tories, Tuckahoe, N. Y. The latter product was not pure and had to be purified by paper chromatography, using solvent 1 (see below). Thereafter, this compound gave the same quantitative yield of 6-thiouric acid as 6-thioxanthine. IV was made according to the method of Loo, *et al.*[3a] The synthetic product was in all respects identical with the material isolated from the enzymatic oxidation of I, II or III.

Milk xanthine oxidase was a gift of Prof. F. Bergel and Dr. R. C. Bray, Chester Beatty Institute of Cancer Research, London, England. This preparation, when diluted 1:4800, produced at *p*H 8.0 and 28° 1γ of uric acid/ml. min., with $6.5 \times 10^{-5}$ *M* xanthine as substrate. In order to prevent inactivation by $H_2O_2$, all solutions of XO contained also catalase (Worthington), 1:500.

The enzyme experiments were carried out in a Beckman ultraviolet spectrophotometer, equipped with a thermospacer. The changes in optical density represent the difference between the readings with the reaction mixture and a control vessel, containing all components besides XO. The *p*H was kept at 8.0 by the use of 0.01 *M* phosphate buffer. All purines used in the present investigation are stable in solution. Therefore, no change in the absorption of the controls was detected.

For paper chromatography on Whatman paper No. 1, the descending method was used with the following solvents:

Solvent 1—95% ethanol, 85 vols.; acetic acid, 5 vols.; water, 10 vols.

Solvent 2—2-propanol, 65 vols.; dimethyl formamide (DMF), 25 vols.; water, 10 vols.

Solvent 3—2-propanol, 65 vols.; DMF, 25 vols.; 25% ammonia, 10 vols.

The $R_f$ values of the purines are included in Table I. For separation of I from II, solvent 3 is most suitable.

For location of the spots, a Mineralight ultraviolet lamp, which emits radiation of about 255 mμ, was used.

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[Contribution from the Department of Chemistry of the University of Wisconsin]

# Piperidine Derivatives. XXXI. Certain 6-Oxo-octahydro- and Decahydroisoquinolines and Related Compounds

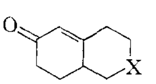
By S. M. McElvain and David C. Remy[1]

Received November 30, 1959

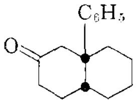
$\Delta^{1(9)}$-Octalone-2 (III) yields *cis*-9-phenyldecalone-2 (IV) by the 1,4-addition of phenylmagnesium bromide in the presence of catalytic amounts of cuprous salts. Under these conditions the 2-acetyl-6-oxo-octahydroisoquinoline II shows no 1,4 addition of the Grignard reagent; II is hydrogenated in acidic methanol to approximately equal amounts of *cis*- and *trans*-2-acetyl-6-oxo-decahydroisoquinoline XI and XII which show anomalous behavior with most of the ordinary carbonyl reagents. The amido ketone II shows an ultraviolet absorption maximum in ethanol at 241 mμ, which corresponds closely to the calculated value (244 mμ); the absorption maximum does not vary significantly with the polarity of the solvent. The amino ketone I yields an allylic chloride XVI that reacts readily with phenol to yield 2-methyl-6-(*o*-hydroxyphenyl)-1,2,3,4,6,7,8,9-octahydroisoquinoline (XVII).

Earlier work in this Laboratory showed that phenyllithium and phenylmagnesium bromide added to the carbonyl group of the 6-oxo-octahydroisoquinoline I with no indication of any 1,4-addition to give the 10-phenylated saturated ketone.[2] Subsequent experiments to promote 1,4-addition by use of catalytic amounts of cuprous salts[3] were unsuccessful due to complexing of the basic amino group with the catalyst.

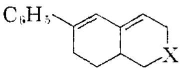
It appeared that this deactivation of the catalyst might be circumvented by the use of the N-acetyl compound II, but before undertaking this project it seemed desirable to determine whether phenylmagnesium bromide could be made to add in the 1,4-manner to the octalone III, to which Birch and Robinson had added methylmagnesium iodide in the presence of cuprous bromide and obtained *cis*-9-methyl-2-decalone in 60% yield.[4]



I, X = $NCH_3$
II, X = $NCOCH_3$
III, X = $CH_2$



IV



Va, X = $CH_2$
Vb, X = $NCH_3$

It was found possible to phenylate the angular position of III with phenylmagnesium bromide in the presence of cuprous chloride to obtain *cis*-9-phenyl-2-decalone (IV) in 25% yield. The major product (66%) was the hydrocarbon Va, which had a broad band in its ultraviolet spectrum at 284 mμ (log ε 4.16) that is indicative of the phenylbutadiene chromophore.[5] The formation of Va doubtless results from the 1,2-addition of the Grignard reagent to III followed by an allylic rearrangement of the resulting carbinol and subsequent dehydration in the same manner that Vb was formed from I.[2] The similarity of the ultraviolet absorption maxima of the two dienes Va and Vb was quite close. No satisfactory analyses could be obtained for Va; on standing it became increasingly viscous and finally turned to a polymeric gel. During this process its weight increased probably by absorption of oxygen.

When the reaction of III with phenylmagnesium bromide was carried out in the absence of the cuprous salt, none of the ketone IV was obtained.

The ketone IV had a sharp melting point and was quite probably stereochemically homogeneous. It was reduced by the Wolff–Kishner reaction to one of the 9-phenyldecalins, whose homogeneity was shown by distillation into fractions of identical refractive index, and its conversion to a single crystalline sulfonamide, m.p. 196°. The *cis* structure VI was assigned to this hydrocarbon after a comparison of its properties with those of the 9-phenyl-

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(1) Wisconsin Alumni Research Foundation Research Assistant 1956–1958; du Pont Summer Research Assistant 1958.

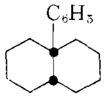
(2) S. M. McElvain and P. H. Parker, This Journal, **78**, 5312 (1956).

(3) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice–Hall, Inc., New York, N. Y., 1954, p. 219.

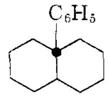
(4) A. J. Birch and R. Robinson, *J. Chem. Soc.*, 501 (1943).

(5) E. A. Braude, *et al.*, *J. Chem. Soc.*, 1087 (1947); O. Grummitt and F. J. Cristoph, This Journal, **73**, 3497 (1951).

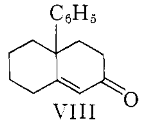
decalin previously reported by Boekelheide.[6] Although this author gave no stereochemical consideration to the hydrocarbon he prepared, it seems quite certain that it has the *trans* structure VII since one of the steps in its preparation involved the hydrogenation of the $\alpha,\beta$-unsaturated ketone VIII. An examination of the molecular model of VIII shows that the side of the molecule containing the phenyl substituent is quite crowded, while the other side of the molecule is flat and relatively unhindered. It would be expected that the hydrogenation would occur on the unhindered side of the molecule to give the *trans* structure VII.



