[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Some Stilbestrol-like Analogs of Desoxycorticosterone and Progesterone

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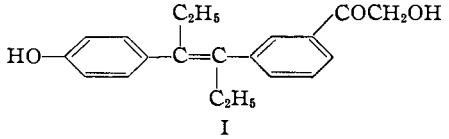
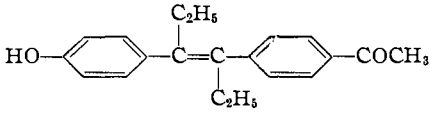
The discovery of the highly potent synthetic estrogen diethylstilbestrol[3] stimulated interest in preparing structurally related analogs of the other steroidal hormones. In 1941 Linnell and Roushdi[4] reported the preparation of the *m*-hydroxyacetyl derivative I (as a glass) and claimed that it possessed activity in the life-



I



II

maintenance test, although less than 0.005 that of desoxycorticosterone acetate.[5] Jaeger and Robinson[6] reported the synthesis of the *p*-acetyl derivative II, also as a glass. While this material failed to show progestational activity in a 70-mg. dose, it was pointed out that its estrogenic activity could be inhibiting the progestational effect if any. The synthesis of a number of other simple analogs of progesterone and desoxycorticosterone has been reported, although physiologically active compounds apparently have not been obtained as yet.[7,8]

In view of the uncertain nature of the glassy product of Jaeger and Robinson, we have been interested in synthesizing the *p*-acetyl derivative II in pure crystalline form for further tests and as a preliminary to the preparation of closer analogs of progesterone, etc., with the aromatic rings hydrogenated. In addition the synthesis of the *p*-acetoxyacetyl analog of II seemed attractive for adrenal cortical tests, particularly since Linnell and Sharma[9] had found that the *m*-hydroxy isomer of diethylstilbestrol was much less active as an estrogen than the *p*-isomer. These compounds have now been synthesized in crystalline form, as have their reduced analogs related to hexestrol.

The cyano ketone (V) employed by Jaeger and Robinson was also used in the present work. The procedures for its preparation were improved, starting with ethyl α-(*p*-aminophenyl)-butyrate (III)[10] as shown in the Flow Sheet. Selective reaction of the keto group with ethylmagnesium bromide (1.25 equivalents) as described by Jaeger and Robinson followed by dehydration gave the oily stilbene derivative VI which was hydrolyzed and demethylated in one step to the stilbene acid VII using the attractive method of Neher and Miescher.[11] The crystalline acid VII (m. p. 143–146.5°) was obtained in 26–33% over-all yields from the cyano ketone V, or as high as 50% if the oily isomeric acids were isomerized by repeated treatment with *p*-toluenesulfonic acid.[10]

When only one equivalent of Grignard reagent was employed with the cyano ketone V and the product carried through the subsequent treatment with alkali at 220°, a different acid, m. p. 143°, was obtained. From the analytical values for carbon–hydrogen and neutralization equivalent, leading to the formula $C_{10}H_{12}O_2$, it was apparent that this acid was the result of cleavage of the molecule; it was obtained in as high as 70% yield by similar alkaline cleavage of the cyano ketone V. The acid was identified as *p*-*n*-propylbenzoic acid, identical with an authentic sample; the other cleavage product (presumably *p*-hydroxybenzoic acid or perhaps phenol) was not isolated.[12]

For preparing the pure acetyl derivative II, the crystalline acid VII provided an intermediate superior to the oily cyano derivative VI (undoubt-

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(3) Dodds, Golberg, Lawson and Robinson, *Nature*, **141**, 247 (1938); *Proc. Roy. Soc. (London)*, **B127**, 140 (1939).

(4) Linnell and Roushdi, *Quart. J. Pharm. Pharmacol.*, **14**, 270 (1941).

(5) These authors also claimed the preparation of the corresponding *m*-acetyl analog (of progesterone); since, however, their method of synthesis involved treating the methyl ester of an acid with methylmagnesium iodide, it seems more probable that the resulting glass contained the tertiary carbinol (and possibly its dehydration product).

(6) Jaeger and Robinson, *J. Chem. Soc.*, 744 (1941).

(7) (a) Linnell and Roushdi, *Quart. J. Pharm. Pharmacol.*, **12**, 252 (1939); Kaikini and Linnell, *ibid.*, **20**, 113 (1947); (b) Brownlee and Duffin, U. S. Patent 2,376,415 (May 22, 1945); British Patent 550,262 (May 22, 1945); (c) Ross, *J. Chem. Soc.*, 536, 538 (1945); (d) Hager and Shonle, THIS JOURNAL, **68**, 2167 (1946); (e) Walker, *J. Chem. Soc.*, 347 (1942); (f) Long and Burger, *J. Org. Chem.*, **6**, 852 (1941); (g) Price, Enos and Kaplan, THIS JOURNAL, **69**, 2261 (1947); (h) Fieser and Turner, *ibid.*, **69**, 2338 (1947); (i) Kornfeld, *ibid.*, **70**, 1373 (1948); (j) Buu-Hoï and Royer, *Bull. soc. chim. France*, 820 (1947).

