methyl-4-piperidone[7] and 1,3-dimethyl-4-piperidone,[3] each of which is as basic as III, XI or XXII, add the Grignard reagent or phenyllithium to give good yields of the corresponding carbinols. It would appear that the various 3-substituents of the 4-piperidones reported in this paper have an associated steric factor which interferes with the normal addition to the carbonyl group, possibly by the interaction of the polar group of the substituent with carbonyl group.

Pharmacological Data.—1-[β-(1-Methyl-4-acetoxy-4-phenyl-3-piperidyl)-propionyl]-piperidine hydrochloride (XIIa) prepared from the crystalline salt of XII and the 1-methyl-3-(3-benzoyloxypropyl)-4-acetoxy-4-phenyl-piperidine hydrochloride (XXIIIa) derived from XXIII were screened for local anesthetic and analgesic action by Messrs. C. L. Rose and E. B. Robbins of The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana. They report for XIIa: LD_{50} mice, 43.9 ± 2.1 mg./kg. (intravenous), 748 ± 43 mg./kg. (subcutaneous), and anesthesia for 16 min. in 1.00% solution in guinea pigs' eyes; XIIa in subcutaneous doses of 10–160 mg./kg. produced no analgesia in rats. For XXIIIa: LD_{50} mice, 35.2 ± 0.07 mg./kg. (intravenous), 765 ± 30 mg./kg. (subcutaneous), and anesthesia for 61 min. in 0.25% solution in guinea pigs' eyes; XXIIIa in doses of 10–160 mg./kg. produced a just measurable analgesia in rats throughout the dose range.

Experimental

1-Methyl-3-carbethoxy-3-(β-carbethoxyethyl)-4-piperidone (II).—In a 500-ml. three-necked flask equipped with a condenser, Hershberg stirrer and dropping funnel was placed 10.8 g. of sodium hydride. After the flask was swept for five minutes with dry nitrogen, 160 ml. of dry, thiophene-free benzene was added to the reaction vessel. From the dropping funnel containing 46.2 g. (0.2 mole) of methyldi-(β-carbethoxyethyl)-amine[8] about 5 ml. of the amine was added to the vigorously stirred suspension of sodium hydride in benzene and 0.4 ml. of absolute ethanol was added through the condenser in order to initiate the reaction. Gentle external heating was employed until the evolution of hydrogen became noticeable. The remainder of the diester was added dropwise at a rate sufficient to keep the benzene at a steady reflux. After the addition of the diester was complete, the flask was heated gently on the steam-bath for one hour, at the end of which time no more hydrogen was evolved. The flask was immersed in a crock of crushed ice and the contents cooled to 5°. Twenty-seven grams of glacial acetic acid was added to neutralize all of the sodium hydride used. A seed crystal of sodium acetate trihydrate was introduced into the flask, followed by dropwise addition of 24.6 ml. of water; crystallization of sodium acetate trihydrate resulted. The solid salt was removed by filtration and washed with two 75-ml. portions of benzene. The washings were combined with the original portion and the benzene–alcohol azeotrope distilled out on the steam-bath. After 215 ml. of distillate had been removed, the refractive index of the distillate indicated that pure benzene was distilling over. Then 5 mole % of sodium hydride (0.25 g.) was added to the alcohol-free solution, and when this had dissolved, 20 g. of freshly distilled ethyl acrylate was added. The reactants were thoroughly mixed and allowed to stand at room temperature for three days and then warmed on the steam-bath for one hour. The product was fractionated from a 125-ml. Claisen flask at reduced pressure. The following fractions were taken: (1) 2.1 g., b.p. up to 145° (1.5 mm.), $n^{25}\text{D}$ 1.4713; (2) 33 g., b.p. 143–145° (0.9 mm.), $n^{25}\text{D}$ 1.4662; (3) 3.9 g., b.p. 143–145° (0.8 mm.), $n^{25}\text{D}$ 1.4646. The last two fractions were taken as **1-methyl-3-carbethoxy-3-(2-carbethoxyethyl)-4-piperidone**. The yield was 65%, based on the amount of methyl di-(β-carbethoxyethyl)-amine used.

Anal. Calcd. for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.13; N, 4.91; C_2H_5O, 31.6. Found: C, 58.85; H, 8.15; N, 5.08; C_2H_5O, 31.5.

A methiodide was prepared in the usual manner and recrystallized twice from absolute ethanol–absolute ether. The solid, after drying two days in a vacuum desiccator, melted at 132–133° (uncor.) when immersed in a bath already heated to 125°.

Anal. Calcd. for $C_{15}H_{26}INO_5$: C, 42.16; H, 6.13. Found: C, 42.03; H, 6.19.

The above reaction was run and sufficient glacial acetic acid (25 g.) was added to the basic reaction mixture to neutralize 92% of the sodium hydride used. Then 20 g. of ethyl acrylate was added and the resultant mixture stirred for 19 hours at room temperature, after which time it was refluxed for 30 minutes. To the cooled benzene solution 2 g. of acetic acid was added to neutralize the remaining base and the product worked up as above to give 50 g. of a pale yellow oil, b.p. 145–160° (0.5 mm.), $n^{25}\text{D}$ 1.4489. A 8.45-g. sample of this liquid was mixed with 100 ml. of water and concentrated hydrochloric acid added to make the solution acid to congo red paper. The solution was shaken vigorously for five minutes, after which it was extracted twice with 75-ml. portions of ether. The acidic solution was made basic with cold potassium hydroxide solution and the separated free amine extracted with ether. The ether extract was dried over anhydrous calcium sulfate and, after removal of the ether, the residual oil was distilled under diminished pressure; 5.53 g. of **methyl-2-carbethoxyethyl 2,4-dicarbethoxybutylamine** (IV), b.p. 137° (0.25 mm.), $n^{25}\text{D}$ 1.4460, d^{25}_4 1.0428, was obtained.

Anal. Calcd. for $C_{16}H_{29}NO_6$: C, 57.98; H, 8.82; C_2H_5O, 40.8. Found: C, 57.98; H, 8.85; C_2H_5O, 40.5.

