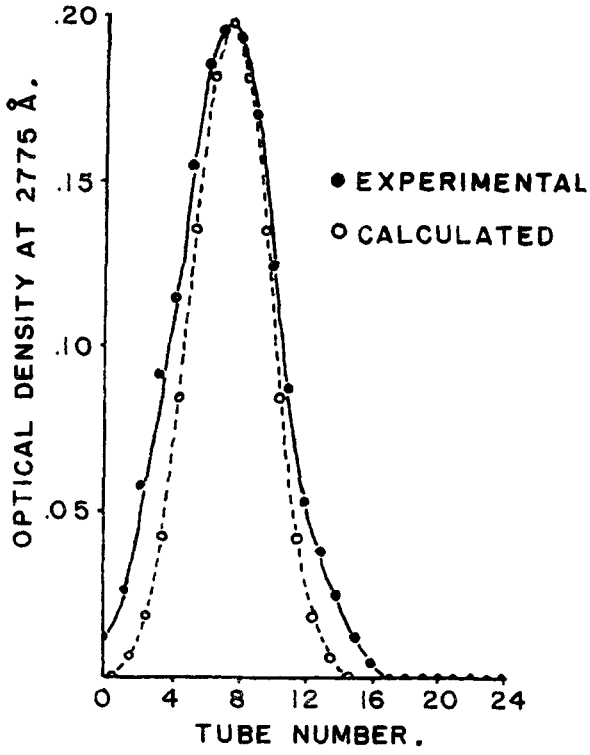


Fig. 1.--Analytical redistribution of hog melanophore hormone.

The contents of tubes numbers 166 to 168 in the larger countercurrent apparatus were found to have the highest ACTH potency ($K = 7.0$). The mixed contents of these tubes, after being concentrated and treated as previously described, were subjected to a 24-tube distribution between 0.1% trichloroacetic acid and secondary butyl alcohol. The ACTH preparation thus obtained was not pure and gave an approximate partition ratio of 1.0.

TABLE II

AMINO ACID COMPOSITION OF MELANOPHORE-EXPANDING HORMONE FROM HOG PITUITARY GLAND

The amino acids and amide ammonia account for 95.2% (uncorrected for moisture and ash) of the total nitrogen of the sample.

| | Per cent. | Molar ratio | Minimum residues per molecule |
|---|---|---|---|
| Alanine | 0.2 | 0.2 | .. |
| Arginine | 4.2 | 1.9 | 2 |
| Aspartic acid | 5.8 | 3.5 | 4 |
| Cystine | 0.3 | 0.1 | .. |
| Glutamic acid | 7.3 | 4.0 | 4 |
| Glycine | 2.2 | 2.3 | 2 |
| Histidine | 2.9 | 1.5 | 2 |
| Isoleucine | .. | .. | .. |
| Leucine | 0.2 | 0.2 | .. |
| Lysine | 6.7 | 3.7 | 4 |
| Methionine | 1.6 | 0.9 | 1 |
| Phenylalanine | 3.7 | 1.8 | 2 |
| Proline | 4.9 | 3.4 | 3 |
| Serine | 2.2 | 1.7 | 2 |
| Threonine | .. | .. | .. |
| Tryptophan | 5.3 | 2.1 | 2 |
| Tyrosine | 3.8 | 1.7 | 2 |
| Valine | 0.5 | 0.3 | .. |
| Amide ammonia | 0.5 | 4.4 | 4 |

The amino acid composition was determined according to the method of Wellington.[11] The acid hydrolysate of the melanophore material from the "peak" tubes of the 24-tube transfer was chromatographed on paper and the amino acids were stained with ninhydrin. The optical density of the respective eluates was read in a Beckman spectophotometer. Tryptophan was determined according to the method of Spies and Chambers.[12] Amide ammonia was determined by the method of Conway.[13] The results of the analyses are given in Table II.

The above amino acid analyses differ considerably from those reported by Lerner and Lee[5] for their purified hog melanophore preparation. The present authors find only trace amounts, or complete absence, of the following amino acids reported present by Lerner and Lee: alanine, cystine, leucine, threonine and valine. Furthermore, histidine and methionine are definitely present in our material whereas Lerner and Lee found the former to be absent from their preparation and did not analyze for the latter amino acid.

(11) E. F. Wellington, *Can. J. Chem.*, **30**, 581 (1952).
(12) J. R. Spies and D. C. Chambers, *Anal. Chem.*, **20**, 30 (1948).
(13) E. J. Conway, "Micro-Diffusion Analysis and Volumetric Error," Crosby Lockwood and Sons, Ltd., Great Britain, 1939.

DEPARTMENTS OF PHARMACOLOGY AND BIOCHEMISTRY
MCGILL UNIVERSITY
MONTREAL, CANADA

## The Reaction of the Chloromagnesium Derivative of Chloromagnesium Phenylacetate with Basic Ketones

BY F. F. BLICKE AND HAROLD ZINNES

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It was found that the Mannich base, 4-diethylamino-2-butanone, reacted with the chloromagnesium derivative of chloromagnesium phenylacetate (an Ivanov reagent) to yield α-phenyl-β-methyl-β-hydroxy-δ-diethylaminovaleric acid.

