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.

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

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

BY J. H. BURCKHALTER AND P. KURATH

RECEIVED AUGUST 4, 1958

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-

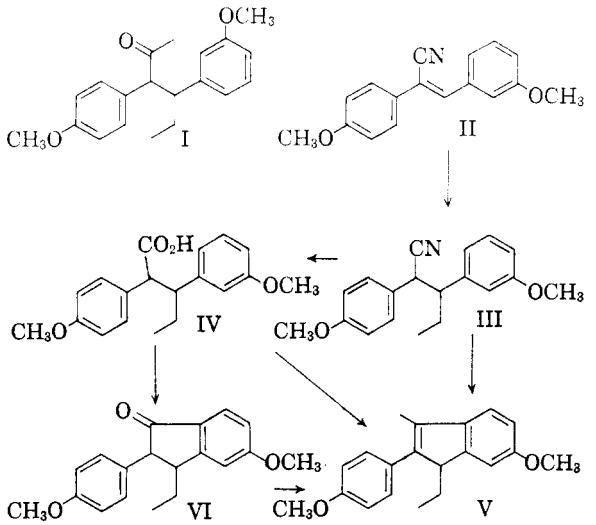
(1) Previous papers: (a) J. H. Burckhalter and J. Sam, THIS JOURNAL, **74**, 187 (1952); (b) J. H. Burckhalter, P. H. Jackson, J. Sam and H. R. Meyer, *ibid.*, **76**, 4112 (1954); (c) J. H. Burckhalter, J. Sam and L. Hall, *ibid.*, **81**, 394 (1959).

(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).

oxyphenyl)-2-(*p*-methoxyphenyl)-valeronitrile. Alkaline hydrolysis of either the solid or liquid nitrile (IIIa or b) by the general method of Hunter and Korman[4b] produced equal amounts of solid and liquid 3-(*m*-methoxyphenyl)-2-(*p*-methoxyphenyl)-valeric acids (IVa and b).



Two different approaches to the preparation of 4-(*m*-methoxyphenyl)-3-(*p*-methoxyphenyl)-2-hexanone (I) from IIIa led to the isolation of a cyclized product, 1-ethyl-6 methoxy-2-(*p*-methoxyphenyl)-3-methylindene (V). The reaction of IIIa with methylmagnesium iodide, followed by hydrolysis of the Grignard complex by means of concentrated hydrochloric acid at room temperature, gave the indene V instead of the ketone I. The same product (V) resulted from the reaction of the acid chloride of IV with diethyl ethoxymagnesium malonate followed by hydrolysis and decarboxylation in an acidic medium, using the general procedure of Walker and Hauser.[5]

That the indene V was obtained instead of the ketone I is not surprising in view of the acidic conditions employed in both reactions which produced the indene. It is likely that the ketone was present in each case but could not be isolated because of its cyclization in the acidic media which were used in order to hydrolyze the Grignard complex and hydrolyze and decarboxylate the substituted malonic ester. In attempting to find a method for the synthesis of I which does not employ acidic conditions, acid IV was treated with methyllithium.[6] However, only the starting acid was recovered in excellent yield. The similar use of dimethylcadmium has not yet been attempted.

It was desirable to prepare V by an independent route. Solid acid IVa on cyclization with polyphosphoric acid[7] gave rise to the ketone VI.[8] This ketone was treated with methylmagnesium iodide and the resulting crude carbinol was dehydrated to yield a compound identical with V. In analogy with examples cited in the literature,[9] the cyclization of the acid IV would be expected to take place at the position *para* to the activating methoxy group, and consequently VI has been formulated as 3-ethyl-5-methoxy-2-(*p*-methoxyphenyl)-1-indanone. Since VI was converted to V, the structure of the latter is obvious. Further, it will be noted that V has the same nucleus as the steroid alkaloid jervine except that ring B is open.[10] Also, it has the same oxygen functions as jervine at positions 3 and 11.

Acknowledgment.—These studies were supported through the General Research Fund of the University of Kansas.

Experimental[11,12]

***m*-Methoxy-α-(*p*-methoxyphenyl)-cinnamonitrile (II).**—The general procedure of Frost[2] was followed. To a well stirred mixture of 54 g. of *p*-methoxyphenyl-acetonitrile[1c] and 52 g. of *m*-methoxybenzaldehyde,[13] 40 ml. of a 20% sodium ethoxide solution in alcohol was added dropwise. The reaction mixture was heated and stirred for 30 minutes and was then left standing at room temperature overnight. The compound was taken up in ether and the ether extract was washed until neutral with water, dried and concentrated. The residue was distilled under reduced pressure to yield 90 g. (92%) of II, b.p. 194–197° (0.1 mm.). The compound solidified on standing. A part of the product was recrystallized from alcohol for analysis, m.p. 43–45°.

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70. Found: C, 76.86; H, 5.65.

