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 μ; the ultraviolet absorption spectrum showed $\lambda_{max}^{95\% EtOH}$ 274 mμ (log ϵ 3.32) and 280 mμ (log ϵ 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 μ, while the ultraviolet spectrum showed a $\lambda_{max}^{95\% EtOH}$ 223 mμ (log ϵ 4.23) and a shoulder at 260 mμ (log ϵ 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 $\lambda_{max}^{95\% EtOH}$ 232 mμ (log ϵ 4.08); λ_{max}^{calcd} for the heteroannular diene 237 mμ, for the homoannular diene 273 mμ.

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.

[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]

Received November 30, 1959

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

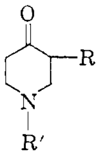
(2) S. M. McElvain, *et al.*, (a) This Journal, **72**, 3134 (1950); (b) **78**, 3140 (1956); (c) A. Ziering and J. Lee, *J. Org. Chem.*, **12**, 911 (1947).

greater amount of addition to the carbonyl group and less of the other reactions than did phenylmagnesium bromide. This was particularly evident with those piperidones whose 3-substituents possessed a polar group.[3] A similar observation has been made with a series of 2-substituted cyclohexanones and the differences in the behavior of the organometallic reagents with these ketones were related to the greater ability of the magnesium to coördinate with the carbonyl oxygen to produce a carbonium center with which the polar group of the substituent might interact.[4]

Inasmuch as a basic amino group was the most effective polar group in causing the enolization reaction with these ketones,[3,4] it appeared that the basic ring nitrogen of the 1-methyl-4-piperidones might promote the enolization of these ketones when they react with the Grignard reagent.[5] For this reason it seemed desirable to study the reaction of phenylmagnesium bromide and phenyllithium with some 1-acetyl-4-piperidones, in which the basic character of the ring nitrogen is masked in the amide function.

The four amides Ia-d, which were used in this study, were prepared from 1-benzoyl-3-carbethoxy-4-piperidone by modifications of procedures previously described. The results of the reactions of these amido ketones with phenylmagnesium bromide and phenyllithium are summarized in Table I. For comparison, previously reported data on the reaction of analogous 1-methyl-4-piperidones Ie-f are included in this table. In order to minimize any possible addition of the organometallic reagent to the amide function the reactions were run at 0° and the technique of inverse addition was used. Also, because of the ether insolubility of Ia and Ic, the reactions were carried out in a benzene–ether solvent pair which permitted homogeneous solution to be maintained at 0°. Therefore, the comparisons of the reactions of the amido ketones Ia-d and the amino ketones Ie-g are not strictly valid because of solvent and temperature differences in the reaction conditions.

Ia, R = H; R' = CH_3CO
Ib, R = $CH_3(CH_2)_3$; R' = CH_3CO
Ic, R = $C_6H_5CH_2$; R' = CH_3CO
Id, R = $C_6H_5CH_2$; R' = C_6H_5CO
Ie, R = H; R' = CH_3
If, R = $CH_3(CH_2)_2$; R' = CH_3
Ig, R = $C_6H_5CH_2$; R' = CH_3



The results of these reactions, shown in Table I, lead to two general conclusions: (1) the reaction of both of the organometallic reagents with the 1-acyl-4-piperidones proceeds in the opposite manner to what would be expected if the basic nitrogen were involved in promoting the enolization reaction and thereby hindering the addition of the reagent to the ketone function; and (2) with the amidopiperidones Ia-d phenylmagnesium bromide gives from one and one-half to three times better yield of addition compound than does phenyllithium, whereas the converse is true with the amino ketones Ie-g.

