TABLE III

CONVERSION OF DICHLOROPHENYLHYDRAZONES (TABLE II) TO DICHLOROINDOLES

Dichlorophenylhydrazone no.	Procedure	Reaction temp., °C.	Solvent	Dichloroindole	Yield, %	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
I[a]	A	200	None	2-Phenyl-5,7-[d]	7	142	$C_{14}H_9NCl_2$[h]	64.14	3.46	64.10	3.37
	B	180	Nitrobenzene	2-Phenyl-5,7-	11	142					
	B	170	Phenol	2-Phenyl-5,7-	16	142					
	B	200	*p*-Cresol	2-Phenyl-5,7-	26	142					
VII	A	210	None	2-Phenyl-5,7-	22	142					
II	A	200	None	2-Methyl-5,7-[e]	0.5	66.5	$C_9H_7NCl_2$	54.03	3.53	54.33	3.40
	B	165	Nitrobenzene	2-Methyl-5,7-	22	66.5					
VIII	A	190	None	2-Methyl-5,7-	9[g]	66.5[g]					
	B	150	Nitrobenzene	2-Methyl-5,7-	43	66.5					
III	A	260	None	2-(*p*-Biphenylyl)-5,7-[f]	33	214	$C_{20}H_{11}NCl_2$	71.01	3.87	71.59	3.86
IX	A	230	None	2-(*p*-Biphenylyl)-5,7-[f]	50	214					
IV	A	300	None	2-(*p*-Chlorophenyl)-5,7-[d]	21	166	$C_{14}H_8NCl_3$	56.69	2.72	56.41	2.69
X	A	285	None	2-(*p*-Chlorophenyl)-5,7-[d]	36	166					
V	B	60	Nitrobenzene	2,3-Tetramethylene-5,7-[f]	0.3	68	$C_{12}H_{11}NCl_2$	60.04	4.59	59.90	4.36
XI	B	*ca.* 100[b]	Aq. ethanol[c]	2,3-Tetramethylene-5,7-[f]	97	68					
	B	98	Nitrobenzene	...	0	...					
XII	A	225	None	2-Phenyl-4,7-[e]	33	106	$C_{14}H_9NCl_2$	64.14	3.46	64.16	3.19
XIII	A	277	None	2-Phenyl-4,6-[d]	11	115	$C_{14}H_9NCl_2$	64.14	3.46	64.02	3.64

[a] No rearrangement in α-methylnaphthalene or tetralin at 200° could be detected. [b] On steam-bath. [c] Hydrochloric acid was used in place of zinc chloride as the reaction promoter. [d] Needles from ethanol. [e] High-vacuum distilled from oily product, then recrystallized from petroleum ether (b. p. 65–110°). [f] Plates from ethanol. [g] Bülow, *Ber.*, **51**, 399 (1918), reported a 5% yield of a product, m. p. 61°, from this reaction. [h] *Anal.* Calcd.: N, 5.34; Cl, 27.05. Found: N, 5.07; Cl, 26.55.

material was dissolved in ether. Removal of the ether gave a crude product from which 0.25 g. (>90%) of 2-phenylindole, m. p. 188–189°, was obtained by recrystallization from ethanol. A mixture of this compound with an authentic sample[9] of 2-phenylindole showed no melting point depression.

Summary

1. Five 2,6-dichlorophenylhydrazones have been converted to 5,7-dichloroindoles under the conditions of the Fischer indole synthesis. The same 5,7-dichloroindoles have also been prepared from the corresponding 2,4-dichlorophenylhydrazones.

2. The 2,5- and 3,5-dichlorophenylhydrazones of acetophenone have been converted to dichloroindoles which are different from each other and from that obtained from the 2,4- and 2,6-dichlorophenylhydrazones of acetophenone; therefore, only the 2,6-dichlorophenylhydrazones undergo halogen migration under conditions of the Fischer indole synthesis.

3. The conversion of 2,6-dichlorophenylhydrazones to 5,7-dichloroindoles is not analogous to any recorded benzidine or Claisen rearrangement, despite the fact that the simple Fischer indole synthesis, benzidine rearrangement and Claisen rearrangement are formally similar.

PITTSBURGH 13, PA. RECEIVED MAY 19, 1948

(9) Shriner, Ashley and Welch, "Organic Syntheses," **22**, 98 (1942).

