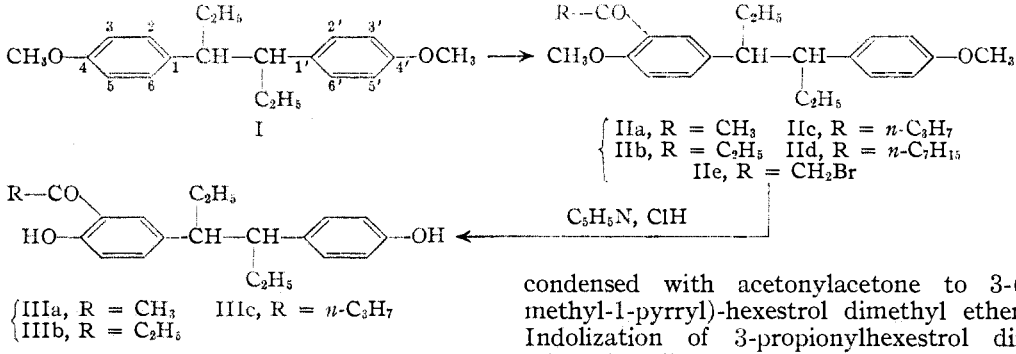
[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

# The Chemistry of Some Ketones Derived from Hexestrol

BY NG. PH. BUU-HOÏ,[1] NG. HOÁN AND NG. D. XUONG

Ketones[2] and α-hydroxyketones[3] whose molecular structures are more or less related to known synthetic estrogens have frequently been prepared and biologically investigated as potential analogs of progesterone and of desoxycorticosterone. In spite of the great variety of the substances thus studied, no compound with an unequivocal activity in these respects has yet been obtained.[4] Nevertheless, the recent discovery by Wilds, Shunk and Hoffman[5] of relatively simple synthetic molecules endowed with androgenic activity is now bringing renewed interest to that field of research. An important incentive for the investigation of ketones related to estrogenic molecules lies in the observation[6] that 4-hydroxypropiophenone, although but feebly estrogenic, readily impairs the gonadotropic and growth-stimulating functions of the pituitary gland.

A very convenient intermediate for synthetic work in this field is hexestrol dimethyl ether (I),




which now can be easily prepared in quantity by the Sisido–Nozaki method[7] as modified by Buu-Hoï and Hoán.[8] This compound was found readily susceptible to Friedel–Crafts reactions with various aliphatic acid chlorides, and gave the following ketones in high yields: 3-acetylhexestrol dimethyl ether (IIa), 3-propionylhexestrol dimethyl ether (IIb), 3-*n*-butyrylhexestrol dimethyl ether (IIc) and 3-*n*-octanoylhexestrol dimethyl ether (IId). Demethylation of these ketones by means of anhydrous pyridine hydrochloride[8] yielded the corresponding 3-acylhexestrols (III) characterized by the yellow coloration of their alkali salts in aqueous solutions; further, bromination of (IIa) gave 3-bromoacetylhexestrol dimethyl ether (IIe).

Some other transformations were undertaken with the ketones (II), resulting in nitrogen-containing substances related to hexestrol. Hitherto, the introduction of nitrogen in estrogenic molecules has always had a marked unfavorable effect upon estrogenicity while in some instances (for example stilbamidine, aminostilbenes, etc.) bringing to light other interesting activities. Beckmann rearrangement of the oxime of (IIa) readily gave 3-acetaminohexestrol dimethyl ether (IV), a substance which is being tested for carcinogenic activity. Analogous amides were also obtained from the higher members of the ketone series (II). Alkaline hydrolysis of these amides yielded 3-aminohexestrol dimethyl ether (V), which condensed with acetonylacetone to 3-(2,5-dimethyl-1-pyrryl)-hexestrol dimethyl ether (VI). Indolization of 3-propionylhexestrol dimethyl ether phenylhydrazone according to a convenient recently described procedure,[9] readily gave 3-(3-methyl-2-indolyl)-hexestrol dimethyl ether (VIIa), from which 3-(3-methyl-2-indolyl)-hexestrol (VIIb) was obtained by the pyridine hydrochloride method.

