[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

A Total Synthesis of Estrone and 14-Isoestrone

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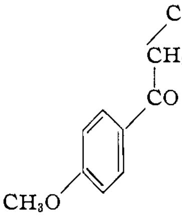
Dieckmann cyclization of the triester III ($R = CH_3$)—obtained by reduction and esterification of the Stobbe condensation product II of the keto ester I ($R = CH_3$)—afforded the keto diester V, which alternatively could be prepared by a combined Stobbe–Dieckmann condensation to give IX ($R = H$), followed by reduction of the olefinic bond. Methylation (preferably *in situ*) of the keto diester V gave a mixture of epimers VI and VII. The former, which was isolated readily by crystallization, on submission to the Reformatsky reaction was converted into a mixture of lactone X and hydroxy ester XI, readily convertible into the isomeric lactone XII. Both lactones were cleaved with base to the same unsaturated diester acid XIII which, on cyclization, was converted into the ketone XVII. Catalytic reduction effected hydrogenolysis of the carbonyl group and stereoselective hydrogenation of the olefinic bond to yield the known diester XIX. Partial saponification of XIX, followed by Arndt–Eistert homologation and ketonic ring closure of the dibasic acid afforded *dl*-estrone methyl ether. Hydrogenation of the unsaturated diester acid XIII proceeded stereoselectively to yield mainly the substance XIV (14-iso configuration). Cyclization to give XX, followed by hydrogenolysis, yielded the diester XXI ($R = CH_3$). Completion of ring D as described above gave 14-isoestrone by the steps: XXI ($R = CH_3$) → XXI ($R = H$) → XXII → XXIII ($R = CH_3$) → XXIII ($R = H$). This substance proved to be identical with Anner and Miescher's estrone-a. In attempts to improve the stereoselectivity of the estrone synthesis, the hydrogenation of the methylated unsaturated half-ester XXIV and of the dienol lactone XXVI was studied which, however, led to the 14-iso series. Some preliminary experiments on the hydroxylation of XXVI were carried out. One isomeric form of the glycol XXVIII was isolated but failed to undergo dehydration to XXIX in preliminary experiments.

The attractive objective of producing the estrone structure *via para*-substituted anisoles rather than from the less accessible *meta* derivatives has already received some attention,[3] and the present report concerns a continuation of our study which has culminated in a highly stereoselective approach to that (of eight possible racemates) isomer corresponding to the natural product.[4]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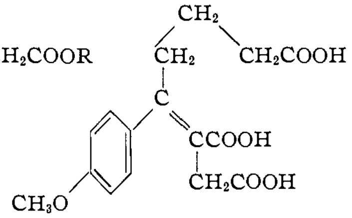
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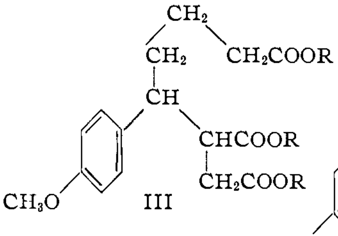
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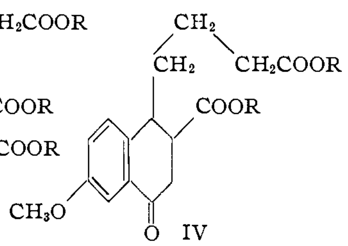
IV

In a previous report[3] we had shown that γ-anisoylbutyrate (I)—readily available *via* the Friedel–Crafts acylation of anisole with glutaric anhydride or (as described in the Experimental part of the present work) with the half-ester acid chloride of glutaric acid—undergoes the Stobbe condensation in high yield to give, after saponification, the unsaturated tricarboxylic acid II[5] which can be reduced to III ($R = H$) with nickel–aluminum alloy and sodium hydroxide. It had been demonstrated that acid-catalyzed cyclization of the saturated acid III ($R = H$) or of its derivatives gave, in addition to the expected α-tetralone derivative IV, an appreciable amount of the undesired isomeric ketone arising from five-ring cyclization. In an effort to circumvent this difficulty, we undertook a modification of the approach so as to reserve the cyclization to produce ring B until after ring C had been completed, thus precluding the five-ring cyclization. To this end we undertook a study of the Dieckmann cyclization of the triester III ($R = CH_3$).

Treatment of the triester III ($R = CH_3$) with sodium hydride in benzene effected cyclization to give the sodio derivative of the β-keto ester, V, which could be treated *in situ* with methyl iodide to yield a mixture of epimeric methylation products VI ($R = CH_3$) and VII ($R = CH_3$).[6] The natural stereoisomer, in which the aryl and methyl groups are on the same side of the cyclohexane ring (Ar/CH_3 *cis*) as shown in formula VI ($R = CH_3$), melted at 95° and crystallized directly from the mixture in 36% yield. An additional 7% of material was isolated as the half-ester VI ($R = H$), m.p. 183°, after selective saponification of the residues. Chromatography of the remaining noncrystalline material afforded the unnatural stereoisomer (Ar/CH_3 *trans*) VII ($R = H$), m.p. 142°, in 29% yield. That the 95° diester was indeed the natural stereoisomer VI ($R = CH_3$) was demonstrated by the subsequent reactions which led to estrone (see below). Before considering this phase of the synthesis, the results of further studies directed toward the improvement in the preparation of VI ($R = CH_3$) will be described.