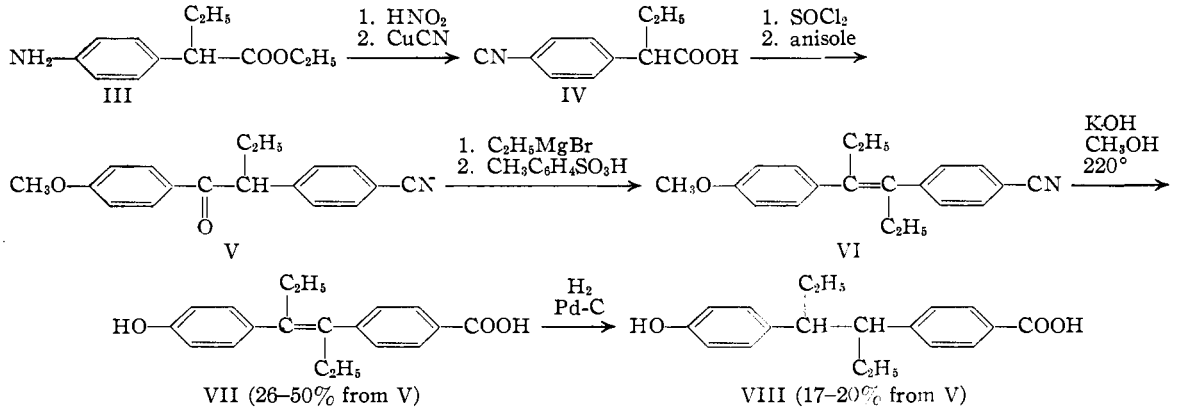
(8) The apparently indiscriminate claims for cortical and progestational activity in the patents of Brownlee and Duffin (ref. 7b) may be discounted until evidence is presented.

(9) Linnell and Sharma, *Quart. J. Pharm. Pharmacol.*, **14**, 259 (1941).

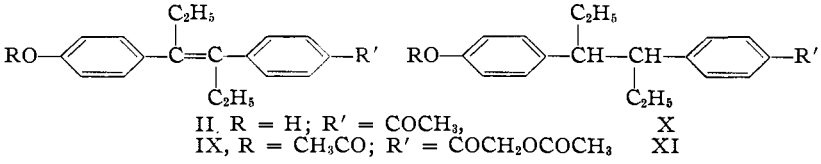
(10) Wilds and Biggerstaff, THIS JOURNAL, **67**, 789 (1945).

(11) Neher and Miescher, *Helv. Chim. Acta*, **29**, 449 (1946).

(12) This cleavage acid seems to be the same as the product (m. p. 142°) obtained by Jaeger and Robinson in low yield by alkaline hydrolysis of the oily cyano carbinol, and to which they assigned the structure of the corresponding α-hydroxy-*p*-methoxy acid ($C_{20}H_{24}O_4$). The acid (m. p. 144–146°) obtained by Neher and Miescher by the action of methanolic alkali at 200° on the same carbinol and considered by them to be the α,*p*-dihydroxy acid ($C_{19}H_{22}O_4$), may also be *p*-*n*-propylbenzoic acid, in view of its markedly greater volatility (in sublimation) than VII. The carbon-hydrogen values do not distinguish decisively between these acids, and in neither case was the neutralization equivalent reported.



edly a mixture of isomers) employed by Jaeger and Robinson. The acid VII was converted *via* the acid chloride of the acetate to the methyl ketone II in two ways, using either dimethylcadmium[13] or sodiomalonic ester[14] followed by hydrolysis. The first method was superior in this example. Reaction of the same acid chloride with diazomethane followed by decomposition of the diazoketone in acetic acid provided the acetoxyacetyl derivative IX. In each case the desired compound was obtained in a pure crystalline state.



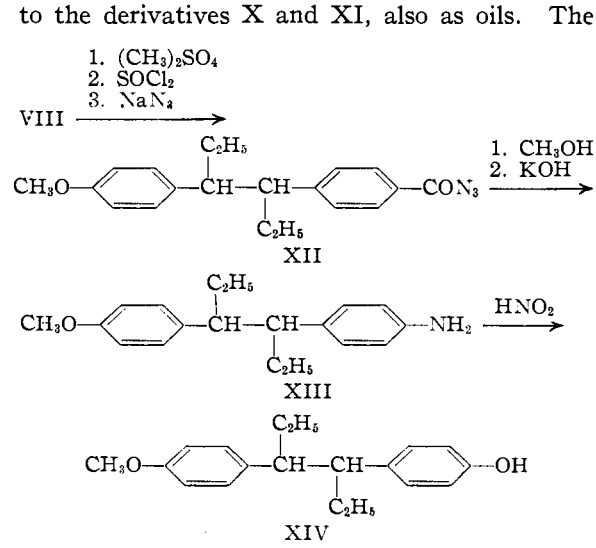
II, R = H; R′ = $COCH_3$,
IX, R = CH_3CO; R′ = $COCH_2OCOCH_3$ X XI

In order to prepare similar analogs related to hexestrol, it was necessary to obtain the corresponding reduced acid VIII. Neher and Miescher[11] carried out hydrogenation experiments with the crystalline acid VII, but were unable to separate the mixture of stereoisomers which resulted. It has been found that hydrogenation of *trans*-diethylstilbestrol gives predominately the lower-melting DL-hexestrol while the *cis*-isomer (and double bond isomers) give mainly *meso*-hexestrol.[15] We therefore turned to hydrogenation of the oily mixture of acids left after removal of the crystalline isomer VII (which probably is the more stable *trans*-isomer, if the analogy to diethylstilbestrol holds). After reduction using a palladium catalyst one of the pure isomers of VIII (m. p. 171.5–172.5°) could be isolated by means of its insoluble sodium salt, and in approximately 17–20% over-all yield based upon the cyano ketone V. A similar reduction of the solid isomer of VII gave a mixture from which could be isolated some (21%) of the 172° acid and in addition, the other isomer, m. p. 126–128°.

