[CONTRIBUTION FROM THE LABORATORY OF PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF KANSAS SCHOOL OF PHARMACY]

# Steroidal Hormone Relatives. III. The Synthesis of 4-(*m*-Acetylphenyl)-3-(*p*-methoxyphenyl)-2-hexanone

BY J. H. BURCKHALTER, JOSEPH SAM AND LUTHER A. R. HALL

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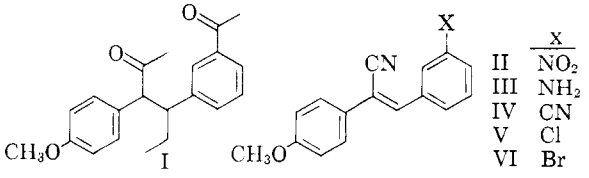
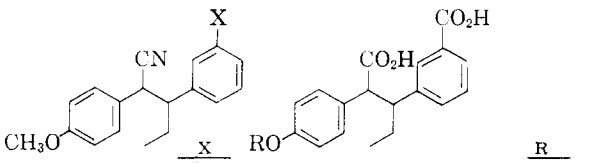
The title compound has been synthesized. It is an open model steroid analog containing oxygen functions in positions corresponding to C-3, 11 and 20 of the steroids.

As a continuation of syntheses of open model steroid analogs which provide a carbonyl in a position corresponding to C-11 of cortisone,[1,2] our attention was directed to the synthesis of 4-(*m*-acetylphenyl)-3-(*p*-methoxyphenyl)-2-hexanone (I), which contains three oxygen functions at positions corresponding to C-3, 11 and 20 of the steroids.



| | X |
|---|---|
| II | $NO_2$ |
| III | $NH_2$ |
| IV | CN |
| V | Cl |
| VI | Br |



| | X |
|---|---|
| VII | Br |
| VIII | CN |

| | R |
|---|---|
| IX | $CH_3$ |
| X | H |

As a starting point, α-(*p*-methoxyphenyl)-3-nitrocinnamonitrile (II) was reduced to the corresponding amine (III) in a yield of 90% by means of either stannous chloride or platinum oxide. The corresponding nitrile IV—actually a dinitrile—was obtained by diazotization of III and treatment of the diazonium salt with cuprous cyanide. However, the yield of IV was only 20%. Condensation of *p*-methoxyphenylacetonitrile and *m*-cyanobenzaldehyde using alcoholic sodium ethoxide gave only a 35% yield of IV, probably because of the impure *m*-cyanobenzaldehyde, an intermediate which was difficult to obtain.[3] A better approach to IV appeared to be through a *m*-halo-α-(*p*-methoxyphenyl)-cinnamonitrile. The chloro compound V was obtained in 83% yield from *m*-chlorobenzaldehyde and *p*-methoxyphenylacetonitrile, but the bromo compound VI[2] was used because of its greater yield and reactivity. However, treatment of VI with cuprous cyanide in a high-boiling solvent gave only a poor yield of IV. Reaction of the unsaturated dinitrile IV with ethylmagnesium bromide gave some of the desired 1,4-addition, for a small amount of the diacid IX could be isolated after alkaline hydrolysis.

Because of the low yields in making and using the unsaturated nitrile IV, we turned to the saturated series in which the ethyl group had already been introduced. Treatment of the solid isomer of the bromonitrile VII[2] with cuprous cyanide in quinoline gave an 85% yield of β-(*m*-cyanophenyl)-α-(*p*-methoxyphenyl)-valeronitrile (VIII). Alkaline hydrolysis of the dinitrile VIII by the general procedure of Hunter and Korman[4] gave a 42% yield of a high melting dicarboxylic acid IXa and an additional 32% yield of a low-melting dicarboxylic acid IXb. Using the procedure of Walker and Hauser,[5] the diacid chloride of IXa and diethyl ethoxymagnesium malonate gave diketone I in 80% yield. Finally, IXa was demethylated with pyridine hydrochloride to X, and the acetate of X was prepared.

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## Experimental

***m*-Amino-α-(*p*-methoxyphenyl)-cinnamonitrile (III).** **Method A.**—To five grams of α-(*p*-methoxyphenyl)-3-nitrocinnamonitrile (II)[6] in 100 ml. of glacial acetic acid, a solution of 20 g. of stannous chloride in 50 ml. of concentrated hydrochloric acid was added. The mixture was heated for 90 minutes during which time the yellow II was converted to a white tin double salt of III. After standing for two hours, the mixture was filtered for removal of the salt. An aqueous solution of the salt was made basic with dilute alkali whereupon a yellow flocculent solid was precipitated. Collected, dried and recrystallized from alcohol, 4 g. (90%. yield) of III was obtained, m.p. 107–108°.

*Anal.* Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64. Found: C, 76.90; H, 5.41.