When the Ivanov reagent was allowed to react with 1-methyl- and with 1-ethyl-4-piperidone, the products were α-phenyl-α-(1-alkyl-4-hydroxy-4-piperidyl)-acetic acids. The methyl esters of these acids were prepared.

### Experimental

**α-Phenyl-β-methyl-β-hydroxy-δ-diethylaminovaleric Acid.**—Isopropylmagnesium chloride was prepared from 14.6 g. of magnesium, 70 cc. of isopropyl chloride and 100 cc. of ether. After the addition of 150 cc. of ether and 40.8 g. of phenylacetic acid, dissolved in 300 cc. of benzene, the mixture was refluxed for 18 hours. A solution of 28.6 g. of 4-diethylamino-2-butanone[1] in 100 cc. of benzene was added and the material was refluxed for 4 hours. The mixture was poured into an ice-cold solution of 60 cc. of concentrated hydrochloric acid in 300 cc. of water. The layers were separated and the organic layer was extracted with 10% hydrochloric acid. The combined aqueous layers were washed with ether and the solvent was removed under reduced pressure. The residue was extracted with chloroform at room temperature. After removal of the solvent under reduced pressure, the gummy residue was dissolved in 200 cc. of water and the solution was stirred with freshly prepared silver oxide which had been obtained from 51 g. of

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

silver nitrate. After 12 hours the precipitate was removed, the filtrate was treated with hydrogen sulfide, charcoal was added and the mixture was filtered. The water was removed by distillation under reduced pressure and the red, gummy residue was refluxed for 30 minutes with 200 cc. of reagent acetone. The white solid, obtained when the mixture was cooled, was dissolved in a hot mixture of 85 cc. of acetone and 20 cc. of absolute methanol. After several days the precipitate weighed 11.0 g. (20%), m.p. 163–165° dec. after an additional recrystallization.

*Anal.* Calcd. for $C_{16}H_{25}O_3N$: C, 68.78; H, 9.02; N, 5.02. Found: C, 68.80; H, 9.05; N, 5.01.

**α-Phenyl-α-(1-methyl-4-hydroxy-4-piperidyl)-acetic Acid.**—After isopropylmagnesium chloride had been prepared from 29.2 g. of magnesium, 130 cc. of isopropyl chloride and 300 cc. of ether, an additional 300 cc. of ether was added. Phenylacetic acid (81.6 g.), dissolved in 500 cc. of benzene, was added and the material was refluxed for 24 hours. Then 45.2 g. of 1-methyl-4-piperidone,[2] dissolved in 500 cc. of benzene, was added and the mixture was refluxed for 4 hours. It was poured into an ice-cold solution of 120 cc. of concentrated hydrochloric acid in 500 cc. of water. The layers were separated and the organic layer was extracted with 10% hydrochloric acid. The combined aqueous layers were washed with ether and evaporated to dryness under reduced pressure. The residue was refluxed with 250 cc. of nitromethane for 30 minutes and the hot mixture was filtered through a sintered glass funnel. After this extraction process had been repeated four times, the combined nitromethane solutions were concentrated under reduced pressure. The hydrochloride of the product, which separated, was recrystallized from nitromethane as solvent, yield 70.9 g. Treatment of this salt with silver oxide, prepared from 62 g. of silver nitrate, yielded an aqueous solution of the free basic acid. The solution was concentrated under reduced pressure and the precipitate was removed at intervals. A gummy residue of unknown nature remained in the distillation flask; yield 50.9 g. (51% based on the piperidone); when heated, the product started to decompose at 231°.

*Anal.* Calcd. for $C_{14}H_{19}O_3N$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.14; H, 7.56; N, 5.63.

**α-Phenyl-α-(1-ethyl-4-hydroxy-4-piperidyl)-acetic Acid.**—This compound was prepared in the manner described above except that 51.5 g. of 1-ethyl-4-piperidone[3] was employed. The hydrochloride, which separated from the nitromethane solution, was recrystallized from isopropyl alcohol; yield 87.0 g. (72%); after further recrystallization it melted at 201–207° dec.

*Anal.* Calcd. for $C_{15}H_{22}O_3NCl$: C, 60.08; H, 7.40; N, 4.67; Cl, 11.83. Found: C, 59.60; H, 7.27; N, 4.68; Cl, 11.77.

The hydrochloride (60.0 g.) was dissolved in 250 cc. of water and treated with silver oxide which had been prepared from 38.0 g. of silver nitrate. The acid, isolated as described above, weighed 40.0 g. (75%). After recrystallization from absolute methanol, it began to decompose at 229° and melted at 234° dec.

*Anal.* Calcd. for $C_{15}H_{21}O_3N$: C, 68.40; H, 8.04; N, 5.33. Found: C, 67.94; H, 8.30; N, 5.39.