The new substances described in this work are under biological investigation in this Institute by Professor A. Lacassagne and Dr. L. Corre. The Friedel–Crafts reactions of hexestrol dimethyl ether with aromatic and heterocyclic acid chlorides and with cyclic acid anhydrides are under examination.

## Experimental

**3-Acetylhexestrol (IIIa).**—A solution of 50 g. of hexestrol dimethyl ether (sample recrystallized from ethanol) and 15 g. of redistilled acetyl chloride in 150 ml. of anhydrous nitrobenzene was cooled in iced water, and 25 g. of finely powdered aluminum chloride were gradually stirred in. The mixture was kept at room temperature for three hours, then poured onto cracked ice, and the nitrobenzene removed by steam. The resulting dark oil

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(2) Jaeger and Robinson, *J. Chem. Soc.*, 744 (1941); Ross, *ibid.*, 536 (1945); Buu-Hoï and Royer, *Bull. soc. chim. France*, [5] **14**, 820 (1947).

(3) Linnell and Roushdi, *Quart. J. Pharm. Pharmacol.*, **14**, 270 (1941); Ross, *J. Chem. Soc.*, 538 (1945); Biggerstaff and Wilds, THIS JOURNAL, **71**, 2132 (1949).

(4) See Biggerstaff and Wilds (ref. 3); Buu-Hoï, *Bull. soc. chim. biol.*, **27**, 393 (1945).

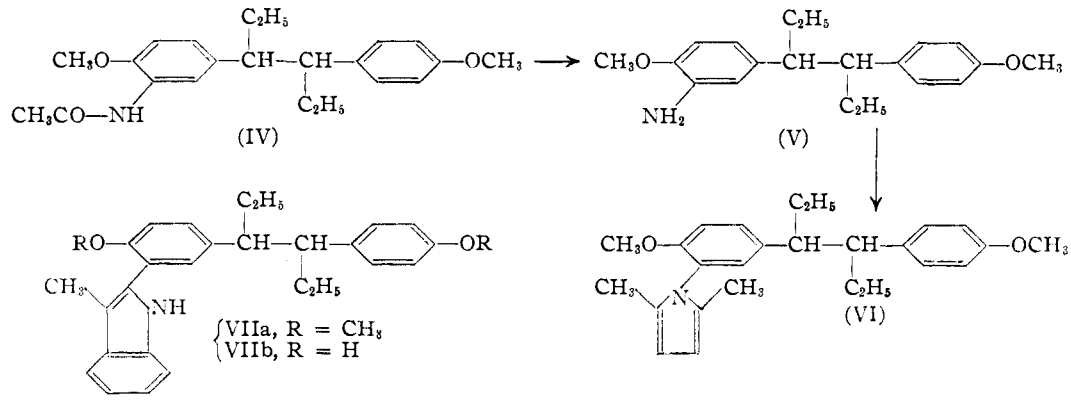
(5) Wilds, Shunk and Hoffman, THIS JOURNAL, **71**, 3266 (1949).

(6) Lacassagne, Chamorro and Buu-Hoï, *Compt. rend. soc. biol.*, in press (1950).

(7) Sisido and Nozaki, THIS JOURNAL, **70**, 778 (1948).

(8) Buu-Hoï and Hoán, *J. Org. Chem.*, **14**, 1023 (1949).

(9) Buu-Hoï, *J. Chem. Soc.*, 2882 (1949).




was taken up in ether and washed thoroughly with a dilute aqueous solution of sodium hydroxide (to remove the phenolic impurities) then with water. The ether solution was dried over sodium sulfate and the solvent removed. The residue gave on vacuum fractionation in a flask fitted with a Vigreux column, 46 g. of a thick yellow jelly b. p. about 265–270° at 18 mm., which solidified on prolonged standing. After two recrystallizations from methanol, **3-acetylhexestrol dimethyl ether (IIa)** was obtained in fine colorless needles, m. p. 97°.

*Anal.* Calcd. for $C_{22}H_{28}O_3$: C, 77.6; H, 8.2. Found: C, 77.4; H, 8.2.

