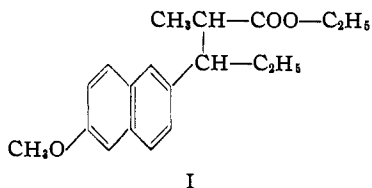


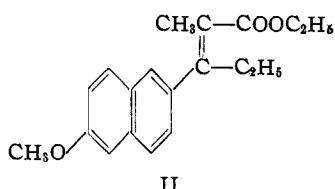
Intermediates for Synthetic Hormones

BY HERBERT E. UNGNADE¹ AND NORMAN L. JENNINGS²

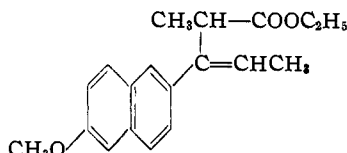
In connection with another problem it became necessary to prepare the ester (I) of the allenolic acid which has been described by Jacques and Horeau³ as an active estrogen.⁴



In the course of this investigation it has been possible to isolate the hitherto unknown unsaturated intermediates (II) and (III) which have been

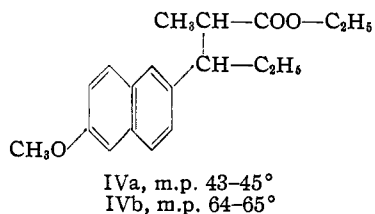


M. p. 103–104° and m. p. 94–96°



M. p. 78–80°

identified on the basis of their absorption spectra (Fig. 1).⁵ Each of the three isomers has been hydrogenated over platinum catalyst, yielding the two expected racemates (IV). The order of the



hydrogenation rates of the isomers was (II) > (III). Hydrolysis of the esters (IV) gave oils with molecular formulas corresponding to C₁₇H₂₀O₃ which have failed to crystallize and have been used without further purification.

Model experiments have shown that (I) can be converted to the corresponding methyl ketone by treating its acid chloride with dimethylcadmium. The methoxyl group is cleaved during the reaction. When the phenolic ketone is reduced with Raney nickel catalyst as described recently,⁶ the phenolic

ring is saturated without the hydrogenolysis of the hydroxyl group which has been observed by other investigators.^{6a,b}

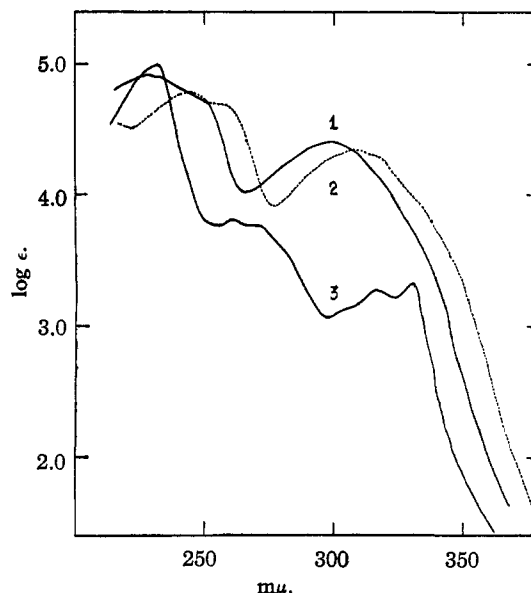


Fig. 1.—Ultraviolet absorption spectra (Beckman quartz spectrophotometer): curve 1, unsaturated ester (II) m. p. 94–96°; curve 2, unsaturated ester (II) m. p. 103–104°; curve 3, ester (III).

Experimental⁷

The unsaturated esters (II) and (III) were synthesized from 2-methoxy-6-propionaphthone⁸ through the Reformatsky reaction and also by use of the Grignard reaction. Since the resultant hydroxy ester could not be crystallized, it was dehydrated in the crude state. The two procedures furnished different ratios of the unsaturated esters.

Reformatsky Reaction.—Ethyl α-bromopropionate (20 g.) was added to a boiling solution of 2-methoxy-6-propionaphthone (16 g.) in 100 ml. of benzene and 100 ml. of toluene containing 25 g. of granulated zinc. A crystal of iodine was added, the reaction was allowed to subside and the mixture was refluxed for 1 hour. The reaction mixture was decomposed with ice and dilute hydrochloric acid, extracted with benzene and the extract was dried and distilled. The oily residue consisting of hydroxy ester was heated with 20 g. of potassium bisulfate for 15 minutes at 190°. The mixture was treated with water and extracted with ether. The extract was dried and the solvent was displaced with Skellysolve B.^{8a} The resultant solution was adsorbed on aluminum oxide. The Skellysolve B eluate contained 10.35 g. of (II), m. p. 103–104°.

Anal. Calcd. for C₁₉H₂₂O₃: C, 76.51; H, 7.38. Found: C, 76.53; H, 7.34.

The column contained two additional bands visible under ultraviolet light. The lower one yielded 0.35 g. of isomer (II), m. p. 94–96°.