3-(*m*-Methoxyphenyl)-2-(*p*-methoxyphenyl)-valeronitrile (IIIa and IIIb).—The general method of Kohler[4a] was followed. From 148 g. of 3-methoxy-α-(*p*-methoxyphenyl)-cinnamonitrile (II), 142 g. of an oil was obtained, b.p. 180–185° (0.3 mm.). Upon crystallization of this product from alcohol, 67 g. (41%) of a solid nitrile IIIa was isolated, m.p. 93–98°. A part of this sample was recrystallized for analysis, m.p. 99–101°.

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17. Found: C, 77.58; H, 7.16.

The mother liquors were concentrated and the residue was distilled under high vacuum to yield 66 g. (40%) of a liquid nitrile IIIb, b.p. 178–180° (0.2 mm.). A part of the compound was fractionated twice giving an analytical sample, b.p. 165–169° (0.1 mm.), $n^{20}D$ 1.5635.

Anal. Found: C, 77.68; H, 7.31.

3-(*m*-Methoxyphenyl)-2-(*p*-methoxyphenyl)-valeric acid (IVa and IVb).—The general method of Hunter and Korman was followed.[4b] A mixture of 17 g. of solid nitrile IIIa, 11g. of sodium hydroxide, 15 ml. of water and 150 ml. of ethylene glycol was heated at reflux temperature for 48 hours. After cooling the mixture to room temperature, it was filtered and the filtrate acidified whereupon a gum precipitated. The gum was dissolved in chloroform and the solution extracted with 10% sodium hydroxide solution. Acidification of the combined extracts gave a gum which was dissolved in hot alcohol. Cooling gave a solid which was recrystallized from alcohol or acetone–Skelly C to yield 6.5 g. (35%) of solid acid IVa, m.p. 156–158°.

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.60; H, 7.00.

The initial alcoholic liquor was concentrated and the residue, from which no further solid separated, was distilled to

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

(6) *Cf.* D. A. van Dorp and J. F. Arens, *Rec. trav. chim.*, **65**, 338 (1946); C. Tegner, *Acta Chem. Scand.*, **6**, 782 (1952).

(7) J. Koo, THIS JOURNAL, **75**, 1891 (1953).

(8) In a cyclization experiment by H. C. Scarborough, Jr., liquid acid IVb gave essentially equal amounts of solid ketone VI and a liquid ketone assumed to be its diastereoisomer, as indicated by elementary and infrared absorption spectra.

(9) F. D. Popp and W. E. McEwen, *Chem. Revs.*, **58**, 321 (1958), particularly pp. 349–363; *cf.* W. S. Johnson, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 124.

(10) J. Fried, *et al.*, THIS JOURNAL, **73**, 2970 (1951).

(11) Microanalyses by Mr. C. W. Beazley, Skokie, Ill.

(12) The melting points are not corrected.

(13) Prepared by the procedure of R. B. Woodward, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 453; and R. N. Icke, C. E. Redemann, B. B. Wisegarver and G. A. Alles, *ibid.*, p. 564.

yield 6.5 g. (35%) of liquid acid IVb, b.p. 200–201° (0.2 mm.).[14]

Anal. Found: C, 72.91; H, 7.31.

Similar hydrolytic treatment of the liquid nitrile IIIb gave a 45% yield of the solid acid IVa, m.p. 153–155°, and 43% yield of the liquid acid IVb, b.p. 201° (0.2 mm.).[14]

3-Ethyl-5-methoxy-2-(*p*-methoxyphenyl)-1-indanone (VI).—According to the general method of Koo,[7] a mixture of 5.8 g. of solid acid IVa and 62 g. of polyphosphoric acid[15] was heated and stirred at 70° for 30 minutes. The reaction mixture was worked up as previously described[7] and 2.2 g. (39% yield) of the ketone VI, m.p. 90–92°, was obtained. Recrystallization of the sample from methanol–water yielded the pure compound VI, m.p. 92–94°.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.87; H, 7.04.

The 2,4-dinitrophenylhydrazone of VI was prepared and recrystallized from chloroform–methanol, m.p. 186–187°.

Anal. Calcd. for $C_{25}H_{24}N_4O_6$: C, 63.01; H, 5.08. Found: C, 62.94; H, 5.31.

From the basic extract of the reaction just described, 2.5 g. (43%) of starting material IVa, m.p. 152–155°, was recovered through acidification.

1-Ethyl-6-methoxy-2(*p*-methoxyphenyl)-3-methylindene (V). (a) From the Nitrile IIIa.—The general procedure of Kohler[4a] was employed. To the Grignard reagent prepared from 12 g. of magnesium and 70 g. of methyl iodide in 150 ml. of anhydrous ether, a solution of 25 g. of the nitrile IIIa in 150 ml. of dry benzene was added slowly with stirring. After completion of the addition, the ether was removed and the resulting mixture heated at reflux temperature for three hours. After cooling, it was added slowly and with stirring to a mixture of 100 ml. of concentrated hydrochloric acid and cracked ice. After being allowed to reach room temperature to ensure complete hydrolysis of the Grignard complex, the mixture was extracted with ether containing a small amount of methanol, the ethereal solution was washed with saturated sodium chloride solution, dried further over sodium sulfate, and filtered. After removal of the ether, the residue distilled from a Hickman flask yielded 21 g. of an oil, b.p. 165–175° (0.3 mm.). The product was crystallized twice from alcohol to give 8 g. (32% yield) of needles, m.p. 97–99°. An analytical sample was prepared, m.p. 99–101°.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.69; H, 7.70.

