2 ml. of dry benzene and two drops of pyridine was ground to a fine suspension with a glass rod, cooled in an ice-bath and treated with 1 ml. of redistilled oxalyl chloride. After the immediate evolution of gas slowed, the mixture was allowed to come to 15° and after five minutes the excess oxalyl chloride and benzene removed as described above, keeping the temperature below 15°. The acid chloride in 2 ml. of benzene was filtered and added to sodiomalonic ester (from 3 g. of malonic ester, 0.23 g. of sodium powder and 15 ml. of ether), stirring overnight at room temperature. Hydrolysis of the product with 2.5 ml. of acetic acid, 2.5 ml. of hydrochloric acid and 1 ml. of water at reflux for two hours, working up the mixture as described above, gave 240 mg. of a reddish oil. This was adsorbed on 5 g. of alumina from benzene–petroleum ether (1:1) and fractionally eluted. From the later eluates with the same mixture, followed by benzene and benzene–ether (1:1) was obtained solid material which was recrystallized from ether–petroleum ether giving 53 mg. (18%) of the diketone XIV (Isomer A), micro m. p. 92–97°. Further recrystallization from the same solvent gave stout prisms, micro m. p. 96–98°, with an absorption maximum at 239 mμ (E = 16,400).

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.8; H, 9.6. Found: C, 79.0; H, 9.6.

The bis-2,4-dinitrophenylhydrazone of XIV (Isomer A), prepared in alcohol containing hydrochloric acid, was obtained originally as a red solid, micro m. p. 125–129°. Recrystallization from chloroform–alcohol raised the micro m. p. to 220–221°. It is not known whether this large change was due to impurities or to polymorphic forms.

Anal. Calcd. for $C_{30}H_{34}O_8N_8$: C, 56.8; H, 5.4. Found: C, 56.8; H, 5.3.

(b) **Dimethylcadmium Method.**[25]—A solution of dimethylcadmium was prepared from 30 ml. of 0.24 *N* methylmagnesium bromide and 0.75 g. of cadmium chloride, refluxing and stirring under nitrogen until the Gilman test for the Grignard reagent was negative. The ether was distilled and replaced by 10 ml. of benzene and a benzene solution of the acid chloride prepared from 1.00 g. of the acid VIIa (Isomer A) was added. After refluxing and stirring one hour the mixture was cooled, hydrolyzed and the organic portion isolated as a reddish oil. This was adsorbed from benzene on a column of 20 g. of alumina and fractionally eluted with the same solvent; from the middle fractions crystalline material was obtained and recrystallized from ether–petroleum ether, affording 132 mg. (13%) of the same diketone XIV (Isomer A) as in (a), micro m. p. 95–97°, mixed m. p. 96–98°.

6-(4′-Acetoxyacetylcyclohexyl)-Δ^{1-9}-octalone-2 (Isomer A) (XV).—The acid chloride from 1.00 g. of the acid VIIa (Isomer A) was treated with diazomethane as described for the phenyl derivative XIa, and the oily diazoketone added to boiling acetic acid, heating for three minutes. After removing the solvent under reduced pressure the residue was triturated with methanol giving 500 mg. of brown solid, micro m. p. 100–105°, which was evaporatively distilled at 115–140° (0.001 mm.) and recrystallized from methanol to give 225 mg., m. p. 115–120° and 110 mg., m. p. 100–115°, corresponding to 28% yield. Two recrystallizations from methanol raised the micro m. p. to 123–124.5°; the absorption spectrum showed a maximum at 239 mμ (E = 16,900).

Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.3; H, 8.5. Found: C, 72.6; H, 8.6.

Summary

Procedures have been developed for the synthesis of some analogs of progesterone and desoxycorticosterone lacking ring C, and with a six-membered ring D. The method involves the Robinson–Mannich base procedure for synthesizing α,β-unsaturated cyclic ketones, modified for application to hydroxymethylene ketones. The progesterone analogs were physiologically inactive; further tests are underway.

MADISON 6, WIS. RECEIVED NOVEMBER 11, 1949

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[25] Cason, *Chem. Rev.*, **40**, 15 (1947).

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

The Stobbe Condensation with Ethyl γ-Anisoylbutyrate. A New Route to Some Estrone Intermediates

BY WILLIAM S. JOHNSON, A. RUSSELL JONES[1] AND WILLIAM P. SCHNEIDER[2]

In work directed toward the total synthesis of estrone various investigators—notably Robinson[3] and Bachmann[4] and their respective collaborators—have developed methods for the synthesis of ketooctahydrophenanthrene derivatives like VIII in which the keto group serves as a site for attachment of the final five-membered ring D. The keto ester VIII ($R^1 = CH_3$, $R^2 = COOCH_3$), which was first prepared by Robinson and Walker[3b,d] (as the ethyl ester, $R^2 = COOC_2H_5$) and later made more readily available by a new method of Bachmann, Kushner and Stevenson,[4,5] has more recently gained particular prominence due to the work of Anner and Miescher[6] who obtained three of the four possible racemic modifications in crystalline form, one of which was converted into estrone by the Bachmann method for introducing ring D.[7]

The present work involves the study of a completely new approach to these important intermediates. The scheme, which is outlined in the accompanying flow sheet, avoids the necessity of relatively inaccessible meta substituted anisoles as starting materials by employing a cyclization directed into the meta position (IV → V). The method involves the first (to our knowledge) successful application of the Stobbe condensation to a keto ester.