By analogy with the hexestrols, it would be concluded that the higher-melting acid VIII possessed the same bridge configuration as *meso*-hexestrol. In order to establish this point more rigorously, this isomer was subjected to a Curtius degradation through the acid azide of the methyl ether XII to the amine XIII in good yield. By diazotization and hydrolysis this provided the monomethyl ether (XIV) of *meso*-hexestrol, identical with an authentic sample.

The 172° isomer of VIII was converted to the acetyl derivative X and the acetoxyacetyl derivative XI using the methods employed with the stilbene acid VII. In each case a pure crystalline compound could be obtained.

Physiological tests have been carried out under the direction of Drs. R. K. Meyer and Elva G. Shipley of the Department of Zoology. Since it was desirable to have these tests on all of the possible isomers, the oily acidic mixture left after removal of the crystalline (and presumably *trans*) isomer of VII was converted to the acetyl and acetoxyacetyl derivatives II and IX, as oils. Similarly the oil mixture of acids remaining after isolation of the 172° isomer of VIII was converted to the derivatives X and XI, also as oils. The



(13) Cason, *Chem. Revs.*, **40**, 15 (1947).
(14) *Cf.* Wilds and Beck, THIS JOURNAL, **66**, 1692 (1944).
(15) Wessely, Kerschbaum, Kleedorfer, Prillinger and Zajik, *Monatsh.*, **73**, 127 (1940); Wessely and Welleba, *Ber.*, **74**, 777 (1941).

128° isomer of VIII has not yet been used in similar syntheses. In preliminary estrogenic assays in ovariectomized rats, the crystalline isomers of IX, X and the oily isomeric mixtures corresponding to IX, X and XI were active in about 100 γ doses. The oil corresponding to II was active at 50 γ. Diethylstilbestrol and hexestrol showed comparable activity in about 0.5–1 γ doses. On the other hand the crystalline isomers of II and XI were inactive at 200 γ and 100 γ, respectively, but appear to be active at a higher level (about 500–1000 γ). The higher estrogenic activity of the oils, particularly II and XI, is unexpected, since the solid isomers correspond to the more active configurations for diethylstilbestrol and hexestrol. While the activity of the oils might be due in part to the presence of a contaminant, this is not derived from the cleavage acid *p*-*n*-propylbenzoic acid, since *p*-*n*-propylacetophenone and α-acetoxy-*p*-*n*-propylacetophenone, obtained as oils, were inactive in 500 γ doses. The aminophenol corresponding to XIII, which is the monoamino analog of hexestrol, was only about one-twentieth as active (20 γ) as the latter.

The compounds were screened for progestational activity using the copulatory response in guinea pigs, which does not seem to be inhibited by estrogens. Both the crystalline and oily isomers of II and X were inactive in 2-mg. doses, while 0.1 mg. of progesterone gave an 80% response. *p*-*n*-Propylacetophenone and α-acetoxy-*p*-*n*-propylacetophenone were inactive at 2-mg. and 5-mg. doses, respectively. In the rabbit test also, the crystalline isomer of II showed no activity (25 mg.—one animal); *p*-*n*-propylacetophenone was inactive at a 50 mg. dose. Life-maintenance tests on adrenalectomized rats indicated the crystalline and oily isomers of IX and XI to be inactive at doses of 2 mg. per day, and the isomers of II and X inactive at 0.5 mg. per day, with most of the animals failing to survive as long as the controls. The crystalline isomers of II and IX failed to show activity in the glycogen deposition test (mice) in doses of 0.5 mg.

Experimental[16]

α-(*p*-Cyanophenyl)-butyric Acid (IV).—Ten grams (0.048 mole) of pure ethyl α-(*p*-aminophenyl)-butyrate[10] was refluxed for twelve hours with 60 cc. of 1:1 hydrochloric acid, then cooled to 0° and diazotized with 3.0 g. of sodium nitrite in 20 cc. of water. After the addition was complete, the solution was stirred one-half hour longer, neutralized with solid sodium carbonate and then added slowly to a vigorously stirred, cold (0–5°) solution of 13.0 g. (0.145 mole) of cuprous cyanide, and 19.1 g. (0.29 mole) of potassium cyanide in 100 cc. of water.[17] After the addition was complete, the mixture was stirred for an additional one-half hour and allowed to come to room temperature. Finally the mixture was warmed to 50°, strongly acidified (hood) and the resulting suspension was stirred at 60–70° for two hours, cooled and extracted with ether. The extract was washed with 1:1 hydrochloric acid, water, dried and concentrated to a cherry-red oil which crystallized to give 8.44 g. (92%) of the crude cyano acid, m. p. 74–82°. Several recrystallizations from benzene together with evaporative distillation of the filtrates gave materials of m. p. 83–87° in 93% recovery. Further recrystallization gave the pure acid as large irregular plates, m. p. 86.5–87.5°.