1-Methyl-3-(2-carbethoxyethyl)-4-piperidone (III).—One mole (285 g.) of 1-methyl-3-carbethoxy-3-(β-carbethoxyethyl)-4-piperidone (II) was placed in a 3-l. flask equipped with a reflux condenser and 950 ml. of 25% hydrochloric acid added. The resulting solution was maintained at a gentle reflux for 27 hours. The remaining hydrochloric acid and water were then removed completely at reduced pressure from the steam-bath. The brown, semi-crystalline solid thus obtained was dissolved in 2.3 l. of absolute ethanol containing 15 ml. of concentrated sulfuric acid and the resulting solution gently refluxed for 30 hours. The condenser then was arranged for downward distillation and about half the alcohol was removed from the steam bath at atmospheric pressure and the remainder removed under reduced pressure. The residual oil was cooled and dissolved in 500 ml. of ice-water. This solution was then saturated with potassium carbonate and the liberated amine extracted with four 250-ml. portions of benzene. Twenty-five grams of Filter-cel was then stirred into the aqueous layer and the mixture filtered to remove the suspended particles of potassium carbonate. The filtrate was extracted again with two 250-ml. portions of benzene. The combined benzene extracts were filtered, and 350 ml. of the solvent was distilled at atmospheric pressure. The remainder was removed at reduced pressure and the residual oil was distilled. The **1-methyl-3-(2-carbethoxyethyl)-4-piperidone** boiling at 106–109° (0.25 mm.) weighed 186 g. (87.5%), $n^{25}\text{D}$ 1.4650.

Anal. Calcd. for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; C_2H_5O, 21.1. Found: C, 61.84; H, 9.20; C_2H_5O, 21.4.

A methiodide of this amine was prepared in the usual manner and recrystallized twice from absolute ethanol–absolute ether. The solid, after thorough drying in a vacuum desiccator, melted at 163–164° when immersed in a bath already heated to 160°.

Anal. Calcd. for $C_{12}H_{22}INO_3$: C, 40.57; H, 6.24. Found: C, 40.79; H, 6.71.

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[6] S. M. McElvain and R. E. Lyle, This Journal, **72**, 384 (1950), *cf.* footnote 8.

[7] S. M. McElvain and J. Safranski, *ibid.*, **72**, 3134 (1950).

[8] S. M. McElvain and K. Rorig, *ibid.*, **70**, 1820 (1948).

Reaction of 1-Methyl-3-(2-carbethoxyethyl)-4-piperidone (III) with Phenylmagnesium Bromide.—To 69.75 ml. of a 1.43 *N* solution of phenylmagnesium bromide in ether under nitrogen was added a solution of 21.3 g. (0.1 mole) of III in 50 ml. of dry ether with stirring and the contents of the flask then refluxed briskly for 30 minutes. The reaction mixture was cooled and decomposed with 50 ml. of 20% hydrochloric acid. The acid solution of the reaction product was poured into a separatory funnel and the solvent layer separated. The acid solution was extracted once with 25 ml. of ether, the two portions of ether were combined and dried over anhydrous calcium sulfate. The dried ether was fractionated through a six-inch column packed with stainless steel wire mesh saddles. The portion boiling at 34°, $n^{25}\text{D}$ 1.3495, was pure ether. The residue was distilled from a small pear-shaped flask through a short Vigreux column; the yield of benzene, b.p. 75–80°, $n^{25}\text{D}$ 1.4884, was 3.7 g. (48%).

Sufficient potassium carbonate solution was added to the acid solution of reaction products to cause precipitation of magnesium carbonate. This solid was separated by filtration and washed once with 20 ml. of water and once with 20 ml. of benzene. Solid potassium carbonate was dissolved in the combined filtrate and washings until an insoluble amine appeared. The upper layer was separated and the remaining alkaline solution extracted three times with 75-ml. portions of ether. These extracts were combined and dried over anhydrous calcium sulfate. Removal of the solvent left 15 g. of oil which was fractionated to yield 7.9 g. (37%) of III, b.p. 92–96° (0.2 mm.), $n^{25}\text{D}$ 1.4669, The residue from this fractionation, which weighed 7.2 g., was dissolved in benzene and placed in the refrigerator. The crystals of 1-methyl-3-(3,3-diphenyl-3-hydroxypropyl)-4-piperidone (VI), which separated from this solution melted at 104–115° and weighed 0.76 g. (4.7%). A sample recrystallized from benzene and dried under reduced pressure at 76° over phosphorus pentoxide melted at 126.5–127°.

Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.40; H, 7.72; N, 4.02.

When the Grignard reagent was added to III and the reaction mixture worked up as described above, a 48% recovery of III and 45% yield of benzene were obtained. When a standardized solution of methylmagnesium iodide in di-*n*-butyl ether was added to III, 54% the theoretical amount of methane was evolved.

Reaction of 1-Methyl-3-(2-carbethoxyethyl)-4-piperidone (III) with Phenyllithium.—To a stirred solution of 21.3 g. of III in 50 ml. of dry ether was added over a period of 45 minutes 103.7 ml. of a freshly prepared 0.965 *N* solution of phenyllithium in ether. The resulting ether suspension of a precipitate was heated at reflux for 30 minutes. The contents of the flask were chilled in an ice-bath and treated with 40 ml. of 20% hydrochloric acid, which converted the reaction mixture to a white, gummy suspension that was difficult to stir; therefore 60 ml. of water was added to the suspension and the product stirred for 1 hour. This mixture, after centrifuging for 20 minutes, separated into three distinct phases: an ether layer, an aqueous acid layer and a solid precipitate. The ether layer was drawn off with a pipet, washed once with 5 ml. of 20% hydrochloric acid and dried over anhydrous calcium sulfate. This solvent portion was fractionated through a six-inch column packed with stainless steel wire mesh saddles. The fraction boiling at 34° (732.2 mm.), $n^{25}\text{D}$ 1.3497, was diethyl ether; the residue was transferred to a small pear-shaped flask and distilled through a short Vigreux column to yield 2.6 g. (33%) of benzene, b.p. 73–79°, $n^{25}\text{D}$ 1.4930.

The acid solution of reaction products was decanted from the precipitated solid in the centrifuge bottle, the solid was washed twice with 10-ml. portions of water, and the washings were combined with the aqueous centrifugate. Sufficient solid potassium carbonate was added to the centrifugate to neutralize the acid and cause separation of a light orange layer of amine. This amine was extracted from the aqueous layer with five 15-ml. portions of benzene, which were combined and dried over anhydrous calcium sulfate. The benzene was removed on the steam-bath, leaving a residue of 5.6 g. of an orange liquid. Fractionation of this liquid gave 3.67 g. (17%) of the original III, b.p. 83–86° (0.07 mm.), $n^{25}\text{D}$ 1.4660.

The remaining aqueous solution from which III had been recovered was filtered and solid potassium carbonate was added until a second oily layer separated from the concentrated aqueous solution. This oil was extracted from the concentrated carbonate solution with two 10-ml. portions of ethanol. The ethanol extracts were combined, dried over anhydrous calcium sulfate and filtered from the potassium carbonate which had precipitated from the ethanol solution. The solvent was removed by a stream of air on the steam-bath. The residual light yellow oil, which weighed 10 g., was not soluble in benzene or ether, nor would it crystallize when dissolved in ethanol and stored in the refrigerator for several weeks. Although this oil could be evaporatively distilled, the distillate was a resinous material which was not identified. The yield of this material calculated on the basis of the weight of the possible organic products was about 30%.