VI



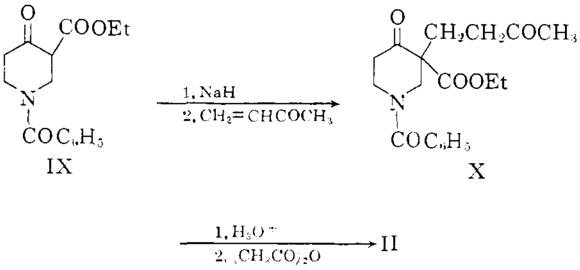
VII



VIII

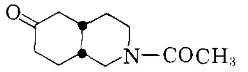
The boiling point and refractive index of the *cis* compound VI compares quite closely to the values reported by Boekelheide for the *trans* compound. The sulfonamide derivatives of VI and VII melt at 196° and 162°, respectively. A comparison of the infrared spectra of the two hydrocarbons VI and VII[7] shows that although they are similar, there is no doubt that they are different. The *cis* configuration for VI establishes the same configuration for the precursor ketone IV, an assignment that is consistent with the stereochemistry noted by Birch and Robinson[4] for the product resulting from the addition of methylmagnesium iodide to III.

The 2-acetyl-6-oxo-octahydroisoquinoline II, required for the next phase of this study, was prepared by the addition of methyl vinyl ketone to 1-benzoyl-3-carbethoxy-4-piperidone (IX) in the manner used for the preparation of I from 1-methyl-3-carbethoxy-4-piperidone.[2] The adduct X was not purified but was treated directly with acid and the intermediate 6-oxoöctahydroisoquinoline acetylated to give II in over-all yields of 16–25%.

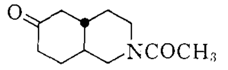


The basic ring structure of II was shown by its hydrogenation in weakly acidic methanol to approximately equal amounts of the *cis*- and *trans*-ketones XI, and XII, which were then converted to the known *cis*- and *trans*-decahydroisoquinolines.

The non-stereospecific hydrogenation of II to XI and XII is of interest in the light of previous work. The hydrogenation of I in dilute acid gives only *cis*-2-methyl-6-oxo-decahydroisoquinoline.[2] Similar exclusive *cis*-hydrogenation has been observed with III in either neutral, acidic or basic solutions[8]; it was only by a chemical reduction with lithium and liquid ammonia that any of the *trans*-2-decalone could be obtained.



XI



XII

The unsaturated ketone II readily forms a bright red 2,4-dinitrophenylhydrazone. However, the corresponding saturated ketones XI and XII, whose infrared spectra have strong carbonyl bands at 5.88 and 5.87 $\mu$, show peculiar behavior with carbonyl reagents. Neither ketone appears to react normally with 2,4-dinitrophenylhydrazine. With phenylhydrazine the *cis*- ketone XI gave no product under conditions that readily gave the phenylhydrazone of cyclohexanone; the *trans*-ketone XII with this reagent did give a crystalline precipitate, but attempted recrystallization converted it to a red oil. The *cis*-ketone reacted with phenylhydrazine in toluene to give a crystalline product, but as in the case of the *trans*-ketone derivative, attempted recrystallization converted the product to an orange oil. However, the *p*-nitrophenylhydrazone of XI could be prepared in toluene as a crystalline product which could be recrystallized from ethanol; the same derivative of XII could be prepared by the standard procedure, but was obtained as a powder that was quite difficult to purify. In connection with this anomalous behavior of XI and XII, it is of interest to note that Georgian[9] encountered no difficulty in the preparation of the phenylhydrazone or the *o*-methoxyphenylhydrazone of the isomeric (probably *trans*) 2-acetyl-5-oxo-decahydroisoquinoline.

The ultraviolet absorption spectrum of the amido ketone II in ethanol shows a maximum at 241 m$\mu$ (log $\epsilon$ 4.06).[10] Although this value is in good agreement with the maximum (244 m$\mu$) predicted from Woodward's rules,[11] it stands in marked contrast to the hypsochromic shift (12 m$\mu$) of the ultraviolet absorption maximum of the amino ketone I. The $\lambda_{max}$ of 232 m$\mu$ (log $\epsilon$ 4.15) for I has been observed by three independent groups.[2,12,13a] More recently Georgian[13b] has extended the study of such spectra to include derivatives and analogs of I and drew certain conclusions which since have been discussed critically by Kosower and Remy.[14] While the absorption maximum of I varies considerably with the solvent polarity,[14] the maximum for II is

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[6] V. Boekelheide, THIS JOURNAL, **69**, 790 (1947).

[7] This comparison was kindly made by Dr. V. Boekelheide. From an independent examination of the model of VIII, he is inclined to agree with the assignment of the *trans* configuration (VII) to the hydrocarbon he prepared.

[8] E. E. van Tamelen and W. C. Proost, Jr., THIS JOURNAL, **76**, 3632 (1954).

[9] Personal communication from Dr. V. Georgian, Department of Chemistry, Northwestern University, Evanston, Ill.

[10] C. B. Clarke and A. R. Pinder, *J. Chem. Soc.*, 1967 (1958), report an ultraviolet absorption maximum in methanol of 234 m$\mu$ for the ketone II, which represents about the same hypsochomic shift from the predicted value as that shown by the amino ketone I (*cf.* ref. 14). It should be noted, however, that the compound II used in the present work was a crystalline solid, m.p. 108°, while the material described by Clarke and Pinder was a liquid, b.p. 146–148° (0.7 mm.).

[11] R. B. Woodward, THIS JOURNAL, **63**, 1123 (1941); **64**, 76 (1942).

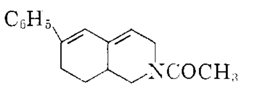
[12] A. Marchant and A. R. Pinder, *J. Chem. Soc.*, 327 (1956).

[13] (a) V. Georgian, *Chemistry & Industry*, 930 (1954); (b) 1480 (1957).

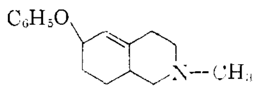
[14] E. M. Kosower and D. C. Remy, *Tetrahedron*, **5**, 281 (1959).

relatively independent of the nature of the solvent. This fact indicates that the molecule of II is able to accommodate the increased charge separation in the excited state formed by light absorption in the $\alpha,\beta$-unsaturated ketone moiety, quite likely by the existence of the hetero ring in a boat conformation that permits the electron-rich amide oxygen to attain sufficiently close proximity for interaction with the positive center being developed at the bridgehead carbon.