Table I

Reaction Products of Certain 4-Piperidones with Organometallic Compounds

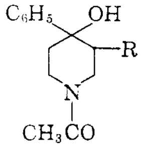
Ketone	Phenylmagnesium bromide Recovd. ketone, %	Addition prod., %	Material balance, %	Phenyllithium Recovd. ketone, %	Addition prod., %	Material balance, %
Ia	35[a]	25	60	32[a]	9	41
Ib	43	27	70	61	10	71
Ic	41	44[b]	85	65	26	91
Id	35	40	75	65	19	84
Ie		57	57[c]		76	84[c,d]
If	40	35	75[e]	23	65	88[f]
Ig	44	33	77[e]	24	64	88[f]

[a] This ketone recovered as 2,4-dinitrophenylhydrazone. [b] When this reaction was run with 2 moles of phenylmagnesium bromide, the yield of addition product was 41%. [c] Ref. 2a. [d] This material balance includes an 8% yield of 1-methyl-3-(1'-methyl-4'-hydroxy-4'-piperidyl)-4-hydroxy-4-phenylpiperidine. [e] M. D. Barnett, Research Report, University of Wisconsin, 1956. [f] Ref. 2b.

In the reactions of Ia with the two organometallic reagents, the solubility of this ketone in water necessitated its recovery as the derivative indicated in Table I. Pure Ia in water forms an insoluble 2,4-dinitrophenylhydrazone in 90% yield. The poor material balances shown for Ia are due to the formation in these reactions of considerable amounts of intractable oily residual materials, which presumably are aldol types of condensation products of Ia.

1-Acetyl-3-*n*-butyl-4-phenyl-4-piperidinol (IIb), as obtained from the addition of phenyllithium to Ib, was a mixture of stereoisomers.

IIa, R = H
IIb, R = $CH_3(CH_2)_3$
IIc, R = $C_6H_5CH_2$



By fractional crystallization 80% of this mixture was obtained as a sharp-melting α-isomer. The remainder of the material, although crystalline, melted over a wide range. By a lengthy fractional crystallization of this material, a pure sample of the β-isomer was obtained. The infrared spectra of these two isomers show bands at 2.99 and 6.20 μ, but the regions between 9 and 11 μ are different. The alcohol IIb obtained from the reaction of phenylmagnesium bromide with Ib was exclusively the α-isomer. The formation of two steroisomeric carbinols from the reaction of phenyllithium with 1-methyl-3-*n*-butyl-4-piperidone has been noted.[6]

A single carbinol IIc was obtained from the reaction of Ic with either of the organometallic reagents. This result also parallels the report that 1-methyl-3-benzyl-4-piperidone gave a single product with phenyllithium.[6]

It has been observed in this Laboratory that phenylmagnesium bromide reacts with 1-acetylpiperidine *at room temperature* to give a 43% yield of acetophenone and 41% of recovered 1-acetylpiperidine.[7] The latter product is doubtless the

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(3) S. M. McElvain, W. B. Dickinson and R. J. Athey, This Journal, **76**, 5625 (1954).

(4) S. M. McElvain and R. B. Clampitt, *ibid.*, **81**, 5590 (1959).

(5) *Cf.* S. M. McElvain and R. E. Lyle, *ibid.*, **72**, 384 (1950).

(6) A. Zerring, A. Motchane and J. Lee, *J. Org. Chem.*, **22**, 1521 (1957).

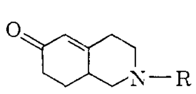
(7) R. J. Athey, Ph.D. Thesis, University of Wisconsin, 1953.

result of an enolization reaction at the 1-acetyl group. In order to exclude the possibility that the recovered ketone yields in Table I were not due to a similar enolization reaction of the 1-acetyl group of the ketones Ia-c, 1-benzoyl-4-piperidone (Id) was included in the study. Since the results with this piperidone, which is incapable of enolization at the amide function, are essentially the same as those with Ic, it seems safe to conclude that the enolization reaction that led to the recovered ketone in the reactions of Ia-c involved the ketone group of these piperidones.