Anal. Calcd. for C₁₉H₂₂O₃: C, 76.51; H, 7.38. Found: C, 76.40; H, 7.43.

The third isomer (III) was recovered from the top band. It melted at 78–80° and weighed 1.20 g.

Anal. Calcd. for C₁₉H₂₂O₃: C, 76.51; H, 7.38. Found: C, 76.27; H, 7.21.

Grignard Reaction.—Magnesium (2.3 g.) was activated by treating with ethyl iodide (1.2 ml.) and ether (20 ml.). The

(6a) Julia, Jacques and Horeau, *Compt. rend.*, **230**, 660 (1950).(6b) NOTE ADDED IN PROOF: Analogous compounds have been reported more recently by Horeau and Jacques, *Compt. rend.*, **230**, 1667, 2029 (1950).

(7) All temperatures uncorrected. Analyses by R. Carpenter and J. S. Finney.

(8) Haworth and Sheldrick, *J. Chem. Soc.*, 864 (1934).

(8a) Petroleum ether, b. p. 60–80°.

(1) New Mexico Highlands University, Las Vegas, New Mexico.

(2) From the master's thesis of N. L. Jennings, 1950.

(3) Jacques and Horeau, *Bull. soc. chim.*, 714 (1948).

(4) The racemate melting at 128–128.5° is reported to be active in doses of 100 γ.

(5) An analogous interpretation of the absorption spectra of similar unsaturated isomers was given by Johnson and Graber (*THIS JOURNAL*, **72**, 929 (1950)).(6) Ungnade and Morriss, *ibid.*, **72**, 2112 (1950).

solution was decanted and the residue was washed with dry ether. To the prepared magnesium was added 20 ml. of anhydrous ether, 13.6 g. of ethyl α -bromopropionate, 30 ml. of dry benzene and 16 g. of 2-methoxy-6-propionaphthone. The mixture was refluxed for 3 hours and decomposed with ice and hydrochloric acid. The reaction product was isolated and dehydrated as described above. The mixture of unsaturated esters was separated by chromatographic adsorption. The isomers obtained in 51% yield were identical with the substances described above: (II), m. p. 103–104°, yield 1.90 g.; (II), m. p. 94–96°, yield 8.45 g.; (III), m. p. 78–80°, yield 2.25 g.

Ethyl 2-Methyl-3-(6-methoxy-2-naphthalene)-pentanoate.—The unsaturated esters (1.75 g. each), dissolved in 80 ml. of acetic acid, were hydrogenated with 200 mg. of platinum oxide at room temperature. Under identical conditions (II), m. p. 103–104°, m. p. 94–96°, and (III) required 70, 15 and 360–480 minutes, respectively, to take up the theoretical amount of hydrogen.

The oily products, after removal of solvent and catalyst, were taken up in Skellysolve B and were chromatographed on aluminum oxide. Two bands were visible under ultraviolet light. They were cut apart and extracted with hot methanol. Crystallization from aqueous methanol yielded the racemate melting at 43–45° (IVa) from the lower band and the isomer, m. p. 64–65° (IVb) from the upper band (Table I).

TABLE I
HYDROGENATION RESULTS

Unsaturated ester	Yield (IVa), g.	Yield (IVb), g.	Total yield, %
II, m.p. 103–104°	1.32	0.25	90
II, m.p. 94–96°	0.25	1.40	95
III, m.p. 78–80°	0.75	0.65	80

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 76.00; H, 8.00. Found: (IVa) C, 76.09; H, 8.07; (IVb) C, 76.10; H, 8.03.

2-Methyl-3-(6-methoxy-2-naphthalene)-pentanoic Acid.—The mixture of isomeric esters (IVa and IVb, 12.0 g.) was hydrolyzed by refluxing for 3 hours with 125 ml. of 30% aqueous sodium hydroxide and 300 ml. of propylene glycol. After cooling, 200 ml. of water was added, the mixture was acidified with hydrochloric acid and extracted with ether. The extract yielded 10.8 g. of a glassy product which resisted all attempts at crystallization.

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 74.72; H, 9.80. Found: C, 74.39; H, 9.73.

Several attempts to obtain crystalline acids by hydrolyzing crystalline esters only gave non-crystallizable glassy substances.

3-Methyl-4-(6-hydroxy-2-naphthalene)-2-hexanone.—The glassy acid mixture (IV) (8.0 g.) was converted to the acid chloride with oxalyl chloride according to Wilds.⁹ The acid chloride (7.8 g.), dissolved in 50 ml. of dry ether, was added to a solution of dimethylcadmium prepared from 1.0 g. of cadmium chloride and methylmagnesium iodide (from 1.0 g. of methyl iodide). After the reaction subsided, the mixture was warmed on a steam-bath for 1 hour. Dilute sulfuric acid was added to the cooled mixture until the white precipitate dissolved. The mixture was extracted with ether, separated, and the ether layer was washed successively with water, dilute base and water, dried and evaporated. Attempts to crystallize the resulting reddish oil failed. The oil was taken up in Skellysolve B and chromatographed on aluminum oxide. The single main band yielded 3.35 g. of oily product. Further purification by conversion to the oily oxime and hydrolysis only gave an oily ketone, yield 3.0 g.