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[1] Wisconsin Alumni Research Foundation Research Assistant, 1948–1950. Research Fellow on funds provided by E. I. du Pont de Nemours and Co., summers 1950 and 1951. Sterling–Winthrop Research Institute Fellow, 1951.

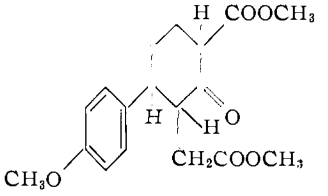
[2] Wisconsin Alumni Research Foundation Research Assistant, 1951–1953. Carbide and Carbon Chemical Corporation Fellow, 1953–1954.

[3] W. S. Johnson, A. R. Jones and W. P. Schneider, THIS JOURNAL, **72**, 2395 (1950).

[4] A preliminary account of a portion of this work has appeared: W. S. Johnson and R. G. Christiansen, *ibid.*, **73**, 5511 (1951).

[5] The location of the olefinic bond in this acid, m.p. 163°, has been confirmed in the present study by permanganate oxidation to give the keto acid I ($R = H$).

[6] The conditions were critical and with excess sodium hydride, a product of dimethylation was isolated. This substance, m.p. 67°, may correspond to formula VI ($R = CH_3$) or VII ($R = CH_3$) in which the methyne hydrogen alpha to the keto group is substituted by methyl.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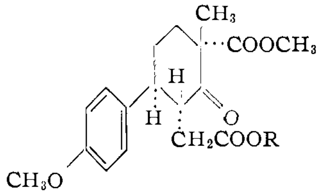
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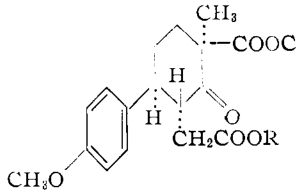
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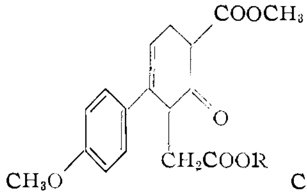
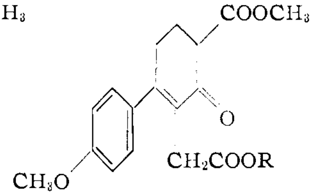
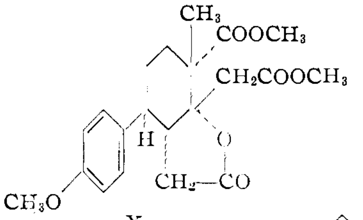

VIII

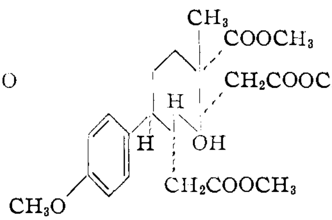

IX

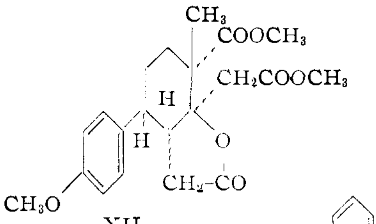
Turner[7] has reported a modified approach to the diester VI (R = CH_3). For the Stobbe condensation with I (R = CH_3), he employed a higher temperature than we had used[3] and in addition to the normal condensation product II, isolated a cyclized unsaturated half-ester, m.p. 168°, in low (15%) yield which he formulated as VIII (R = H). As is shown below, this 168° half-ester is undoubtedly the isomer IX (R = H). Turner also reported that catalytic hydrogenation of his 168° half-ester, followed by esterification and methylation, afforded the 95° diester VI (R = CH_3) in 36% yield. The combined Stobbe–Dieckmann condensation requires 2^+ mole-equivalents of base instead of the 1 employed by Turner. By modifying the procedure accordingly, we obtained the crystalline half-ester IX (R = H) in 49% yield after one week at room temperature in the presence of potassium *t*-butoxide or in 58% yield after 7 hr. at 40° in the presence of excess sodium hydride.[8] When the condensation was carried out with 4 mole-equivalents of potassium *t*-butoxide in refluxing *t*-butyl alcohol, the product of decarbomethoxylation (IX, R = H and with H in place of $COOCH_3$) was produced in 48% yield. The significant spectral properties of its methyl ester were the same as those of the half-ester IX (R = H), indicating an analogous disposition of the olefinic bond (see below).

Concerning the position of the olefinic bond in the 168° half-ester, the structure IX (R = H) is preferred to VIII (R = H), because the ultraviolet spectrum—λ_{max} 226 mμ (log ϵ 4.08), 292 (4.10)—is of the *p*-anisalacetone type appropriately modified (hypsochromic shift) by inclusion of the α,β-unsaturated ketone portion of the chromophore in a six-membered ring.[9] The infrared spectrum, moreover, exhibits strong absorption at 6.04 μ characteristic of an α,β-unsaturated ketone. The susceptibility of the olefinic bond to hydrogenation as compared with that of II may be due either to a lower steric interference in the cyclic form or to the possibility that IX (R = H) may undergo reduction by a different mechanism (*e.g.*, a 1,4-addition involving the enol form).

The Reformatsky reaction of the keto diester VI (R = CH_3) gave a mixture of a γ-lactone (λ_{max} 5.65 μ), m.p. 113°, and a hydroxy ester, m.p. 102°, separable in 29 and 28% yields, respectively, by crystallization. The hydroxy ester, on treatment with formic acid, was converted to an isomeric γ-lactone (λ_{max} 5.65 μ), m.p. 137°. The hydroxy ester precursor of the 113° lactone was not found, which indicates a facile lactonization during the Reformatsky reaction, a fact consistent with the formulation of a *cis*-fused lactone ring, formula X.[10] The hydroxy ester is formulated accordingly as XI and the 137° lactone derived therefrom as XII with the *trans*-fused lactone ring.


