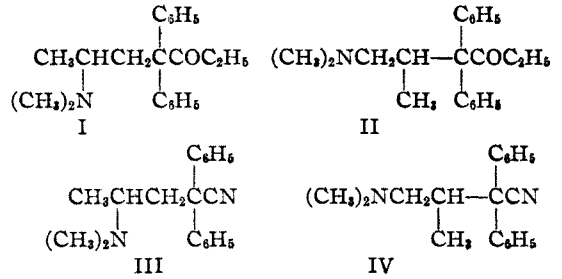
[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

# The Resolution of Methadone and Related Compounds

BY A. A. LARSEN, B. F. TULLAR, B. ELPERN AND J. S. BUCK

In a British Intelligence report[1] it was stated that the levo[2] isomer of the German analgesic drug methadone possessed greater activity than the racemic[3] modification. Since that time this report has been substantiated and several brief procedures for obtaining *l*-methadone have been published.[4] In connection with work in this Laboratory we have resolved methadone (I), the isomeric methylhexanone (II) and in addition the two nitriles (III and IV) related to these aminoketones.



To obtain the resolved aminoketones two methods were employed. The first was to prepare the *dl*-ketone from the *dl*-nitrile and then resolve the ketone. The second was to resolve the nitrile and then allow the optically active nitriles to react with ethylmagnesium bromide to give the desired ketones. Interestingly enough, it was observed that *l*-6-dimethylamino-4,4-diphenyl-3-heptanone, *l*-methadone, was obtained from 1,4-dimethylamino-2,2-diphenylpentanenitrile, whereas *l*-6-dimethylamino-4,4-diphenyl-5-methyl-3-hexanone was obtained from *d*-4-dimethylamino-2,2-diphenyl-3-methylbutanenitrile.

In all four cases resolution could be accomplished readily by use of *d*-tartaric acid. The initial seed crystals were obtained by mixing equimolar quantities of the racemic base and *d*-tartaric acid on a watch glass, adding and evaporating various common solvents and scratching vigorously. Upon the appearance of a solid phase any excess solvent present was decanted, the solid material leached several times with the crystallizing solvent and filtered off.

This paper describes in some detail these resolutions. The physical properties of the various isomers and their salts are given in Table I.

## Experimental

**Resolution of *dl*-6-Dimethylamino-4,4-diphenyl-3-heptanone (I).**—A solution of 620 g. (2 moles) of racemic aminoketone and 310 g. (3.05 moles) of *d*-tartaric acid in 2.4 l. of propanol was seeded with *l*-aminoketone *d*-bitartrate and maintained at −10° for twenty-four hours. The white solid (A) was filtered off, washed with cold propanol and dried *in vacuo*. It weighed 320 g. and melted at 143–147°. A recrystallization from 1.5 l. of propanol gave 250 g. of *l*-aminoketone *d*-bitartrate, m. p. 147–148°, [α] −85°. This recrystallization could also be accomplished by using 3 parts by weight of water to 1 part by weight of the salt to give the hemihydrate, m. p. 90–92°, [α] −84°.

After the filtrate from the crystals (A) had stood for several hours at room temperature a second crop of crystals (B) weighing 200 g. was obtained which was essentially a 1:1 mixture of the diastereoisomers, m. p. 128–130°, [α] +12°. This material was dried and resolved by recrystallization from propanol to yield another 50 g. of *l*-aminoketone *d*-bitartrate.

The filtrate from the crystals (B) was diluted with 140 ml. of water and kept at 5° for several hours. The resultant third crop of crystals (C), impure *d*-aminoketone *d*-bitartrate monohydrate, weighed 145 g. and melted at 93–96°. This material (C) was recrystallized several times from an equal weight of water and dried *in vacuo* at 80° to give the anhydrous salt, m. p. 107–109°, [α] +104°.

The filtrate from the crop (C) was concentrated and cooled to yield another 100 g. of *d*-aminoketone *d*-bitartrate monohydrate (D). When the filtrate from the monohydrate (D) was diluted with water and made alkaline with ammonia, there was obtained 100 g. of base having slight optical activity.