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.81. Found: C, 79.49; H, 7.58.

Catalytic Hydrogenation.—The oily ketone (3 g.) was hydrogenated with Raney nickel (W-2, aged three weeks under absolute alcohol) at 240 atm. and 165° in sodium ethoxide solution containing 0.02 g. of sodium.⁶ After removal of catalyst and solvent, the product was taken up in benzene and chromatographed on alumina. One single major band was eluted with the same solvent and yielded 2.7 g. of glassy product which was Folin-negative.

(9) Wilds and Shunk, *THIS JOURNAL*, **70**, 2427 (1948).

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 77.27; H, 11.08. Found: C, 77.10; H, 10.86.

Absorption Spectra.—The ultraviolet absorption spectra of (II) and (III) were determined in 95% ethanol in concentrations of 6.29, 9.73 and 8.66 mg. per 25 ml.¹⁰

(10) Absorption spectra by Dr. E. E. Pickett, University of Missouri, Columbia, Missouri.

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A Simple Acetolysis of Nitrate Esters¹

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The nitrate esters of carbohydrates may be effectively denitrated by any of several methods involving metallic agents such as alkali metal hydro-sulfides,² aluminum and mercuric chloride,³ Devarda's alloy in a highly alkaline medium,⁴ and iron dust (or zinc and iron dust) in glacial acetic acid.^{5,6} A combined denitration and acetylation can be produced with zinc and anhydrous hydrogen chloride (or dry pyridine) in acetic anhydride.⁷ A catalytic regeneration of the original alcohol from a nitrate ester has been effected by high pressure hydrogenolysis⁸ and by the employment of hydrazine.⁹ All of these methods employ reducing agents.

This report concerns a very simple acetolysis applicable to nitrate esters of small carbohydrate units. It has been developed from the observations of Kuhn¹⁰ that ethyl nitrate in cold sulfuric acid produces considerable amounts of NO_2^+ and from the observations of Wolfrom and Montgomery¹¹ that in cold absolute sulfuric acid carbohydrate sulfate esters are converted to the acetates in the presence of acetic anhydride. The nitrate ester is dissolved in a small amount of sulfuric acid-acetic anhydride reagent in the cold and after subsequent hydrolysis of excess reagent, the acetate is separated by extraction of the hydrolyzate with some suitable solvent. No reducing environment is needed. Acetate derivatives were obtained in good yield (Table I) from the nitrates of cellobiose, D-glucose, pentaerythritol, erythritol, D-mannitol and levoglucosan (1,6-anhydro- β -D-glucopyranose). These acetolysis conditions are similar to those employed to anomerize β -acetates to the α -forms.^{12,13} Thus the isolation of members of the α -D-series is to be expected. Our procedure is somewhat related to that of Clémente and Rivière¹⁴ for producing cellulose acetate from cellulose nitrate. These authors employed acetic acid, acetic anhydride and

(1) This work was carried out under a contract (W33-019ord-6279; supervising agency, Ballistic Research Laboratory, Aberdeen Proving Ground, Maryland) between the Ordnance Department and The Ohio State University Research Foundation (Project 313).

(2) H. de Chardonnet, German Patent 56,655 (1890).

(3) B. Rassow and E. Dörr, *J. prakt. Chem.*, **216**, 113 (1924).

(4) A. Devarda, *Z. anal. Chem.*, **33**, 113 (1894).

(5) J. W. H. Oldham, *J. Chem. Soc.*, **127**, 2840 (1925).

(6) J. Dewar and G. Fort, *ibid.*, 492, 496 (1944); J. Dewar, G. Fort and N. McArthur, *ibid.*, 499 (1944).

(7) D. O. Hoffman, R. S. Bower and M. L. Wolfrom, *THIS JOURNAL*, **69**, 249 (1947).

(8) L. P. Kuhn, *ibid.*, **68**, 1761 (1946).

(9) L. P. Kuhn, *Abstracts Papers Am. Chem. Soc.*, **117**, 2-0 (1950).

(10) L. P. Kuhn, *THIS JOURNAL*, **69**, 1974 (1947).

(11) M. L. Wolfrom and R. Montgomery, *ibid.*, **72**, 2859 (1950).

(12) Edna Montgomery and C. S. Hudson, *ibid.*, **56**, 2463 (1934).

(13) K. Freudenberg and K. Soff, *Ber.*, **69**, 1245 (1936).

(14) L. Clémente and C. Rivière, U. S. Patent 1,168,164 (1916).