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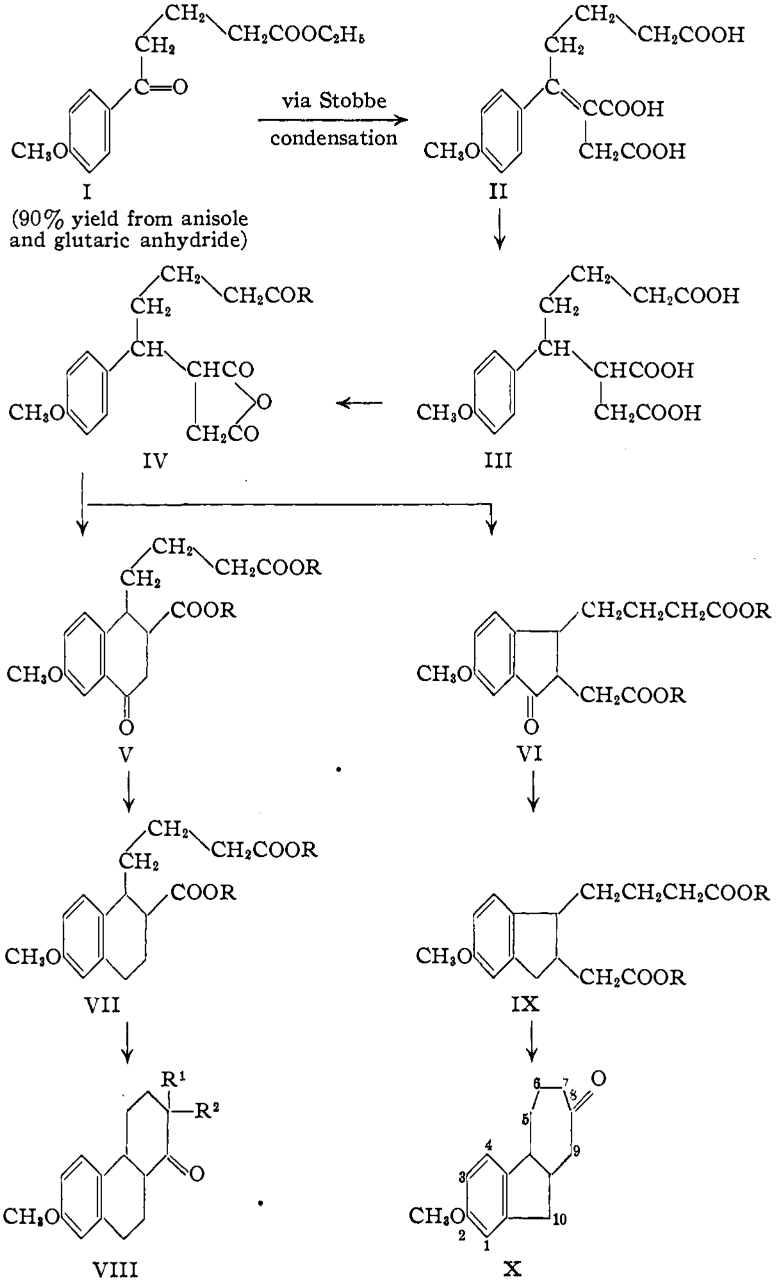
[3] (a) Robinson and Schlittler, *J. Chem. Soc.*, 1288 (1935); (b) Robinson and Walker, *ibid.*, 192, 747 (1936); (c) 60 (1937); (d) 183 (1938).

[4] Bachmann, Kushner and Stevenson, THIS JOURNAL, **64**, 974 (1942).

[5] See also Wilds and T. L. Johnson, *ibid.*, **70**, 1166 (1948).

[6] Anner and Miescher, *Helv. Chim. Acta*, **30**, 1422 (1947).

[7] Anner and Miescher, *Experientia*, **4**, 25 (1948); *Helv. Chim. Acta*, **31**, 2173 (1948).



Ethyl γ-anisoylbutyrate (I) which can be prepared readily in about 90% over-all yield by the Friedel–Crafts acylation of anisole with glutaric anhydride, followed by esterification, failed to react with diethyl succinate under the conditions of the modified Stobbe condensation.[8] However, when the reaction was conducted at room temperature instead of at the boiling point, the desired condensation proceeded in practically quantitative yield to give an oily mixture of acid esters. Saponification yielded a mixture of tribasic acids from which one of the isomers was readily separated in 62% yield by crystallization. The ethylenic bond of this product was unusually resistant to catalytic hydrogenation, the benzene nucleus apparently being attacked at a comparable rate. This behavior is consistent with the alkylidenesuccinic acid structure II having an ethylenic bond that carries no hydrogen atoms and which is involved in a *p*-methoxycinnamic acid system. This bond could be reduced readily, however, by the method of Schwenk, Papa, Whitman and Ginsberg[9] employing nickel–aluminum alloy and sodium hydroxide. A crystalline racemate of the tribasic acid III was thus obtained in 77% yield. This same acid, m. p. 155.5–156.5° (pure), could be obtained from the crude Stobbe condensation product in 41–47% yield by direct treatment with nickel–aluminum alloy and alkali without isolation of the unsaturated acid II. Of a variety of methods which were tried, the best procedure for the cyclization of the acid III consisted in treatment with thionyl chloride to produce the acid chloride anhydride IV (R = Cl) which, without isolation, was treated with 2 moles of piperidine for each of acid. The anhydride piperidide IV ($R = NC_5H_{10}$) thus produced was cyclized in nitrobenzene solution with aluminum chloride at room temperature, and the product of ring closure was isolated by extraction from aqueous solution at a *p*H > 5.50, which was shown by control experiments to retain the dibasic acid piperidide, allowing the less acidic, cyclized material to go into the organic layer. Acid hydrolysis of the oily product to eliminate the piperidide residue, followed by esterification gave a mixture of isomeric keto esters V ($R = CH_3$) and VI[10] ($R = CH_3$) in 51% over-all yield from III. The keto group was hydrogenated smoothly to the methylene group in the presence of palladium catalyst and a trace of perchloric acid.[11] The reduced mixture of keto esters gave after saponification, a mixture of dibasic acids

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(8) Johnson, Petersen and Schneider, THIS JOURNAL, **69**, 74 (1947).

(9) Schwenk, Papa, Whitman and Ginsberg, *J. Org. Chem.*, **9**, 175 (1944).