The corresponding **oxime**, prepared in the usual way, crystallized from ethanol in colorless needles m. p. 154°.

*Anal.* Calcd. for $C_{22}H_{29}O_3N$: N, 3.9. Found: N, 4.0.

The demethylation of (IIa) was effected by gently refluxing a mixture of 8 g. of the ketone and 50 g. of redistilled pyridine hydrochloride for twenty minutes. After cooling, water was added, and the precipitate formed was collected, dried, and recrystallized from benzene (charcoal). A 90% yield of **3-acetylhexestrol** was obtained in long colorless glinting needles, m. p. 208°, which sublimed above 204–205° when heated in the open air, and readily dissolved in aqueous sodium hydroxide solution with a bright yellow coloration.

*Anal.* Calcd. for $C_{20}H_{24}O_3$: C, 76.9; H, 7.7. Found: 76.8; H, 7.9.

**3-Aminohexestrol Dimethyl Ether (V).**—Five grams of the foregoing oxime was suspended in 30 ml. of anhydrous ether, and 4.5 g. of finely powdered phosphorus pentachloride was stirred in small portions, the temperature being kept below 0°. The stirring was continued for ten minutes, and the mixture was poured onto cracked ice. The organic layer was washed with dilute aqueous sodium carbonate solution and then with water; after removal of the solvent, the residue was crystallized twice in ether; 4 g. of **3-acetaminohexestrol dimethyl ether** was obtained in the form of fine colorless glinting prisms, m. p. 160°.

*Anal.* Calcd. for $C_{22}H_{29}O_3N$: N, 3.9. Found: N, 3.9.

Two grams of the foregoing amide was refluxed for two hours with 50 ml. of 10% methanolic sodium hydroxide solution; the solvent was distilled off in vacuum, and water was added. The precipitate of **3-aminohexestrol dimethyl ether** crystallized from a mixture of benzene and ligroin in fine colorless prisms, m. p. 146°.

*Anal.* Calcd. for $C_{20}H_{27}O_2N$: N, 4.4. Found: N, 4.2.

**3-(2,5-Dimethyl-1-pyrryl)-hexestrol Dimethyl Ether (VI).**—A mixture of 1 g. of the amine (V) and 1 g. of acetonylacetone with one drop of acetic acid was refluxed overnight, and poured into water after cooling; the precipitate crystallized from ethanol in fine colorless glistening prisms, m. p. 152°.

*Anal.* Calcd. for $C_{26}H_{33}O_2N$: C, 79.6; H, 8.4. Found: C, 79.4; H, 8.7.

**3-Bromoacetylhexestrol Dimethyl Ether (IIe).**—To an ice-cooled solution of 10 g. of the ketone (IIa) in 60 ml. of dry chloroform, 4.8 g. of bromine (dissolved in 5 ml. of chloroform) was added dropwise with stirring. Discoloration occurred immediately; after removal of chloroform, and repeated crystallizations of the residue from ethanol, colorless prisms, m. p. 96°, were obtained. The location of the bromine atom in the side-chain was shown by refluxing for one hour the compound with sodium acetate in ethanol, a bromine-free compound being obtained.

*Anal.* Calcd. for $C_{22}H_{27}O_3Br$: C, 63.0; H, 6.4. Found: C, 63.1; H, 6.6.

**3-Propionylhexestrol (IIIb).**—The dimethyl ether (IIb) (35 g.; b. p. about 280° at 18 mm.) was prepared from hexestrol dimethyl ether (50 g.) and propionyl chloride (17 g.) as described for the lower homolog; it crystallized from ethanol in lustrous colorless leaflets, m. p. 96°.

*Anal.* Calcd. for $C_{23}H_{30}O_3$: C, 77.9; H, 8.5. Found: C, 78.0; H, 8.7.

Demethylation of (IIb) as for the lower homolog yielded (IIIb) which formed from benzene colorless glistening needles, m. p. 168°, giving with aqueous sodium hydroxide a yellow coloration.

*Anal.* Calcd. for $C_{21}H_{26}O_3$: C, 77.3; H, 7.9. Found: C, 77.1; H, 8.0.