The white solid remaining in the centrifuge bottle was transferred to an evaporating dish and dried under diminished pressure over phosphorus pentoxide. The melting point of the resulting solid was 237–239°, but after standing for a week it melted at 227–229° and weighed 7.7 g.

This solid was mixed with 150 ml. of 20% hydrochloric acid and the mixture heated to reflux. The solid melted to an insoluble oil, which after an hour resolidified into light tan lumps; after 24 hours, however, the solid was entirely in the form of fine white needles. The contents of the flask were cooled, the crystals removed by filtration, washed once with cold water and dried under reduced pressure over phosphorus pentoxide. The yield of **1-methyl-3-(3,3-diphenyl-2-propenyl)-4-phenyl-4-hydroxypiperidine** (VIII) hydrochloride, m.p. 234–236°, was 6.2 g. (45%). A 1-g. sample of this solid was recrystallized from 75 ml. of hot water. The snow-white solid was recovered by filtration and dried carefully at 76° under reduced pressure in the presence of phosphorus pentoxide. This solid, m.p. 238–240°, was taken for analysis.

Anal. Calcd. for $C_{27}H_{20}ClNO$: C, 77.21; H, 7.20; Cl, 8.44. Found: C, 77.28; H, 6.97; Cl, 8.67.

The infrared spectra of VIII and its hydrochloride showed a hydroxyl band at 3.0–3.1 μ and a double bond absorption at 6.1 μ; the ultraviolet spectrum was typical of the benzhydrylidene grouping[9] with a single band at 240 mμ (log $\epsilon_{\text{max.}}$ 4.37) in ethanol.

A solution of 0.173 g. of the hydrochloride of VIII in 10 ml. of ethyl acetate was treated with oxygen containing about 3% ozone at −70° until a blue color[10] appeared (about 10 min.). This solution then was allowed to stand for 30 minutes with 2 ml. of 30% hydrogen peroxide and 3 ml. of a 10% solution of sodium hydroxide, after which the mixture was steam distilled. The distillate was extracted with ether and this extract, after drying, concentrated. The residue on treatment with 2,4-dinitrophenylhydrazine reagent yielded 0.066 g. (43%) of crude 2,4-dinitrophenylhydrazone of benzophenone, m.p. 233–236°, which was not depressed when this material was mixed with an authentic sample, m.p. 237–238°.[11]

1-Methyl-3-(2-carbethoxyethyl)-4,4-diethoxypiperidine (V).—A solution of dry hydrogen chloride in absolute ethanol was prepared and titrated against standard sodium hydroxide. Exactly 17.60 ml. of this 2.86 *N* solution was added slowly to a constantly swirled 200-ml. balloon flask containing a solution of 10.66 g. (0.05 mole) of 1-methyl-3-(2-carbethoxyethyl)-4-piperidone (III) in 25 ml. of dry ethanol. This was just sufficient hydrogen chloride to convert the amine into its salt; an additional 1.00 ml. of the acid solution and 8.9 g. of ethyl orthoformate were added, the contents of the flask heated at gentle reflux for 6 hours and then allowed to stand overnight. About half of the alcohol was removed by distillation and the residue cooled to room temperature. By means of a buret exactly 19.77 ml. of a previously standardized 2.67 *N* solution of sodium ethoxide in dry ethanol was added to neutralize the catalyst and liberate the amine from its salt. Most of the remaining ethanol was removed by distillation under diminished pressure, and the precipitated sodium chloride was separated by centrifugation. The residual salt was washed twice with 10-ml. portions of warm ethanol. The combined centrifugates were distilled at the water-pump to remove the remaining ethanol and ethyl orthoformate, leaving a brown

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(9) *Cf.* E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 2014 (1950).

(10) E. R. H. Jones, *et al.*, *ibid.*, 4890 (1952).

(11) The authors are indebted to Mr. E. J. Eisenbraun for conducting this ozonolysis.

oily amine. This amine, when distilled under vacuum, boiled at 87–92° (0.1–0.2 mm.) and weighed 9.60 g. (67%). A redistilled sample of this material boiling at 88–91° (0.15 mm.), $n^{25}\text{D}$ 1.4567, was analyzed.

Anal. Calcd. for $C_{15}H_{29}NO_4$: C, 62.68; H, 10.17; C_2H_5O, 47.0. Found: C, 62.03; H, 9.73; C_2H_5O, 44.2.

1-Methyl-3-(2-carbethoxyethyl)-4,4-diethoxypiperidine (V) Hydrochloride.—To a solution of 2.87 g. of 1-methyl-3-(2-carbethoxyethyl)-4,4-diethoxypiperidine (V) in 7 ml. of dry ether was added from a buret 5.13 ml. of a 1.95 *N* solution of hydrogen chloride in dry ethanol with continuous swirling. The resulting solution was tightly stoppered and stored in the refrigerator for 45 minutes. The crystals which formed were removed by filtration and washed once with dry ether containing a little ethanol. The solid was dried over phosphorus pentoxide at 76° under diminished pressure for 3.5 hours. The yield of white crystals melting at 135.5–137° was 1.430 g.

The mother liquor from this crystallization was diluted with anhydrous ether and returned to the refrigerator. The resulting crystals were isolated by filtration, washed with anhydrous ether containing a little ethanol and dried under vacuum as before. The white solid weighed 1.252 g., bringing the total yield to 2.682 g. (83%).

Anal. Calcd. for $C_{15}H_{30}ClNO_4$: Cl, 10.95; C_2H_5O, 41.7. Found: Cl, 11.00; C_2H_5O, 41.3.

The above hydrochloride of V also was obtained when the preparation of the hydrochloride of III was attempted by dissolving III in dry ethanol solution of hydrogen chloride. The product that crystallized from this solution on standing had the same m.p. and analyses as the sample described above.

Reaction of Phenyllithium with V.—To a solution of 10.0 g. (0.035 mole) of V in 50 ml. of ether was added 37.7 ml. of a 0.928 *N* solution of phenyllithium (0.035 mole) in ether. No precipitate was formed during this addition. The ether was removed from the resulting solution by distillation to leave a hard yellow resin; this was treated with 50 ml. of Skellysolve A, which dissolved most of the resin in about 2 hours, leaving a light yellow precipitate. The solid was separated after centrifugation and washed four times with 10-ml. portions of Skellysolve A, which were combined with the original centrifugate. The light yellow solid (2.7 g.) was lithium ethoxide.