The actual yield of the desired *l*-aminoketone *d*-bitartrate was 300 g. (65%). When allowance was made for the recovered racemic base and recycling of the liquors in subsequent runs, the yield amounted to about 85%. The yield of the *d*-aminoketone *d*-bitartrate monohydrate was 245 g. (42%).

***l*-6-Dimethylamino-4,4-diphenyl-3-heptanone Hydrochloride.**—A solution of 240 g. of recrystallized *l*-aminoketone *d*-bitartrate in 1.5 l. of water was cooled at 15° and slowly made alkaline with ammonia. The white solid was filtered off, washed with water, dried *in vacuo*, and weighed 158 g. (97%), m. p 96–98°. Recrystallization of a sample of this material from isopropanol gave the base which melted at 100–101°, [α] −26°.

A solution of 158 g. of *l*-aminoketone in 100 ml. of water and 40 ml. of concentrated hydrochloric acid was filtered and then kept at 5° for several hours. The crystalline hydrochloride, after drying *in vacuo*, weighed 168 g. (95%), and melted at 243–245°, [α] −125°. A small portion when recrystallized from isopropanol melted at 244–245° with no change in rotation.

***d*-6-Dimethylamino-4,4-diphenyl-3-heptanone Hydrochloride.**—The method for preparing this hydrochloride and the corresponding base from the *d*-bitartrate was the same as that employed for the *l*-aminoketone. The *d*-aminoketone melted at 100–101°, [α] +26°, the hydrochloride melted at 243–244°, [α] +125°.

**Resolution of *dl*-6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexanone (II).**—A solution of 775 g. (2.5 moles) of racemic aminoketone and 390 g. (2.6 moles) of *d*-tartaric acid in 8 l. of warm water was cooled to room temperature, seeded with *l*-aminoketone *d*-bitartrate and let stand for twenty-four hours. A heavy crop of crystals (A) was collected, dried on the filter, dissolved in 2 l. of warm water and kept at room temperature overnight. The glistening crystals (B) so obtained were collected and air dried. Recrystallization of this material (B) from 2 l. of water yielded 345 g. of *l*-aminoketone *d*-bitartrate (C), m. p. 115–120°, [α] −43°.

(1) British Intelligence Objectives Sub-committee, Final Report No. 116, Item No. 24, pp. 51, 52 and 65.

(2) The use of levo, dextro, "*l*" and "*d*" is restricted to designation of the direction of rotation.

(3) No distinction is made in this paper between racemic and "*dl*."

(4) Thorp, Walton and Ofner, *Nature*, **159**, 679 (1947); **160**, 605 (1947); Brode and Hill, *J. Org. Chem.*, **13**, 191 (1948).

TABLE I

COMPOUNDS RELATED TO METHADONE[a]