The reaction of II with phenylmagnesium bromide in the presence of cuprous chloride gave a product that showed no carbonyl or hydroxy band in its infrared spectrum. The ultraviolet spectrum had a broad maximum at 281 m$\mu$ (log $\epsilon$ 4.17) which is indicative of the phenylbutadiene chromophore (*cf.* Va and Vb) and on this basis the reaction product, which was obtained in 60% yield, was assigned the structure XIII. As in the reaction of III with phenylmagnesium bromide, the diene XIII quite likely is formed by a 1,2-addition of the Grignard reagent to II followed by an allylic rearrangement of the 6-hydroxyl group to the 10-position and subsequent dehydration. Also, as in the case of V, no satisfactory analyses could be obtained for XIII. The compound, which could not be distilled or crystallized, on standing for a few days became a green polymeric material. In addition to XIII, 17% of the starting ketone II was recovered from the aqueous solution resulting from the hydrolysis of the Grignard reaction. It is apparent from these results that the unsaturated ketone II, in contrast to its carbocyclic analog III, gives no 1,4-addition of the Grignard reagent.

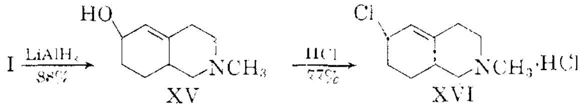


XIII



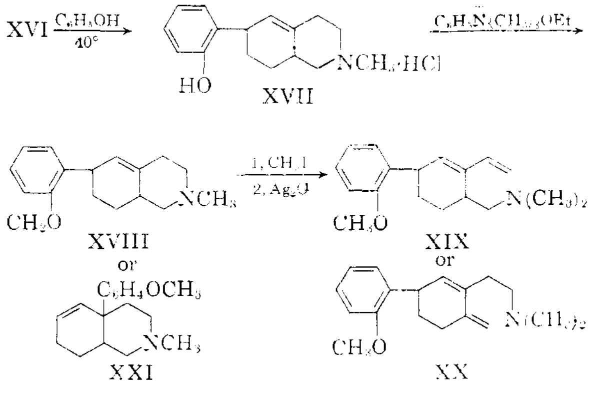
XIV

An attempt was made to prepare the 6-phenoxyoctahydroisoquinoline XIV in the hope that it might undergo a Claisen rearrangement to phenylate the 10-angular position. To this end the amino ketone I was reduced to the allylic alcohol XV. Treatment of this alcohol with hydrogen chloride converted it in 77% yield to a single allylic chloride hydrochloride, to which the structure XVI is assigned. This salt was added to a twenty molar excess of sodium phenoxide in ethylene glycol dimethyl ether[15] and the reaction mixture worked up to isolate any basic compound such as XIV as well as amphoteric material. No significant amount of basic product was obtained. A small amount (6.7%) of an amphoteric product, the nature of which is described below, was isolated as a crystalline, high melting hydrochloride. The remainder of the reaction products were water soluble, indicating that the amino chloride underwent rapid polymeric quaternization as it was liberated from its salt XVI by the sodium phenoxide. Such a reaction course was substantiated by the behavior of XVI when treated with a solution of sodium hydroxide. At first a marked turbidity developed due to precipitation of the free base of XVI. This precipitate rapidly redissolved due to the quaternization of the chloroamine.[16] The resulting solution again became turbid when excess base was added, but dilution with water immediately produced a clear solution.



Allylic chlorides are known to react with phenols under very mild conditions to give nuclear allylation.[17] When the salt XVI was mixed with phenol, an extremely facile reaction occurred at 40° with the formation of a homogeneous solution and the evolution of hydrogen chloride. The product, isolated in 86% yield as a crystalline hydrochloride, was identical with the salt of the amphoteric material obtained when XVI was treated with sodium phenoxide. This compound was shown to have the structure XVII by oxidation of its methyl ether XVIII to *o*-methoxybenzoic acid and by the Hofmann decomposition of the methiodide of this ether to a product (77% yield) that showed a maximum in its ultraviolet absorption spectrum at 223 m$\mu$ (log $\epsilon$ 4.23), which is indicative of the butadiene chromophore. The decomposition of the methiodide of XVIII could yield either XIX or XX which have calculated maxima of 227 and 237 m$\mu$, respectively. The observed value for the reaction product is in quite good agreement with the calculated value for XIX and establishes XVIII as the structure of the methyl ether of the condensation product of XVI with phenol. The methiodide of the isomeric 10-(*o*-anisyl)-$\Delta^5$-structure XXI obviously could not yield a conjugated diene by the Hofmann reaction.

The validity of structure XVIII is also shown by its n.m.r. spectra, which was kindly run and interpreted by Professor John D. Roberts at the California Institute of Technology. These spectra showed that the ratio of vinyl hydrogens to aromatic hydrogens approach 1:4 as required by structure XVIII and, therefore, exclude XXI in which the ratio is 1:2.



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[15] *Cf.* N. Kornblum and A. Lurie, This Journal, **81**, 2705 (1959).

[16] This behavior is analogous to that of 1-(2-chloroethyl)-2,2,5,5-tetramethylpiperazine dihydrochloride when treated with base; *cf.* S. M. McElvain and E. H. Pryde, This Journal, **71**, 326 (1949).

[17] L. I. Smith, *Chem. Revs.*, **27**, 295 (1940).

An attempt was made to prepare the methyl ether XVIII directly by the condensation of anisole with XVI. In contrast to the facile reaction of phenol, a temperature of 125° was required to produce evolution of hydrogen chloride and a homogeneous solution of the salt XVI in anisole. The reaction product, however, was not XVIII but a dehydrohalogenated XVI, which was quite probably 2-methyl-1,2,3,7,8,9-hexahydroisoquinoline hydrochloride, $\lambda_{\max}^{\text{EtOH}}$ 232 m$\mu$ (log $\epsilon$ 4.08).

## Experimental

**$\Delta^{1(9)}$-Octalone-2(III).**—The following procedure is an adaptation of the method used by McElvain and Parker[2] to prepare I. A solution of 65.0 g. (0.382 mole) of ethyl 2-oxocyclohexanecarboxylate in 320 ml. of dry benzene was placed in a 3-necked flask equipped with stirrer, dropping funnel and condenser. This solution was then boiled to eliminate all traces of moisture. After flushing the system with nitrogen, 0.28 g. (3 mole %) of sodium hydride was added and the solution stirred until all of the sodium hydride had dissolved. After cooling to room temperature, 28.4 g. (0.405 mole) of freshly distilled methyl vinyl ketone in 60 ml. of dry benzene was added dropwise over a period of 30 minutes. The exothermic reaction was stirred for 2 hr. The benzene solution was washed with two 15-ml. portions of water, dried over magnesium sulfate, and the benzene removed under reduced pressure. The pale yellow oil remaining was mixed with 500 ml. of boiling water containing 5.15 g. of potassium hydroxide, and the solution was refluxed for 2 hr. At this time, an additional 13.95 g. of potassium hydroxide in 126 ml. of water was added, and the solution was allowed to reflux another 6 hr. After cooling, the reaction mixture was extracted with five 200-ml. portions of ether. The combined ether extracts, after drying over magnesium sulfate, were evaporated to dryness leaving an orange mobile oil. This oil was distilled under reduced pressure, and a center fraction which weighed 15.83 g. (28%) and boiled at 134–139° (14 mm.) was taken as pure III; $n^{25}$D 1.5220 (reported b.p. 101–102° (2–3 mm.), $n^{18}$D 1.5238[18]; b.p. 91.5–92.0° (1 mm.), $n^{25}$D 1.5204[19]).