X


XI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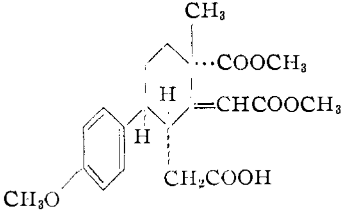
XIII

On treatment with one mole-equivalent of methanolic sodium hydroxide, the 113° γ-lactone X was transformed readily by a β-elimination into the unsaturated acid diester XIII.[11] A single geometric isomer, m.p. 122°, was isolated in 77% yield.[12,13] This same acid was produced, although

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[7] D. L. Turner, This Journal, **73**, 1284 (1951).

[8] *Cf.* G. H. Daub and W. S. Johnson, *ibid.*, **70**, 418 (1948).

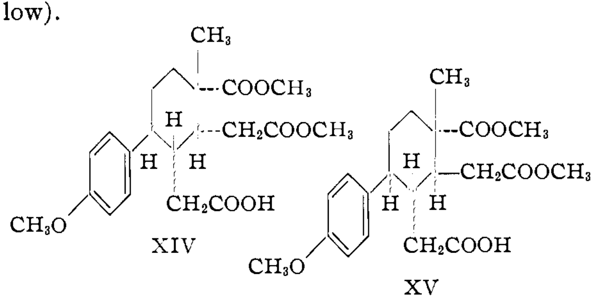
[9] *Cf.* the similar system of H. J. E. Loewenthal, *J. Chem. Soc.*, 3962 (1953): λ_{max} 233 mμ (log ϵ 4.2), 287 (3.9).

[10] *Cf.* the facile formation of a *cis*-fused γ-lactone as compared with the *trans*-fused system, M. S. Newman and C. A. VanderWerf, This Journal, **67**, 233 (1945). See also J. H. Brewster and C. H. Kucera, *ibid.*, **77**, 4564 (1955), regarding the stability of these rings toward cleavage.

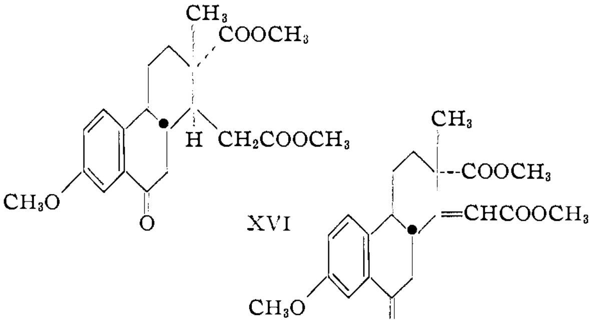
[11] For similar types of cleavage of lactones by hydroxide, see for example W. E. Bachmann and G. D. Johnson, *ibid.*, **71**, 3463 (1949), and B. Belleau, *ibid.*, **73**, 5149 (1951).

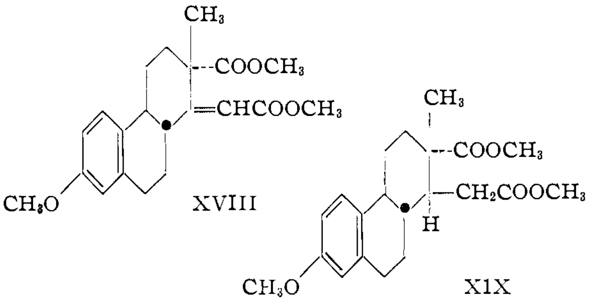
[12] The stereoselectivity of this type of reaction has been well demonstrated; *cf.*, for example, the conversion of the lactone $OCOCH_2CH_2CHCH_2CO_2CH_3$ to methyl hydrogen *trans*-Δ^{α}-dihydromuconate, J. A. Elvidge, R. P. Linstead, B. A. Orkin, P. Sims, H. Baer and D. B. Pattison, *J. Chem. Soc.*, 2228 (1950). For other

in lower (40%) yield, by the action of hydroxide on the 137° lactone XII. In this case a hydroxy acid, m.p. 182°, was also isolated, evidently formed by a competing hydrolysis reaction.[13] The behavior toward hydroxide is also consistent with the postulated configurations of the two lactones, since the *trans*-fused isomer would be expected to be more susceptible than the *cis*- to hydrolysis.[10] For preparative purposes the crude mixture from the Reformatsky reaction could be treated directly with formic acid (to lactonize XI), then with methanolic sodium hydroxide to give the unsaturated acid XIII in 39% over-all yield.[13] The exocyclic position of the olefinic bond as shown in formula XIII is preferred, since this substance is the precursor of and is spectrographically similar to the tricyclic unsaturated ester XVIII (see below).


XIV XV

Catalytic hydrogenation of the unsaturated acid diester XIII over 30% palladium-on-strontium carbonate proceeded stereoselectively to give in 79% yield a dihydro compound, m.p. 174°, which as shown below belongs to the unnatural (14-iso by steroid numbering) stereochemical series and therefore corresponds to formula XIV. From the mother liquors the epimeric substance XV, m.p. 126°, was isolated in 5% yield. Cyclization of this latter isomer through the acid chloride[14] afforded in 77% yield a keto diester XVI, m.p. 104°, which on hydrogenolytic reduction[15] was transformed (93% yield) into a diester, m.p. 99°, that proved (see below) to be the known[16] isomer XIX of natural configuration.