From the mother liquors no other compound could be identified. Treatment of the liquid nitrile IIIb under similar conditions led to a mixture, and no pure product could be isolated.

(b) From the Acid IVa.—The acid chloride was prepared from 6.3 g. of IV with 10 ml. of thionyl chloride under conditions previously employed.[16] The crude acid chloride (6 g.) was treated with diethyl ethoxymagnesium malonate[5] and the resulting substituted malonic ester was hydrolyzed and decarboxylated. Upon distillation of the product, 2 g. (32% yield) of an oil, b.p. 185–195° (0.5–1 mm.), was obtained. The compound was crystallized from acetone–Skellysolve C and was finally recrystallized from methanol to give a sample melting at 100–101°. Admixture of this compound with V, obtained from nitrile IIIa, did not depress the melting point.

(c) From the Ketone VI.—The ketone VI (3 g.) was allowed to react with methylmagnesium iodide[17] and the resulting crude carbinol was dehydrated by heating it at reflux temperature with 0.8 g. of *p*-toluenesulfonic acid in 40 ml. of acetic acid for 2.5 hours.[18] The crude reaction product, 2 g. (67%), crystallized after seeding it with a crystal of V obtained from the nitrile IIIa. The compound was recrystallized for analysis, m.p. 99–101°. Admixture of this compound with V, obtained from nitrile IIIa, did not depress the melting point.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.64; H, 7.59.

(14) Experiment carried out by H. C. Scarborough, Jr.

(15) Obtained through the courtesy of Victor Chemical Works, Chicago 4, Ill.

(16) R. C. Fuson and J. T. Walker, ref. 13, Coll. Vol. II, 1943, p. 169.

(17) *Cf.* W. Voser, D. E. White, H. Heusser, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **35**, 830 (1952).

(18) *Cf.* A. Eschenmoser, J. Schreiber and S. A. Julia, *ibid.*, **36**, 482 (1953).

LAWRENCE, KANS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Studies in the Synthesis of the Antirachitic Vitamins. VII. The Synthesis of 2,1′-*cis* and 2,1′-*trans* Isomers of 1-Cholestanylidene-2-(5′-methoxy-2′-methylene-1′-cyclohexylidene)-ethane

BY NICHOLAS A. MILAS AND CHARLES P. PRIESING[1]

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The synthesis of 2,1′-*cis*(VII) and 2,1′-*trans*(VIII) isomers of 1-cholestanylidene-2-(5′-methoxy-2′-methylene-1′-cyclohexylidene)-ethane, two homologs of vitamin D, from the corresponding isomeric dienones is described. During the purification of these homologs, a product was isolated which was chemically related to them but exhibited an abnormal ultraviolet spectrum. When tested on rachitic rats both the homologs and the third product were biologically active with the 2,1′-*cis*-homolog and the third product nearly as active as crystalline vitamin D_2, while the 2,1′-*trans*-homolog had very much less activity.

In connection with a long range program on the total synthesis of vitamin D_3 we had occasion to synthesize various homologs of this vitamin in order to study the influence of constitution on antirachitic activity. With the single exception of the calcium salt of the enol of 9,10-*seco*-cholest-5-en-7-one-3,10-diol[2] no biologically active antirachitic products of high activity have been obtained heretofore without the use of ultraviolet light or other high energy producing sources to activate the provitamin D intermediates which usually possess no antirachitic properties. It has already been established that high biological activity is associated with the stereochemical configuration of the triene system of the vitamin D molecule,[3a,b] and that the hydrocarbon side chain on carbon atom 17 is essential for this activity.[4] In view of the latter fact no attempt was made to assay biologically our simple homolog.[3b,5] However, in a recent communication[3a] we have announced the synthesis of a homo-

(1) From the Ph.D. Thesis of C. P. Priesing, M.I.T., April, 1957; presented before the 132nd Meeting of the A. C. S., New York, September 8–13 (1957).

(2) Y. Raoul, N. Le Boulch, C. Baron, R. Bazier and A. Gueriollot-Vinet, *Compt. rend.*, **242**, 3004 (1956).

(3) (a) N. A. Milas and C. P. Priesing, THIS JOURNAL, **79**, 3610 (1957); (b) **79**, 6295 (1957).

(4) N. A. Milas and R. C. Milone, *ibid.*, **68**, 738 (1946).

(5) N. A. Milas, L. C. Chiang, C. P. Priesing, A. A. Hyatt and J. Peters, *ibid.*, **77**, 4180 (1955).