**Method B.**—Five grams of II dissolved in 200 ml. of absolute alcohol was reduced in a low-pressure hydrogenator using Adams catalyst. After 10 minutes the theoretical drop in hydrogen pressure had occurred. After removal of the catalyst and concentration of the solvent to one-half volume, 4 g. (90% yield) of III was obtained, m.p. 108–109°.

***m*-Cyano-α-(p-methoxyphenyl)-cinnamonitrile (IV).** **Method A.**—By following the general method of Linnell and Roushdi,[7] 10 g. of amine III was converted to 2 g. (20% yield) of yellow crystalline nitrile IV, m.p. 138–139°. There was no depression upon admixture with a sample prepared by method B.

**Method B.**—A solution of 1 g. of sodium in 25 ml. of absolute alcohol was added to a solution of 7.3 g. (0.05 mole) of *p*-methoxyphenylacetonitrile[8] and 5 g. (0.033 mole) of crude *m*-cyanobenzaldehyde[8] in 35 ml. of absolute alcohol. The mixture was allowed to stand overnight whereupon the light yellow precipitate was collected by filtration. After recrystallization from alcohol, 3 g. (35% yield) of IV, m.p. 143–144°, was obtained.

*Anal.* Calcd. for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65. Found: C, 78.50; H, 4.71.

**Method C.**—The procedure of Hager and Burgison[9] was applied to *m*-bromo-α-(*p*-methoxyphenyl)-cinnamonitrile (VI).[2] From 6.3 g. of VI, 5.4 g. of cuprous cyanide and 50

(1) J. H. Burckhalter and J. Sam, THIS JOURNAL, **74**, 187 (1952).

(2) J. H. Burckhalter, P. H. Jackson, J. Sam and H. R. Meyer, *ibid.*, **76**, 4112 (1954).

(3) K. H. Slotta and R. Kethur, *Ber.*, **71**, 61 (1938).

(4) J. H. Hunter and J. Korman, THIS JOURNAL, **70**, 3426 (1948).

(5) H. G. Walker and C. R. Hauser, *ibid.*, **68**, 1386 (1946).

(6) J. B. Niederl and A. Ziering, *ibid.*, **64**, 886 (1942).

(7) W. H. Linnell and I. M. Roushdi, *Quart. J. Pharm. Pharmacol.* **14**, 277 (1941).

(8) K. Rorig, *et al.*, *Org. Syntheses*, **36**, 50 (1956); Trubek Laboratories, East Rutherford, N. J.

(9) G. P. Hager and R. H. Burgison, *J. Am. Pharm. Assoc.*, **39**, 7 (1950).

ml. of quinoline, less than a gram of yellow product IV was obtained, m.p. 134–137°. There was no depression upon admixture with a sample prepared by method B.

***m*-Chloro-α-(*p*-methoxyphenyl)-cinnamonitrile (V).**—By replacing *m*-cyanobenzaldehyde with the same amount of *m*-chlorobenzaldehyde[10] in the procedure of IVB, 8 g. (83% yield) of yellow crystalline V was obtained, m.p. 83.5–84°.

*Anal.* Calcd. for $C_{16}H_{12}ClNO$: C, 71.24; H, 4.49. Found: C, 71.15; H, 4.40.

**β-(*m*-Cyanophenyl)-α-(*p*-methoxyphenyl)-valeronitrile (VIII). Method A.**—An adaptation of the procedure of Hager and Burgison, as described for the preparation of 4-(*m*-cyanophenyl)-3-(*p*-methoxyphenyl)-2-hexanone of a previous paper,[2] was used.

From 7 g. of solid β-(3-bromophenyl)-α-(*p*-methoxyphenyl) valeronitrile (VII),[2] 5.4 g. of cuprous cyanide and 50 ml. of quinoline, 5 g. (85% yield) of VIII was obtained, b.p. 223–230° (1–1.5 mm.).

*Anal.* Calcd. for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25. Found: C, 78.72; H, 6.33.

**Method B.**[11]—To 0.031 mole of freshly prepared ethylmagnesium bromide in 50 ml. of dry ether solution, there was added with stirring over a 10 minute period 3.5 g. (0.014 mole) of *m*-cyano-α-(*p*-methoxyphenyl)-cinnamonitrile (IV). After a mildly exothermic reaction had subsided, the stirring was continued for 15 minutes at room temperature, at reflux for 90 minutes and finally at room temperature for an hour. The complex was hydrolyzed with ice and concentrated hydrochloric acid and the ether layer dried over magnesium sulfate. Evaporation of the ether and treatment of the tarry residue with methyl alcohol gave about 0.2 g. of a yellow solid, m.p. 136–136.5°, which by mixed m.p. was shown to be identical with starting material IV. Evaporation of the filtrate gave about 2 g. of oily material which was assumed to contain VIII because it was hydrolyzed by the procedure of the following section to give 0.15 g. of acid, m.p. 258–260°, shown to be identical with IXa (*vide infra*) by mixed m.p. determination. In this experiment, the dicarboxylic acid IXa was isolated by trituration of the resinous product with benzene. The mother liquor of the benzene was concentrated to an oil which presumably contained the low melting isomer IXb.