The Skellysolve A solution of the reaction products was evaporated on the steam-bath and the residue dissolved completely by shaking with 25 ml. of cold 15% hydrochloric acid for 10 minutes. The solution was transferred to a separatory funnel and solid potassium carbonate was added portionwise until all the acid had been neutralized and a red organic oil separated. The water layer was drawn off, and the red oil was diluted with 25 ml. of benzene. The benzene solution soon became cloudy, and within a minute a precipitate had formed in the solution. This insoluble solid was filtered from the benzene solution and washed once with 10 ml. of benzene. When dried under reduced pressure this solid IX melted at 144–147°, and was obtained in 36% yield based on the phenyllithium used. The solid was dissolved in absolute ethanol, filtered and diluted with absolute ether. The resulting crystals, however, even after careful drying, gave a wider melting range (114–140°) than did the unrecrystallized material. Exactly 0.4440 g. of this material melting at 114–140° was placed in a centrifuge tube and washed twice with 7-ml. portions of boiling benzene to leave 0.4276 g. of undissolved **1-methyl-3-(3,3-diphenyl-3-hydroxypropyl)-4,4-dihydroxypiperidine hydrochloride (IX)**, m.p. 150.5–151.5°.

Anal. Calcd. for $C_{21}H_{28}ClNO_3$: C, 66.74; H, 7.47; Cl, 9.38. Found: C, 66.89; H, 7.11; Cl, 9.05.

The benzene solution from which IX was isolated was heated on a steam-bath to remove the solvent. After standing three days this oil deposited a small quantity of white crystals which were isolated by filtration and dried under reduced pressure. The crystals, which weighed 1.2 g., were recrystallized once from benzene and dried at 76° under diminished pressure in the presence of phosphorus pentoxide. The recrystallized solid, m.p. 126.5–127.5°, when mixed with a sample of 1-methyl-3-(3,3-diphenyl-3-hydroxypropyl)-4-piperidone (VI), m.p. 126.5–127.5°, prepared by the action of phenylmagnesium bromide on 1-methyl-3-(2-carbethoxyethyl)-4-piperidone (III), melted at 126.5–127.5°.

Distillation of the residual oil from which VI had crystallized gave 3.00 g. of a liquid boiling at 80–83° (0.05 mm.), $n^{25}\text{D}$ 1.4683. This is a 40% recovery of 1-methyl-3-(2-carbethoxyethyl)-4-piperidone (III) based on the amount of ketal V used.

The Interconversion of VI and IX.—To a solution of 0.5000 g. of IX in 50 ml. of water was added about 0.5 g. of solid potassium carbonate. A gummy precipitate was formed immediately, which on standing for 1 hour in the solution became solid. The solid was broken up with a small glass rod and filtered and dried over phosphorus pentoxide to yield 0.3497 g. (82%), m.p. 122–125°. A single recrystallization from benzene gave VI, m.p. 126.5–127.5°. Mixed melting points with a sample obtained from the reaction of phenylmagnesium bromide with III were not depressed. The reverse transformation was accomplished by dissolving 0.2112 g. of VI in a mixture of 4 ml. of water and 0.8 ml. of concentrated hydrochloric acid. After about a minute, crystals were observed in the clear solution, and after 10 minutes the solid was isolated by filtration and dried over phosphorus pentoxide at reduced pressure. The yield of crude IX was 0.2163 g. (88%), m.p. 146–147°. When mixed with an authentic sample of IX obtained from the action of phenyllithium on V, the m.p. of the mixture was 150–151.5°.

β-(1-Methyl-4-ethoxy-1,2,5,6-tetrahydro-3-pyridyl)-propionylpiperidine (X).—A solution of 10 g. (0.0348 mole) of V in 30 ml. of piperidine, to which 1% water had been added, was heated at 175° for 12 hours in a bomb. The bomb was cooled, opened and the contents distilled from a modified Claisen flask. Two fractions were collected: (a) 2.0 g., b.p. 88–110° (0.15 mm.); (b) 7.0 g., b.p. 130–160°. Fraction a was largely unchanged V (20%); fraction b represented a 72% yield of X. This amide, on redistillation through a 30-cm. Podbielniak column, was a clear, yellow oil, b.p. 147–151° (0.15 mm.), $n^{25}\text{D}$ 1.5080.

Anal. Calcd. for $C_{16}H_{28}N_2O_2$: C, 68.5; H, 10.05; N, 9.96; C_2H_5O, 16.0. Found: C, 68.7; H, 10.02; N, 9.64; C_2H_5O, 16.0.

The methiodide, recrystallized from ethanol–ether, melted at 195–196°.

Anal. Calcd. for $C_{17}H_{31}IN_2O_2$: C, 48.4; H, 7.40; I, 30.0; C_2H_5O, 10.68. Found: C, 48.3; H, 7.65; I, 30.0; C_2H_5O, 11.00.

It was found that little reaction occurred when the experiment was conducted at 150°, and that there was extensive decomposition at 200°.

1-[β-(1-Methyl-4-keto-3-piperidyl)-propionyl]-piperidine (XI).—A solution of 5.0 g. of X in 50 ml. of 5% hydrochloric acid was allowed to stand at room temperature for 45 minutes. It was then treated with a large excess of potassium carbonate, extracted with four 50-ml. portions of benzene and dried over potassium carbonate. On distillation, 3.68 g. (82%) of XI, b.p. 155–160° (0.15 mm.), $n^{25}\text{D}$ 1.5098, was obtained as a yellow oil.

Anal. Calcd. for $C_{14}H_{24}N_2O_2$: C, 66.6; H, 9.57; N, 11.10. Found: C, 66.3; H, 9.40; N, 11.32.

The infrared spectrum contained a strong ketone carbonyl band at 5.90 μ, and a strong amide carbonyl band at 6.16 μ.

The methiodide recrystallized from ethanol–ether had the correct analysis for a dihydrate, and melted at 125–130° with effervescence.

Anal. Calcd. for $C_{15}H_{27}IN_2O_2 2H_2O$: I, 29.6; N, 6.51. Found: I, 29.5; N, 6.35.

A sample of the methiodide, when heated at 90° for 18 hours (0.1 mm.), changed to a hard, extremely hygroscopic glass, with an indefinite, but effervescent, melting point.

Anal. Calcd. for $C_{15}H_{27}IN_2O_2 \cdot H_2O$: I, 30.8. Found: I, 30.6.

Further heating at 135° for 2 hours (0.1 mm.) did not change this analysis.

1[β-(1-Methyl-4-phenyl-4-hydroxy-3-piperidyl)-propionyl]-piperidine (XII) (α-Isomer).—In a 1-l., three-necked flask, equipped with a reflux condenser, stirrer and dropping funnel, 100 ml. of 0.572 *N* phenylmagnesium bromide (0.057 mole) was treated dropwise with 14.36 g. (0.057 mole) of XI, dissolved in 200 ml. of dry ether, over a period of 30 minutes. A white precipitate formed immediately. The precipitate was allowed to settle, and the basicity of a 5-ml. aliquot of the supernatant liquid determined with standard acid, using methyl red as indicator; only one drop of 0.1 *N* hydrochloric acid was required.