XVI XVII


XVIII XIX

In view of the unfavorable stereochemical course of the hydrogenation of the unsaturated acid XIII which gave mainly the unnatural series (XIV), we undertook a study of cyclization (to form ring B) prior to reduction of the olefinic bond. Ring closure[14] of XIII proceeded in 88% yield to give the unsaturated keto diester XVII, m.p. 148°. Hydrogenolytic reduction[15] of the carbonyl group could be effected without attacking the olefinic bond to produce the unsaturated diester XVIII, m.p. 112–112.2°, in 76% yield.[17] Anner and Miescher[16] have described an unsaturated diester of this structure, m.p. 113–115°, and we presumed that the products were identical,[4] since they both gave the same diester XIX on hydrogenation. One subtle difference in behavior was noted, namely, our 112° ester underwent hydrogenation in ethyl acetate solution over 30% palladium-on-strontium carbonate at room temperature and atmospheric pressure to give an 84% yield of the stereoisomer XIX, m.p. 98°, having the natural configuration. Some of the epimer (14-iso series) may have been formed but was not easily isolated. The 115° ester of Anner and Miescher,[16] in contrast, appeared to be more resistant to hydrogenation, since they employed more vigorous conditions (60° and acetic acid solvent.)[18] In addition to the preponderant product XIX, they isolated an isomer, m.p. 75–77°, but no yields were reported. Since our preliminary publication,[4] we have had the opportunity to make a direct comparison of the two unsaturated diesters.[19] The m.p. of a mixture showed a marked depression and the infrared spectra were clearly different. Ultraviolet and infrared spectroscopy, however, showed clearly (see below) that the olefinic bond was conjugated with the carbomethoxy group (exocyclic); hence the

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examples see J. A. Elvidge, R. P. Linstead and P. Sims, *ibid.*, 3386 (1951); R. P. Linstead, L. N. Owens and R. F. Webb, *ibid.*, 1225 (1953), and related papers.

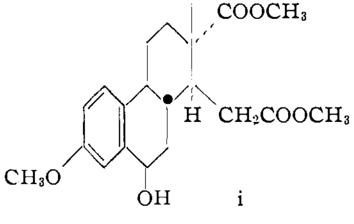
[13] The yield of unsaturated acid undoubtedly could be improved by the choice of a more appropriate reagent, *e.g.*, alkoxide to minimize competing hydrolysis reactions (*cf.* ref. 12).

[14] The inverse Friedel–Crafts technique was employed, W. S. Johnson and H. J. Glenn, THIS JOURNAL, **71**, 1092 (1949).

[15] Over palladium catalyst in the presence of a trace of perchloric acid—the method of K. Kindler as described by K. W. Rosenmund and E. Karg, *Ber.*, **75**, 1850 (1942).

[16] G. Anner and K. Miescher, *Helv. Chim. Acta*, **31**, 2173 (1948).

[17] When the unsaturated keto diester XVII was hydrogenated over 30% palladium-on-strontium carbonate, two mole-equivalents of hydrogen was absorbed and the saturated hydroxy diester (i) was isolated. This substance was transformed into the keto diester XVI by Oppenauer oxidation.


i

[18] G. Anner and K. Miescher, *Helv. Chim. Acta*, **32**, 1957 (1949).

[19] We wish to thank Drs. Anner and Miescher for sending us a specimen of their substance.

two substances must be geometric isomers.[20] The ultraviolet spectrum of our unsaturated diester (curve 1, Fig. 1) and of Anner and Miescher corresponded closely to the superposition of the absorption of an authentic α,β-unsaturated ester of the same type (curve 4)[21] as that of the substituted anisole system (curve 2). The intense absorption in the short wave length region is characteristic of the α,β-unsaturated ester system.[22] If the olefinic bond were in the endocyclic (1,10a) position, the spectrum would resemble that of the saturated ester (curve 2) with a pronounced minimum in the 247 mμ region. If the bond were between rings B and C in conjugation with the aromatic nucleus, the spectrum would be expected to have a single strong band at about 275 mμ (ε 16,000–18,000).[23] Further evidence for the exocyclic position of the olefinic bond was provided by the infrared spectrum which exhibited a relatively intense band in the 6.10 μ region, characteristic of the stretching vibration of a *conjugated* olefinic bond.

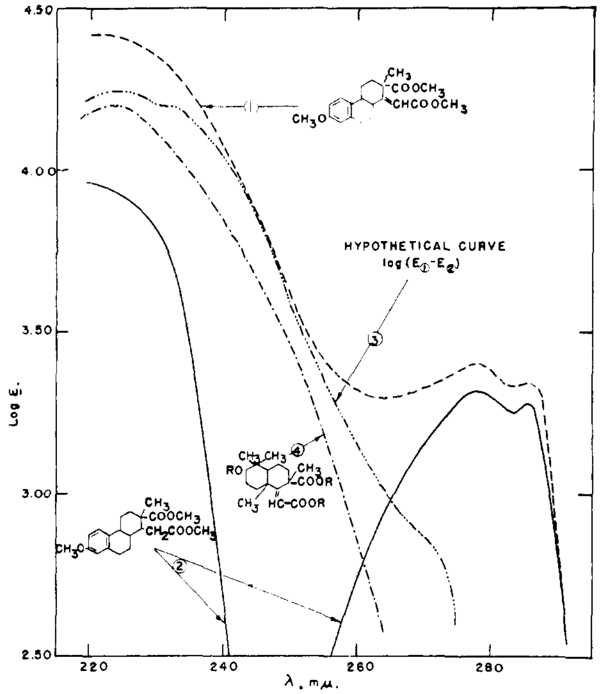
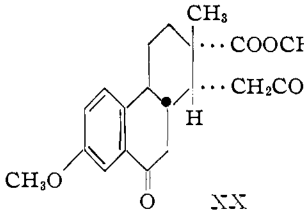


Fig. 1.