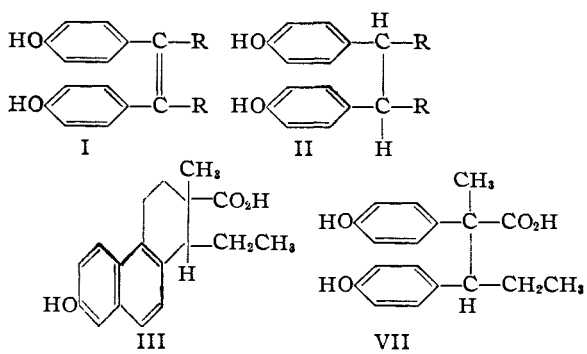
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

α-Methyl-α,β-di-(*p*-hydroxyphenyl)-valeric Acid, an Active Estrogen

BY JAMES H. HUNTER AND JEROME KORMAN

Researches of Dodds and co-workers[1] provided ground work for numerous investigations[2] of synthetic estrogens of the di-*p*-hydroxyphenylethylene (I) and the related ethane (II) types. More recently, extensive studies by Miescher *et al.*[3] have led to potent estrogenic substances of the bis-dehydrodoisynolic acid class (III).

In continuation of studies on synthetic estrogens in this Laboratory,[4] it was considered worth



while to incorporate into a single molecule certain of the salient features of II and III above. Ac-

(1) Dodds, Goldberg, Lawson and Robinson, *Proc. Roy. Soc. London*, **B127**, 140 (1939).

(2) Solmssen, *Chem. Rev.*, **37**, 481 (1945).

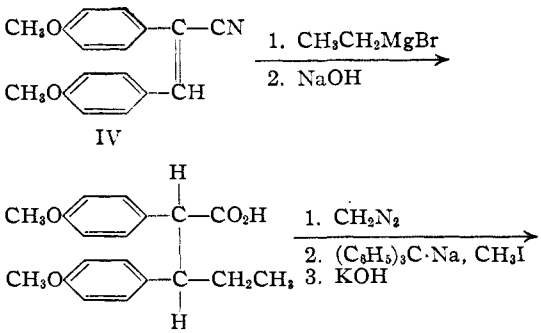
(3) (a) Miescher, *Helv. Chim. Acta*, **27**, 1727 (1944); (b) Heer, Billeter and Miescher, *ibid.*, **28**, 1342 (1945); (c) Heer and Miescher, *ibid.*, **28**, 1506 (1945); (d) Anner and Miescher, *ibid.*, **29**, 586 (1946).

(4) Hunter and Korman, THIS JOURNAL, **69**, 2124 (1947).

cordingly, α-methyl-α,β-di-(p-hydroxyphenyl)-valeric acid (VII) has been synthesized and shown to be a moderately active estrogenic agent.

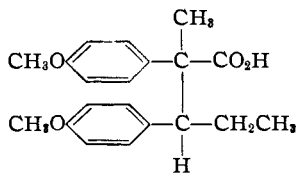
Several unsuccessful approaches were made to the synthesis of VII from desoxyanisoin and α-ethyldesoxyanisoin. With the objective of preparing an α-carbalkoxydesoxyanisoin which could be converted into VII by the method used previously,[4] desoxyanisoin was glyoxalated in good yield; however, attempts to decarbonylate the crude material in the presence of powdered soft glass gave none of the expected carbomethoxy compound. Instead, decomposition products of unknown constitution were formed. Furthermore, analytically pure samples of the glyoxalate did not lose carbon monoxide smoothly to give the desired product. Attempts to carboxylate or carbalkoxylate by the method of Levine and Hauser[5] using sodamide and either solid carbon dioxide or ethyl carbonate failed, as did the method of Wallingford and co-workers,[6] using ethyl carbonate and removing ethyl alcohol formed in the reaction. In a recent patent[7] Wallingford obtained only a 5% yield of α-carbethoxydesoxybenzoin by his procedure. This is not surprising since Rattner[8] reported that distillation of the corresponding desoxybenzoin derivative gave stilbene as one of the decomposition products, and that cold alcoholic alkali caused decomposition to yield, among other products, desoxybenzoin, benzoin and benzhydrol.

Efforts to prepare α-hydroxy-α,β-di-(p-methoxyphenyl)-valeronitrile, a potential intermediate to VII, by the action of hydrogen cyanide on α-ethyl-desoxyanisoin were likewise ineffectual. These unpromising routes were finally abandoned in favor of a more indirect method:



IV

V



VI

(5) Levine and Hauser, THIS JOURNAL, **66**, 1768 (1944).

(6) Wallingford, Homeyer and Jones, *ibid.*, **63**, 2252 (1941).

(7) Wallingford and Homeyer, U. S. Patent 2,407,942, September, 1946.

(8) Rattner, *Ber.*, **21**, 1316 (1888).