**The oxime of 3-propionylhexestrol dimethyl ether** formed from methanol colorless microcrystals, m. p. 140°.

*Anal.* Calcd. for $C_{23}H_{31}O_3N$: N, 3.7. Found: N, 3.8.

The Beckmann rearrangement of this oxime yielded **3-propionylaminohexestrol dimethyl ether** which formed from ether colorless leaflets, m. p. 122°.

*Anal.* Calcd. for $C_{23}H_{31}O_3N$: N, 3.7. Found: N, 3.4.

**3-(3-Methyl-2-indolyl)-hexestrol (VIIb).**—Four grams of 3-propionylhexestrol dimethyl ether was heated for some minutes at about 150° with 2 g. of phenylhydrazine, steam being allowed to escape. To the crude phenylhydrazone thus obtained, 20 ml. of a saturated solution of hydrogen chloride in acetic acid were added, and the mixture refluxed for two minutes. The hot mixture was poured into water, the sticky mass extracted with benzene, the benzene solution washed with water and dried over sodium sulfate. The solvent was removed, and the residue vacuum-distilled. A 90% yield of the **indole (VIIa)** was obtained; crystallization from methanol gave yellow-tinged prisms, m. p. 128°.

*Anal.* Calcd. for $C_{29}H_{33}O_2N$: N, 3.2. Found: N, 3.1.

The demethylation of this compound was effected with pyridine hydrochloride in the usual way; after crystallization from toluene (VIIb) formed fine yellowish prisms, m. p. 186°, giving a yellow coloration with aqueous sodium hydroxide, and a brown-violet molecular compound with picric acid.

*Anal.* Calcd. for $C_{27}H_{29}O_2N$: N, 3.5. Found: N, 3.3.

**3-*n*-Butyrylhexestrol (IIIc).**—The dimethyl ether (IIc) (38 g.; b. p. 285° at 16 mm.), obtained as usual from hexestrol dimethyl ether (50 g.) and *n*-butyryl chloride (27 g.), formed from methanol lustrous colorless leaflets, m. p. 72°.

*Anal.* Calcd. for $C_{24}H_{32}O_3$: C, 78.2; H, 8.7. Found: C, 78.0; H, 8.8.

**3-*n*-Butyrylhexestrol,** produced by demethylation of (IIc), crystallized from a mixture of benzene and ligroin in fine colorless needles, m. p. 134°.

*Anal.* Calcd. for $C_{22}H_{28}O_3$: C, 77.6; H, 8.2. Found: C, 77.4; H, 8.3.

**The oxime of 3-*n*-butyrylhexestrol dimethyl ether** formed from ethanol fine colorless needles, m. p. 135°.

*Anal.* Calcd. for $C_{24}H_{33}NO_2$: N, 3.6. Found: N, 3.5.

The Beckmann rearrangement readily yielded **3-*n*-butyrylaminohexestrol dimethyl ether,** crystallizing from ether in lustrous colorless leaflets, m. p. 150°.

*Anal.* Calcd. for $C_{24}H_{33}O_3N$: N, 3.6. Found: N, 3.4.

**3-*n*-Octanoylhexestrol Dimethyl Ether (IId).**—This compound (17 g., b. p. about 300° at 15 mm.) crystallized from ligroin in light colorless leaflets, m. p. 67°; its demethylation gave a greasy mass which could not be purified, but which apparently contained **3-*n*-octanoylhexestrol,** since it gave a yellow coloration with aqueous sodium hydroxide.

*Anal.* Calcd. for $C_{28}H_{40}O_3$: C, 79.2; H, 9.4. Found: C, 79.0; H, 9.6.

## Summary

1. The Friedel–Crafts reactions of hexestrol dimethyl ether and various acid chlorides are described.

2. Several ketones and nitrogen-containing substances derived from hexestrol have been prepared for biological investigation.