**The Reaction of III with Phenylmagnesium Bromide in the Presence of Cuprous Chloride.**—A solution of phenylmagnesium bromide, prepared from 12.5 g. (0.080 mole) of bromobenzene and 1.95 g. (0.080 atom) of magnesium in 60 ml. of ether, was transferred by means of nitrogen pressure through a dry glass tube, containing a piece of glass wool to filter off any unreacted particles of magnesium, into a 3-necked round-bottom flask equipped with condenser, dropping funnel and stirrer. To this solution was added 0.11 g. of freshly prepared cuprous chloride,[20] and the mixture was cooled to 0° in an ice-bath. A solution of 9.408 g. (0.0626 mole) of III in 50 ml. of ether was then added to this vigorously stirred solution over a period of 1 hr. After the addition was complete, the flask was allowed to warm to room temperature while stirring was continued. After 1 hr., 25 ml. of 6 *N* hydrochloric acid was added slowly, and the ether phase separated. The aqueous acid phase was washed with ether and the combined ether phases evaporated to approximately 100 ml. After drying over magnesium sulfate, the ether was evaporated leaving 14.00 g. of a mobile orange oil. The infrared spectrum of this oil showed strong absorption at 5.87 $\mu$.

This oil was taken up in petroleum ether and chromatographed on almost neutral Woelm aluminum oxide, activity grade 1. On eluting the column with petroleum ether, a total of 8.790 g. (66%) of **2-phenyl-3,4,5,6,7,10-hexahydronaphthalene (Va)** was obtained; $\lambda_{\max}^{95\%\ \text{EtOH}}$ 284 m$\mu$ (log $\epsilon$ 4.16), 236 m$\mu$ (log $\epsilon$ 3.89). The infrared spectrum (liquid film) showed bands at 5.15, 6.16, 6.28, 6.39, 6.74, 11.23, 12.55 and 13.28 $\mu$. On attempted distillation, only 60% of the material distilled, b.p. 120–125° (0.25 mm.). The pot residues were an orange, polymeric material. The distillate was analyzed. Found: C, 89.06; H, 7.55. Calcd. for Va: C, 91.37; H, 8.63.

On standing, this distillate became increasingly viscous and after standing for 2 months had become a stiff polymeric gel. An increase in weight of the material occurred during this standing. The ultraviolet absorption spectrum of this gel showed $\lambda_{\max}^{95\%\ \text{EtOH}}$252 m$\mu$ (log $\epsilon$ 3.98 if the molecular weight of the hydrocarbon $C_{16}H_{18}$ is used).

On further elution of the column with ether, 3.532 g. (24.7%) of 9-phenyldecalone-2 (IV) was obtained as an oil that rapidly crystallized. This ketone could be purified by distillation at reduced pressure, b.p. 117–120° (0.25 mm.), or by recrystallization from aqueous ethanol, m.p. 68–69°. The infrared spectrum ($CHCl_3$) showed a strong band at 5.89 $\mu$. The ultraviolet absorption spectrum (95% ethanol) showed bands at 253.3 (log $\epsilon$ 2.41), 255.2 (log $\epsilon$ 2.40), 258.6 (log $\epsilon$ 2.47), 261.7 (log $\epsilon$ 2.44), 264.8 (log $\epsilon$ 2.37), and 268.5 m$\mu$ (log $\epsilon$ 2.31).

*Anal.* Calcd. for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.07; H, 8.89.

When the reaction of III with phenylmagnesium bromide was carried out as previously described except that no cuprous chloride was added to the solution of phenylmagnesium bromide, the infrared absorption spectrum of the crude reaction product failed to show any band in the 5.87 $\mu$ region that could be interpreted as being a carbonyl band. The infrared spectrum was almost identical to that of V which was obtained from the chromatographic separation described in the previous experiment.

**The Wolff–Kishner Reduction of 9-Phenyldecalone-2 (IV) to *cis*-9-Phenyldecalin (VI).**—A solution of 2.032 g. (8.9 mmoles) of IV and 1.0 ml. of 99% hydrazine hydrate in 5 ml. of absolute ethanol was refluxed gently for 4 hr. The volatile material was then evaporated off and 4.35 g. of solid powdered potassium hydroxide added. The flask was placed in a heating bath and the temperature raised slowly to 230°. The almost solid reaction mixture began nitrogen evolution at about 120°. At 230° the reaction appeared complete as there was no further evidence of nitrogen evolution in the homogeneous melt. After cooling, water was added and the organic material extracted with two 50-ml. portions of benzene. After drying over magnesum sulfate, the benzene was evaporated off and the residue distilled through a short Vigreux column to give the fractions: (a) 0.207 g., b.p. 97–98° (0.25 mm.), $n^{20}$D 1.5536; (b) 0.177 g., b.p. 97–98° (0.25 mm.), $n^{20}$D 1.5536; (c) 0.260 g., b.p. 97–98° (0.25 mm.), $n^{20}$D 1.5536; (d) 0.598 g., b.p. 97–98° (0.25 mm.), $n^{20}$D 1.5542. Fractions a through d showed no tendency to crystallize on standing or on cooling. The infrared absorption spectrum ($CHCl_3$) of fraction c showed bands at 6.25, 6.65, 6.75, 9.00 and 10.22 $\mu$. Fractions a through d amounted to 1.242 g. (65%) of ***cis*-9-phenyldecalin (VI)**. Fraction c was taken for analysis.

*Anal.* Calcd. for $C_{16}H_{22}$: C, 89.65; H, 10.35. Found: C, 89.78; H, 10.35.

The sulfonamide derivative of VI was prepared by the method of Huntress and Carten.[21] Recrystallization from aqueous ethanol gave the pure sulfonamide as lustrous white needles, m.p. 195–196°.

*Anal.* Calcd. for $C_{16}H_{23}NO_2S$: C, 65.50; H, 7.90. Found: C, 65.40; H, 7.94.