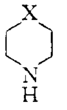
In the reactions of Ia-d with phenylmagnesium bromide and phenyllithium, one equivalent of the organometallic compound was added slowly to the solution of the piperidone. In each case a precipitate occurred almost immediately. Certain ketones are known to react with Grignard reagents to give insoluble coördination complexes, which yield the ketone on hydrolysis and which require an excess of the Grignard reagent to give the normal addition to the carbonyl group. The possibility that such a reaction was the source of the recovered ketones listed in Table I was eliminated when it was found that Ic gave essentially the same results with two moles of the Grignard reagent as with one mole (*cf.* footnote *b*, Table I).

From the results shown in Table I, it is apparent that masking the basicity of the nitrogen of 4-piperidones does not decrease the amount of the enolization reaction that these ketones give with organometallic compounds, as the relatively non-basic 1-acyl-4-piperidones Ia-d show this reaction to an even greater extent than do the more basic piperidones Ie-g. While the mechanism by which the amide moiety operates is not known, two rationalizations of its behavior may be considered.

First, it has been shown from spectral data that the hetero ring of the bicyclic ketoamide IIIa quite probably exists in the boat conformation.[8a] This compound is a vinylog of the 1-acetyl-4-piperidones Ia-c and the possibility exists that these simpler structures might also exist in a boat conformation. To the extent that the amide oxygen can supply electrons to the developing carbonium center of the carbonyl carbon, nucleophilic attack at that carbon by the organometallic reagent will be diminished.



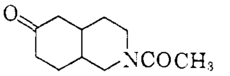
IIIa, R = CH_3CO
IIIb, R = CH_3



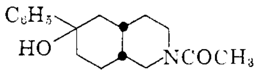
IV, X = CH_2, NH, NH_2^+, O, S, $NCOCH_3$, $NCOC_6H_5$, $NCOOC_2H_5$, or $NSO_2C_7H_7$

A second possibility derives from the work of Hall,[9] in which it was found that the direct field effect of the hetero group X constitutes a significant factor in determining the base strength of the series of cyclic amines IV. The direct field effect, together with the inductive effect, of the hetero atom has been used to explain the hypsochromic shift observed in the ultraviolet absorption maximum of the amino ketone IIIb[8b] in non-polar media.[10] If the direct field effect is operative in the 1-acyl-4-piperidones Ia-d, it, together with the normal inductive effect of the amide moiety, should decrease the electrophilic character of the carbonyl carbon while increasing the acidic character of the hydrogen atoms in the α-position to this carbonyl group.

When it was found that the amide function of the 1-acyl-4-piperidones Ia-d diminished the tendency of the carbonyl group to add the organometallic reagents, it seemed of interest to determine the course of reaction of the 2-acetyl-6-oxo-*cis*- and *trans*-decahydroisoquinolines Va and b with such reagents, particularly since these ketones had shown anomalous behavior toward the ordinary carbonyl reagents.[8a] The 6-oxo-octahydroisoquinoline IIIa had been found to react with phenylmagnesium bromide in the presence of cuprous chloride to give a product in 60% yield, whose formation required the addition of the Grignard reagent to the carbonyl group.[8] Similarly, the 2-methyl analog IIIb as well as the corresponding saturated compound, 2-methyl-6-oxo-*cis*-decahydroisoquinoline, readily add organometal reagents at the ketonic function.[8b]



Va, *cis*; Vb, *trans*



VI

Phenylmagnesium bromide reacted with Va to give two stereoisomeric forms of the carbinol VI in 8 and 31% yields, respectively; 11% of Va was recovered from the reaction. The remainder of the reaction product was an intractable oil. When the *trans*-ketone Vb was used in a similar reaction none of the carbinol corresponding to VI could be found. All of the reaction products, even after extensive chromatography, remained as intractable oils and gums, indicating that the basic reagent had caused extensive polycondensation of the ketone.