Anal. Calcd. for $C_{11}H_{11}O_2N$: C, 69.8; H, 5.9; neut. equiv., 189. Found: C, 69.9; H, 5.9; neut. equiv., 191.

Alkaline hydrolysis of the cyano acid gave **α-(*p*-carboxyphenyl)-butyric acid** which crystallized from acetone as colorless leaflets, m. p. 186–187.5°.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.5; H, 5.8; neut. equiv., 104. Found: C, 63.5; H, 5.6; neut. equiv., 104.

1-(*p*-Anisyl)-2-(*p*-cyanophenyl)-1-butanone (V).—The acid chloride was prepared from 65.2 g. of the cyano acid IV and condensed with anisole in the presence of stannic chloride following the same general procedure previously employed in the synthesis of α-ethyldesoxyanisoin.[10] The resulting crude ketone was obtained as an oil which crystallized from twice its volume of 95% ethanol to give in two crops 79.3 g. (82%) of the solid ketone, m. p. 64–70.5°. Another recrystallization gave material of m. p. 69–72° in 96% recovery. In the early runs a lower melting form of the ketone was obtained, m. p. 61–63° (reported,[6] 60–62°); the higher melting form (m. p. 71–73°) was obtained in the later runs. Seeding a melt of the lower form at 67° converted it to the higher melting solid.

The analytical sample was obtained as colorless prisms with the broad m. p. 70–74°, unchanged by numerous recrystallizations from alcohol or prolonged drying at 50° and 0.1 mm.

Anal. Calcd. for $C_{18}H_{17}O_2N$: C, 77.4; H, 6.1. Found: C, 77.0; H, 5.9.

Alkaline hydrolysis of the cyano ketone gave **1-(*p*-anisyl)-2-(*p*-carboxyphenyl)-1-butanone**, which melted at 130.5–131.5° after several recrystallizations from benzene–petroleum ether.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.5; H, 6.1; neut. equiv., 298. Found: C, 72.4; H, 6.0; neut. equiv., 297.

α,α′-Diethyl-4′-hydroxy-4-stilbenecarboxylic Acid (VII).—Ten grams of the cyano ketone V was converted to the cyano carbinol using 1.25 equivalents of ethylmagnesium bromide following essentially the procedure of Jaeger and Robinson,[6] except the Grignard reagent was added to the cyano ketone. The oily carbinol was not distilled but dehydrated directly by heating with 1 g. of *p*-toluenesulfonic acid[10,18] at 130° under reduced pressure (water pump) for thirty minutes. The resulting oily mixture was transferred to a steel reaction bomb with 120 cc. of methanol, and 50 g. of potassium hydroxide pellets added. The bomb was heated at 220° with shaking for fifteen hours, cooled and the mixture worked up by a modification of the method described by Neher and Miescher.[11] A negligible amount (0.1 g.) of neutral material was separated from 10.8 g. of an acidic oil; the latter was dissolved in about 35 cc. of hot 2 *N* sodium hydroxide and cooled in the refrigerator to give a solid sodium salt which was filtered, suspended in water and acidified. The resulting hydroxystilbene acid was filtered and dried to constant weight, 2.81 g. (26%), m. p. 135–146°. Other runs gave yields of 30–33% at this stage. One recrystallization from benzene–petroleum ether gave material of m. p. 143–146° (dried at 85° and 0.2 mm. for one hour) in 70% recovery.

The analytical sample, prepared by hydrolysis of the pure methyl ester described below, was obtained after recrystallization from acetone–petroleum ether in the form of colorless plates, m. p. 143–146.5°. Neher and Miescher[11] reported the m. p. 144–146°.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.0; H, 6.8; neut.

(16) All melting points are corrected.

(17) With smaller proportions of cuprous and potassium cyanides the yields were considerably lower, *e. g.*, 76% with 2 and 4 mole-equivalents, respectively.

(18) Dehydration with this reagent gave a purer product than with iodine in xylene

equiv., 296. Found: C, 77.2; H, 6.9; neut. equiv., 292, 294.

Acidification of the alkaline filtrate from the insoluble sodium salt (above) gave 6.46 g. of an oil consisting mainly of isomeric hydroxystilbene acids. In similar runs it was found possible to isomerize this oily mixture to the solid hydroxystilbene acid by repeating the treatment with *p*-toluenesulfonic acid as above, separating the product as the insoluble sodium salt; the total yield of crude acid after three such treatments was 49%, m. p. 135–142°.

Reaction of the hydroxystilbene acid, m. p. 137–144°, with diazomethane followed by two recrystallizations from benzene–petroleum ether gave the methyl ester as colorless blades, m. p. 116–117°, in 87% yield. Further recrystallization did not change the melting point.

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.4; H, 7.2. Found: C, 77.6; H, 7.2.

α,α′-Diethyl-4′-acetoxy-4-stilbenecarboxylic Acid.—A solution of 2.56 g. of crude hydroxystilbene acid VII, m. p. 135–142°, in 8 cc. of acetic acid, 2 cc. of pyridine and 2 cc. of acetyl chloride was allowed to stand overnight, and then filtered to give 2.01 g. of the acetate, m. p. 178–180.5°. An additional 0.61 g., m. p. 175–180°, was obtained by extraction of the filtrate bringing the total yield to 90%. Recrystallization from benzene–petroleum ether gave the pure acetate as colorless diamond-shaped plates, m. p. 181–182.5° (reported[11] 182–183°).