(10) Presumed structure, see below.

(11) The method of Kindler; see Rosenmund and Karg, *Ber.*, **75**, 1850 (1942).

from which the known isomer of VII (R = H), m. p. 156.5–157.5°, could be crystallized in low (7–14%) yield. The identity of this product was established by a mixed melting point determination with authentic VII (R = H).[12] The remaining acidic mixture was treated with diazomethane giving a mixture of the esters, VII and IX[10] (R = CH_3), from which one form of the latter crystallized in 42% yield. The remaining liquid fraction (obtained also in 42% yield) contained considerable diester VII (R = CH_3) as shown by its conversion into the known crystalline methoxyketoöctahydrophenanthrene VIII ($R^1 = R^2 = H$) by Dieckmann cyclization followed by hydrolysis and decarboxylation. The identity of this product was confirmed by comparison of the ketone with an authentic specimen.[12] The yield of VIII ($R^1 = R^2 = H$) in the present study was 32% as compared with the 57% yield reported by Bachmann, Kushner and Stevenson[4] from pure VII (R = CH_3). Since it is known that methylation *in situ* of the product of the Dieckmann cyclization of VII (R = CH_3) (see above) gives rise to the keto ester VIII ($R^1 = CH_3$, $R^2 = COOCH_3$),[4] the present scheme affords a new route to this important substance. Although this step has not been performed with the products of the present study, the application is obvious, particularly in view of the favorable difference in rates of Dieckmann cyclization of VII (R = CH_3) and IX[10] (R = CH_3) (see below) for effecting selective cyclization of V (R = CH_3).

Dieckmann cyclization of the crystalline diester (presumably IX, R = CH_3) described above with sodium hydride proceeded much more slowly than with VII (R = CH_3) as estimated by the rate of evolution of hydrogen gas. This behavior is consistent with the proposed seven-membered ring cyclization IX→X.[13] The crystalline ketone obtained in 50% yield upon hydrolysis and decarboxylation melted at 110° after purification, but was different from the ketoöctahydrophenanthrene VIII ($R^1 = R^2 = H$), m. p. 107°, as shown by the depression of melting point on admixture. Attempts to interconvert the two ketones by the action of alkoxides failed, thus precluding the likelihood that they are diastereoisomeric. This implication that the 110° ketone is a structural isomer of VIII ($R^1 = R^2 = H$) suggests that the cyclization of the anhydride piperidide IV (R = NC_5H_{10}) proceeded to give five as well as six-ring closure. While this was unexpected behavior on the basis of the studies of von Braun,[14] it is not without precedent,[15] and the formulation of steps IV → VI → IX → X are therefore entirely plausible. Preliminary attempts to prove conclusively the structure of the 110° ketone have failed. Reduction with aluminum isopropoxide gave a crystalline carbinol which was dehydrated to give what is presumed to be a methoxybenzhexahydroazulene. Dehydrogenation experiments with this product, however, yielded only dark intractable tars from which neither methoxybenzazulene nor methoxyphenanthrene was isolated. This behavior is not inconsistent with the proposed benzazulene structure.[16]

Experimental[17]

γ-Anisoylbutyric Acid.—By a modification of the procedure of Banerjee[18] the yield of this acid was improved somewhat. A solution of 56 g. of anhydrous aluminum chloride in 200 ml. of dry nitrobenzene in a three-necked flask equipped with a stirrer, thermometer and dropping funnel was cooled to 5° with stirring, and 21.60 g. of anisole was added. A solution of 24.0 g. of glutaric anhydride[19] in 50 ml. of nitrobenzene was then added dropwise at such a rate that the temperature was maintained below 3°. After this addition was complete, stirring was continued for five minutes, then the stirrer was removed, the flask protected with a soda-lime tube and stored in a refrigerator at 3°.

After twelve days the dark red solution was poured onto ice and hydrochloric acid. The suspension was shaken thoroughly, the solid separated by suction filtration, and the aqueous layer of the filtrate was separated and extracted with ether. The combined ether and nitrobenzene layers were washed with water, then extracted thoroughly with 10% sodium hydroxide solution. The solid portion separated as described above was dissolved in the combined alkaline extracts, which were then washed with ether, heated to drive off dissolved ether, cooled, and acidified with 6 *N* hydrochloric acid. The product was filtered off, washed with water and dried at 55°; yield 42.76 g. (96%) of light tan solid, m. p. 136–139°. This material was satisfactory for the esterification.

In another run in which 129.6 g. of anisole, 145 g. of glutaric anhydride and 336 g. of aluminum chloride were employed, the yield of crude acid after eight days was 276.3 g. Recrystallization from water gave a total of 241.5 g. (90% yield) of colorless plates, m. p. 138.5–141° (reported,[20] 137°).

Ethyl γ-Anisoylbutyrate (I).—A solution of 42.76 g. of the crude acid, m. p. 136–139°, in 320 ml. of benzene, 40 ml. of ethanol, and 1 ml. of concentrated sulfuric acid was refluxed in a system containing a continuous water separator[21] previously filled with benzene. After seven hours water was no longer separating, and the solution was cooled, washed with saturated sodium bicarbonate solution, followed by water and saturated salt solution. The benzene solution was filtered through a bed of anhydrous sodium sulfate, concentrated, and distilled at reduced pressure. The product, a pale yellow crystalline solid, m. p. 57–59°, was collected at 170–185° (0.15–0.20 mm.); yield 44.91 g. (93%). This material was suitable for use in the next step. A sample after recrystallization from dilute alcohol had the m. p. 58.5–59.5° (reported,[18] 59–60°).

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[12] Prepared by Dr. W. E. Shelberg according to the Bachmann method, refs. 4 and 5.

[13] Dieckmann, *Ber.*, **55**, 2470 (1922); *Ann.*, **317**, 27 (1901), found that diethyl suberate cyclized in about 0.5% yield under conditions which effected cyclization of diethyl pimelate in at least 60% yield. Note, however, that the suberate could be cyclized satisfactorily upon prolonged treatment.