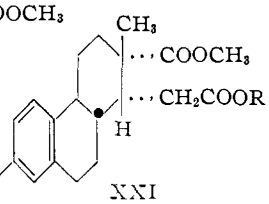
For the preparation of estrone from the unsaturated diester XVII, obviously the two reduction steps can be combined to produce XIX. To demonstrate the identity of our 98° saturated ester with that (XIX) of Anner and Miescher, m.p. 96°, it was converted as already described,[16] to the half-ester, m.p. 175° (reported[16] 173°). Application of the Arndt–Eistert sequence, followed by saponification, afforded *dl*-homomarrianolic acid methyl ether, m.p. 226°, undepressed on admixture with an authentic specimen from an independent synthesis.[24] Cyclization afforded *dl*-estrone methyl ether, m.p. 144°, undepressed on admixture with authentic material.[24]

A highly stereoselective approach to estrone is defined by the foregoing. Our method of producing the saturated diester XIX coupled with the elegant scheme of Sheehan, Coderre and Cruickshank[25] for converting this substance into estrone or estradiol constitutes the most practical totally synthetic pathway to these hormones known to date.

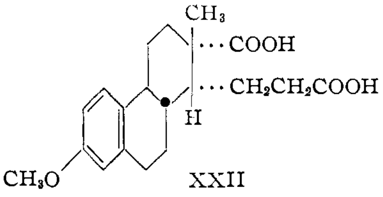
14-Isoestrone.—The major product XIV, produced stereoselectively on hydrogenation of the unsaturated diester XIII (see below), was cyclized[14] in 94% yield to the keto diester XX, m.p. 154°, which on hydrogenolysis[15] was transformed in 84% yield into the diester XXI (R = CH_3), m.p. 89.5–90° (*cf.* the Anner and Miescher product, m.p. 75–77°[26]). Selective saponification afforded in 73% yield the half-ester XXI (R = H), m.p. 167–167.8° (*cf.* the Anner and Miescher product, m.p. 154–155°),[26] which was submitted to the Arndt–Eistert reaction to give, after saponification, the homo diacid XXII, m.p. 233.5–234.5° (*cf.* the Anner and Miescher product, m.p. 225–227°[26]). Cyclization by pyrolysis with lead carbonate[16] afforded in 79% yield *dl*-14-isoestrone methyl ether (XXIII, R = CH_3), m.p. 120.6–121° (*cf.* the



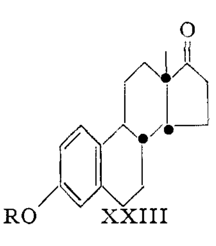
XX



XXI



XXII



XXIII

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[20] If the lactone opening step (X or XII → XIII) proceeded by the same stereochemical path as had been demonstrated for simpler cases (ref. 12), then our substance corresponds to that isomer in which the carbomethoxy group attached to the trigonal carbon atom is oriented toward the carbon (C_2) holding the methyl group. The isomer of Anner and Miescher would accordingly have the alternative configuration. Until further evidence is available, the configurations may be thus assigned tentatively.

[21] R. Ruegg, J. Dreiding, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **33**, 889 (1950).

[22] Cf. J. L. H. Allen, E. R. H. Jones and M. C. Whiting, *J. Chem. Soc.*, 1862 (1955).

[23] For spectra of model compounds having the *p*-methoxystyrene chromophore, see D. Banes and J. Carol, *J. Biol. Chem.*, **204**, 509 (1953); J. Heer and K. Miescher, *Helv. Chim. Acta*, **31**, 219, 1289 (1948).

[24] W. S. Johnson, D. K. Banerjee, W. P. Schneider, C. D. Gutsche' W. E. Shelberg and L. J. Chinn, THIS JOURNAL, **74**, 2832 (1952).

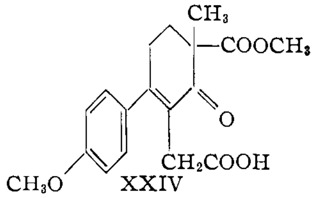
[25] J. C. Sheehan, R. A. Coderre and L. A. Cruickshank, *ibid.*, **75**, 6231 (1953); J. C. Sheehan, W. F. Erman and P. A. Cruickshank, *ibid.*, **79**, 147 (1957).

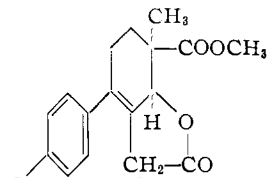
[26] This m.p. was reported by Anner and Miescher (ref. 18) for an intermediate that led to an estrone isomer apparently identical with our 14-isoestrone (see below). The discrepancy in the melting points may be due to polymorphism or to the possibility that their material was contaminated with some of the natural epimer.