Anal. Calcd. for $C_{21}H_{22}O_4$: C, 74.5; H, 6.6. Found: C, 74.4; H, 6.6.

***p*-*n*-Propylbenzoic Acid. (a). By Alkaline Cleavage.**—When 2.00 g. of the cyano ketone V was treated with 1.0 instead of 1.25 equivalents of ethylmagnesium bromide and the resulting product dehydrated and treated with methanolic alkali at 220° as described above, only a small amount (0.06 g.) of the solid hydroxystilbene acid II could be isolated through its sodium salt. Acidification of the filtrate gave a solid which was separated with 5% sodium bicarbonate into 0.1 g. of crude phenolic material, m. p. 130–145°, and an acidic portion which upon recrystallization from benzene–petroleum ether gave 0.15 g. of solid, m. p. 141–143°. Evaporative distillation and recrystallization gave the acid as colorless blades, m. p. 141.5–143°. Unlike the hydroxystilbene acid this acid was soluble in cold 2 *N* sodium hydroxide and depressed the melting point of the former to 110–140°. The m. p. of a mixture of this acid with authentic *p*-*n*-propylbenzoic acid was undepressed (141.5–143°).

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.1; H, 7.4; neut. equiv., 164. Found: C, 73.0; H, 7.4; neut. equiv., 161.

When the cyano ketone V was treated directly with methanolic alkali at 200°, the acid was obtained in 70% yield, m. p. 138–141°. Another recrystallization gave material of m. p. 140–142.5°, which did not depress the melting point of the above acid.

(b) **From *p*-Bromo-*n*-propylbenzene.**—The Grignard reagent prepared from 10 g. of this bromide was poured upon Dry Ice and allowed to stand overnight. Acidification of the salt gave 4.8 g. (58%) of acid, m. p. 138–141°. Several recrystallizations from benzene–petroleum ether gave the pure acid, m. p. 142–143° (reported[19] 142.5°).

***p*-*n*-Propylbenzamide**, prepared from the authentic acid and recrystallized from acetone–petroleum ether, formed colorless prisms, m. p. 153–154.5°. The amide prepared from the acid obtained in (a) melted at 152.5–154° and showed no depression in melting point when mixed with the known derivative.

Anal. Calcd. for $C_{10}H_{13}ON$: C, 73.6; H, 8.0. Found: C, 73.3; H, 7.7.

The Higher Melting Isomer of 3-(*p*-Carboxyphenyl)-4-(*p*-hydroxyphenyl)-hexane (VIII).—The oily hydroxystilbene acid (6.46 g.) obtained above after removal of the solid isomer as the sodium salt, was hydrogenated in 40 cc. of glacial acetic acid with 3 g. of 5% palladium-on-carbon[20] and hydrogen at atmospheric pressure for twelve hours. At the end of this time the absorption of hydrogen had become very slow and the total uptake was 90–95% of the theoretical. The oil obtained by diluting and extracting with ether was dissolved in hot 2 *N* sodium hydroxide solution. Upon cooling, a solid salt separated from which was obtained on acidification 3.05 g. of crude acid VIII, m. p. 160–170°, corresponding to 28% over-all yield from the cyano ketone. The total yield of the two crude acids VII and VIII was usually 52–55%.

The crude reduced acid from three runs was combined (7.68 g.), taken up in ether and washed with several portions of dilute hydrochloric acid to free a portion present as sodium salt (0.5–0.6 g.). The dried ether solution was evaporated and the solid acid recrystallized from benzene to give in two crops, 5.50 g., m. p. 170–172.5° (after drying at 90° and 0.1 mm). The combined filtrates were evaporatively distilled at 0.2 mm. and the distillate recrystallized from benzene to give an additional 0.34 g., m. p. 170–172.5°. The over-all yield of the pure reduced acid was 17–21% from the cyano ketone. Repeated recrystallizations raised the melting point to 171.5–172.5°. A different crystallographic form of the acid, thick, colorless prisms, m. p. 180–182°, softening at 171°, was obtained by hydrolysis of the pure acetate methyl ester (below) followed by recrystallization from acetone–petroleum ether. The higher melting point, 181–182.5°, was observed when the two forms were mixed.

Anal. Calcd. for $C_{19}H_{22}O_3$: C, 76.5; H, 7.4. Found: C, 76.3; H, 7.5.

The acetate was prepared in 92% yield from the crude saturated acid VIII by the procedure already described for the stilbene acid. Several recrystallizations from benzene gave the pure acetate as colorless, elongated plates, m. p. 176.5–178.5°.

Anal. Calcd. for $C_{21}H_{24}O_4$: C, 74.1; H, 7.1. Found: C, 73.9; H, 7.2.

The methyl ester of the acetate, prepared using diazomethane, was recrystallized from benzene–petroleum ether and then from methanol as thin, irregular platelets, m. p. 126.5–128°.

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.5; H, 7.4. Found: C, 74.3; H, 7.3.

The methyl ester of the hydroxy acid VIII, prepared using diazomethane, crystallized from acetone–petroleum ether in the form of colorless blades which melted at 143–146°; when the melt was induced to resolidify it remelted at 155–157°. Another recrystallization did not change these melting points.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.9; H, 7.7. Found: C, 77.0; H, 7.8.