4,4′-Dimethoxy-α-cyanostilbene (IV)[9] was added to a refluxing ethereal solution of ethylmagnesium bromide and heated for twenty-four hours[10] to give two isomeric α,β-di-(p-methoxyphenyl)-valeronitriles, a liquid and a solid form, which are probably diastereoisomers. The solid nitrile was hydrolyzed with sodium hydroxide in ethylene glycol containing 10% water[11] to give the isomeric acids (V). Generally the nitriles, without preliminary separation, were hydrolyzed to the mixture of the same acids. Attempts to separate the acids by direct fractional crystallization from 95% ethanol gave only one crystalline form (A), m.p. 177.5–179°. The oily semi-solid material obtained after removal of the solvent was treated with diazomethane and the resulting methyl ester of the isomeric acid (B) melted at 93–94.5° after recrystallization from ethanol. A sample of this ester was hydrolyzed with potassium hydroxide to give the free acid (B), m.p. 163–164.5°.

The methyl ester of A was alkylated with methyl iodide in the presence of triphenylmethyl sodium, and hydrolyzed with potassium hydroxide in methyl alcohol. The dimethyl ether (VI) was cleaved with pyridine hydrochloride to yield VII, which was obtained pure as the diacetate.

Preliminary tests[12] by the Kahnt–Doisy method, employing white rats, have indicated that the dimethyl ether (VI) is inactive in doses up to 500 gamma, while VII produces the full estrus response in doses of 20 gamma.

Experimental[13,14]

4,4′-Dimethoxy-α-cyanostilbene (IV).—This compound was prepared by the method of Niederl and Ziering[9] in 91.5% yield. After two additional recrystallizations from methanol, a sample formed needles, m. p. 108–109.5°.

α,β-Di-(p-methoxyphenyl)-valeronitrile.—To a refluxing solution of ethylmagnesium bromide prepared from 4.86 g. of magnesium and 21.8 g. of ethyl bromide in 200 ml. of anhydrous ether was added 26.5 g. of the above nitrile in small portions. After refluxing for twenty-four hours, the reaction mixture was cooled and decomposed with ice and dilute acetic acid. The ethereal layer was washed with saturated sodium bicarbonate solution, water, and dried over sodium sulfate. Removal of the ether gave a red viscous oil which solidified partially on cooling and scratching. Recrystallization from 95% ethanol gave 10 g. of needles, m. p. 130–131° (A).

Removal of alcohol from the mother liquor and distillation of the residue at 0.03 mm. (bath temperature 220–230°) gave 13 g. of a yellow, viscous oil (B) which failed to crystallize.

Anal. Calcd. for $C_{19}H_{21}O_2N$: C, 77.26; H, 7.17; N, 4.74. Found: (A) C, 77.53; H, 7.23; N, 4.82. (B) C, 77.29; H, 7.27; N, 4.25.

(9) Niederl and Ziering, THIS JOURNAL, **64**, 885 (1942).

(10) Kohler, *Am. Chem. J.*, **35**, 391 (1906).

(11) This procedure was adopted in order to eliminate the use of the Carius bomb as recommended by Kohler who reported that the corresponding α,β-diphenylvaleronitriles could be hydrolyzed only by concentrated hydrochloric acid at 180° for five hours.

(12) We are indebted to Mr. S. C. Lyster of our Department of Pharmacology and Endocrinology for conducting these bioassays.

(13) All melting points are uncorrected.

(14) Microanalyses were performed by Mr. Harold Emerson and staff of our microanalytical laboratories.

α,β-Di-(p-methoxyphenyl)-valeric Acid (V).—A mixture of 12.1 g. of the solid nitrile, 4 g. of sodium hydroxide, 8 ml. of water and 75 ml. of ethylene glycol was refluxed for thirty-six hours.[15,16] An equal volume of water was added and the solution filtered while hot. Acidification of the cooled solution with dilute hydrochloric acid yielded a mixture of isomeric acids. Recrystallization from 95% ethyl alcohol gave 4.65 g. of white product (A), m. p. 177.5–179°.

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.58; H, 7.05. Found: C, 72.53; H, 6.90.

Hydrolysis of the liquid nitrile likewise yielded an acid which showed no melting point depression on admixture with A above.

The crude residue (6.0 g.) after removal of alcohol was dissolved in ether and esterified with diazomethane. After standing for two hours, the ether was removed and the residue, which solidified immediately, was recrystallized three times from 95% ethanol. There was obtained 4.92 g. of crystalline methyl ester of the isomeric α,β-di-(p-methoxyphenyl)-valeric acid, m. p. 93–94.5°.

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.12; H, 7.33.

Seven hundred milligrams of the above ester was allowed to stand at room temperature for four hours and then heated on the steam-bath for one hour with 15 ml. of 15% methanolic potassium hydroxide. Water was added and the alcohol removed in a current of air on the steam-bath. Acidification of the cooled solution with hydrochloric acid gave 610 mg. of crude product. Recrystallization from benzene–petroleum ether gave 400 mg. of the isomeric acid (B), m. p. 163–164.5°.