**2-Acetyl-6-oxo-1,2,3,4,6,7,8,9-octahydroisoquinoline (II).**—A solution of 161 g. (0.585 mole) of 1-benzoyl-3-carbethoxy-4-piperidone (IX)[22] in 500 ml. of dry benzene was placed in a dry 3-necked flask equipped with stirrer, dropping funnel and condenser. After flushing the system with nitrogen, 0.45 g. (3 mole %) of sodium hydride was added. The solution was heated and stirred until all of the sodium hydride had reacted. After cooling to room temperature, 43.4 g. (0.62 mole) of freshly distilled methyl vinyl ketone in 90 ml. of benzene was added dropwise over a period of 35 min. The slightly exothermic reaction was allowed to stir for an additional 2 hr. at which time a ferric chloride test was negative. The benzene solution was washed with two 20-ml. portions of water, dried over magnesium sulfate, and the benzene removed under reduced pressure. There remained 200 g. of a pale yellow oil which was mixed with 1080 ml. of 6 *N* hydrochloric acid and refluxed vigorously for 4–5 hours. After cooling, the crystalline benzoic acid was filtered off.

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(18) F. C. du Feu, F. J. McQuillin and R. Robinson, *J. Chem. Soc.*, 53 (1937).

(19) W. T. Tsatsos, Ph.D. Thesis, University of Wisconsin, 1954.

(20) R. N. Keller and H. D. Wycoff, "Inorganic Syntheses," McGraw-Hill Book Co., Inc., New York, N. Y., 1946. Vol. II, p. 1.

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The aqueous acid solution was washed with two 100-ml. portions of ether and was then evaporated to dryness under reduced pressure. The dark red residue of crude amine hydrochloride was dissolved in 150 ml. of water and warmed to 50°. While stirring rapidly, 71.5 g. (0.70 mole) of acetic anhydride was added, and then 102 g. of sodium acetate in 300 ml. of water. After stirring for an hour, the solution was cooled, saturated with potassium carbonate, and extracted with four 200-ml. portions of benzene. After drying over magnesium sulfate, the benzene was chromatographed over Fisher alumina, 80–200 mesh. Evaporation of the benzene left a thick red oil which was distilled through a short Vigreux column to give 22.10 g. (19.5%) of a thick green oil, b.p. 160–170° (0.25 mm.), which slowly crystallized. Almost all of the color could be removed from this distillate by rechromatographing a benzene solution of it over alumina. After evaporation of the benzene, the residue was crystallized from ethyl acetate and petroleum ether to give 17.8 g. of pure **2-acetyl-6-oxo-1,2,3,4,6,7,8,9-octahydroisoquinoline** (II) as small colorless needles, m.p. 107–108°. The ultraviolet absorption maxima of II in various solvents were: water, 244 m$\mu$ (log $\epsilon$ 4.14); methanol, 240 m$\mu$ (log $\epsilon$ 4.08); 95% ethanol, 241 m$\mu$ (log $\epsilon$ 4.06); 2-propanol, 241 m$\mu$ (log $\epsilon$ 4.06); acetonitrile, 244 m$\mu$ (log $\epsilon$ 4.03); dichloromethane, 244.5 m$\mu$ (log $\epsilon$ 4.02); cyclohexane, 243 m$\mu$ (log $\epsilon$ 3.95). The infrared absorption spectrum (mull) showed bands at 6.05 (ketone) and 6.17 $\mu$ (amide).

*Anal.* Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.40; H, 7.57.

The **2,4-dinitrophenylhydrazone**, prepared in ethanol and recrystallized from chloroform and petroleum ether, was obtained as sparkling ruby red plates, m.p. 235–236.5° dec.

*Anal.* Calcd. for $C_{17}H_{19}N_5O_5$: C, 54.68; H, 5.13. Found: C, 54.29; H, 4.97.

**2-Acetyl-6-oxo-*cis*-decahydroisoquinoline** (XI).—To a solution of 18.23 g. (0.0945 mole) of II in 183 ml. of absolute methanol containing 18 drops of concentrated hydrochloric acid was added 0.60 g. of 10% palladium-on-charcoal catalyst. The mixture was shaken with hydrogen at an initial pressure of 38 pounds until hydrogen was no longer being absorbed (20–30 min.). The catalyst was removed by filtration, the solution was evaporated *in vacuo*, and the residue taken up in ethyl acetate and petroleum ether. On standing, 5.91 g. (32%) of the *cis*-ketone XI crystallized in almost pure form. Concentration of the mother liquors gave an additional 0.34 g. (1.9%) of XI. Recrystallization of the combined crops of XI from ethyl acetate and petroleum ether gave glistening white needles, m.p. 114–115°. The infrared spectrum ($CHCl_3$) showed bands at 5.88 and 6.18 $\mu$.

*Anal.* Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78. Found: C, 67.55; H, 8.90.

The preparation of the 2,4-dinitrophenylhydrazone derivative was attempted according to the procedure of Shriner and Fuson.[23] The solution became progressively darker, but no derivative precipitated. After two months, a black coating covered the walls of the flask. This material was not investigated.

A solution of 0.280 g. (0.00143 mole) of XI, 0.155 g. (0.00143 mole) of phenylhydrazine and 2 drops of glacial acetic acid in 2 ml. of 95% ethanol was heated on a steam-bath for 10 min. The solution was allowed to cool, but no precipitation of a derivative occurred. Several drops of water was added to the solution, but on further cooling no precipitation occurred. The use of cyclohexanone, rather than the ketone XI, under identical reaction conditions readily gave the phenylhydrazone of cyclohexanone.

To a solution of 0.500 g. (0.00256 mole) of XI and 0.292 g. (0.00270 mole) of phenylhydrazine in 3 ml. of toluene was added 3 drops of glacial acetic acid. After heating at 105° for 20 min., the solution was allowed to cool, and upon trituration of the solution with petroleum ether, crystallization occurred. This solid material was removed by filtration and dried. There was obtained 0.556 g. of material that melted at 130–140°. On attempted recrystallization, the material became increasingly yellow and within 2–3 days became an orange oil, which was not further characterized.

To a solution of 0.5215 g. (0.00268 mole) of XI in 6 ml. of toluene was added 0.422 g. (0.00276 mole) of *p*-nitrophenylhydrazine. After adding 3 drops of glacial acetic acid, the mixture was boiled gently for 15 min., and, after cooling, the solid material was collected on a filter and dried. There was obtained 0.823 g. (92%) of the ***p*-nitrophenylhydrazone of XI** as golden clumps of crystals, and which, after recrystallization from 95% ethanol, melted at 204–206°.

*Anal.* Calcd. for $C_{17}H_{22}N_4O_3$: C, 61.80; H, 6.71. Found: C, 61.87; H, 6.72.

**2-Acetyl-6-oxo-*trans*-decahydroisoquinoline** (XII).—After the *cis*-ketone XI had been removed by filtration from the above hydrogenation reaction, the filtrate was evaporated to dryness leaving an oily residue which could not be crystallized even after rechromatographing its benzene solution. Distillation of this oil gave 6.10 g. (33%) of the *trans*-ketone XII as a colorless oil, b.p. 142–150° (0.20 mm.). The infrared spectrum ($CHCl_3$) showed bands at 5.87 and 6.18 $\mu$.

*Anal.* Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78. Found: C, 67.84; H, 8.47.