[14] See Johnson in Adams, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, pp. 116–118.

[15] See Johnson and Graber, THIS JOURNAL, **72**, 925 (1950).

[16] *Cf.* the failure in attempts to aromatize both a hexa- and an octahydrobenz[*e*]azulene by Cook, McGinnis and Mitchell, *J. Chem Soc.*, 286 (1944).

[17] All melting points are corrected.

[18] Banerjee, *J. Ind. Chem. Soc.*, **17**, 573 (1940).

[19] Prepared from glutaric acid obtained by the method of Bachmann, Kushner and Stevenson, ref. 4, or of Otterbacher, *Org. Syn.*, Coll. Vol. I, 290 (1941).

[20] Plant and Tomlinson, *J. Chem. Soc.*, 856 (1935).

[21] Cope, Hofmann, Wyckoff and Hardenbergh, THIS JOURNAL, **63**, 3452 (1941).

The Stobbe Condensation with Ethyl γ-Anisoylbutyrate.—Diethyl succinate (40 ml.) was added to a solution of 6.5 g. of potassium in 50 ml. of dry *t*-butyl alcohol at room temperature (nitrogen atmosphere) and the mixture stirred until homogeneous. To this solution was added 30.00 g. of ethyl γ-anisoylbutyrate with 40 ml. of *t*-butyl alcohol, and the mixture was stirred for twenty minutes. As the yellow solution stood for twelve hours at room temperature (nitrogen atmosphere) it gradually turned to a clear red color. A solution of 15 ml. of concentrated hydrochloric acid in 100 ml. of water was then added with stirring, and most of the alcohol distilled off at reduced pressure. The pale yellow oily residue was taken up in ether and extracted with saturated sodium bicarbonate solution. The combined extracts were acidified, the precipitated oil taken up in ether, washed with water, followed by saturated salt solution and dried over anhydrous sodium sulfate. The yellow oily product obtained on evaporation of the ether and removal of traces of solvent at the water pump amounted to 44.6 g. (98% yield). A sample of material thus prepared was evaporatively distilled at 180° (0.05 mm.).

Anal. Calcd. for $C_{20}H_{26}O_7$: C, 63.48; H, 6.92. Found: C, 63.85; H, 6.44.

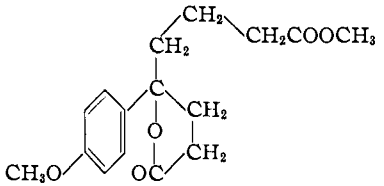
The triethyl ester was prepared from 4.00 g. of the crude condensation product, 20 ml. of benzene, 5 ml. of ethanol and a few drops of concentrated sulfuric acid. A continuous water separator[21] was used and after four hours of refluxing the reaction was apparently complete. The product was isolated in the usual manner. It distilled as a colorless oil, b. p. about 215° (0.6 mm.).

Anal. Calcd. for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44. Found: C, 65.07; H, 6.97.

6,7-Dicarboxy-5-*p*-anisyl-5-heptenoic Acid (II).—A 20.26-g. sample of the crude Stobbe condensation product in 200 ml. of 1.5 *N* sodium hydroxide was warmed on the steam-bath for one hour, allowed to stand for two days at room temperature, then warmed for another hour. The cooled solution was acidified with hydrochloric acid, saturated with sodium chloride and extracted with three 100-ml. portions of ether. The combined ether extracts were washed with saturated salt solution and dried over anhydrous sodium sulfate. Evaporation of the solvent left 17.55 g. of an orange glassy product which upon trituration with a warm mixture of 25 ml. each of benzene and chloroform, first dissolved, then yielded a colorless precipitate. After standing twenty-four hours the precipitate was separated by suction filtration, and washed twice with a mixture of 5 ml. each of benzene and chloroform containing 4 drops of acetone. The yield of acid, m. p. 152.5–154° (dec.), was 10.88 g. (62%). Repeated recrystallization from a mixture of benzene, methanol and 60–68° petroleum ether gave small colorless prisms, m. p. 162.4–163° (dec.).

Anal. Calcd. for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63; neut. equiv., 107. Found: C, 59.82; H, 5.66; neut. equiv., 108.

Decarboxylation of the acid II was effected by the hydrobromic acid method.[22] A solution of 4.00 g. of the acid II in 75 ml. of acetic acid, 50 ml. of 48% hydrobromic acid, and 25 ml. of water was boiled under reflux for two hours. The solvents were removed under reduced pressure, and the residue methylated with dimethyl sulfate and dilute sodium hydroxide. The basic solution was finally heated to saponify any ester groups, cooled, and extracted with ether to remove some tarry material. The aqueous solution was acidified, warmed to complete the lactonization, and the oil taken up in ether, washed with water and dried. The product obtained on evaporation of the ether was evaporatively distilled at 220–235° (0.1 mm.), the yellow distillate treated with diazomethane, and the resulting ester distilled in a two-bulb flask at 0.3 mm. to yield 1.19 g. of an oil, probably the lactone of **methyl 5-*p*-anisyl-5-hydroxy-7-carboxyheptanoate** (XI).



XI

Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.85; H, 6.91.