Anner and Miescher product, m.p. 114–116°[26]). Demethylation with pyridine hydrochloride gave in 89% yield *dl*-14-isoestrone (XXIII, R = H), m.p. 216–217° (reported[18] 214–216°). Specimens of this material and the methyl ether were compared with the corresponding products of Anner and Miescher. Dr. Anner, who kindly performed the experiment, reported that there was no melting point depression on admixture. The proof that our material is in fact *dl*-14-isoestrone is the subject of another communication.[27]

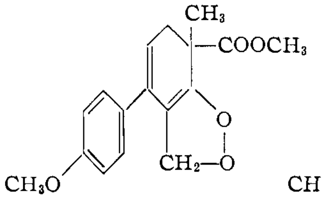
On the basis of the close agreement of the melting points of the free hydroxy compound and its benzoate, Anner and Miescher[18] proposed tentatively that their estrone isomer, m.p. 214–216°, was identical with the "estrone a" of Bachmann, Kushner and Stevenson.[28] All efforts by Anner and Miescher or by us to obtain specimens of authentic Bachmann material for comparison with our products have failed. In view of the discrepancy in melting points of our (120.6–121°) and Bachmann's (101.5–102.5°) methyl ethers and considering the fact that in other work yet to be reported[29] we have discovered another estrone isomer, the properties of which are in closer agreement with those of "estrone a," we are inclined to feel that the latter isomer is not *dl*-14-isoestrone. This matter will receive further attention.

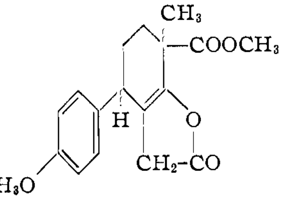
Attempts to Improve the Stereoselectivity of the Synthesis.—The synthetic scheme delineated above is stereoselective except for the step involving the methylation of the keto ester V which gave both epimers VI and VII. Some further studies aimed at improvement at this stage were undertaken and, although the objective was not realized in the present investigation, some interesting behaviors were noted which are recorded herewith.


XXIV


XXV

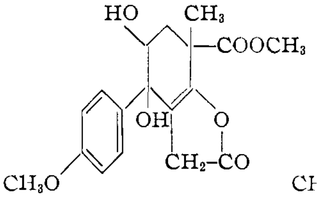
With the view to changing the order of introduction of the asymmetric centers, the keto half-ester IX (R = H) was converted to the tetrahydropyranyl ester IX (R = tetrahydropyranyl),[30] then methylated with sodium hydride and methyl iodide. After acid-catalyzed cleavage of the blocking group,[30] the methylated keto half-ester XXIV, m.p. 130°, was obtained in 73% over-all yield. Hydrogenation of this substance over 10% palladium-on-carbon ceased after the absorption of one mole-equivalent of hydrogen and yielded a mixture from which a γ-lactone (λ_{max} 5.60 μ), m.p. 110°, was isolated in 49% yield. Since this substance exhibited absorption at 256 mμ typical of the *p*-methoxystyrene chromophore, it may be formulated as the unsaturated lactonic ester XXV. The stereochemical configuration shown in formula XXV is tentatively suggested, because the hydrogenation appears to involve preferential attack of the molecule on the side of the molecule carrying the methyl group (see below). Also isolated (in 27% yield) was the 142° keto half-ester VII (R = H) of unnatural configuration. None of the desired product was found. Esterification of XXIV with diazomethane followed by hydrogenation over 10% palladium-on-carbon in the presence of a trace of potassium hydroxide gave, after selective saponification, an 85% over-all yield of this same half-ester VII (R = H).

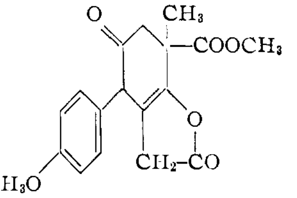

XXVI


XXVII

Treatment of the unsaturated keto half-ester XXIV with acetyl chloride and acetic anhydride afforded the dienol-lactone XXVI, m.p. 134°, in 69% yield. On selective hydrogenation over 10% palladium-on-carbon this substance was transformed in 94% yield into an enol-lactone, m.p. 128°, which was different from the enol-lactone, m.p. 117°, obtained from the half-ester VI (R = H). That the 128° compound was, indeed, the epimeric enol-lactone XXVII, was confirmed by alkaline hydrolysis to the 142° half-ester VII (R = H).

Preliminary attempts to reduce the methylated half-ester XXIV with alkali metals in ammonia under conditions for selective attack of a conjugated olefinic linkage[31] were unpromising. Although the olefinic bond was thus reduced, it was not possible, under the conditions examined, to prevent carbonyl reduction.


XXVIII


XXIX

A preliminary study was initiated with the view to introducing a carbonyl group at the position corresponding to C_{11} (steroid numbering), to produce an intermediate like XXIX which, by virtue of the stereochemically labile carbon holding the aryl group, would undoubtedly assume the natural configuration. A compound like XXIX, moreover, would serve as a potentially useful intermediate for the production of 11-oxygenated-19-norsteroids. Performic acid hydroxylation of the dienol-lactone XXVI yielded, after hydrolysis of the formate esters, two glycols (presumably stereoisomers repre-

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[27] W. S. Johnson and W. F. Johns, THIS JOURNAL, **79**, 2005 (1957).

[28] W. E. Bachmann, S. Kushner and A. C. Stevenson, *ibid.*, **64**, 974 (1942).

[29] W. S. Johnson and I. David.