The preparation of the 2,4-dinitrophenylhydrazone derivative was undertaken.[23] The solution became progressively darker on standing, but no precipitation occurred. After two months, a reddish-black coating covered the walls of the flask.

A solution of 0.280 g. (0.001431 mole) of XII, 0.155 g. (0.00143 mole) of phenylhydrazine and 2 drops of glacial acetic acid in 2 ml. of 95% ethanol was heated on a steam-bath for 10 min. The solution was allowed to cool, and small crystals began to form. The addition of 2 drops of water completed the crystallization. The solid material, after removal of filtrate, melted at 131–143°. On attempted recrystallization, this material became increasingly colored, and within 1–2 days became an orange oil.

A solution of 0.510 g. (0.00261 mole) of XII, 0.440 g. (0.00287 mole) of *p*-nitrophenylhydrazine and 2 drops of glacial acetic acid in 10 ml. of 95% ethanol was heated on a steam-bath for 10 min. Water was added dropwise to the hot solution until it became slightly turbid. After cooling, the precipitate which had formed was removed by filtration and dried. This material, the ***p*-nitrophenylhydrazone of XII**, was quite difficult to purify, but after repeated recrystallization from dimethylformamide and water was obtained as a copper colored powder melting at 239–241°.

*Anal.* Calcd. for $C_{17}H_{22}N_4O_3$: C, 61.80; H, 6.71. Found: C, 61.91; H, 6.01.

**The Clemmensen Reduction of 2-Acetyl-6-oxo-*cis*-decahydroisoquinoline (XI).**—The procedure reported here is an adaptation of that of Clemo, Cook and Raper.[24] A mixture of 10 g. of mossy zinc, 1.0 g. of mercuric chloride, 15 ml. of water and 15 drops of concentrated hydrochloric acid was shaken for 5 minutes. The supernatant liquid then was decanted and replaced by 16 ml. of concentrated hydrochloric acid. After the initial vigorous bubbling had subsided, 2.08 g. (0.01065 mole) of XI was added. The mixture was refluxed gently for 24 hr. after which time an additional 10 g. of zinc, amalgamated as described above, and 20 ml. of concentrated hydrochloric acid were added. The solution was refluxed another 24 hr. and, after cooling, filtered through a plug of glass wool to remove the metallic solids. A large excess of 50% sodium hydroxide solution was added, while cooling, to render the solution distinctly basic. After steam distillation of this solution, the 300–350 ml. of distillate collected was saturated with sodium chloride and extracted with two 50-ml. portions of ether. Evaporation of the ether left 0.52 g. (35%) of *cis*-decahydroisoquinoline as a clear, mobile oil. The hydrochloride of this amine, prepared in ether and recrystallized from ethanol and ether, melted at 181–182.5° (reported[25] 183°). The picrate of this amine, prepared in ethanol and recrystallized from methanol, was obtained as yellow aggregates melting at 150–151° (reported[25] 150°). Authentic *cis*-decahydroisoquinoline picrate was prepared by the method of Witkop,[25] m.p. 150–153°. A mixed melting point of the authentic picrate of *cis*-decahydroisoquinoline and the picrate obtained from the Clemmensen reduction of XI was not depressed, m.m.p. 150–153°. The infrared absorption spectra (Nujol mull) of both picrates were identical in every respect.

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**The Clemmensen Reduction of 2-Acetyl-6-oxo-*trans*-decahydro-isoquinoline (XII).**—The Clemmensen reduction of 2.09 g. (0.01065 mole) of XII was carried out exactly as previously described for the *cis* isomer. There was obtained 0.393 g. (27%) of *trans*-decahydroisoquinoline as a clear mobile oil. The picrate of this amine, prepared in ethanol and recrystallized from methanol, was obtained as small golden prisms melting at 177–179.5° (reported[25] 175–178°). Authentic *trans*-decahydroisoquinoline picrate was prepared by the method of Witkop,[25] m.p. 176–179°. A mixed melting point of authentic *trans*-decahydroisoquinoline picrate and the picrate obtained from the Clemmensen reduction of XII was not depressed, m.p. 176.5–179°. The infrared absorption spectra (Nujol mull) of both picrates were identical in every respect.

**The Reaction of II with Phenylmagnesium Bromide in the Presence of Cuprous Chloride.**—A solution of phenylmagnesium bromide, prepared from 0.63 g. (0.0259 g. atom) of magnesium and 4.06 g. (0.0259 mole) of bromobenzene in 26 ml. of ether, was transferred by means of nitrogen pressure through a dry glass tube, containing a piece of glass wool to filter off any unreacted particles of magnesium, into a 3-necked round-bottom flask equipped with condenser, dropping funnel and stirrer. To this solution was added 0.06 g. of freshly prepared cuprous chloride, and the mixture was cooled to 0° in an ice-bath. To this solution was added rapidly 5.00 g. (0.0259 mole) of II dissolved in 50 ml. of benzene. After stirring for 30 min. the reaction was allowed to warm to room temperature over a period of 30 min. After hydrolysis of the reaction with 50 ml. of 6 *N* hydrochloric acid, the organic phase was separated, and the aqueous acid phase was washed with 50 ml. of benzene. The combined benzene–ether phase was evaporated to dryness leaving 4.51 g. of an amber oil. This oil was taken up in benzene and chromatographed on almost neutral Woelm aluminum oxide, activity grade 1. A total of 0.168 g. of material was obtained from this chromatogram by eluting with benzene and ether. On eluting the column with acetone, 3.95 g. (60%) of **2-acetyl-6-phenyl-1,2,3,7,8,9-hexahydroisoquinoline (XIII)** was obtained. The ultraviolet absorption spectrum showed a $\lambda_{\max}^{95\%\,\mathrm{EtOH}}$ at 281 mμ (log ε 4.17). The infrared spectrum (mull) showed bands at 6.11, 11.29, 13.12 and 14.30 μ. This material could neither be distilled nor recrystallized. No satisfactory elemental analysis was obtained for the compound and, on standing, it rapidly became a green polymeric glass.

The aqueous acid phase from the Grignard hydrolysis reaction was neutralized with sodium hydroxide, and the solution then was saturated with sodium carbonate. This mixture was extracted with two 50-ml. portions of benzene. After drying over magnesium sulfate, this benzene solution was chromatographed over a short column of alumina. On development of the column with benzene, there was obtained 0.849 g. (17%) of recovered ketone II, which after recrystallization from ethyl acetate and petroleum ether melted at 104–107°.