6,7-Dicarboxy-5-*p*-anisylheptanoic Acid (III). (*a*) *From the Pure Unsaturated Acid II.*—A solution of 10.00 g. of the acid II, m. p. 148–151°, in 300 ml. of 10% sodium hydroxide was heated to 90°, 3 drops of octanol-2 was added, then 30 g. of Raney nickel alloy was introduced into the well stirred solution in portions over a period of forty-five minutes. Additional traces of octanol-2 were added as needed to decrease foaming. A second 200 ml. of 10% sodium hydroxide was added followed by an additional 30-g. charge of the alloy in exactly the same manner, and then the solution was stirred for an additional hour at 90°, the volume of the mixture being kept approximately constant by the addition of water. The hot mixture was filtered, and the nickel residue washed with three 100-ml. portions of boiling water. The combined filtrate and washings were cooled and poured slowly into a separatory funnel containing 400 ml. of concentrated hydrochloric acid and 400 g. of ice. The mixture was saturated with sodium chloride and extracted thoroughly with ether. The glassy product obtained on evaporation of the ether was dissolved in 50 ml. of warm water, treated with 0.5 g. of Norit, and filtered, an additional 50 ml. of water being used in washing and transferring. Seed crystals were added to the warm solution which was then stirred continuously overnight as the product slowly crystallized. Without agitation the crystallization took several days to weeks. Colorless crystals amounting to 7.14 g. were thus obtained, m. p. 153–154.6°. An additional 0.64 g. of material m. p. 152–153° was isolated from the mother liquors, making the total yield 7.78 g. or 77%. Repeated recrystallization from water gave colorless crystals, m. p. 155.5–156.5°, depressed to 141–144° on admixture with the starting acid II.

Anal. Calcd. for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22; neut. equiv., 108. Found: C, 59.46; H, 6.21; neut. equiv., 107.

(*b*) *Directly from the Crude Stobbe Condensation Product.*—A 9.60-g. sample of the oily condensation product was treated exactly as described above for the reduction of the pure acid II, except that the amounts of 10% sodium hydroxide and Raney nickel alloy used in the *second* charge were reduced to 100 ml. and 10 g., respectively. For the recrystallization the total volume of water was reduced to 50 ml. The product crystallized more slowly in this case, the first crop amounting to 3.64 g., m. p. 150.4–152.8°. An additional 0.24 g., m. p. 152–154.5° was obtained from the mother liquor, making the total yield 3.88 g. (47%). Another reduction carried out with 31.70 g. of crude condensation product gave a total of 11.11 g. (41% yield).

6,7-Dicarboxy-5-*p*-anisylheptopiperidide Anhydride (IV, R = NC_5H_{10}).—A mixture of 4.828 g. of the reduced tribasic acid III, m. p. 153–154°, 10 ml. of thionyl chloride[23] and 20 ml. of anhydrous ether was heated under reflux for one hour in an apparatus protected from atmospheric moisture. The solvents were removed at reduced pressure, and traces of thionyl chloride eliminated by codistillation with three 25-ml. portions of dry benzene. The oily residue, probably consisting largely of the chloride anhydride IV (R = Cl) (Calcd. for $C_{16}H_{17}O_5Cl$: Cl, 10.9. Found: Cl, 11.6) was dissolved in a mixture of 50 ml. of dry ether and 25 ml. of dry benzene, then a solution of 2.530 g. of anhydrous piperidine in 50 ml. of dry benzene was added dropwise at room temperature with

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[22] *Cf.* Johnson and Jones, THIS JOURNAL, **69**, 792 (1947).

[23] Purified by the method of Cottle, *ibid.*, **68**, 1380 (1946).

good stirring, an additional 50 ml. of benzene being used to wash in the piperidine solution. Without filtering off the precipitated piperidine hydrochloride (which amounted to 95% of the calculated quantity in experiments where this separation was effected), the mixture was washed with 25 ml. of saturated sodium bicarbonate solution, water, saturated salt solution, and finally dried over Drierite. Evaporation and removal of traces of solvent at reduced pressure gave 5.54 g. (99% yield) of viscous oily piperidide anhydride which was suitable for cyclization (see below).

The crude piperidide anhydride could be hydrolyzed to the bicarbonate-soluble oily dibasic acid piperidide by warming with aqueous alkali. The product could be at least partly reconverted to the anhydride with acetyl chloride, and material thus treated was submitted to evaporative distillation at 170–175° (< 1 micron). Considerable decomposition occurred even under these conditions, and therefore it is not surprising that the analysis of the oily distillate was not satisfactory.

Anal. Calcd. for $C_{21}H_{27}O_5N$: C, 67.54; H, 7.29. Found: C, 66.27; H, 6.98.

After redistillation of the above material, the analysis for carbon dropped to 65.12%. When the crude piperidide anhydride was treated with dilute sodium hydroxide about 10% of the material remained undissolved. This neutral fraction (2.64 g.) obtained from 25.00 g. of the tribasic acid was submitted to evaporative distillation. The fraction obtained at 155–170° (0.2 mm.) amounted to 0.40 g. of crystalline product, m. p. 117–121.5°. Repeated recrystallization from 60–68° petroleum ether gave colorless needles, m. p. 126.5–127°. This substance of unknown structure did not contain nitrogen or sulfur.

Anal. Found: C, 73.05, 73.05; H, 7.26, 7.32.

Further evaporative distillation of the residue at 180–190° (< 1 micron) for nineteen hours gave 0.66 g. of a nearly colorless glassy product. The analysis was in fair agreement with that calculated for the tripiperidide of the tribasic acid III.

Anal. Calcd. for $C_{31}H_{47}O_4N_3$: C, 70.82; H, 9.01. Found: C, 70.48; H, 8.79.

Cyclization of 6,7-Dicarboxy-5-*p*-anisylheptopiperidide Anhydride.—The crude piperidide anhydride prepared from 20.00 g. of the tribasic acid III as described above was dissolved in 40 ml. of dry nitrobenzene, the solution was cooled, and maintained at 0–5° while a solution of 28.0 g. of anhydrous aluminum chloride in 125 ml. of dry nitrobenzene was slowly added with stirring. After the addition was complete, the solution was allowed to stand for two and one-half days at 27° protected from atmospheric moisture by a soda-lime tube. It was then poured onto a mixture of 15 ml. of concentrated hydrochloric acid and 150 g. of ice. After thorough shaking, the layers were separated, the aqueous layer was extracted with ether, and the combined organic layers were washed with water followed by 1.5 *N* sodium hydroxide solution. The combined alkaline solutions (about 200 ml.) were placed in a 1-l. beaker, 100 ml. of chloroform added, and the electrodes of a Macbeth *p*H meter were immersed in the aqueous solution. While the solution was vigorously stirred with a Hershberg wire stirrer, 6 *N* hydrochloric acid was added dropwise until the *p*H (determined upon interrupting the stirring and allowing the layers to separate) dropped to 5.40. The layers were then separated and the aqueous layer extracted first with 50 ml. of chloroform, then with 25 ml. of ether. The combined organic layers were washed with water, dried over anhydrous sodium sulfate, and evaporated. After removal of traces of solvent at reduced pressure (steam-bath temperature) there remained 20.27 g. of a red glassy product, neut. equiv. 390 (calcd. for the keto-acid piperidide, 373).