Experimental

1-Acetyl-4-piperidone (Ia).—A slurry of 74.7 g. (0.272 mole) of 1-benzoyl-3-carbethoxy-4-piperidone[11] and 750 ml. of 6 *N* hydrochloric acid was heated under reflux with vigorous stirring for 3 hr. After cooling, the crystalline benzoic acid was removed by filtration, and the solution was extracted with two 100-ml. portions of ether. The clear aqueous solution then was evaporated to dryness on a steam-bath under reduced pressure. The crystalline residue (36.3 g.) was dissolved in 500 ml. of water and cooled to 0°. While stirring rapidly, 32.6 g. (0.319 mole) of acetic anhydride was added. Solid potassium carbonate then was added slowly until the solution was saturated. After continuous extraction of this solution for 72 hr. with benzene, evaporation of the benzene left an amber oil. Distillation of this oil through a short Vigreux column gave 12.4 g. (33%) of Ia, b.p. 120–128° (0.2 mm.), $n^{25}D$ 1.5029 (reported[11] b.p. 124–128° (0.2 mm.), $n^{25}D$ 1.5023). The 2,4-dinitrophenylhydrazone, obtained in 90% yield, was recrystallized from ethanol–ethyl acetate; m.p. 212–214° (reported[11] 212–213°).

1-Benzoyl-3-butyl-3-carbethoxy-4-piperidone was prepared by the procedure of Trimble[12]: To a hot solution of potassium *t*-butoxide prepared from 14.1 g. (0.362 g. atom) of potassium and 300 ml. of dry *t*-butyl alcohol was added dropwise with stirring a solution of 99 g. (0.36 mole) of 1-benzoyl-3-carbethoxy-4-piperidone in 50 ml. of dry *t*-butyl alcohol.

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[8] (a) S. M. McElvain and D. C. Remy, This Journal, **82**, 3960 (1960); (b) S. M. McElvain and P. H. Parker, *ibid.*, **78**, 5312 (1956).

[9] H. K. Hall, *ibid.*, **78**, 2570 (1956).

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

[11] S. M. McElvain and R. E. McMahon, This Journal, **71**, 901 (1949).

[12] A. T. Trimble, Jr., Ph.D. Thesis, University of Wisconsin, 1952, p. 44.

The suspension was heated on a sand-bath for 15 minutes. After cooling under a tap, 100 ml. of diethyl ether was added, and the mixture centrifuged, extracted with 100 ml. of diethyl ether, and again centrifuged. The resulting solid was rinsed into the Parr pressure reaction bomb with a total of 225 ml. (2.1 moles) of freshly distilled butyl bromide. The bomb was sealed and heated at 130° until the solids no longer showed a basic reaction to litmus and a purple coloration to ferric chloride test solution (12 hours). The phases were separated by suction filtration with the aid of Filter-cel and the filter cake rinsed with 100 ml. of ethyl acetate. The combined ester solutions were transferred to a separatory funnel and washed successively with 100-ml. portions of 1% sodium hydroxide, 1% hydrochloric acid, dilute sodium bicarbonate and water. The final washings gave a neutral reaction to litmus. Removal of low-boiling material under reduced pressure left 88 g. (75%) of a light amber oil, $n^{25}\text{D}$ 1.5257. A small portion was distilled to yield a yellow oil, b.p. 170–175° (0.1 mm.), $n^{25}\text{D}$ 1.5296.

Anal. Calcd. for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60. Found: C, 68.64; H, 7.75.

1-Acetyl-3-*n*-butyl-4-piperidone (Ib).—A slurry of 265 g. (0.80 mole) of 1-benzoyl-3-*n*-butyl-3-carbethoxy-4-piperidone in 2700 ml. of 6 *N* hydrochloric acid was hydrolyzed in the manner previously described for the preparation of Ia. The 123.0 g. of salt residue was dissolved in 1300 ml. of water and warmed to 50°. While stirring rapidly, 81.6 g. (0.80 mole) of acetic anhydride was added, followed by the addition of 59.04 g. (0.72 mole) of sodium acetate dissolved in 400 ml. of water. After cooling to room temperature, sodium bicarbonate was added until the reaction mixture was basic to litmus. After extraction of this solution with four 250-ml. portions of benzene, evaporation of the benzene left a red oil which was distilled through a small Vigreux column to give 34.1 g. (22%) of Ib as a clear colorless liquid, b.p. 132–135° (0.15 mm.), $n^{25}\text{D}$ 1.4868. The infrared spectrum (liquid film) showed bands at 5.85 and 6.10 μ.