**2-Methyl-6-hydroxy-1,2,3,4,6,7,8,9-octahydroisoquinoline (XV).**—A solution of 28.77 g. (0.174 mole) of 2-methyl-6-oxoöctahydroisoquinoline (I)[2] in 250 ml. of ether slowly was added to a rapidly stirred slurry of 6.60 g. (0.174 mole) of lithium aluminum hydride in 300 ml. of ether. The gummy precipitate which first formed broke apart when the solution was gently refluxed for 1 hr. At this time, the excess lithium aluminum hydride was decomposed with 100 ml. of 20% potassium hydroxide. The organic phase was decanted, and the aqueous residue extracted with two 100-ml. portions of ether. The combined ether fractions, after drying over magnesium sulfate, were distilled to yield 25.71 g. (88%) of XV, b.p. 96–98° (0.15 mm.), $n^{25}\mathrm{D}$ 1.5239. The infrared spectrum (liquid film) showed a wide band at 2.9–3.1 μ and a sharp small band at 6.01 μ. The picrate, recrystallized from methanol, melted at 160–162° (reported[12] m.p. 163°).

**2-Methyl-6-chloro-1,2,3,4,6,7,8,9-octahydroisoquinoline Hydrochloride (XVI).**—A stream of dry hydrogen chloride was passed into a solution of 4.70 g. (0.0281 mole) of XV in 94 ml. of chloroform by means of a fritted glass tube. The vigorously shaken solution became warm and cloudy, and within 1 to 2 minutes water droplets began to precipitate. At the end of 5 minutes, the reaction was stopped, and the solution then was heated on a steam-bath until the water had been removed by azeotropic distillation and the solution was clear. Ether was added and on cooling 3.29 g. of XVI crystallized. Concentration of the mother liquors yielded two additional crops of crystals. The combined weight of the three crops, all of which melted between 128–138°, was 4.77 g. (77%). Recrystallization from chloroform–ether gave pure XVI, m.p. 138–139°. The infrared spectrum (Nujol mull) showed a wide band at 4.1 μ and small sharp bands at 6.06 and 12.41 μ.

*Anal.* Calcd. for $C_{10}H_{17}Cl_2N$: C, 54.06; H, 7.71; Cl, 31.92. Found: C, 54.47; H, 7.47; Cl, 31.77.

**The Reactions of XVI. (a) With Sodium Phenoxide.**—Into a dry 3-necked flask equipped with stirrer, condenser and dropping funnel was placed 12.88 g. (0.536 mole) of sodium hydride. After overlaying the sodium hydride with 150 ml. of ethylene glycol dimethyl ether, a solution of 50.0 g. (0.532 mole) of phenol in 100 ml. of ethylene glycol dimethyl ether was added slowly while stirring. After all of the phenol had reacted, the solution of sodium phenoxide was transferred through a glass tube by means of nitrogen pressure into a dry 3-necked flask equipped with condenser and stirrer; a small piece of glass wool in the glass tubing prevented the transfer of small particles of sodium hydride. To this solution of sodium phenoxide was then added a slurry of 5.95 g. (0.0268 mole) of XVI and 50 ml. of ethylene glycol dimethyl ether. The solution was heated on the steam-bath for 1 hr. After cooling a large volume of ether was added and the solution was extracted with three 100-ml. portions of 6 *N* hydrochloric acid. The combined acid extracts were made basic by the addition of solid sodium bicarbonate, and the mixture was extracted with three 50-ml. portions of ether. These combined ether extracts were extracted with two 50-ml. portions of 10% aqueous potassium hydroxide. The alkaline extracts were designated solution A while the residual ether solution was designated solution B.

Solution A was made acid by addition of 6 *N* hydrochloric acid, and then made basic by the addition of solid sodium bicarbonate. This solution then was extracted with two 50-ml. portions of ether. After drying over magnesium sulfate, an ethereal solution of hydrogen chloride was added to the ethereal amine solution. After removing the resulting precipitate by filtration, the material was dried to give 0.499 g. (6.7%) of the hydrochloride XVII, m.p. 299–301° (see below). The infrared spectrum (mull) showed bands at 3.15, 3.75, 3.88, 6.29, 6.65 and 13.17 μ.

Solution B was dried over magnesium sulfate. The addition of ethereal hydrogen chloride solution resulted in the precipitation of 0.600 g. of a brown, intractable gum which could not be characterized.

**(b) With Base.**—A solution of 1.51 g. (0.0068 mole) of XVI in 15 ml. of water was prepared and to it was added dropwise 10% aqueous potassium hydroxide; there was decided turbidity, indicating precipitation of the free base of XVI, but the solution cleared within a few seconds. After neutralization of all of the hydrochloride, continued addition of alkali caused the solution to become turbid. The addition of a few drops of water, however, completely cleared the solution.

**(c) With Phenol. 2-Methyl-6-(*o*-hydroxyphenyl)-1,2,3,4,6,7,8,9-octahydroisoquinoline Hydrochloride (XVII).**—Into a dry 3-necked flask, which was being swept with a stream of nitrogen, were placed 3.17 g. (0.0142 mole) of XVI and 15.85 g. (0.168 mole) of phenol. The stirred mixture, which immediately began melting with the evolution of hydrogen chloride, was warmed to 40°. At the end of 90 minutes, no further halide could be detected in the effluent gases by silver nitrate. The reaction mixture was cooled and on addition of a large volume of ether, 3.43 g. (86%) of the hydrochloride XVII precipitated. Recrystallization from absolute ethanol yielded the pure salt, m.p. 298–301°. Infrared spectrum (Nujol mull) showed bands at 3.14, 3.75, 3.88, 6.29, 6.65 and 13.20 μ; ultraviolet spectrum: $\lambda_{\max}^{95\%\,\mathrm{EtOH}}$ 274 (log ε 3.34), inflection, 280 mμ (log ε 3.29).

*Anal.* Calcd. for $C_{16}H_{22}ClNO$: C, 68.68; H, 7.93. Found: C, 69.08; H, 8.06.

The free base of XVII was obtained by neutralizing the hydrochloride salt with sodium bicarbonate, and was crystallized from benzene–petroleum ether as fine needles containing one mole of benzene of crystallization, m.p. 105–106°. The infrared spectrum (chloroform) showed a wide spreading in the region 2.9–4.3 μ. As a Nujol mull, bands were observed at 3.3–4.3, 6.27, 12.50 and 13.34 μ.

*Anal.* Calcd. for $C_{16}H_{21}NO\cdot C_6H_6$: C, 82.20; H, 8.47. Found: C, 82.28; H, 8.74.

**2-Methyl-6-(*o*-anisyl)-1,2,3,4,6,7,8,9-octahydroisoquinoline (XVIII).**—To a solution of 1.11 g. (0.0206 mole) of sodium methoxide in 5.0 ml. of absolute ethanol was added a solution of 5.75 g. (0.0197 mole) of trimethylphenylammonium benzenesulfonate dissolved in 14 ml. of absolute ethanol. The salt which precipitated was removed by filtration and then washed with a few milliliters of absolute ethanol. To this solution then was added 3.54 g. (0.0145 mole) of the free base of XVII. The reaction was heated in an oil-bath until all of the ethanol had distilled and only an oily residue remained. After heating an additional hour at 110–120°, the flask was cooled and the residue acidified with 200 ml. of 15% acetic acid. This mixture was steam distilled until no further precipitation of dimethylaniline occurred when the distillate was made basic. A large volume of 20% potassium hydroxide was added to the non-volatile residue, and the resulting precipitate was extracted with two 100-ml. portions of ether. After drying over magnesium sulfate, evaporation of the ether left 2.80 g. (75%) of XVIII as a viscous oil which slowly crystallized. Sublimation of this material gave pure XVIII, m.p. 77–78.5°.