**Methyl α-Phenyl-α-(1-methyl-4-hydroxy-4-piperidyl)-acetate.**—(A) The required acid (20.0 g.) was dissolved in 100 cc. of absolute methanol and treated with ethereal diazomethane until the yellow color became permanent. The mixture was filtered immediately and the solvent and excess diazomethane were removed by distillation. The residue was extracted with three 200-cc. portions of boiling petroleum ether (60–75°). A considerable amount of residue remained. Upon concentration of the extract, 5.5 g. (21%) of the ester was obtained; m.p. 82–83° after recrystallization from petroleum ether (60–75°).

*Anal.* Calcd. for $C_{15}H_{21}O_3N$: C, 68.40; H, 8.05. Found: C, 68.57; H, 8.24.

The hydrochloride melted at 133–135° after recrystallization from absolute methanol–ether.

*Anal.* Calcd. for $C_{15}H_{22}O_3NCl$: N, 4.68; Cl, 11.82. Found: N, 4.66; Cl, 11.64.

(B) Ten grams of the acid chloride, 70 cc. of absolute methanol and 5 cc. of concentrated sulfuric acid were refluxed for 18 hours and most of the methanol was removed by distillation under reduced pressure. The residue was dissolved in water and the solution, after it had been washed with ether, was cooled in an ice-bath, made alkaline and extracted with ether. The solvent was removed from the dried extract and the oily residue was extracted with three 50-cc. portions of boiling petroleum ether (60–75°). After the extract had been concentrated to a volume of 50 cc. the solution was placed in a refrigerator; yield 7.5 g. (82%), m.p. and mixed m.p. 82–83° after recrystallization from petroleum ether (60–75°).

**Methyl α-Phenyl-α-(1-ethyl-4-hydroxy-4-piperidyl)-acetate.**—By the use of procedure A, 11.2 g. (71%) of ester was obtained from 15.0 g. of the required acid; m.p. 70.5–71.5° after recrystallization from petroleum ether (40–60°).

*Anal.* Calcd. for $C_{15}H_{21}O_3N$: C, 68.40; H, 8.04; N, 5.33. Found: C, 67.94; H, 8.30; N, 5.39.

The hydrochloride melted at 162–164° after recrystallization from absolute methanol–ether.

*Anal.* Calcd. for $C_{16}H_{24}O_3NCl$: N, 4.46; Cl, 11.30. Found: N, 4.44; Cl, 11.35.

The methobromide melted at 204–205° dec. after recrystallization from absolute methanol–ether.

*Anal.* Calcd. for $C_{17}H_{26}O_3NBr$: N, 3.76; Br, 21.47. Found: N, 3.77; Br, 21.35.

COLLEGE OF PHARMACY
UNIVERSITY OF MICHIGAN
ANN ARBOR, MICHIGAN

(2) S. M. McElvain and K. Rorig, THIS JOURNAL, **70**, 1820 (1948); R. Mozingo and J. H. McCracken, *Org. Syntheses*, **20**, 35 (1940).

(3) R. C. Fuson, W. E. Parham and L. J. Reed, THIS JOURNAL, **68**, 1239 (1946); H. M. Cardwell and F. J. McQuillin, *J. Chem. Soc.*, 708 (1949).

## Endocyclic α,β-Unsaturated Ketones. IV. Reaction of 4,4-Dimethyl-1-keto-1,4-dihydronaphthalene with Cyclohexylmagnesium Bromide

BY RICHARD D. CAMPBELL[1a] AND NORMAN H. CROMWELL[1b]

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The previous papers of this series[2] point out the importance of steric restrictions in the reactions of endocyclic α,β-unsaturated carbonyl systems. The present note extends the study of 4,4-dimethyl-1-keto-1,4-dihydronaphthalene (VI).

A new synthesis of 4,4-dimethyltetralone-1 (IV) is presented, employing a route used by Barnes[3] for a similar compound. Each step gives excellent yields. The procedure of Arnold[4] for converting IV to the desired unsaturated ketone VI was modified and simplified with some increase in yield.

In paper I of this series[2a] the action of organometallic reagents with the endocyclic α,β-unsaturated ketone VI was described. In the instances cited, the reaction of Grignard reagent with VI was nearly quantitative. Addition was mainly, if not exclusively, to the carbonyl group. The resulting carbinols dehydrated and rearranged in the presence of acid. A mechanism of the retropinacol type was proposed.

In the present study the ketone VI was treated with a four-mole excess of cyclohexylmagnesium bromide. The reaction was not quantitative. Instead, a 30% yield of the starting material VI

(1) (a) du Pont Teaching Fellow 1954–1955. (b) To whom correspondence regarding this article should be addressed.

(2) (a) N. H. Cromwell, D. B. Capps and H. H. Eby, THIS JOURNAL, **73**, 1224 (1951); (b) N. H. Cromwell, D. B. Capps and S. E. Palmer, *ibid.*, **73**, 1226 (1951); (c) N. H Cromwell, D. B. Capps and H. H. Eby, *ibid.*, **73**, 1230 (1951).

(3) R. A. Barnes and G. R. Buckwalter, *ibid.*, **73**, 3858 (1951).

(4) R. T. Arnold, J. S. Buckley and J. Richter, *ibid.*, **69**, 2322 (1947).