The reaction mixture was treated with 200 ml. of 2.5% hydrochloric acid, and the liquid layers separated. The aqueous layer was extracted once with 100 ml. of ether (discarded), then neutralized with excess potassium carbonate, and extracted with six 100-ml. portions of benzene. It was generally necessary to filter the magnesium carbonate in order to prevent emulsion formation. The benzene solutions were combined, dried over potassium carbonate and distilled. Two fractions were obtained: (a) 10.1 g. (70%) of unchanged XI, b.p. 150–170° (0.15 mm.); (b) 2.49 g. (13%) of XII, b.p. 225–230° (0.15 mm.). This material did not crystallize, but cooled to a soft, yellow glass.

A 4.64-g. sample of XII, obtained from additional runs of the above experiment, was converted to the hydrochloride, and recrystallized from amyl acetate or acetone–ether, to avoid ethanol of crystallization. The maximum weight of the hydrochloride that could be crystallized was 2.29 g. (45%), m.p. 181–181.5°.

Anal. Calcd. for $C_{20}H_{31}ClN_2O_2$: C, 65.5; H, 8.52; N, 7.64; Cl, 9.68. Found: C, 65.47; H, 8.52; N, 7.70; Cl, 9.46.

The free base α-XII was liberated from this hydrochloride and, on recrystallization from 90–100° petroleum ether, melted at 109.5–110.5°.

Anal. Calcd. for $C_{20}H_{30}N_2O_2$: C, 72.7; H, 9.15; N, 8.50. Found: C, 72.49; H, 9.37; N, 8.63.

The infrared spectrum of this material in carbon disulfide showed an hydroxyl band at 3.00 μ, and a strong amide carbonyl band at 6.16 μ.

The mother liquor from the recrystallizations of the hydrochloride was concentrated, but the residues could not be induced to crystallize. The free base was liberated from this hydrochloride, redistilled and converted to the hydrochloride, hydrobromide, picrate and trichloroacetate, but none would crystallize. The infrared spectrum of the free base from this hydrochloride proved to be virtually indistinguishable from that of the crystalline isomer.

The methiodide of XII, as obtained from the Grignard reaction, was recrystallized from ethanol–ethyl acetate in 42% yield, m.p. 196–197°.

Anal. Calcd. for $C_{21}H_{33}IN_2O_2$: C, 53.4; H, 7.04; N, 5.93; I, 26.9. Found: C, 53.03; H, 7.12; N, 5.33; I, 26.8.

The crude, distilled amide XII was converted to the picrate, but the only material that could be obtained crystalline was 1,1-diphenyl-3-(1-methyl-4-keto-3-piperidyl)-1-propene (XII), m.p. 231–232°, in 1% yield, based on the Grignard reagent used in the reaction.

Anal. Calcd. for $C_{27}H_{26}O_8N_4$: C, 60.7; H, 4.91; N, 10.50. Found: C, 60.26; H, 5.05; N, 10.70.

When a sample of the crude, distilled amide was dissolved in petroleum ether, and seeded with the crystalline α-isomer of XII, no additional crystallization took place.

The Grignard reaction with XI was repeated, with the following variations: (a) the phenylmagnesium bromide was added to XI; (b) phenyllithium was substituted, using both normal and reverse addition; (c) the temperature was varied over a range of −50 to +80°, the latter using benzene as solvent, in the case of phenylmagnesium bromide; (d) the ketone XI was added to a fivefold excess of phenylmagnesium bromide. However, none of these variations caused any change in ratio of yields of either XI, or the carbinol XII separated from the reaction mixture. In one experiment, the precipitate was filtered before neutralization. On distillation through a 30-cm. Heli-pack column, a 60% yield of benzene was obtained, m.p. *m*-dinitro derivative 88–89°.

1-[β-(1-Methyl-4-phenyl-4-acetoxy-3-piperidyl)-propionyl]-piperidine Hydrochloride (XIIa).—A solution of 3.0 g. of crystalline α-XII hydrochloride, and 1.68 g. of freshly distilled acetic anhydride in 50 ml. of dry pyridine was refluxed for 4.5 hours. The pyridine was then removed from a steam-bath under 15 mm. pressure. The residue was recrystallized once from ethanol–ethyl acetate, and 2.40 g. (72%) of XIIa, m.p. 208–209°, was obtained. The solvent was concentrated and a second crop of 0.93 g. (27%), m.p. 206–209°, was obtained.

The analytical sample, recrystallized from ethanol–ethyl acetate, melted at 208.5–209.5°.

Anal. Calcd. for $C_{22}H_{33}ClN_2O_3$: C, 64.7; H, 8.14; N, 6.86; Cl, 8.69. Found: C, 64.34; H, 8.17; N, 6.56; Cl, 8.62.

The uncrystallizable hydrochloride of XII was acetylated under similar conditions, but the acetate ester failed to crystallize. Similarly, the distilled mixture of the isomeric forms of XII also was acetylated, but no crystalline material could be obtained.

Reaction of XI with Methylmagnesium Iodide.—In a 250-ml., three-necked flask, equipped with dropping funnel, sealed stirrer and reflux condenser, was placed a solution of 1.81 g. (0.00719 mole) of XI in 200 ml. of dry ether. A gas-measuring apparatus was connected to the reflux condenser, and from the dropping funnel was added 22.6 ml. (0.00719 mole) of 0.318 *N* methylmagnesium iodide, over a period of 5 minutes. The volume of methane evolved was 105 ml. (0.00415 mole, 58%), measured over saturated brine at 22° and 740 mm. pressure.

1-(1-Methyl-4-ethoxy-1,2,5,6-tetrahydro-3-pyridyl)-3-(1-piperidyl)-propane (XVI).—A solution of 5.0 g. of the enol ether X in 50 ml. of dry ether was added dropwise to a stirred solution of 0.5 g. of lithium aluminum hydride in 100 ml. of dry ether, in a 250-ml. three-necked flask equipped with a stirrer, reflux condenser and dropping funnel. When the addition of the amide was complete, the suspension was stirred for 30 minutes, after which time 50 ml. of water was added cautiously. The solutions were separated in a separatory funnel, and the aqueous layer extracted with four 50-ml. portions of ether. The organic layers were combined and dried over potassium carbonate. On distillation, 419 g. (88%) of the diamine XVI, b.p. 127–128° (0.2 mm.), $n^{25}D$ 1.4861, was obtained.

The methiodide, recrystallized from ethanol–ethyl acetate, melted at 189–189.5° with effervescence.

Anal. Calcd. for $C_{18}H_{36}I_2N_2O \cdot EtOH$: C_2H_6O, 15.1; I, 42.6. Found: C_2H_6O, 14.6; I, 42.4.