**β-(*m*-Carboxyphenyl)-α-(*p*-methoxyphenyl)-valeric Acid (IX).**—The general method of Hunter and Korman was followed.[4] A mixture of 4.2 g. of VIII, 3 g. of sodium hydroxide, 60 ml. of ethylene glycol and 5 ml. of water was heated for 36 hours at reflux temperature. Solution was effected as soon as the mixture became hot, and the color lightened as heating was continued. An equal volume of water was added and the clear solution filtered while hot. The cooled filtrate was acidified with dilute hydrochloric acid. The white precipitate was removed by filtration and recrystallized thrice from diluted alcohol. Two grams (42% yield) of acid IXa was obtained, m.p. 258–260°. The compound readily sublimed at about ten degrees below the melting point; neut. equiv.: calcd. 164, found 162.

*Anal.* Calcd. for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.16; H, 6.34.

Two grams of oily solid acid, recovered by evaporation of the filtrate of IXa, was crystallized from benzene to give 1.5 g. (32% yield) of isomeric acid IXb, m.p. 146–147°.

*Anal.* Found: C, 69.75; H, 6.26.

**β-(*m*-Chlorocarbonylphenyl)-α-(*p*-methoxyphenyl)-valeryl Chloride.**—A mixture of 1.5 g. of IXa and 10 ml. of thionyl chloride was heated to boiling for four hours. The excess thionyl chloride was removed *in vacuo*. A small amount of the residue was crystallized from Skellysolve but was not analyzed, m.p. 145–146°.

**4-(*m*-Acetylphenyl)-3-(*p*-methoxyphenyl)-2-hexanone (I).**—The method used was that of Walker and Hauser[5] for the preparation of methyl ketones. The acid chloride was not isolated.

From 1.5 g. of diacid IXa, 1.2 g. (80% yield) of pure diketone I was obtained after recrystallization from dilute alcohol, m.p. 112–114°.

*Anal.* Calcd. for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.88; H, 7.46.

**β-(*m*-Carboxyphenyl)-α-(*p*-hydroxyphenyl)-valeric Acid (X).**—A mixture of 1 g. of diacid IXa and 25 g. of pyridine hydrochloride was heated at reflux temperature for three hours. After cooling the flask, an equal volume of water was added. The mixture was extracted several times with ether. Evaporation of the ether from the combined extracts gave a residue which was recrystallized from dilute alcohol. The yield of X was 0.6 g. (62%), m.p. 330° dec.

*Anal.* Calcd. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.82; H, 5.91.

**The acetate** of X was prepared by means of acetic anhydride and sodium acetate. It was recrystallized first from dilute alcohol and then from benzene, m.p. 216–217°.

*Anal.* Calcd. for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66. Found: C, 67.43; H, 5.88.

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(10) J. S. Buck and W. S. Ide, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 130.

(11) This experiment was carried out by H. C. Scarborough, Jr.

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# Steroidal Hormone Relatives. IV.[1] The Synthesis of 1-Ethyl-6-methoxy-2-(*p*-methoxyphenyl)-3-methylindene

BY J. H. BURCKHALTER AND P. KURATH

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Attempts to prepare 4-(*m*-methoxyphenyl)-3-(*p*-methoxyphenyl)-2-hexanone (I) led to a cyclized product of I, the structure of which was established as 1-ethyl-6-methoxy-2-(*p*-methoxyphenyl)-3-methylindene (V) by an independent synthesis from an indanone (VI) which is related structurally to jervine.

As a part of a continuing program[1] to synthesize analogs of the steroidal hormones, we have attempted the synthesis of I which carries an oxygen function at the position corresponding to C-11 in the steroid nucleus.

The condensation of *p*-methoxyphenylacetonitrile with *m*-methoxybenzaldehyde by the general procedure of Frost[2,3] gave *m*-methoxy-α-(*p*-methoxyphenyl)-cinnamonitrile (II) in 92% yield. The latter compound (II), when treated with ethylmagnesium bromide,[4] was converted in 41% yield to a solid IIIa and in 40% yield to a liquid IIIb, which represent the diastereoisomeric forms of 3-(*m*-meth-

(1) Previous papers: (a) J. H. Burckhalter and J. Sam, THIS JOURNAL, **74**, 187 (1952); (b) J. H. Burckhalter, P. H. Jackson, J. Sam and H. R. Meyer, *ibid.*, **76**, 4112 (1954); (c) J. H. Burckhalter, J. Sam and L. Hall, *ibid.*, **81**, 394 (1959).

(2) H. V. Frost, *Ann.*, **250**, 156 (1889).

(3) *Cf.* S. Wawzonek and E. M. Smolin, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 715.

(4) *Cf.* (a) E. P. Kohler, *Am. Chem. J.*, **35**, 386 (1906); (b) J. H. Hunter and J. Korman, THIS JOURNAL, **70**, 3424 (1948).