The methyl ether of the acid VIII was prepared using 10% potassium hydroxide and dimethyl sulfate, warming on the steam-bath for one hour; then the ester was hydrolyzed by refluxing with additional potassium hydroxide for one hour. When the clear solution was cooled, shining crystals of the potassium salt of the methoxy acid separated. Acidification of the suspension and extraction with ether gave a 94% yield of the methoxy acid, m. p. 169–171.5° (softening at 166°). Repeated recrystallizations of the solid from acetone–petroleum ether did not improve the melting point; vacuum sublimation gave prisms, m. p. 170.5–172.5° (softening at 166°). The acid melted completely when inserted in a bath preheated to 168°, suggesting the existence of polymorphic forms. A mixed melting point with the hydroxy acid (VIII) gave a marked depression, m. p. 150–160°.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.9; H, 7.7. Found: C, 77.1; H, 7.6.

The Lower Melting Isomer of 3-(*p*-Carboxyphenyl)-4-(*p*-hydroxyphenyl)-hexane (VIII).—Hydrogenation of 1.64 g. of the solid hydroxystilbene acid VII (m. p. 143–144°) in 15 cc. of glacial acetic acid with 0.8 g. of 5% palladium-on-carbon[20] at atmospheric pressure gave a nearly quantitative uptake of hydrogen after three and one-half hours. Removal of the catalyst, dilution and extraction with ether gave an oil from which was obtained through its so-

(19) Kindler, *Ber.*, **69**, 2801 (1936).

(20) Mozingo, *Org. Syntheses*, **26**, 78 (1946), procedure B.

dium salt 0.34 g. (21%) of the higher melting acid VIII, m. p. 169–172° (mixed melting point undepressed). Acidification and extraction of the filtrate from the sodium salt gave an oily acid which crystallized from benzene after long standing in the refrigerator. This solid, when dried at 0.2 mm. and 75° to remove benzene of crystallization, amounted to 0.88 g., m. p. 120–128°. After three more recrystallizations followed by drying *in vacuo*, 0.63 g. (38%) of the acid VIII, m. p. 125–127°, was obtained. Hydrolysis of the pure acetate (see below) followed by recrystallization from benzene gave the analytical sample as colorless needles. After prolonged drying (vacuum) this melted at 126–128° when the bath temperature was raised slowly; more rapid heating gave the m. p. 114–116° to a cloudy liquid becoming clear at 125°.

Anal. Calcd. for $C_{19}H_{22}O_3$: C, 76.5; H, 7.4. Found: C, 76.3; H, 7.3.

The acetate of the lower melting racemic acid VIII was prepared by the method described for the higher melting form. Repeated recrystallization from acetone–petroleum ether gave colorless blades, m. p. 132–134°.

Anal. Calcd. for $C_{21}H_{24}O_4$: C, 74.1; H, 7.1. Found: C, 73.9; H, 6.8.

Conversion of the Higher Melting Isomer of 3-(*p*-Carboxyphenyl)-4-(*p*-hydroxyphenyl)-hexane to *meso*-Hexestrol.—One-half gram of the pure methyl ester of VIII (m. p. 155–157°) was hydrolyzed with alkali and the resulting hydroxy acid was methylated to give 0.51 g. of crude solid methoxy acid. This was converted to the acid chloride by the usual procedure employing thionyl chloride, and then dissolved in 5 cc. of acetone; to the solution was added 0.13 g. of sodium azide followed by 0.5 cc. of water. The flask was swirled for twenty minutes at room temperature and then diluted to 30 cc. with water. The crystalline **acid azide**, after drying *in vacuo*, weighed 0.47 g. (87%), m. p. 94–96° (dec.). The azide was refluxed with 5 cc. of methanol and 5 cc. of toluene for four hours, forming the **methyl urethan derivative**. When pure this derivative formed clusters of fine needles from benzene, m. p. 145.5–146.5°.

Anal. Calcd. for $C_{21}H_{27}O_3N$: C, 73.9; H, 8.0. Found: C, 73.9; H, 7.8.

The entire amount of the methyl urethan from the above procedure was hydrolyzed by refluxing with 3 cc. of 45% potassium hydroxide and 5 cc. of methanol under nitrogen for forty-five hours. At the end of this time the suspension was diluted and extracted with ether, giving the crude solid amine, 0.36 g. (91% based on the azide), m. p. 95–100°, which was only slightly soluble in warm dilute hydrochloric acid. Sublimation and recrystallization from methanol gave **3-(*p*-aminophenyl)-4-(*p*-methoxyphenyl)-hexane (XIII)** as slender needles, m. p. 103–105°.

Anal. Calcd. for $C_{19}H_{25}ON$: C, 80.5; H, 8.9. Found: C, 80.6; H, 8.7.

To 50 mg. of the methoxyamine dissolved in 0.5 cc. of glacial acetic acid was added a mixture of 0.2 cc. of concentrated sulfuric acid and 0.3 cc. of glacial acetic acid with stirring. The pasty mixture was then diazotized using 14 mg. of sodium nitrite in 0.5 cc. of water, continuing stirring for one and one-half hours. The cold diazonium solution was then added dropwise to 10 cc. of boiling 15% sulfuric acid and after heating for several minutes the mixture was cooled and extracted with ether. Evaporative distillation at 0.1 mm. of the resulting brown oil followed by recrystallization from benzene–petroleum ether gave 15 mg. of solid, m. p. 110–115°. Another distillation produced 10 mg. (20%) of solid *meso*-hexestrol monomethyl ether, m. p. 117–119°. Admixture with a known sample, m. p. 118–120°,[21] showed no melting point depression.