1-(1-Methyl-4-keto-3-piperidyl)-3-(1-piperidyl)-propane (XVII).—A solution of 13.0 g. of the enol ether X, in 100 ml. of dry ether, was added dropwise to a solution of 1.5 g. of lithium aluminum hydride in 100 ml. of dry ether, in a 500-ml. three-necked flask, equipped with a stirrer, dropping funnel and reflux condenser. The reaction was allowed to stir for 30 minutes, and was then neutralized with 100 ml. of water containing 10 ml. of concentrated hydrochloric acid (caution). The layers were separated and the aqueous solution allowed to stand for 15 minutes, after which time it was treated with a large excess of potassium carbonate and extracted with five 100-ml. portions of benzene. The benzene solutions were combined and dried over potassium carbonate. Upon distillation, 7.83 g. (62%) of the ketone XVII, b.p. 127–130° (0.2 mm.), $n^{25}D$ 1.4908, was obtained as a clear viscous liquid.

Anal. Calcd. for $C_{14}H_{26}N_2O$: C, 70.5; H, 11.00; N, 11.75; neut. equiv., 119. Found: C, 70.26; H, 10.91; N, 11.58; neut. equiv., 121.

Reaction of Phenylmagnesium Bromide with XVII.—To 23.4 ml. (0.0210 mole) of 0.896 *N* phenylmagnesium bromide was added dropwise a solution of 5.00 g. (0.0210 mole) of XVII in 50 ml. of dry ether. A white precipitate formed immediately, and did not appear to undergo any change. After 10 minutes additional stirring, the reaction was neutralized with 50 ml. of water containing 10 ml. of concentrated hydrochloric acid. The solutions were separated and the aqueous layer extracted once with ether (discarded). The aqueous solution was treated with a large excess of potassium carbonate, the magnesium carbonate filtered, and the solution extracted with four 100-ml. portions of benzene. The combined benzene solutions were dried over potassium carbonate, and upon distillation, 4.10 g. (82%) of the ketone XVII, b.p. 125–130° (0.2 mm.), $n^{25}D$ 1.4925, was obtained. No higher-boiling product was present.

β-(1-Methyl-4-phenyl-4-hydroxy-3-piperidyl)-propionic Acid (XIV).—A solution of 1.60 g. of the α-form of XII in 15.00 ml. of 2.990 *N* sulfuric acid was refluxed for 7 hours. The solution was neutralized with 150.0 ml. of 0.3454 *N* barium hydroxide, and extracted with four 100-ml. portions of benzene. Evaporation of this benzene extract left no noticeable residue. The aqueous solution was steam distilled until the distillate was no longer alkaline to litmus; the residual solution was then treated with 2.31 ml. of 2.990 *N* sulfuric acid, and the barium sulfate filtered. The filtrate had a *p*H of approximately 5 (*p*H paper). The water was evaporated, and the residue converted to the picrate. Upon recrystallization from toluene–acetone, 1.74 g. (73%) of the picrate of the hydroxyacid XIV, m.p. 189–190°, was obtained.

Anal. Calcd. for $C_{21}H_{24}N_4O_{10}$: C, 51.30; H, 4.91. Found: C, 51.44; H, 5.17.

The distillate was neutralized to methyl red with standard hydrochloric acid, and was found to contain 0.00428 mole (89%) of piperidine. The hydrochloride was recovered by evaporation, and on recrystallization from ethanol–ethyl acetate, melted at 244–245°. The melting point of authentic material was not depressed.

A sample of the uncrystallizable isomer of XII was subjected to the above hydrolysis, and a 75% yield of a picrate, m.p. 189–190°, was obtained on recrystallization from toluene–acetone. It did not depress the melting point of the picrate from the α-isomer described above.

β-(1-Methyl-4-phenyl-4-hydroxy-3-piperidyl)-propionic Acid Lactone (XV).—A solution of 0.5 g. of the hydrochloride of the α-isomer of XII and 3 ml. of water in 3 ml. of concentrated sulfuric acid was refluxed for 2.5 hours, during which time the solution turned a deep purple. This solution was cooled and diluted with 50 ml. of water, made strongly alkaline with potassium carbonate and extracted with four 50-ml. portions of benzene. The benzene solution was dried over potassium carbonate, evaporated and the residue dissolved in ether and converted to the hydrochloride. On filtration, 0.12 g. (31%) of the lactone hydrochloride was obtained. On recrystallization from ethanol–ethyl acetate, pale yellow plates, m.p. 282–283°, were obtained.

Anal. Calcd. for $C_{15}H_{20}ClNO_2$: C, 64.0; H, 7.16. Found: C, 63.45; H, 7.24.

1-Methyl-3-(3-hydroxypropyl)-4,4-diethoxypiperidine (XVIII).—A solution of 7.5 g. of lithium aluminum hydride in 500 ml. of dry ether was placed in a 1-l. three-necked flask, equipped with dropping funnel, reflux condenser with calcium chloride tube and stirrer. From the dropping funnel was added dropwise a solution of 75 g. of the ketal ester V in 100 ml. of dry ether. The precipitate was gelatinous, and efficient stirring was difficult toward the end of the reaction. When the addition of V was complete, the suspension was allowed to stir for 15 minutes and then was treated with 100 ml. of water (caution). The layers were separated in a separatory funnel and the aqueous layer extracted with four 100-ml. portions of ether. The combined ethereal solutions were dried over potassium carbonate, and upon distillation, 55.3 g. (87%) of XVIII, b.p. 113–115° (0.2 mm.), $n^{25}\text{D}$ 1.4683, was obtained as a colorless liquid.

Anal. Calcd. for $C_{13}H_{27}NO_3$: C, 63.7; H, 11.10; N, 5.71; C_2H_5O, 36.8. Found: C, 63.2; H, 11.0; N, 5.75; C_2H_5O, 36.0.

The methiodide, recrystallized from ethanol–ethyl acetate, melted at 158–159°.

Anal. Calcd. for $C_{14}H_{30}INO_3$: C, 43.50; H, 7.77; N, 3.62; C_2H_5O, 23.2; I, 32.8. Found: C, 43.30; H, 7.82; N, 3.55; C_2H_5O, 23.6; I, 32.6.

1-Methyl-3-(3-hydroxypropyl)-4-piperidone Hemiacetal (XIX).—XVIII was prepared as described above from 50 g. of V, and 5 g. of lithium aluminum hydride. At the point where the reaction mixture had been treated with water, the aqueous solution was made acid to congo red with hydrochloric acid, and the solutions thoroughly shaken. The organic layer was discarded, and the aqueous solution allowed to stand for 30 minutes. It was then treated with an excess of potassium carbonate, extracted with four 150-ml. portions of benzene and the benzene solution dried over potassium carbonate. On evaporation, 23.5 g. (80%) of the hemiacetal XIX was obtained. On recrystallization from 90–100° petroleum ether, the material was obtained as a white granular solid, m.p. 110–111°, with previous softening. This compound could be sublimed readily at 110° (0.1 mm.).