The combined aqueous layer and water washing (*p*H 5.52) was acidified with concentrated hydrochloric acid until it turned congo red test paper blue, and extracted with chloroform followed by ether. From the organic layers which were combined, washed and dried as above, there was obtained 2.61 g. of dark red glassy material, neut. equiv. 197 (calcd. for dibasic acid piperidide, 196). Control experiments with the dibasic acid piperidide prepared from the anhydride (see above) showed that it could not be extracted from an aqueous solution at *p*H > 5.40.

There is some doubt as to whether the 2.61 g. of more strongly acidic material isolated above was indeed the dibasic acid piperidide, because an attempt to cyclize this product after treatment with acetyl chloride, presumably to reform the anhydride, gave only 0.50 g. of the desired product, considerable tarry material being formed. The exact course of the reaction of acetyl chloride with the dibasic acid piperidide, however, is somewhat uncertain (see above).

Since attempts to crystallize the cyclized material failed, it was hydrolyzed and esterified as follows. A mixture of 20.37 g. of crude keto acid piperidide, 100 ml. of concentrated hydrochloric acid and 35 ml. of water was boiled under reflux for four hours. The cooled mixture was extracted *thoroughly* with chloroform, and the combined organic solutions were washed with water and evaporated, leaving 12.45 g. of an orange glassy material which was esterified with ethanol, benzene and sulfuric acid in a continous water separator[21] as described above for the preparation of I. After the reaction was complete, the benzene solution was extracted with saturated sodium bicarbonate solution which removed 0.10 g. of glassy acidic material; then with 1.5 *N* sodium hydroxide which removed 0.43 g. of more weakly acidic (phenolic ?) material. The neutral fraction remaining in the benzene layer was washed with water, followed by saturated salt solution, and dried over anhydrous potassium carbonate. The solvent was removed, and the residue distilled in a modified Claisen flask giving 11.43 g. (51% yield from the tribasic acid III) of yellow mixture of keto di-esters, b. p. 215–240° (0.2 mm.) mostly at 230–235° (0.2 mm.). Redistillation gave fraction (a) 0.36 g., b. p. 181–210° (0.2 mm), (b) 10.34 g., b. p. 210–220° (0.2 mm.) and (c) 0.45 g., b. p. about 210–220° 0.2 mm.). The analysis was performed on fraction (b).

Anal. Calcd. for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.30; H, 7.08.

Attempts to prepare the semicarbazone, thiosemicarbazone and 2,4-dinitrophenylhydrazone gave oily products.

Reduction of the Keto Diester Mixture and Separation of the Products.—An 11.71-g. sample of the distilled keto diester mixture described above was dissolved in 50 ml. of acetic acid, 3.00 g. of 5% palladium-charcoal[24] and 2.0 ml. of 60% perchloric acid were added and the mixture was stirred in the presence of hydrogen at room temperature and atmospheric pressure. After two and one-half days the calculated amount of gas was absorbed (80% by the end of the first day). The mixture was filtered, the filtrate evaporated in a current of air to a volume of about 30 ml., 100 ml. of water and 50 g. of sodium hydroxide were added and the mixture was boiled for three hours. The salt which precipitated on cooling was separated and dissolved in water. Acidification of this solution gave 1.50 g. of a cloudy colorless glassy product which on trituration with a mixture of 1 ml. each of benzene and acetone, gave 0.68 g. of γ-(2-carboxy-6-methoxy-1,2,3,4-tetrahydro-1-naphthyl)-butyric acid (V, R = H), m. p. 156.5–157.3°, undepressed on admixture with authentic material[12] (m. p. 155.5–156.9°).

The residue from the trituration was combined with the 9.40 g. of orange oil obtained by acidification of the aqueous alkaline filtrate described above, and treated with excess diazomethane. Distillation afforded 8.67 g. of colorless mixture of dimethyl esters, b. p. 195–200° (0.2 mm.).

Anal. Calcd. for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.16; H, 7.32.

Trituration with 60–68° petroleum ether gave 1.33 g. of colorless needles, m. p. 60.5–64°. The oily residue obtained on evaporation was dissolved in 10 ml. of alcohol, and seeds of the solid isomer added. On chilling, additional product, m. p. 58.5–61°, crystallized raising the

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[24] Catalyst B, Mozingo, *Org. Syn.*, **26**, 77 (1946).

total yield to 4.33 g. (42%). This crystalline ester, presumably **methyl γ-(2-carbomethoxymethyl-5-methoxy-1-hydrindanyl)-butyrate (IX, R = CH_3)**, was obtained as long, colorless, silky needles, m. p. 64–66° after repeated recrystallization from alcohol.

Anal. Calcd. for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.58; H, 7.34.