| Compound | Optical form | Salt | $[\alpha]^{26}D$[b] | M. p., °C.[c] | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|---|---|
| 6-Dimethylamino-4,4-diphenyl-3-heptanone | *dl* | Base | ... | 79–81 | 81.50 | 81.30 | 8.80 | 8.68 | 4.53 | 4.45 |
| | *d* | Base | + 26 | 100–101[d] | 81.50 | 81.47 | 8.80 | 8.54 | 4.53 | 4.51 |
| | *l* | Base | − 26 | 100–101[d] | 81.50 | 81.37 | 8.80 | 8.69 | 4.53 | 4.60 |
| | *dl* | HCl | ... | 229–230 | 72.91 | 73.14 | 8.16 | 8.03 | 4.05 | 3.96 |
| | *d* | HCl | +125 | 243–244[e] | 72.91 | 72.77 | 8.16 | 7.98 | 4.05 | 3.88 |
| | *l* | HCl | −125 | 245–246[e] | 72.91 | 73.06 | 8.16 | 8.23 | 4.05 | 4.07 |
| | *d* | Bitartrate | +104 | 107–109[f] | 65.34 | 65.30 | 7.24 | 6.94 | 3.05 | 2.93 |
| | *l* | Bitartrate | − 85 | 147–149[g] | 65.34 | 65.24 | 7.24 | 7.56 | 3.05 | 2.81 |
| 6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexanone | *dl* | Base | ... | Oil | 81.50 | 81.37 | 8.80 | 8.68 | 4.53 | 4.47 |
| | *d* | Base | + 21 | Oil[h] | 81.50 | 81.51 | 8.80 | 8.79 | 4.53 | 4.55 |
| | *l* | Base | − 20 | Oil[h] | 81.50 | 81.87 | 8.80 | 8.65 | 4.53 | 4.38 |
| | *dl* | HCl | ... | 153–155[i] | 69.30 | 69.54 | 8.32 | 8.33 | 3.87 | 3.79 |
| | *d* | HCl | + 66 | 176–177[i] | 69.30 | 69.52 | 8.32 | 8.18 | 3.87 | 3.76 |
| | *l* | HCl | − 70 | 231–233 | 72.91 | 72.98 | 8.16 | 8.04 | 4.05 | 4.02 |
| | *d* | Bitartrate | + 60 | 148–152[k] | 65.34 | 65.33 | 7.24 | 7.06 | 3.05 | 2.95 |
| | *l* | Bitartrate | − 44 | 122–125 | 65.34 | 65.04 | 7.24 | 6.95 | 3.05 | 3.04 |
| 4-Dimethylamino-2,2-diphenylpentanenitrile | *dl* | Base | ... | 91–92 | 81.97 | 82.05 | 7.97 | 8.28 | 10.06 | 9.76 |
| | *d* | Base | + 50 | 100–101[l] | 81.97 | 82.28 | 7.97 | 7.83 | 10.06 | 9.89 |
| | *l* | Base | − 50 | 100–102[l] | 81.97 | 82.19 | 7.97 | 7.85 | 10.06 | 9.87 |
| | *dl* | HCl | ... | 186–188 | 72.48 | 72.76 | 7.36 | 7.23 | 8.89 | 8.77 |
| | *d* | HCl | + 3.6 | 211–212[m] | 72.48 | 72.72 | 7.36 | 7.21 | 8.89 | 8.66 |
| | *l* | HCl | − 3.8 | 211–212[n] | 72.48 | 72.38 | 7.36 | 7.11 | 8.89 | 8.67 |
| | *d* | Bitartrate | + 7 | 87–100[o] | 64.47 | 64.30 | 6.58 | 6.58 | 6.54 | 6.25 |
| | *l* | Bitartrate | + 14 | 116–120[p] | 61.86 | 62.01 | 6.77 | 6.51 | 6.28 | 6.11 |
| 4-Dimethylamino-2,2-diphenyl-3-methylbutanenitrile | *dl* | Base | ... | 68–70 | 81.97 | 82.33 | 7.97 | 7.65 | 10.06 | 9.95 |
| | *d* | Base | + 70 | 101–102 | 81.97 | 82.26 | 7.97 | 7.70 | 10.06 | 9.83 |
| | *l* | Base | − 70 | 102–103 | 81.97 | 82.24 | 7.97 | 7.84 | 10.06 | 9.81 |
| | *dl* | HCl | ... | 227–229 | 72.48 | 72.44 | 7.36 | 7.17 | 8.89 | 8.78 |
| | *d* | HCl | + 75 | 226–228 | 72.48 | 72.44 | 7.36 | 7.32 | 8.89 | 8.64 |
| | *l* | HCl | − 75 | 226–227 | 72.48 | 72.77 | 7.36 | 7.15 | 8.89 | 8.80 |
| | *d* | Bitartrate | + 65 | 95–110 | 64.47 | 64.29 | 6.58 | 6.59 | 6.54 | 6.46 |
| | *l* | Bitartrate | − 45 | 105–107 | 64.47 | 64.33 | 6.58 | 6.69 | 6.54 | 6.37 |