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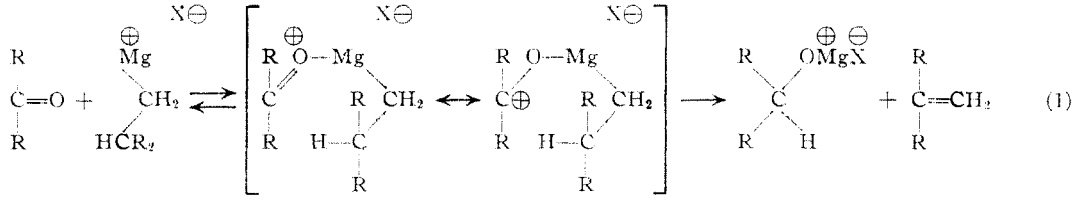
# Asymmetric Reductions. I. The Action of (+)-2-Methylbutylmagnesium Chloride on Methyl *t*-Butyl Ketone[1]

BY HARRY S. MOSHER AND EDWARD LA COMBE

Vavon and co-workers[2,3] have reported the unique action of isobornylmagnesium chloride[4] on a series of six phenyl alkyl ketones to give in each case the reduced phenylalkylcarbinol which was optically active. The optical activity of these products ranged from 19 to 72% of that reported for the pure dextro isomers. With the exception of reactions involving enzyme systems, no other case of an asymmetric reduction by an optically active reducing agent is known to the authors.[5,6]

Whitmore has proposed a common basis for the "abnormal" reactions of the Grignard reagent with carbonyl compounds[7,8] which represents the mechanism for the Grignard reduction reaction proceeding via a six-membered ring complex as formulated in equation 1.[9]



(1)

In an effort to obtain further evidence bearing on this mechanism, a study on the action of the Grignard reagent from (+)-2-methylbutyl chloride on various hindered aliphatic ketones was under-

(1) Presented before the San Francisco Meeting of the American Chemical Society, March 28, 1949. This paper was originally submitted to THIS JOURNAL on April 8, 1949, in the form of a communication.

(2) Vavon and Angelo, *Compt. rend.*, **224,** 1435–1437 (1947).

(3) Vavon, Riviere and Angelo, *ibid.*, **222,** 959 (1946).

(4) The isobornylmagnesium chloride was the Grignard solution obtained by the action of magnesium on "pinene hydrochloride." Vavon and Riviere, [*Compt. rend.*, **220,** 286 (1945); *Ann. chim.*, 1, 157-231 (1946)] have shown by oxidation and carbonation experiments that such a solution contains a mixture of bornylmagnesium and isobornylmagnesium chlorides in approximately equal amounts, and that it was the isobornylmagnesium chloride in this solution which was primarily responsible for the reducing action. Presumably this is because of the greater hindrance existing in the isobornyl structure containing the *cis* methylene bridge.

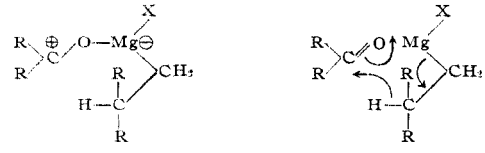
(5) The communication by Doering and Young [THIS JOURNAL, **72,** 631 (1950)], which appeared after the present paper was submitted, describes two successful experiments of this type.

(6) Baker and Linn [*ibid.*, **71,** 1399 (1949)] describe an unsuccessful attempt at the asymmetric reduction of acetophenone using the optically active aluminate from (+)-2-methyl-1-butanol.

(7) Frank C. Whitmore, paper presented before the Atlantic City Meeting of the American Chemical Society, April, 1943.

(8) For a review of this subject, prior references, and some of the experimental basis for this generalization, see the Ph.D. thesis of Richard Stanley George, The Pennsylvania State College, July, 1943, available through the University Microfilm Service, Ann Arbor, Mich. See also the reviews of the Grignard reduction by Kharasch and Weinhouse [*J. Org. Chem.*, **1,** 209 (1936-1937)] and by Runge ["Organometallverbindungen," Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1944, p. 394–404].

(9) In this and the following formulations the ether molecules which are coördinated to the magnesium have been omitted for convenience in representation. Various symbolisms may be used to delineate the postulated intermediate in this reaction. Two other representations would be



All of these are essentially equivalent. The extent of ionic character of the magnesium halogen bond in anhydrous ether is still problematical.