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.58; H, 7.05. Found: C, 72.28; H, 7.20.

Two grams of the higher melting isomer (A, m. p. 177.5–179°), on treatment with diazomethane and recrystallization from 95% ethanol, gave 1.36 g. of the solid methyl ester, m. p. 128.5–130°.

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 72.83; H, 7.15.

α-Methyl-α,β-di-(p-methoxyphenyl)-valeric Acid (VI).—A solution of 5.0 g. of the methyl ester (m. p. 128.5–130°) in 50 ml. of dry ether was treated with 110 ml. of an ethereal solution of triphenylmethyl sodium[17] (0.000162 mole/ml.) in a stoppered Erlenmeyer flask under nitrogen. After standing for three hours at room temperature, 10 ml. of methyl iodide was added and the stoppered flask allowed to stand overnight. Water and a few drops of glacial acetic acid was added and the ether layer separated. After removal of the solvent in a current of air, the crude residue was refluxed for twenty-two hours with a solution of 10 g. of potassium hydroxide in 150 ml. of 95% ethyl alcohol. The solid obtained on acidification amounted to 4.09 g., m. p. 165–175°.

Recrystallization from *n*-butyl alcohol gave a first crop of 2.24 g., m. p. 181–182.5° (A), and a second crop of 0.07 g. of material melting at 154–156° (B). Because of the small amount of the product (B), demethylation and bioassay was carried out only with the higher melting compound.

Anal. Calcd. for $C_{20}H_{24}O_4$: (A) C, 73.14; H, 7.37. Found: C, 72.95; H, 7.15. (B) C, 73.14; H, 7.37. Found: C, 73.13; H, 7.34.

α-Methyl-α,β-di-(p-hydroxyphenyl)-valeric Acid (VII).—A mixture of 1.0 g. of the acid, m. p. 181–182.5°, and 25 g. of pyridine hydrochloride was heated at 185–195° for three hours. After cooling, the melt was dissolved in water and extracted repeatedly with ether. The ethereal layer was washed with dilute hydrochloric acid, water, and dried. Removal of solvent gave 0.8 g. of solid material which melted with decomposition at approximately 225°.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.31; H, 6.71. Found: C, 71.00; H, 7.36.

The **diacetate** after recrystallization from dilute ethyl alcohol melted at 210–212.5°.

Anal. Calcd. for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29. Found: C, 68.57; H, 6.28.

(15) We have found the use of sodium hydroxide in ethylene glycol very satisfactory for the preparation of acids from other difficultly hydrolyzed nitriles and esters.

(16) Original procedure of Snyder and McIntosh, THIS JOURNAL, **63**, 3280 (1941).

(17) "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. 1, p. 286.

Summary

α-Methyl-α,β-di-(p-hydroxyphenyl)-valeric acid, an active estrogen possessing certain of the salient structural features of both hexestrol and bis-dehydrodoisynolic acid, has been synthesized.

KALAMAZOO, MICHIGAN RECEIVED JUNE 1, 1948

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF BROOKLYN COLLEGE]

The Structure of Meldrum's Supposed β-Lactonic Acid

BY DAVID DAVIDSON AND SIDNEY A. BERNHARD

Meldrum[1] observed that malonic acid and acetone react in the cold in acetic anhydride–sulfuric acid medium, eliminating the elements of water to form a crystalline product, $C_6H_8O_4$. Since this proved to be a monobasic acid which could be titrated in aqueous solution, Meldrum concluded that one of the carboxyl groups of the malonic acid molecule remained intact and proposed that the structure of the new compound was β,β-dimethyl-β-propiolactone-α-carboxylic acid (I).

This view is still current[2] although none of the reactions of Meldrum's product or of its homologs studied by Meldrum and by later workers[3,4,5,6] furnished evidence for the new C:C bond found in I. Instead, all its reactions indicated a notable tendency of the substance to regenerate acetone. Thus, **alkaline hydrolysis**[1] yielded acetone and sodium malonate; **acid alcoholysis,**[3,6] acetone and diethyl malonate; **anilinolysis,**[1] acetone, carbon dioxide and acetanilide; **pyrolysis,**[1,3] acetone, carbon dioxide, acetic acid and carbon suboxide.

(1) Meldrum, *J. Chem. Soc.*, **93**, 598 (1908).

(2) Roger Adams, Editor in Chief, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 124.

(3) Ott, *Ann.*, **401**, 159 (1913).

(4) Kandiah, *J. Chem. Soc.*, 1215 (1932).

(5) Michael and Ross, THIS JOURNAL, **55**, 3684 (1933).

(6) Michael and Weiner, *ibid.*, **58**, 680, 999 (1936).