Anal. Calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71. Found: C, 66.93; H, 9.58.

The **2,4-dinitrophenylhydrazone** required several days for precipitation. Recrystallization from benzene and petroleum ether gave yellow clumps, m.p. 137–139°.

Anal. Calcd. for $C_{17}H_{23}N_5O_5$: C, 54.10; H, 6.14. Found: C, 54.36; H, 6.27.

1-Acetyl-3-benzyl-4-piperidone (Ic).—A solution of 10.1 g. (0.045 mole) of pure crystalline 3-benzyl-4-piperidone hydrochloride[13] in 125 ml. of water was treated with 5.5 g. (0.054 mole) of acetic anhydride and 4.05 g. (0.0495 mole) of sodium acetate dissolved in 25 ml. of water as previously described in the preparation of Ib. After extracting the solution with benzene, evaporation of the benzene left a colorless oil which was distilled at reduced pressure to give 9.16 g. (88%) of Ic, b.p. 167–172° (0.07 mm.). The distillate crystallized immediately; recrystallization from ethyl acetate–petroleum ether gave white fluffy needles, m.p. 93–94°. The infrared spectrum (CS_2) showed bands at 5.81 and 6.06μ. The molecular weight was determined cryoscopically in benzene; calcd. 231, found 237.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41. Found: C, 72.42; H, 7.30.

The **2,4-dinitrophenylhydrazone** required several days for precipitation. Recrystallization from ethanol and ethyl acetate yielded sparkling golden plates, m.p. 204.5–206°.

Anal. Calcd. for $C_{20}H_{21}N_5O_5$: C, 53.38; H, 5.15. Found: C, 58.19; H, 5.08.

1-Benzoyl-3-benzyl-4-piperidone (Id).—To 2.00 g. of 3-benzyl-4-piperidone hydrochloride[13] dissolved in 50 ml. of water was added 1.50 g. of benzoyl chloride and 10 ml. of 5% sodium hydroxide. The solution was shaken vigorously for several minutes, another 15 ml. of 5% sodium hydroxide added, and the solution was shaken vigorously again. The solution was extracted twice with 25-ml. portions of benzene which then were washed with water and dried over potassium carbonate. Evaporation of the benzene left a clear colorless oil which was crystallized easily from ethyl acetate–petroleum ether to give 2.45 g. (95%) of Id as fluffy white needles, m.p. 97–98.5°.

Anal. Calcd. for $C_{19}H_{19}NO_2$: C, 77.77; H, 6.53. Found: C, 77.54; H, 6.46.

The Reaction of 1-Acetyl-4-piperidone (Ia) with Phenyllithium.—A solution of 5.92 g. (0.0420 mole) of Ia in 75 ml. of dry benzene was placed in a 3-necked flask equipped with stirrer, condenser and dropping funnel. To this solution, cooled to 0°, was added dropwise an ethereal solution of phenyllithium prepared from 0.75 (0.108 g. atom) of lithium and 7.06 g. (0.045 mole) of bromobenzene. In this and the following experiments in which inverse additions of organometallic compounds were employed, the organometallic reagent was transferred directly into the dropping funnel through a dry glass tube by means of nitrogen pressure. A piece of glass wool was used to filter off any unreacted particles of metal. The addition was complete in 1 hr. at which time 40 ml. of 3 *N* hydrochloric acid was added. The benzene–ether phase was separated, filtered through sodium sulfate, and evaporated to dryness. The residual oil was taken up in a minimum quantity of benzene and triturated with petroleum ether. After several days 0.81 g. (9%) of **1-acetyl-4-phenyl-4-piperidinol** (IIa) crystallized. Recrystallization from benzene gave pure IIa, m.p. 149.5–150.5°.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82. Found: C, 71.55; H, 7.61.