When 5 mg. of the monomethyl ether in dilute potassium hydroxide was treated with dimethyl sulfate and allowed to stand overnight, *meso*-hexestrol dimethyl ether was formed. After recrystallization from benzene–petroleum ether this melted at 142.5–143.5° and showed no depression with an authentic sample.

3-(*p*-Aminophenyl)-4-(*p*-hydroxyphenyl)-hexane.—A mixture of 77 mg. of the methoxy amine (see above), 2 cc. of acetic acid and 1 cc. of 48% hydrobromic acid was refluxed for six hours, then diluted, neutralized to litmus paper with 45% potassium hydroxide solution and thoroughly extracted with ether. Crystallization of the product from acetone–petroleum ether gave 20 mg., m. p. 170–185°; an additional 34 mg., m. p. 184–188°, was obtained by subliming the filtrate at 0.1 mm., making the total yield 74% at this stage. By further sublimation at 125° and 0.1 mm., material was obtained with the m. p. 186–188° (vac.).

Anal. Calcd. for $C_{18}H_{23}ON$: C, 80.3; H, 8.6. Found: C, 80.0; H, 8.5.

α,α'-Diethyl-4′-hydroxy-4-acetylstilbene (II). (a) Diethyl Malonate Procedure.—The acid chloride, prepared from 2.00 g. of the acetoxy-stilbene acid with thionyl chloride, was dissolved in 25 cc. of dry thiophene-free benzene and treated with sodiomalonic ester prepared from 0.4 g. of powdered sodium as described by Wilds and Beck.[14] The acylmalonic ester was then refluxed for two hours with 10 cc. of glacial acetic acid, 8 cc. of concentrated hydrochloric acid and 4 cc. of water. The diluted mixture was extracted with ether, washing with 5% sodium bicarbonate; from the latter was obtained only 0.1 g. of acidic material. The oil resulting from the ether layer crystallized from benzene–petroleum ether to give 0.56 g. of the ketone, m. p. 135–140°, and an additional 0.28 g. m. p. 128–138°. Recrystallization gave a total of 0.52 g. (30%), m. p. 141–145°. Four recrystallizations of the solid from acetone–petroleum ether gave small colorless plates of the phenolic ketone II, m. p. 144.5–146.5°.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.6; H, 7.5. Found: C, 81.3; H, 7.6.

(b) **Dimethylcadmium Procedure.**[13]—A solution of dimethylcadmium was prepared by adding 0.30 g. of anhydrous cadmium chloride to 11 cc. of 0.27 *N* methylmagnesium bromide, stirring and refluxing for thirty minutes (test for Grignard reagent negative after twenty minutes); nearly all of the ether was removed and 5 cc. of dry benzene was added. The acid chloride from 500 mg. of the acetoxystilbene acid, dissolved in 5 cc. of dry thiophene-free benzene and filtered through a cotton plug (another 5 cc. benzene used to complete the transfer) was added rapidly to the refluxing benzene solution, and stirring and refluxing were continued for one hour. The suspension was cooled, hydrolyzed with cold, dilute hydrochloric acid and extracted twice with ether. Evaporation of the ether left the oily acetoxy methyl ketone which was hydrolyzed with 2 cc. of 45% potassium hydroxide and 4 cc. of methanol, heating one hour at reflux. The product was extracted with the ether after acidification, washing with 5% sodium bicarbonate solution to separate the acidic material (40 mg.); removal of the ether left 400 mg. of the crude, solid phenolic ketone which after several recrystallizations from acetone–petroleum ether and evaporative distillation of the residues at 0.1 mm. gave a total of 273 mg. (63%) of the same unsaturated ketone as described in (a), m. p. 142–146.5°.

Treatment of the above phenolic derivative with dimethyl sulfate and potassium hydroxide gave the methyl ether (85% yield) which after recrystallization from petroleum ether was obtained as clusters of fine needles, m. p. 104–105.5°.

Anal. Calcd. for $C_{21}H_{24}O_2$: C, 81.8; H, 7.8. Found: C, 81.5; H, 7.6.

3-(*p*-Acetylphenyl-4-(*p*-hydroxyphenyl)-hexane (X).—The methyl ketone was prepared from the higher melting isomer of the reduced acid VIII by either the diethyl malonate or the dimethylcadmium procedure. As was the case with the stilbene analog the second method gave better yields. Thus, when 0.50 g. of the acetoxy satu-

(21) Kindly furnished by Dr. William B. McCormack, *cf.* THIS JOURNAL, **70**, 4129 (1948).

rated acid was converted through its acid chloride to the acylmalonic ester and then hydrolyzed and decarboxylated as previously described, 0.27 g. (62%) of crude crystalline ketone, m. p. 153–158°, was obtained in three crops from 95% ethanol. Recrystallization of this material gave 0.20 g. (46%) of solid, m. p. 158–160°. The analytical sample was obtained from ethanol in the form of thick hexagonal plates, m. p. 159–160°.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.0; H, 8.2. Found: C, 80.9; H, 7.9.