[30] The method of R. E. Bowman and W. D. Fordham, *J. Chem. Soc.*, 3945 (1952).

[31] F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **75**, 1282 (1953).

sented by the structure XXVIII), m.p. 173° and 150°. Preliminary attempts to rearrange the former (preponderant) glycol to XXIX under acidic conditions failed. It is expected that further study will lead to successful conversion of XXVIII to XXIX.

Acknowledgment.—We are indebted to the agencies mentioned in refs. 1 and 2 for providing generous assistance to this program.

Experimental[32]

Methyl γ-Anisoylbutyrate (I, R = CH_3).—The acylation was carried out by the procedure of Papa, Schwenk and Hankin.[33] To a stirred solution (at 0° or below) of 196 g. of anisole in 653 ml. of anhydrous *sym*-tetrachloroethane there was added slowly 425.6 g. of anhydrous granular aluminum chloride, followed by the dropwise addition at 0° of 231.2 g. of γ-carbomethoxybutyryl chloride, b.p. 88–89° (7 mm.). After the addition was complete, the mixture was stirred at 0° for 3.5 hr., then allowed to come to room temperature slowly overnight. The mixture was treated with excess hydrochloric acid and ice, then steam distilled to remove the solvent and excess anisole. The oily residue was extracted with ether and the ether solution washed with water, followed by saturated brine, then dried over anhydrous sodium sulfate. The crude residue obtained on evaporation of the solvent consisted mainly of methyl γ-anisoylbutyrate and some of the acid. This mixture was esterified with a mixture of 153.6 g. of methanol, 4.8 ml. of concentrated sulfuric acid and 480 ml. of ethylene dichloride according to the method of Clinton and Laskowski.[34] The mixture was refluxed overnight, then washed with water, saturated sodium bicarbonate solution, again with water and dried over anhydrous sodium sulfate. The residue obtained on evaporation of the solvent was crystallized from ether–petroleum ether (60–68°) to give 286.4 g. (77% yield) of colorless plates, m.p. 52–54° (reported[7] 49–51°).

Oxidation of 5-*p*-Anisyl-6,7-dicarboxy-5-heptenoic Acid (II).—The following procedure is an adaptation of that of Stobbe.[35] A solution of 2 g. of potassium permanganate in 100 ml. of water was added slowly with stirring to a solution of 2 g. of the tricarboxylic acid,[3] m.p. 160–161°, in 100 ml. of water containing 2 g. of potassium carbonate. The temperature of the mixture was maintained at 5° during the addition and for an additional 2 hr. stirring period thereafter. The mixture was then allowed to come to room temperature, excess sodium bisulfite added, followed by sulfuric acid and a total of 1.15 g. of colorless crystalline material separated, m.p. 138–140°, undepressed on admixture with an authentic specimen of γ-anisoylbutyric acid.

Methyl 5-*p*-Anisyl-6,7-dicarbomethoxyheptanoate (III, R = CH_3).—The following procedure is an adaptation of the method of Clinton and Laskowski.[34] A mixture of 54.0 g. of the triacid III (R = H),[3] m.p. 151–153°, 48 g. of methanol, 150 ml. of ethylene dichloride and 4 ml. of concentrated sulfuric acid was boiled under reflux for 81 hr. The organic layer was separated, 200 ml. of ether added (to minimize emulsion formation) and the mixture washed thoroughly with 10% sodium carbonate solution, followed by saturated brine, then dried over anhydrous magnesium sulfate. The oily residue obtained on evaporation of the solvent was distilled through a Claisen head, b.p. 196–206° (0.35 mm.), reported[7] 195–207° (2 mm.). The yield of colorless viscous distillate was 55.5 g. (91%), $n^{25}\text{D}$ 1.5040.

The respective yields for reaction periods of 20, 44 and 65 hr. were 54, 63 and 85%. By re-esterification of the acidic fractions the triester was obtained in 97% yield.

A sample of the triester prepared by the action of diazomethane was twice distilled, b.p. 208–212° (0.8 mm.), $n^{25}\text{D}$ 1.5022.

Anal. Calcd. for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15. Found: C, 62.3; H, 7.23.

Dieckmann Cyclization and Methylation of Methyl 5-*p*-Anisyl-6,7-dicarbomethoxyheptanoate (III, R = CH_3).—The following reaction was carried out under strictly anhydrous conditions in an apparatus attached to a constant-pressure eudiometer. To a refluxing suspension of 11.62 g. of sodium hydride in 400 ml. of dry benzene (atmosphere of nitrogen) was added (from a pressure-equalized dropping funnel) a solution of 79.8 g. of the triester in 100 ml. of dry benzene containing 2 ml. of methanol. The mixture was stirred continuously during the addition period (about 1 hr.). The commencement of the reaction, as evidenced by the brisk and continual evolution of hydrogen, was capricious but was generally observed at least by the end of the addition period. After about 90% of the calculated volume of gas was evolved (usually about 3–4 hr.) the reaction was proceeding very slowly and was interrupted. The mixture was cooled in an ice-bath (dry nitrogen being admitted), 5 ml. of anhydrous methanol was introduced to react with residual sodium hydride and 85 ml. of methyl iodide was added. After stirring for 30 minutes in the cold, the mixture, with suspended sodium iodide, was allowed to stand overnight at room temperature; then an additional 35 ml. of methyl iodide was introduced and the mixture heated under reflux for 2 hr. with stirring. The excess methyl iodide was removed by distilling off about 200 ml. of solvent; then the mixture was cooled and acidified with 30 ml. of acetic acid. Water was added and the aqueous layer extracted with ether. The combined organic layers were washed thoroughly with 10% sodium carbonate solution, then with saturated brine and dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the solvent was dissolved in 60 ml. of ether, seed crystals (from another run) added and the mixture placed in the refrigerator overnight. Colorless prisms, m.p. 94–95°, amounting to 27.3 g. (36% yield) separated. Repeated recrystallization from petroleum ether (60–68°) or methanol gave a pure specimen of **methyl 6β-*p*-anisyl-3-α-carbomethoxy-2-keto-3β-methylcyclohexane-1α-acetate** (VI, R = CH_3),[36] m.p. 95–95.5°, undepressed on admixture with a sample of the material prepared by Dr. Turner.[7]