After filtering IIa from the reaction mixture the solvents were evaporated to dryness leaving 2.46 g. of a red oil which could not be crystallized or distilled.

A solution of 2,4-dinitrophenylhydrazine reagent sufficient to react with 5.92 g. of Ia was added to the aqueous acid phase of the above phenyllithium hydrolysis reaction. After cooling overnight, there was obtained 4.28 g. (32%) of the 2,4-dinitrophenylhydrazone of Ia, m.p. 211–214°.

The Reaction of Ia with Phenylmagnesium Bromide.—A solution of 6.55 g. (0.0465 mole) of Ia in 75 ml. of benzene was cooled to 0° and treated dropwise with 29.8 ml. of a 1.56 *N* ethereal solution of phenylmagnesium bromide. Hydrolysis was effected after 1 hr. by the dropwise addition of a saturated solution of ammonium chloride until the mixture cleared and a white cake of inorganic salt precipitated. The clear organic phase was decanted and the residues rinsed well with hot benzene. Approximately 100 ml. of ether was added to the benzene solution, and on cooling 2.53 g. (25%) of IIa crystallized.

After IIa had been removed by filtration, the filtrate was evaporated to dryness leaving 1.02 g. of oily material. Distillation of this residue gave 0.13 g. of material that appeared to be the starting ketone Ia, b.p. 108–110° (0.1 mm.). This material and the non-distillable pot residues were not characterized further.

A solution of 2,4-dinitrophenylhydrazine reagent sufficient to react with 6.55 g. of Ia was added to the cake of inorganic salts obtained from hydrolysis of the Grignard reaction. The 2,4-dinitrophenylhydrazone of Ia rapidly precipitated and after removal and drying weighed 5.19 g. (35%), m.p. 208–213°.

The Reaction of 1-Acetyl-3-*n*-butyl-4-piperidone (Ib) with Phenyllithium.—A solution of 16.11 g. (0.0818 mole) of Ib in a mixture of 200 ml. of benzene and 100 ml. of ether was treated with an ethereal solution of phenyllithium prepared from 1.15 g. (0.166 g. atom) of lithium and 13.01 g. (0.083 mole) of bromobenzene as described previously. After hydrolysis of the reaction mixture with 80 ml. of water, the organic phase was withdrawn and the solvent removed under diminished pressure leaving an orange tarry residue. Distillation of this residue yielded 9.84 g. (61%) of recovered Ib, b.p. 119–125° (0.10 mm.). The residue from this distillation was dissolved in benzene and triturated with petroleum ether. The crystalline material which separated was removed by filtration and the solution triturated with additional petroleum ether. By continuing this process, there was obtained a total of 2.14 g. (10%) of crystalline material melting at 95–110°. By fractional crystallization from benzene–petroleum ether, 1.71 g. of the predominant α-form of **1-acetyl-3-*n*-butyl-4-phenyl-4-piperidinol** (IIb) was obtained, m.p. 124–125°. By repeated concentration of the mother liquors and recrystallization of the material obtained, there was obtained 15 mg. of the β-diastereomer of IIb in pure form, m.p. 98.5–100°. The infrared absorption spectra (chloroform) of both diastereomers showed bands at 2.80, 2.99 and 6.20 μ; the regions of 9 to 11 μ were different.

Anal. Calcd. for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15. Found: α; C, 73.68; H, 8.92. β: C, 74.33; H, 9.04.

The Reaction of Ib with Phenylmagnesium Bromide.—To a solution of 7.20 g. (0.0365 mole) of Ib in 135 ml. of a 2:1

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(13) G. Stork and S. M. McElvain, THIS JOURNAL, **68**, 1053 (1946).

mixture of benzene and ether was added an ethereal solution of phenylmagnesium bromide prepared from 0.925 g. (0.038 g. atom) of magnesium and 5.96 g. (0.038 mole) of bromobenzene as previously described. After hydrolysis of the mixture with 100 ml. of 25% sulfuric acid, the organic phase was separated and washed with sodium carbonate. Evaporation of the solvent left an amber oil which was fractionally distilled to give 3.05 (43%) of recovered Ib, b.p. 112–113° (0.06 mm.). The residue from this fractionation was dissolved in benzene and triturated with petroleum ether. Crystallization was rapid and there was obtained 2.66 g. (27%) of IIb, m.p. 119–123°. Recrystallization from benzene and petroleum ether gave the pure α-diastereoisomer, m.p. 123–124.5°.