[a] The values given in the table are for analytically pure compounds and are not necessarily those found in the text. [b] Unless otherwise indicated a 1.5% solution of the salt in water or base in U. S. P. ethanol was employed. [c] All melting points in the table are corrected. Sample in capillary tube immersed in the bath at a temperature 20° below the melting point and the temperature raised at a rate of 3° per minute. Melting points in the text except the final ones that appear in the table are not corrected. [d] Thorp, Walton and Ofner, *Nature*, **160**, 605 (1947), reported $[\alpha]D$ +28° and −32°, no concentration or temperature specified, melting point of both isomers reported as 99°. Brode and Hill, *J. Org. Chem.*, **13**, 191 (1948), reported $[\alpha]^{26}D$ +29.51°, m. p. 98.7–99° and $[\alpha]^{22}D$ −29.91° (concn. 2.66 g., absolute ethanol), m. p. 98.7–99°. [e] Brode and Hill, *loc. cit.*, reported $[\alpha]^{28}D$ 127.5° and −127.8° (concn. 2.96 in water). [f] Brode and Hill, *loc. cit.*, reported m. p. 117.8–118.1°, no rotation or analysis given. A material having the analysis of *d*-methadone *d*-ditartrate was obtained which melted at 121–123°, $[\alpha]$ +79°. *Anal.* Calcd. for $C_{21}H_{27}NO \cdot C_8H_{12}O_{12}$: C, 57.32; H, 6.14; N, 2.30. Found: C, 57.15; H, 6.18; N, 2.21. [g] Brode and Hill, *loc. cit.*, reported $[\alpha]^{26}D$ −84.43° (concn. 3.02 g. in distilled water), m. p. 149.5–151°. [h] Boiling point was 162–165° (0.6 mm.), $n^{25}D$ 1.5575. [i] Monohydrate, Easton, Gardner, Evanick and Stevens, THIS JOURNAL, **70**, 76 (1948), reported melting point as 145–149°. [j] Monohydrate, anhydrous salt melted at 230–231°, $[\alpha]$ +70°. [k] This bitartrate was prepared from a sample of optically pure base and *d*-tartaric acid, since isolation of the bitartrate was unnecessary for the purposes of resolution. [l] Rotation taken in absolute ethanol. In U. S. P. ethanol the values are ±40°. Thorp, *et al.*, *loc. cit.*, reported $[\alpha]D$ +49° and −51°, melting point as 101 and 100°, respectively. [m] Rotation taken with 5% solution in absolute ethanol; $[\alpha]$ −3.2° (4% in 80% ethanol) and −6° (5% in water). [n] Rotation taken with 5% solution in absolute ethanol; $[\alpha]$ +3° (4% in 80% ethanol) and +6° (5% in water). [o] This bitartrate was prepared from a sample of optically pure base and *d*-tartaric acid, since isolation of the bitartrate was unnecessary for the purposes of resolution. Rotation taken with a 5% solution in water. Thorp, *et al.*, *loc. cit.*, reported $[\alpha]^{20}D$ +5° (concn. 1.62 in water) and melting point as 66–70°. [p] Monohydrate, $[\alpha]$ +8° (1.5% in abs. ethanol). Thorp, *et al.*, *loc. cit.*, reported melting point as 109–112°, $[\alpha]^{20}D$ +16° (concn. 1.44 in water).

When the combined filtrates, from the crops (A) and (B), were diluted with 500 ml. of concentrated hydrochloric acid and allowed to stand for several hours there was obtained 300 g. of nearly pure *d*-aminoketone hydrochloride monohydrate (D), $[\alpha]$ +65°. The filtrate from the monohydrate (D) was saturated with sodium chloride and maintained at 5° for several hours to yield 240 g. of hydrochloride (E) having little optical activity.

When the filtrate from the bitartrate (C) was diluted with 200 ml. of concentrated hydrochloric acid there was obtained 35 g. of practically pure *l*-aminoketone hydrochloride monohydrate (F), $[\alpha]$ −66°. The filtrate from the hydrochloride (F) was saturated with sodium chloride to yield another 30 g. of racemic hydrochloride. When this racemic salt was combined with the previous 240 g. of racemic material (E), converted to the base and sub-

jected to a second resolution another 70 g. of *l*-aminoketone hydrochloride monohydrate was obtained. The yield of the *l*-aminoketone was 82%, that of the *d*-isomer 65%.

***l*-6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexanone Hydrochloride.**—A solution of 345 g. of the *l*-aminoketone *d*-bitartrate in 2 l. of water was made alkaline with ammonia and 225 g. (97%) of the free base isolated as an oil. This was dissolved in 500 ml. of water and 60 ml. of concentrated hydrochloric acid at 90°, filtered and diluted with 200 ml. of water. After standing at 5° for several hours the white crystalline hydrochloride was collected, washed with water, with acetone, and finally with ether and dried *in vacuo* at 90°. The recrystallized product weighed 230 g. (91%) and melted at 231–233°, $[\alpha]$ −70°. More conveniently the hydrochloride could be obtained by dissolving the tartrate in water, adding concentrated hydrochloric acid, cooling and collecting the hydrated hydrochloride directly.