*Anal.* Calcd. for $C_{17}H_{23}NO$: C, 79.33; H, 9.01. Found: C, 79.37; H, 8.71.

**The hydrochloride of XVIII**, prepared in ether, was recrystallized from water; m.p. 203–204°. The infrared spectrum ($CHCl_3$) showed bands at 4.2, 6.28, 6.71 and 8.1 $\mu$; the ultraviolet absorption spectrum showed $\lambda_{\max}^{95\%\,\mathrm{EtOH}}$ 274 m$\mu$ (log $\epsilon$ 3.32) and 280 m$\mu$ (log $\epsilon$ 3.30).

*Anal.* Calcd. for $C_{17}H_{24}ClNO$: C, 69.48; H, 8.23. Found: C, 69.37; H, 8.03.

The methiodide of XVIII, prepared in ether, and crystallized from water, melted at 252–253°.

*Anal.* Calcd. for $C_{18}H_{26}INO$: C, 54.14; H, 6.56. Found: C, 54.52; H, 6.64.

**Oxidation of XVIII.**—A solution of 1.0 g. of the phenol XVII and 0.16 g. of sodium hydroxide in 25 ml. of water was warmed on the steam-bath, and 1.04 g. of freshly distilled dimethyl sulfate was added slowly. Alkalinity of the reaction mixture was controlled by testing with *p*H paper and adding 10% sodium hydroxide as needed. To this alkaline solution then was added 17.0 g. of potassium permanganate. After refluxing 2 hr., the excess permanganate was reduced with isopropyl alcohol, the solution filtered and evaporated to a small volume. Dilute sulfuric acid was added until the solution was acid to congo red. Extraction with two 50-ml. portions of ether, drying over sodium sulfate, and subsequent evaporation of the ether yielded 58 mg. of *o*-methoxybenzoic acid, m.p. 98–100°. There was no depression of this melting point when the sample was admixed with authentic *o*-methoxybenzoic acid, m.p. 98–100°

**The Hofmann Degradation of XVIII.**—To a magnetically stirred solution of 1.47 g. of the methiodide of XVIII in 600 ml. of water, cooled in an ice-bath, was added a 5 molar excess of freshly precipitated silver oxide (washed free of excess alkali by eight 100-ml. portions of water). The cooled solution was stirred for 90 min. and then was filtered through Filter-cel. The clear, colorless solution was concentrated *in vacuo* and, when the water was completely removed, the flask was heated to 150° for 20 min. at approximately 15 mm. pressure. After cooling, the flask was rinsed with five 25-ml. portions of ether, which on evaporation left 0.774 g. (77%) of **1,2,3,4-tetrahydro-4-dimethylaminomethyl-5-vinyl-2′-methoxybiphenyl (XIX)** as a clear oil. The infrared spectrum ($CHCl_3$) showed bands at 6.15, 6.28, 6.70 and 11.17 $\mu$, while the ultraviolet spectrum showed a $\lambda_{\max}^{95\%\,\mathrm{EtOH}}$ 223 m$\mu$ (log $\epsilon$ 4.23) and a shoulder at 260 m$\mu$ (log $\epsilon$ 3.99).

**The methiodide of XIX**, prepared in ether, and recrystallized from ethyl acetate and petroleum ether, melted at 170–172°.

*Anal.* Calcd. for $C_{19}H_{28}INO$: C, 55.21; H, 6.83. Found: C, 55.00; H, 6.66.

**The Reaction of XVI with Anisole.**—Into a dry 3-necked flask, through which nitrogen was passing, was placed 4.0 g. (0.018 mole) of XVI and 19.5 g. (0.18 mole) of freshly distilled anisole. The rapidly stirred mixture had to be heated to 125° before the mixture became homogeneous and hydrogen chloride evolution began. At the end of 2.5 hours, hydrogen chloride could no longer be detected in the effluent nitrogen stream and the solution was cooled. A crystalline material began precipitating from solution at about 40°; a small amount of ether was added to complete the precipitation. The crystalline material was removed by filtration, dissolved in water, and solid potassium carbonate was added slowly until the solution was saturated. Extraction of this mixture with four 25-ml. portions of ether, followed by drying over magnesium sulfate and subsequent evaporation of the ether, gave 1.74 g. (65%) of **2-methyl-1,2,3,7,8,9-hexahydroisoquinoline** as a mobile oil.

The hydrochloride of this base was prepared by the addition of an ethereal solution of hydrogen chloride to an ethereal solution of the base. Although this salt could be recrystallized from isopropyl alcohol, the compound was extremely hygroscopic. The ultraviolet absorption showed $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 232 m$\mu$ (log $\epsilon$ 4.08); $\lambda_{\max}^{\mathrm{calcd}}$ for the heteroannular diene 237 m$\mu$, for the homoannular diene 273 m$\mu$.

**The methiodide of 2-methyl-1,2,3,7,8,9-hexahydroisoquinoline** was prepared in ether and recrystallized from absolute ethanol, m.p. 227–228.5° dec.

*Anal.* Calcd. for $C_{11}H_{18}NI$: C, 45.37; H, 6.23. Found: C, 45.06; H, 6.46.

Madison 6, Wisc.

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[Contribution from the Department of Chemistry of the University of Wisconsin]

# Piperidine Derivatives. XXXII. Reaction of 1-Acyl-4-piperidones with Organometallic Compounds

By S. M. McElvain and David C. Remy[1]

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The course of the reactions of phenylmagnesium bromide and phenyllithium with a series of 1-acyl-4-piperidones Ia-d has been determined. These non-basic piperidones give greater amounts of their enolate salts and less addition to the carbonyl group with these organometallic reagents than do the more basic 1-methyl-4-piperidones. 2-Acetyl-6-oxo-*cis*-decahydroisoquinoline likewise gives low yields of the carbinol with phenylmagnesium bromide; the corresponding *trans* isomer gives no recognizable product with this reagent.

Previous work in this Laboratory has shown that the reactions of 1-methyl-3-substituted-4-piperidones with phenylmagnesium bromide and phenyllithium are quite complex. Addition of the organometallic reagent to the carbonyl group, formation of the metal enolate of the ketonic function and an aldol type of condensation of the ketone with itself can occur concurrently to varying extents depending on the nature of the 3-substituent of the ring and the organometallic reagent employed.[2] In general, phenyllithium has been found to give a

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