When 0.40 g. of the acetoxy saturated acid was converted to the acid chloride, treated with dimethylcadmium following the procedure described for the stilbene analog, and the oily acetoxy ketone hydrolyzed, 0.33 g. of crude solid hydroxy ketone was obtained, m. p. 147–153°. Two recrystallizations from 95% ethanol gave 0.22 g. (63%) of the ketone, m. p. 158–160°.

The methyl ether, prepared from the above saturated phenolic ketone with dimethyl sulfate, crystallized from acetone–petroleum ether as colorless platelets, m. p. 135.5–137°.

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.3; H, 8.4. Found: C, 81.0; H, 8.1.

α,α′-Diethyl-4′-acetoxy-4-acetoxyacetylstilbene (IX).—The acid chloride from 1.00 g. of the acetoxystilbene acid dissolved in 10 cc. of dry benzene was added dropwise to a cold (0–5°) ethereal solution of diazomethane (prepared from 4.4 g. of nitrosomethylurea, dried over potassium hydroxide and distilled). After standing at room temperature for nineteen hours, the excess diazomethane and ether were removed leaving the crude solid diazoketone (1.02 g.). Recrystallization from benzene–petroleum ether gave 0.88 g. (82%) of the pale yellow compound, m. p. 152–154° (dec.). To 2 cc. of boiling acetic acid was added 200 mg. of the recrystallized diazoketone. Nitrogen was rapidly evolved and boiling was continued five minutes after the addition was complete. The mixture was chilled, taken up in ether and washed with water. Evaporation of the dried ether extract left a semisolid residue which was recrystallized from ethanol to give in two crops 189 mg. of solid, m. p. 123–137°. Further recrystallization from acetone–petroleum ether resulted in 144 mg. of the stilbene acetoxyacetyl derivative, m. p. 135–138°, corresponding to a 66% yield from the diazoketone or 54% from the acetoxy acid. Further recrystallization gave the pure compound as thick, colorless prisms which showed two melting points, 133.2–134° and 138–140°.

Anal. Calcd. for $C_{24}H_{26}O_5$: C, 73.1; H, 6.6. Found: C, 73.0; H, 6.6.

The over-all yield of the acetoxy ketone was higher (63%) when the intermediate diazoketone was not recrystallized but used directly. An attempt to obtain more crystalline material from the oily residue by chromatographic adsorption on alumina gave only a negligible amount of impure solid, m. p. 100–125°.

3-(*p*-Acetoxyacetylphenyl)-4-(*p*-acetoxyphenyl)-hexane (XI).—One hundred milligrams of the saturated acetoxy acid was converted through the diazoketone to the acetoxyacetyl derivative by the above procedure; a first crop of 36 mg., m. p. 150–152°, was obtained from acetone–petroleum ether and another 41 mg., m. p. 135–147°, in three additional crops. Recrystallization of the latter material brought the yield of saturated acetoxy ketone to 70 mg. (60%), m. p. 149–152°. Several more recrystallizations gave the pure compound as long, colorless blades, m. p. 152–153.5°.

Anal. Calcd. for $C_{24}H_{28}O_5$: C, 72.7; H, 7.1. Found: C, 72.6; H, 7.0.

Summary

Some analogs of progesterone and desoxycorticosterone have been prepared in the stilbestrol and hexestrol series.

These crystalline compounds, as well as mixtures of isomers corresponding to them, were found to be weak estrogens but failed to show progestational or adrenal cortical activity.

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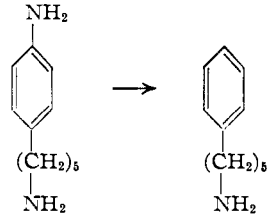
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

The Selective Replacement of the Aromatic Primary Amino Group by Hydrogen in Aromatic–Aliphatic Diamines[1]

BY NATHAN KORNBLUM AND DON C. IFFLAND[2]

It has recently been found in this Laboratory that aliphatic primary amines do not react with nitrous acid at a *p*H below *ca.* 3.[3] Thus, methylamine, ethylamine, *n*-propylamine, *n*-amylamine, benzylamine and cyclohexylamine are not attacked by nitrous acid below this *p*H. In sharp contrast, aromatic primary amines are routinely diazotized at a *p*H below 1, *i.e.*, in relatively strongly acidic solutions.[4] This difference, plus the fact that hypophosphorous acid smoothly replaces a diazonium group by hydrogen,[5] now makes it possible to effect transformations such as



That is, an aromatic primary amino group is replaced by hydrogen without disturbing the aliphatic amino group. The selective deamination reaction is a general one as is demonstrated by its successful application to a total of thirteen aromatic–aliphatic diamines in which the side chains are ortho, meta and para to the aromatic amino group.

The procedure is very simple; hypophosphorous acid being a relatively strong acid[6] is used not only as the reducing agent but also as the source

(1) From the doctoral dissertation of Don C. Iffland, Purdue University, June, 1947.

(2) Present address: University of West Virginia, Morgantown, West Va.

(3) Iffland, Ph.D. thesis, Purdue University, June, 1947.

(4) "Organic Syntheses," Coll. Volume I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 542; Saunders, "The Aromatic Diazo Compounds," Arnold and Co., London, 1936, p. 4.

(5) Kornblum, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1944, Vol. II, pp. 277–282.

(6) $K = 6 \times 10^{-2}$; Kolthoff, *Rec. trav. chim.*, **46**, 350 (1927)