Anal. Calcd. for $C_9H_{17}NO_2$: N, 8.18. Found: N, 8.65.

The infrared spectrum (chloroform) contained a hydroxyl band at 2.81 μ, but only a slight dip in the ketone carbonyl region at 5.90 μ.

The methiodide, recrystallized from ethanol–ether, melted at 177–178°.

Anal. Calcd. for $C_{10}H_{20}INO_2$: I, 40.5. Found: I, 40.3.

The Reaction of Phenylmagnesium Bromide with XIX.—In a 500-ml., three-necked flask, equipped with a stirrer, dropping funnel, and reflux condenser with calcium chloride tube, was placed a solution of 5.0 g. (0.0292 mole) of XIX, in 122 ml. of dry ether and 50 ml. of dry benzene. To it was added 78 ml. of 0.751 *N* phenylmagnesium bromide (0.0584 mole), and the white precipitate that immediately formed stirred for 1 hour. The precipitate was allowed to settle, and an aliquot of the supernatant solution was removed for titration with standard acid. It was found that half the Grignard reagent was still present in the solution. After 4 hours at reflux, the titer did not change. The suspension was treated with 50 ml. of 25% acetic acid, and the layers separated in a separatory funnel. The aqueous layer was extracted once with ether (discarded), treated with excess potassium carbonate and extracted with four 50-ml. portions of benzene. On evaporation, 3.50 g. (70%) of unchanged XIX was obtained. The residue was extracted with 10 ml. of ether, and the ether evaporated, but there was no noticeable residue.

2-Methyl-4a-methoxy-5-oxa-perhydroisoquinoline (XX).—A solution of 10.13 g. (0.0593 mole) of XIX in 100 ml. of dry methanol was treated with 11.00 ml. of 6.67 *N* hydrogen chloride (0.0733 mole) in methanol, and the solution refluxed for 2 hours. It was cooled, treated with a solution of sodium methoxide, prepared from the reaction of 1.69 g. of sodium with 25 ml. of dry methanol, the precipitated sodium chloride was filtered and washed with methanol. On distillation 9.26 g. (85%) of the methyl ether XX, b.p. 67–78° (0.5 mm.), $n^{25}\text{D}$ 1.4751, was obtained.

Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 64.8; H, 10.32; N, 7.56; C_2H_5O, 16.73. Found: C, 64.86; H, 10.31; N, 7.50[12]; C_2H_5O, 14.9.

The methiodide, recrystallized from ethanol–ethyl acetate, melted at 209–210°.

Anal. Calcd. for $C_{11}H_{22}INO_2$: N, 4.28; I, 38.8. Found: N, 4.23; I, 38.7.

1-Methyl-3-(3-benzoyloxypropyl)-4,4-diethoxypiperidine (XXI) Hydrochloride.—A solution of 5.0 g. (0.02 mole) of XVIII in 20 ml. of dry pyridine was carefully treated with a solution of 2.87 g. (0.02 mole) of benzoyl chloride in 10 ml. of dry pyridine. The mixture was then heated on the steam-bath for 1 hour, during which time the solution became a reddish-yellow. The pyridine was removed under aspirator vacuum, and the semi-crystalline residue recrystallized from ethanol–ethyl acetate. On filtration, 5.51 g. (70%) of the hydrochloride of XXI, m.p. 147–147.5°, was obtained. A second crop of 0.83 g. (11%), m.p. 130–138°, was obtained from the mother liquor.

Anal. Calcd. for $C_{20}H_{32}ClNO_4$: Cl, 9.20; C_2H_5O, 23.4. Found: Cl, 9.13; C_2H_5O, 22.8.

1-Methyl-3-(3-benzoyloxypropyl)-4-piperidone (XXII).—A solution of 16.21 g. of XVIII in 75 ml. of dry pyridine was treated with a solution of 9.30 g. of benzoyl chloride in 25 ml. of dry pyridine, as described above. The resulting pyridine solution was concentrated to 50 ml. on a steam-bath under aspirator vacuum, and the hydrochloride of XXI precipitated by the addition of 250 ml. of ether. The salt was dissolved in 100 ml. of water, acidified to congo red with hydrochloric acid and warmed to effect solution. After standing for 1 hour, the solution was extracted once with benzene (discarded), treated with excess potassium carbonate and extracted with four 100-ml. portions of benzene. The benzene solution, after drying, was distilled to yield 15.51 g. (85%) of XXII, b.p. 162–167° (0.1 mm.), $n^{25}\text{D}$ 1.5248.

Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.6; H, 7.69. Found. C, 69.56; H, 8.03.

The methiodide, recrystallized from ethanol–ethyl acetate, melted at 184.5–185.5°.

Anal. Calcd. for $C_{17}H_{24}INO_3$: C, 49.0; H, 5.80; I, 30.4. Found: C, 48.75; H, 5.95; I, 30.3.

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(12) Some of the amines described in the present work gave inconsistently low analyses by the Kjeldahl procedure, but good analyses by the Dumas procedure. The methiodides, in some cases, gave good analyses by the Kjeldahl determination, so the procedure when used with the amines was altered as follows: The weighed sample of the free base, approximately 50 mg., was placed in a Kjeldahl flask and treated with 5 ml. of methyl iodide. The solution was warmed for a moment on the steam-bath, then the excess methyl iodide was distilled. The regular digestion reagents then were added, and the determination carried out in the conventional manner. The analyses of all the amines were not improved by this modification, and since there appeared to be no correlation among them, no attempt was made to classify them.

While XXII usually distilled normally, there were several occasions on which distillation resulted in extensive decomposition. The cause for this inconsistent behavior could not be determined.

1-Methyl-3-(3-benzoyloxypropyl)-4-phenyl-4-hydroxy-piperidine (XXIII).—A solution of 10.0 g. (0.0364 mole) of XXII in 100 ml. of dry ether was treated dropwise with 56 ml. (0.0364 mole) of a 0.649 *N* solution of phenylmagnesium bromide in ether. A white precipitate formed immediately. The suspension was refluxed for an additional 15 minutes, during which time it underwent no apparent change. The mixture was then treated with 100 ml. of water containing 10 ml. of concentrated hydrochloric acid. The layers were separated; the aqueous layer was extracted once with benzene (discarded), neutralized with an excess of potassium carbonate, and extracted with four 100-ml. portions of benzene. The benzene solution, after drying over potassium carbonate, was distilled to yield: (a) 5.49 g. (55%) of XXII, b.p. 165–170° (0.4 mm.); (b) 3.63 g. (28%) of XXIII, b.p. 210–225° (0.5 mm.). Fraction b cooled to a yellow, glassy material, which could not be obtained in the crystalline state. The hydrochloride, obtained in 57% yield, recrystallized from ethanol–ethyl acetate, melted at 159–160°. The remainder of the hydrochloride could not be made to crystallize.