The Reaction of 1-Acetyl-3-benzyl-4-piperidone (Ic) with Phenyllithium.—A solution of 8.0 g. (0.0346 mole) of Ic in a mixture of 100 ml. of benzene and 50 ml. of ether was treated with an ethereal solution of phenyllithium prepared from 0.584 g. (0.0842 g. atom) of lithium and 5.5 g. (0.035 mole) of bromobenzene as previously described. After the reaction was hydrolyzed with 50 ml. of water, it was filtered to remove a voluminous white precipitate, which, after drying, weighed 2.74 g. (26%). Recrystallization of this material from aqueous ethanol gave pure **1-acetyl-3-benzyl-4-phenyl-4-piperidinol** (IIc) as fluffy needles, m.p. 238.5–239.5°. The infrared absorption spectrum (Nujol mull) showed bands at 3.05, 6.21 and 13.15 μ.

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49. Found: C, 77.71; H, 7.48.

The organic phase of the filtrate from the above reaction was separated. After drying over magnesium sulfate, evaporation of the solvent left an oil which was easily crystallized from ethyl acetate–petroleum ether to give 5.17 g. (65%) of recovered Ic.

The Reaction of Ic with Phenylmagnesium Bromide.—A solution of 10.0 g. (0.0433 mole) of Ic in 150 ml. of benzene and 65 ml. of ether was treated with an ethereal solution of phenylmagnesium bromide prepared from 7.23 g. (0.046 mole) of bromobenzene and 1.12 g. (0.046 g. atom) of magnesium and subsequently hydrolyzed as described for the reaction of Ib with phenylmagnesium bromide. The precipitate which formed was removed by filtration. Recrystallization of this precipitate from aqueous ethanol gave 5.81 g. (44%) of pure IIc, m.p. 238–239°. The organic phase of the filtrate was separated from the aqueous acid and washed with a solution of sodium carbonate. After drying over magnesium sulfate, evaporation of the solvent left an oil which was crystallized from ethyl acetate–petroleum ether to give 4.11 g. (41%) of the starting ketone Ic.

This reaction was repeated except that two moles of Grignard reagent was added per mole of the ketone Ic. The reaction followed the same pattern in that the adduct IIc crystallized as a voluminous white precipitate during the hydrolysis. This precipitate was collected by filtration and recrystallized from aqueous ethanol to give a 41% yield of IIc, m.p. 238–239°.

The Reaction of 1-Benzoyl-3-benzyl-4-piperidone (Id) with Phenyllithium.—To a solution of 3.0 g. (0.0102 mole) of Id in 100 ml. of benzene was added an ethereal solution of phenyllithium prepared from 0.181 g. (0.0261 g. atom) of lithium and 1.71 g. (0.0109 mole) of bromobenzene as previously described. After hydrolysis of the mixture with 50 ml. of water, the organic phase was separated, boiled to expel traces of water, and filtered. On cooling, a total of 0.72 g. (19%) of **1-benzoyl-3-benzyl-4-phenyl-4-piperidinol** crystallized. Recrystallization from benzene gave the pure alcohol, m.p. 207–209°.

Anal. Calcd. for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78. Found: C, 80.63; H, 6.56.

After the addition compound had been removed by filtration, the organic filtrate was evaporated to dryness and the residual oil taken up in ethyl acetate–petroleum ether. On cooling, a total of 1.95 g. (65%) of Id crystallized.