1-Keto-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene (VIII, R^1 = R^2 = H) was prepared from the oily fraction remaining after separation of the crystalline isomer (see above). A solution of 10.00 g. of such material in 45 ml. of dry xylene was added dropwise to a stirred refluxing suspension of 2.0 g. of sodium hydride[25] and 1.0 g. of sodium methoxide in 20 ml. of dry xylene (nitrogen atmosphere), and the evolved gas was collected in an eudiometer. The reaction was very rapid and was kept under control by adjusting the rate of addition so that foaming was not excessive. During the one hour required for this addition, 86% of the calculated amount of hydrogen was evolved. Refluxing was then continued and an additional 13% of the gas was collected during the first and none during the second hour of heating. The mixture was cooled, a solution of 10 ml. of acetic acid in 50 ml. of benzene was added slowly with stirring, and the solution was washed with water and concentrated under reduced pressure. The oily residue was refluxed with 320 ml. of acetic acid, 160 ml. of concentrated hydrochloric acid and 80 ml. of water for four and three-quarters hours; then the solvents were removed at reduced pressure, water was added and the mixture extracted with ether. The combined ether extracts were washed in sequence with water, 1.5 *N* sodium hydroxide solution, water, and saturated salt solution. Evaporation of the dried (over anhydrous potassium carbonate) solution gave 6.13 g. of crude pasty solid ketone which was dissolved in alcohol, treated with Norit, recovered and finally triturated with cold ether which gave 2.40 g. of crude colorless ketone, m. p. 88–96°. Crystallization from 10 ml. of alcohol yielded 2.28 g. of colorless needles, m. p. 96–102.5°. Recrystallization raised the m. p. to 103.5–106°. The m. p. was not depressed on admixture with authentic ketone[12] (m. p. 105–107°), but was depressed to 83–87° on admixture with the isomer, presumably X, described below.

The semicarbazone was formed readily in 92% yield and melted at 227–227.5° (dec.) when introduced in bath at 200° (reported m. p. for semicarbazone of VIII, R^1 = R^2 = H, 225° (dec.[3b]).

Cyclization of the Solid Dimethyl Ester (Presumably IX, R = CH_3).—A 10.00-g. sample of the ester, m. p. 58–63°, was cyclized with sodium hydride exactly as described above for the liquid form. During the addition, which required forty minutes, only 32% of the calculated amount of gas was evolved, but after heating for an additional two and one-half hours, a total of 89% of the calculated volume of gas had been liberated. The neutral product obtained after hydrolysis and decarboxylation amounted to 5.76 g. of pale yellow crystals, m. p. 97–107°. After treatment (in methanol solution) with Norit this substance was triturated with cold methanol to give 3.60 g. of colorless material, m. p. 100–105°. Recrystallization from 15 ml. of ethanol yielded 3.18 g., m. p. 107–108.5$_\circ$. After repeated recrystallization from methanol the ketone, presumably **2-methoxy-8-keto-4b,5,6,7,8,9,9a,10-octahydrobenz[*a*]-azulene**, was obtained as colorless prisms, m. p. 109.9–110.8° (depressed to 85–110° on admixture with an authentic sample of VIII, R^1 = R^2 = H[12]).

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.33, 78.39; H, 8.05, 7.71.

The **semicarbazone** was obtained as a colorless powder from *n*-butyl alcohol and melted at 213.7–214.3° (dec.) when introduced in bath at 200°.

Anal. Calcd. for $C_{16}H_{21}O_2N_3$: C, 66.87; H, 7.37. Found: C, 66.98; H, 7.34.

The **2,4-dinitrophenylhydrazone** crystallized from ethyl acetate in the form of yellow prisms, m. p. 222.5–223.5°.

Anal. Calcd. for $C_{21}H_{22}O_5N_4$: C, 61.45; H, 5.40. Found: C, 61.36; H, 5.39.

The **mono-benzylidine derivative** was prepared[26] from 67 mg. of the ketone, 85 mg. of benzaldehyde, 3 ml. of alcohol, 0.5 ml. of water and 0.5 ml. of 45% potassium hydroxide solution. After several days at 26–27° the crude yellow product which had precipitated amounted to 40 mg. (43% yield), m. p. 116–119.3°. After repeated recrystallization from dilute alcohol nearly colorless needles, m. p. 121.9–122.6°, were obtained.

Anal. Calcd. for $C_{22}H_{22}O_2$: C, 82.99; H, 6.97. Found: C, 83.12; H, 6.82.

The formation of the above derivative rather than the dibenzylidene compound does not preclude the structure X which has a carbonyl flanked by two methylene groups, because the course of such a condensation has been shown to vary considerably with minor variations in conditions.[27] The methylene group at 9, moreover, would be expected to be hindered compared with that at 7, and therefore attack at the latter position is preferred, and the product is presumed to be the 7-benzylidene derivative.

The **mono-piperonylidene derivative** was similarly prepared in about 31% yield (crude), and was obtained from dilute alcohol in the form of almost colorless needles, m. p. 138–139°.

Anal. Calcd. for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12. Found: C, 76.35; H, 6.14.

Reduction of the 110° ketone (1.500 g.) with aluminum isopropoxide[28] gave the corresponding carbinol, presumably **2-methoxy-8-hydroxy-4b,5,6,7,8,9,9a,10-octahydrobenz[*a*]azulene**, one form of which was isolated by crystallization from ether-petroleum ether; yield 1.052 g., m. p. 90–93.6°. Repeated recrystallization from ether–petroleum ether (40–60°) gave colorless rods, m. p. 94–95.5°.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.12; H, 8.70.

Dehydration of 1.369 g. of the crude carbinol mixture (see above) was effected by heating with 3 g. of potassium acid sulfate at 160° for one hour. Water was added to the cooled mixture and the organic material taken up in ether. Evaporation of the ether layer gave a red oil which was submitted to evaporative distillation at 75–150° (0.5–0.20 mm.). The **methoxyhexahydrobenz[*a*]azulene** was thus obtained as a yellow oil which solidified on standing; yield 0.790 g., m. p. 45–52°.

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.80; H, 8.51.

Attempts to dehydrogenate this material over palladium–charcoal catalyst gave only intractable dark tars.

Summary

A new approach to the 1-keto-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene (VIII) nucleus is described. The scheme involves a Stobbe condensation between ethyl γ-anisoylbutyrate and diethyl succinate followed by a nickel–alkali reduction to give a tribasic acid (III) which on cyclization and reduction of the keto group yields a mixture of two dibasic acids, one of which (VII) is the precursor of the estrone intermediate (VIII, R^1 = CH_3, R^2 = $COOCH_3$).