***d*-6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexanone Hydrochloride Monohydrate.**—Recrystallization from water of the *d*-aminoketone hydrochloride monohydrate as obtained from the resolution gave a product which melted at 176–178°, $[\alpha]$ +66°.

**Resolution of *dl*-4-Dimethylamino-2,2-diphenylpentanenitrile (III).**—A solution of 110 g. (0.4 mole) of the racemic base and 60 g. (0.4 mole) of *d*-tartaric acid in 400 ml. of acetone and 25 ml. of water was seeded with *l*-aminonitrile *d*-bitartrate and set aside to crystallize overnight at room temperature. The white solid was collected, washed with acetone–Skelly B and dried on the filter. The *l*-aminonitrile *d*-bitartrate monohydrate (A) weighed 84 g. and melted at 110–115°, $[\alpha]$ +11°. Subsequent recrystallizations from acetone–water raised the melting point to 116–120°, $[\alpha]$ +14°. When the tartrate salt (A) was dissolved in water and made alkaline with ammonia the 51 g. of free base separated out as a solid (B), m. p. 93–98°. Recrystallization of the base (B) from 60 ml. and then 50 ml. of isopropyl alcohol gave 31 g. of *l*-aminonitrile, m. p. 100–103°, $[\alpha]$ −50°.

Concentration of the filtrate from the bitartrate (A) followed by dilution with water and addition of aqueous ammonia gave crude *d*-aminonitrile, $[\alpha]$ +34°. Recrystallization first from 60 ml. and then from 50 ml. of isopropyl alcohol gave 35 g. of base, m. p. 96–101°, $[\alpha]$ +47°. The yield of the *l*-aminonitrile was 56%, that of the practically pure *d*-aminonitrile 63%.

***l*-4-Dimethylamino-2,2-diphenylpentanenitrile Hydrochloride.**—The free base was dissolved in ether and the hydrochloride precipitated with alcoholic hydrogen chloride. Two recrystallizations from isopropyl alcohol gave the pure hydrochloride, m. p. 211–212°, $[\alpha]$ −3.8°.

***d*-4-Dimethylamino-2,2-diphenylpentanenitrile Hydrochloride.**—The base as obtained from the resolution was converted to the hydrochloride. Two recrystallizations from isopropyl alcohol gave the pure hydrochloride, m. p. 211–212°, $[\alpha]$ +3.6°. A portion of the hydrochloride was treated with aqueous ammonia and the base was recrystallized from isopropyl alcohol, m. p. 100–102°, $[\alpha]$ +50°.

**Resolution of *dl*-4-Dimethylamino-2,2-diphenyl-3-methylbutanenitrile (IV).**—A solution of 2 kg. (7.2 moles) of racemic aminonitrile and 1120 g. (7.45 moles) of *d*-tartaric acid in 15 l. of 95% ethanol was seeded with *d*-aminonitrile *d*-bitartrate and allowed to stand for two days at 5°. The solid (A) was collected, washed with 2 l. of 95% ethanol and dried on the filter. A solution of the bitartrate (A) in 4 l. of 95% ethanol after standing at 5° for twenty-four hours yielded 1220 g. of *d*-aminonitrile *d*-bitartrate sesquihydrate (B), m. p. 75–95°, $[\alpha]$ +64°.

The recrystallized bitartrate (B) was dissolved in 15 l. of water and slowly made alkaline with ammonia. The base was washed well with water, dried and recrystallized from 2 l. of 95% ethanol to give 610 g. of *d*-aminonitrile, m. p. 101–102°, $[\alpha]$ +70°.