The Reaction of Id with Phenylmagnesium Bromide.—A solution of 3.0 g. (0.0102 mole) of Id in 100 ml. of benzene was treated with an ethereal solution of phenylmagnesium bromide prepared from 1.71 g. (0.0109 mole) of bromobenzene and 0.265 g. (0.0109 g. atom) of magnesium as previously described. After hydrolysis and separation of the organic phase, a total of 1.50 g. (40%) of 1-benzoyl-3-benzyl-4-phenyl-4-piperidinol crystallized. The organic filtrate yielded 1.04 g. (35%) of the starting ketone Id.

The Reaction of 2-Acetyl-6-oxo-*cis*-decahydroisoquinoline (Va) with Phenylmagnesium Bromide.—A solution of 3.00 g. (0.0154 mole) of Va in a mixture of 50 ml. of benzene and 10 ml. of ether was placed in a 3-necked flask equipped with stirrer, dropping funnel and condenser. After cooling to 0° and passing nitrogen through the system, an ethereal solution of phenylmagnesium bromide, prepared from 2.51 g. (0.016 mole) of bromobenzene and 0.393 g. (0.016 g. atom) of magnesium, was added dropwise over a 45-minute period. A yellow precipitate which formed at the start of the reaction continued to accumulate during the addition. After all the Grignard reagent had been added, the solution was allowed to warm to room temperature over an hour while stirring was continued. At this time a saturated solution of ammonium chloride was added dropwise until the reaction cleared and a white cake of inorganic salts formed. The organic layer was decanted and the residues washed with two 20-ml. portions of warm benzene. The combined organic phases were evaporated to approximately 15 ml. On cooling, one of the diastereoisomers (α) of **2-acetyl-6-phenyl-6-hydroxy-*cis*-decahydroisoquinoline** (VI) crystallized; after filtration and drying it weighed 0.339 g. (8%). Recrystallization from benzene gave pure VI, m.p. 213–214°. The infrared absorption spectrum (mull) showed bands at 2.94 and 6.21 μ.

Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48. Found: C, 74.27; H, 8.47.

After the crystalline α-stereoisomer had been removed by filtration, the benzene filtrate was evaporated in a stream of nitrogen. The residue from this evaporation was taken up in ethyl acetate. Upon trituration with petroleum ether, crystallization occurred. After filtration and recrystallization from ethyl acetate and petroleum ether, 1.30 g. (31%) of the β-diastereoisomer of **2-acetyl-6-phenyl-6-hydroxy-*cis*-decahydroisoquinoline** (VI), m.p. 165.5–166.5°, was obtained. The infrared absorption spectrum showed bands at 2.92 and 6.22 μ. The region from 7 to 12 μ was different from that for the α-diastereoisomer.

Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48. Found: C, 74.94; H, 8.23.

The filtrate obtained after removal of the β-diastereoisomer was evaporated in a stream of nitrogen and the residue obtained taken up in benzene. This benzene solution was passed through a short column of Fisher alumina, 80–200 mesh, using benzene as a solvent. Subsequent evaporation of the benzene gave an oil which could be crystallized from ethyl acetate and petroleum ether. After removal by filtration, there was obtained 0.338 g. (11%) of the starting ketone Va, m.p. 111–114°. When the chromatographic column finally was washed with methanol, there was obtained 0.839 g. of an intractable oil that showed no tendency to crystallize after long standing.

The above experiment was repeated using a solution of 4.93 g. (0.0252 mole) of the *trans*-ketone Vb in 60 ml. of dry benzene and 10 ml. of dry ether. It was allowed to react with a solution of phenylmagnesium bromide prepared from 4.25 g. (0.027 mole) of bromobenzene and 0.656 g. (0.027 g. atom) of magnesium. The reaction was carried out and worked up as described for the reaction of Va. No addition product could be isolated from the reaction mixture. When the reaction mixture was chromatographed over a column of Fisher alumina, 80–200 mesh, using benzene to develop the column, a total of 3.62 g. of an oily material was obtained.

When methanol finally was used to elute the column, 1.452 g. of an intractable gummy material was obtained which could not be crystallized, and, therefore, was not further characterized.

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