Anal. Calcd. for $C_{22}H_{28}ClNO_3$: C, 67.8; H, 7.24; N, 3.59; Cl, 9.10. Found: C, 66.81; H, 7.44; N, 3.56; Cl, 9.05.

The methiodide of XXIII, as obtained from the Grignard reaction, was recrystallized from ethanol–ether and melted at 162.5–163.5°.

Anal. Calcd. for $C_{23}H_{30}INO_3$: C, 55.6; H, 6.10. Found: C, 55.09; H, 6.20.

When phenyllithium was added to the ketone XXII, a white precipitate formed, but there was no indication of the phenylcarbinol XXIII; unchanged XXII was the sole product.

1-Methyl-3-(3-benzoyloxypropyl)-4-phenyl-4-acetoxy-piperidine Hydrochloride (XXIIIa).—A solution of 3.40 g. (0.00871 mole) of the hydrochloride of XXIII and 1.00 g. (0.0098 mole) of freshly distilled acetic anhydride in 75 ml. of dry pyridine was refluxed for 4 hours. The pyridine was removed under diminished pressure on a steam-bath, and on recrystallization of the residue from amyl acetate, 2.74 g. (77%) of XXIIIa, m.p. 174–175°, was obtained as a monohydrate. A second crop of 0.33 g. (9%) was obtained from the mother liquor.

Anal. Calcd. for $C_{24}H_{30}ClNO_4 \cdot H_2O$: C, 64.1; H, 7.17; N, 3.11; Cl, 7.89. Found: C, 64.19; H, 6.95; N, 3.07; Cl, 7.90.

The picrate of this acetate of XXIII, recrystallized from ethanol, melted at 201.5–202°.

Anal. Calcd. for $C_{30}H_{32}N_4O_{11}$: C, 57.8; H, 5.17. Found: C, 57.50; H, 5.18.

1-Methyl-3-(3-hydroxypropyl)-4-phenyl-4-hydroxy-piperidine (XXIV).—A solution of 3.53 g. (0.01 mole) of XXIII and 0.80 g. (0.02 mole) of sodium hydroxide in 50 ml. of 80% ethanol was refluxed for 5 hours, after which the solvent was removed on a steam-bath under diminished pressure. The residue was dissolved in 50 ml. of water, made acid to congo red with hydrochloric acid and extracted with four 50-ml. portions of benzene. The benzene solution was extracted once with 50 ml. of water containing 5 g. of sodium hydroxide which was acidified with hydrochloric acid and cooled to 0°. On filtration, 1.00 g. (82%) of benzoic acid, was obtained. The aqueous solution containing the hydrochloride of XXIV was treated with excess potassium carbonate, and the solid which precipitated, filtered. On recrystallization from ethyl acetate, 1.59 g. (64%) of the glycol XXIV, m.p. 160.5–161°, was obtained as white granules; mol. wt. as determined by titration with acid, 248 (calcd. 249).

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.3; H, 9.28; N, 5.61. Found: C, 72.08; H, 9.58; N, 5.54.

The ultraviolet spectrum in ethanol had six maxima, at 241 (log $\epsilon_{\max}$ 1.88), 247 (log $\epsilon_{\max}$ 2.07), 251 (log $\epsilon_{\max}$ 2.22), 257 (log $\epsilon_{\max}$ 2.31), 264 (log $\epsilon_{\max}$ 2.18) and 267 mμ (log $\epsilon_{\max}$ 1.99).

1-Methyl-3-(3-hydroxypropyl)-4-phenyl-1,2,5,6-tetrahydropyridine (XXV) Hydrochloride.—A solution of 0.5 g. (2.0 mmoles) of XXIV in 10 ml. of concentrated hydrochloric acid was refluxed for 1 hour. After cooling to room temperature, the solution was neutralized with an excess of potassium carbonate and extracted with four 50-ml. portions of benzene. The benzene was dried over potassium carbonate, evaporated, the residue dissolved in 50 ml. of dry ether and filtered to remove a trace of insoluble material. The amine was converted to the hydrochloride, and after two recrystallizations from ethanol–ethyl acetate, 0.22 g. (48%) of the hydrochloride of XXV, m.p. 174.5–175.5°, was obtained.

Anal. Calcd. for $C_{15}H_{22}ClNO$: C, 67.4; H, 8.28. Found: C, 66.75; H, 8.12.

The infrared spectrum of this hydrochloride, as a mull, had a definite hydroxyl band at 3.0 μ. The free base, recovered from the hydrochloride, had the same band. The ultraviolet spectrum of the hydrochloride in ethanol had a single maximum at 235 mμ (log $\epsilon_{\max.}$ 4.01), typical of styrenes.

The glycol XXIV, when allowed to stand in concentrated hydrochloric acid, 60% sulfuric acid or 85% phosphoric acid at room temperature, was recovered unchanged.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE FRANCIS EARLE LABORATORIES, INC.]

New Syntheses of Purine

BY ALDEN G. BEAMAN

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Purine has been prepared by the dethiolation of 6-mercaptopurine and 2,6-dimercaptopurine. Although the monomercapto compound can be made directly from hypoxanthine, the analogous treatment of xanthine with phosphorus pentasulfide produced 2-hydroxy-6-mercaptopurine. The dimercapto compound was prepared from 2-mercapto-6-hydroxypurine.

Although substituted purines have been studied extensively, the parent compound, purine, is relatively little known. Unlike the nucleic acid purines and the common alkaloids, caffeine, theobromine and theophylline, purine is quite rare in nature. It was only recently that a natural product, nebularine, obtained from the mushroom *Agarious* (*Clitocybe*) *nebularis* Batsch. was shown by Löfgren and Lüning[1] to produce purine and ribose upon hydrolysis. G. B. Brown and Weliky[2] have demonstrated that 9-β-D-ribofuranosylpurine, which they synthesized, is identical with the natural product.

Purine itself was first prepared in extremely small yield by Emil Fischer[3] by the reduction of 2,6,8-trichloropurine which had been synthesized from uric acid.[4,5] A later method by Isay,[6] involved the conversion of 5-nitrouracil to 4,5-diaminopyrimidine, which was then condensed with

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[1] N. Löfgren and B. Lüning, *Acta Chem. Scand.*, **7**, 225 (1953).

[2] G. B. Brown and V. Weliky, *J. Biol. Chem.*, **204**, 1019 (1953).

[3] E. Fischer, *Ber.*, **31**, 2550 (1898).

[4] E. Fischer and L. Ach, *ibid.*, **30**, 2208 (1897).

[5] E. Fischer, *ibid.*, **30**, 2220 (1897).

[6] O. Isay, *ibid.*, **39**, 250 (1906).