When the combined filtrates from the crops (A) and (B) were allowed to stand for several days at room temperature a heavy crop of *l*-aminonitrile *d*-bitartrate (C) separated out. The filtrate from the crystals (C) was concentrated to 10 l. and after standing for several days at room temperature a second crop of *l*-aminonitrile *d*-bitartrate (D) was obtained. When 120 g. of the crude *l*-aminonitrile *d*-bitartrate was recrystallized from first 450 and then 350 ml. of water, there was obtained 100 g. of *l*-aminonitrile *d*-bitartrate hemihydrate (E). When dried *in vacuo* at 80° the tartrate (E) still contained a trace of moisture, m. p. 105–107°, with softening from 85–105°, $[\alpha]$ −45°.

When the filtrate from the bitartrate (D) was maintained at 5° for twenty-four hours there was obtained 520 g. of crude *d*-aminonitrile *d*-bitartrate. Recrystallization of this salt, liberation of and subsequent recrystallization of the base, as indicated above, gave 250 g. of pure *d*-aminonitrile. The yield of the *d*-aminonitrile was 860 g. (86%) while that of the *l*-aminonitrile *d*-bitartrate hemihydrate was 630 g. (40%).

***d*-4-Dimethylamino-2,2-diphenyl-3-methylbutanenitrile Hydrochloride.**—The recrystallized base was dissolved in ether and alcoholic hydrogen chloride added. The hydrochloride after recrystallization from isopropyl alcohol melted at 226–228°, $[\alpha]$ +75°.

***l*-4-Dimethyl-2,2-diphenyl-3-methylbutanenitrile Hydrochloride.**—The free base when liberated from the bitartrate salt and recrystallized from isopropyl alcohol melted at 102–103°, $[\alpha]$ −70°. The hydrochloride melted at 226–227°, $[\alpha]$ −75° after recrystallization from isopropyl alcohol.

**Preparation of the Ketones From the Nitriles.**[5]—The example given here is for the preparation of *dl*-6-dimethylamino-4,4-diphenyl-5-methyl-3-hexanone. The general procedure was the same for the preparation of the isomeric aminoheptanone except that in the latter case refluxing with the dilute hydrochloric acid was not necessary. The somewhat vigorous decomposition of the Grignard complex is sufficient in the case of the aminoheptanone to hydrolyze the ketimine to the ketone. With the more sterically hindered aminohexanone the ketimine is isolated unless additional heat is supplied by subsequent refluxing.

To a Grignard solution, in a 12-l. flask, prepared from 348 g. (14.3 gram atoms) of magnesium and 1.7 kg. (1190 ml., 15.5 moles) of ethyl bromide and 3 l. of dry ether, was added a solution of 1 kg. (3.6 moles) of *dl*-4-dimethylamino-2,2-diphenyl-3-methylbutanenitrile in 1.5 l. of dry toluene. Heat was applied and the ether distilled. The color of the reaction mixture changed to gray-green at about 100°. The mixture was then refluxed at 106° for three hours. Efficient stirring was necessary to prevent caking of the Grignard complex. The temperature was allowed to drop to 70° and the mixture poured into a well-stirred solution of 4 l. of concentrated hydrochloric acid and 9 l. of water. The reaction was so vigorous that most of the toluene was evaporated. The hydrolysate solution was refluxed for six hours, cooled in an ice-bath and the solid collected. This aminoketone hydrobromide monohydrate was washed with 2 l. of cold water, 500 ml. of 95% ethanol and finally 1 l. of ether. This first crop weighed 1065 g. A second crop of crystals weighing 100 g. was obtained by maintaining the filtrate at 5° for two days. A third crop of crystals was obtained by refluxing the filtrate for an additional six hours and cooling in an ice-bath. The total yield was 1315 g. (89%). The combined crops were recrystallized from 3.5 l. of water with a 92% recovery to give a product which melted at 147–150°.

**Acknowledgments.**—We are indebted to Mrs. M. MacMullin and Messrs. C. J. Smith, W. Wetterau and M. L. Smith for assistance in resolving these compounds and to Mr. Morris Auerbach and staff for the microanalyses and physical data.

(5) Office of the Publication Board, Department of Commerce, Report No. PB-981, p. 97.

Summary

The resolution of the analgesic drug methadone and related compounds has been described.