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[25] Obtained from the Electrochemicals Department, E. I. du Pont de Nemours and Co.

[26] *Cf.* the small-scale procedure described for 9-methyldecalone-1; Johnson, THIS JOURNAL, **65**, 1317 (1943).

[27] *Cf.* the critical study of the condensation of aldehydes with 1-methyl-4-piperidone; McElvain and Rorig, THIS JOURNAL, **70**, 1820 (1948).

[28] Wilds in Adams, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 203.

The second dibasic acid appears to be a product (IX) of five-membered ring closure, and on Dieckmann cyclization of the ester, followed by hydrolysis and decarboxylation gives what is probably a benzazulene derivative X.

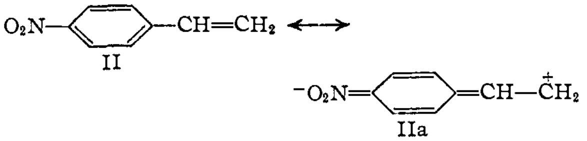
MADISON, WISCONSIN RECEIVED NOVEMBER 5, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

The Reaction of Certain Substituted Styrenes with Dioxane Sulfotrioxide[1]

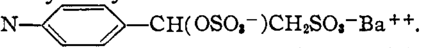
BY WILLIAM E. TRUCE AND PAUL F. GUNBERG[2]

The reaction of dioxane sulfotrioxide (I) with *p*-nitrostyrene (II) and *m*-nitrostyrene (III) has been investigated to determine whether the latter isomer, lacking resonance interaction between the nitro group and the olefinic group, would react more rapidly than II in which resonance of the type IIa should inhibit reaction with an electrophilic reagent at the ω-carbon atom.


II

IIa

Some support for this prediction was furnished by the reactions of 2- and 4-vinylpyridines (where resonance would be expected to impose an electron deficiency on the terminal carbon atoms) with nucleophilic reagents, whereas 3-vinylpyridine failed to react under the same conditions.[3]

The reaction of I and II, surprisingly rapid at 1-7°, led to the isolation of a product (as a barium salt) considered to be the sulfate ester of 2-(*p*-nitrophenyl)-2-hydroxyethane-1-sulfonic acid (IV), *i. e.*, . Barium and nitrogen analyses were consistent with this structure. Since the barium sulfonate(s) gave a very weak reaction with permanganate, the presence of a small amount of barium 2-(*p*-nitrophenyl)-ethene-1-sulfonate (V), was considered. Another component was assumed to be barium 2-(*p*-nitrophenyl)-2-hydroxyethane-1-sulfonate (VI). The small amount of V was determined by titration using a standard bromate–bromide solution.[4] From the barium analyses of the mixed sulfonates the relative amounts of IV and VI were then calculated. On this basis, IV was calculated to be formed in 83–88% yields.

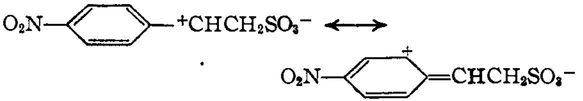
Product IV was converted to the following crystalline derivatives: the corresponding S-benzylthiuronium salt, 2-(*p*-nitrophenyl)-ethene-1-sulfonyl chloride (VII), and 2-(*p*-nitrophenyl)-ethene-1-sulfonamide (VIII). Both VII and VIII are described in the literature, having been prepared via the nitration of 2-phenylethene-1-sulfonyl chloride.[5] Further proof of the structure of VIII was obtained by reducing it to 2-(*p*-aminophenyl)-ethene-1-sulfonamide as described in the literature,[5] and then deaminating it by diazotization in the presence of hypophosphorus acid to 2-phenylethene-1-sulfonamide.[6]

Comparable results were obtained in the sulfonation of III. The sulfate ester of 2-(*m*-nitrophenyl)-2-hydroxyethane-1-sulfonic acid was formed in 69–71.5% yields. Analogous derivatives were prepared and the method of proving the structure was the same as above.

Because of the intermediate effect of a chlorophenyl group, between that of the phenyl and nitrophenyl groups, on the side-chain reactions of certain benzene derivatives,[7] the reaction of I with *m*-chlorostyrene was also investigated. In this case the principal product was 2-(*m*-chlorophenyl)-2-hydroxyethane-1-sulfonic acid. On the basis of analytical data, it was estimated that the corresponding sulfate ester was obtained (as the barium salt) in only 7–15% yields. A water-insoluble crystalline product was also obtained. This was considered to be a sultone analogous to that obtained by the sulfonation of styrene.[4] From the mixed barium sulfonates, 2-(*m*-chlorophenyl)-ethene-1-sulfonyl chloride and the corresponding sulfonamide were prepared.

Although the reaction of I with styrene has been investigated thoroughly,[4] we repeated the sulfonation in an effort to find some evidence for the formation of a sulfate bond. Our findings were essentially the same as described in the literature. The presence of the sulfate ester of 2-phenyl-2-hydroxy-1-ethanesulfonic acid was not detected by the methods used.

Discussion.—In the reaction of I with an α-olefin, the electrophilic agent always attacks the terminal olefinic carbon atom.[8] In the case of styrenes, resonance stabilization of the resulting intermediates would be expected, *e. g.*



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[3] Doering and Weil, THIS JOURNAL, **69**, 2461 (1947).

[4] Bordwell and Rondestvedt, *ibid.*, **70**, 2429 (1948).

[5] Bordwell, Colbert and Alan, *ibid.*, **68**, 1778 (1946).

[6] Bordwell, Suter, Holbert and Rondestvedt, *ibid.*, **68**, 139 (1946), and refs. cited therein.

[7] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 188.

[8] Bordwell, Suter and Webber, THIS JOURNAL, **67**, 827 (1945).