RENSSELAER, N. Y. RECEIVED JUNE 4, 1948

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

# Estrogenic Phenylindane Derivatives[1a]

BY U. V. SOLMSSEN[1b] AND E. WENIS

2-Phenylindene derivatives of the general structure (V, VI) may be considered as analogs to the powerful synthetic estrogens of the stilbene type. For example, 2-(*p*-methoxyphenyl)-3-ethyl-6-methoxyindene (V) may, theoretically, be derived from 4,4'-dimethoxy-α-methyl-β-ethylstilbene by ring closure between the methyl group and a phenyl ring. Because of this structural relationship, a number of 2-phenylindene derivatives were synthesized by Salzer[2a] and Solmssen.[2b]

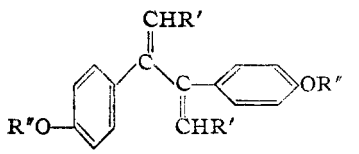
This earlier work, recently reviewed,[3] found that the most active 2-phenylindenes with phenolic hydroxy groups had an estrogenic activity of the same order as the 4,4'-dihydroxystilbene derivatives with isomeric structure. However, such 2-phenylindenes are too unstable for therapeutic usefulness. Acylation of the phenolic hydroxyls resulted in more stable but less active estrogens. Hydrogenation of the indene double bond appeared to be a more promising approach to stable yet highly potent preparations.

In the stilbene series, hydrogenation of the ethylene linkage generally results in unimpaired activity for the *meso* form of the hydrogenation product while the racemic form is much less active. Salzer[2a] reported that hydrogenation of the 2,3-double bond in 2-(*p*-hydroxyphenyl)-3-methyl-6-hydroxy-(2,3)-indene led to complete inactivation. On the other hand, Solmssen[2b] found that saturation of the indene double bond in 2-(*p*-hydroxyphenyl-3-ethyl-6-hydroxy-(2,3)-indene resulted in the corresponding indane (XX) with only slightly decreased activity and satisfactory stability.

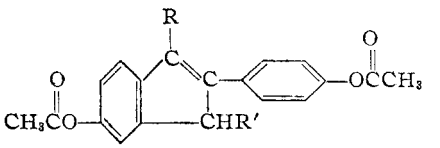
Therefore it was of interest to extend this earlier work[2a] and our first objective was the preparation of a complete series of homologs of the 3-ethylindane (XX). The general method employed for the synthesis is the one described previously[2b] though various steps have been improved materially. Thus, *p*-anisylacetic acid required as an intermediate was prepared from *p*-methoxyacetophenone by Schwenk's[4] variant of the Willgerodt reaction in 49% yield as compared with 18% by the azlactone method from anisaldehyde and hippuric acid, as described previously.[2b] The key intermediate, 2-(*p*-anisyl)-6-methoxyindanone-(3) (II), was obtained in greatly improved yield through Perkin reaction of *p*-anisylacetic acid with *m*-methoxybenzaldehyde, reduction of the resulting crude cinnamic acid by means of Raney nickel, and ring closure of the hydrocinnamic acid (I) with hydrofluoric acid. In analogy with similar observations by Johnson, Anderson and Shelberg[5] this reagent gave practically exclusively the desired isomer (II), m. p. 96°. The other isomer (III) and additional by-products in the ring closure are discussed in the experimental part.

The 3-alkyl substituted dimethoxyindenes (V–X) shown in Table I were again obtained by the Grignard reaction with alkylmagnesium halide. Catalytic reduction of the indene double bond with Raney nickel and demethylation of the crude dimethoxyindanes (XII–XVII) with hydrobromic–acetic acid resulted in the 3-alkyl-2-(*p*-hydroxyphenyl)-6-hydroxy–indanes (XIX–XXIV) as stable, well crystallized substances summarized in Table II.

In the earlier work[2b] five-ring closure had been effected with an unsymmetric starting material and the methoxy or hydroxy group in the fused phenyl ring had been presumed to be in the 6-position. Evidence for the correctness of this assumption has now been furnished by the work of Adler and Hagglund[6] who obtained 2-(*p*-acetoxyphenyl)-3-methyl-6-acetoxy-2,3-indene (XXVII) by means of boron trifluoride cyclization of 2,3-bis-(*p*-acetoxyphenyl)-1,3-butadiene (XXV).



XXV, R' = H, R'' = $CH_3CO$
XXVI, R' = $CH_3$ R'' = $CH_3CO$



XXVII, R = $CH_3$ R' = H

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