Anal. Calcd. for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.7; H, 7.00.

The oily residue (38.0 g.) obtained on evaporation of the mother liquors was dissolved in 400 ml. of methanol and treated with 124 ml. of 0.969 *N* sodium hydroxide solution. After 1 week at room temperature, the solvent was removed by distillation at reduced pressure, water was added and the mixture extracted with ether to remove neutral material. The aqueous solution was acidified, extracted with ether, then the ether solution was washed with saturated brine and dried over anhydrous magnesium sulfate. The ether solution was concentrated to 100 ml., then seeded with pure half-ester VI (R = H) described below. After 3 days in the refrigerator the solution deposited 5.34 g. of this half-ester, m.p. 178–180°.

The Ar/CH_3 *trans*-half-ester VII (R = H) was isolated from the oily residue obtained on evaporation of the mother liquors from the crystallization of VI (R = H). A 0.300-g. sample of this oily residue was chromatographed on 18 g. of Florex (Floridin Co.). The fractions eluted with 1–2% ethanol in ether amounted to 0.150 g. of crystalline material, m.p. 138–139°. Two recrystallizations from benzene–petroleum ether (60–68°) gave pure **6β-*p*-anisyl-3β-carbomethoxy-2-keto-3α-methylcyclohexane-1α-acetic acid** (VII, R = H), as colorless prisms, m.p. 141–142°; $\lambda_{\max}^{95\%\ \text{EtOH}}$ 226 mμ (log ε 4.00), 277 (3.26), 283 (3.19).

Anal. Calcd. for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63. Found: C, 64.8; H, 6.82.

6β-*p*-Anisyl-3α-carbomethoxy-2-keto-3β-methylcyclohexane-1α-acetic Acid (VI, R = H).—A solution of 0.500 g. of the diester VI (R = CH_3), m.p. 94–95°, in 20 ml. of methanol and 1.50 ml. of 1 *N* sodium hydroxide solution was allowed to stand at room temperature for one week. The total crude acidic fraction, isolated as described in the selective saponification reaction described above, amounted to 0.425 g. of colorless solid, m.p. 157–165°. Three recrystallizations from methanol gave colorless prisms, m.p. 181–183°.

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[32] Melting points are corrected for stem exposure. The asymmetric products reported herein are all racemic substances, but the prefix "*dl*" has generally been omitted.

[33] D. Papa, E. Schwenk and H. Hankin, THIS JOURNAL, **69**, 3018 (1947).

[34] R. O. Clinton and S. Laskowski, *ibid.*, **70,** 3135 (1948).

[35] H. Stobbe, *Ann.*, **308, 114** (1899).

[36] To designate stereochemistry, the methyl group is arbitrarily labeled "β" (as in steroid nomenclature) and all groups on the same side of the cyclohexane ring are accordingly assigned the β-configuration while those on the opposite side are designed "α."

Anal. Calcd. for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63. Found: C, 64.95; H, 6.69.

The enol lactone was prepared from 1.00 g. of the half-ester, m.p. 180–182°, 12.5 ml. of acetic anhydride and 5 ml. of acetyl chloride. The mixture was boiled under reflux for 48 hr.; the solvent was removed under reduced pressure. The residue was taken up in ether, washed successively with dilute sodium carbonate solution, water and saturated brine and finally dried over anhydrous magnesium sulfate. The residue obtained upon evaporation of the solvent was triturated with a little methanol giving 0.587 g. (62% yield) of colorless prisms, m.p. 117–117.4°. Recrystallization from methanol did not raise the m.p.

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.3; H, 6.41.

Isolation of the **Dimethylated Product after Dieckmann Cyclization.**[6]—A solution of 77.6 g. of the triester III (R = CH_3) in 150 ml. of benzene containing 5 ml. of methanol was added with stirring over a 30-minute period to a refluxing suspension of 20.4 g. of sodium hydride in 400 ml. of benzene, as described above. After 4 hr. at refluxing temperature 90% of the gas was evolved and the reaction was proceeding very slowly. Glacial acetic acid (60 ml.) was added; then, after gas evolution ceased, the mixture was diluted with water and the aqueous layer extracted with benzene. The combined organic layers were washed thoroughly with 10% sodium carbonate solution, then with water and saturated brine and finally dried over anhydrous magnesium sulfate. This solution contained the cyclization product which gave a mauve color with 1% alcoholic ferric chloride. It was not obtained crystalline, nor could it be distilled without excessive decomposition.

The benzene solution of the cyclized ester was concentrated to a volume of about 200 ml. and added slowly to a stirred and cooled suspension of 7.64 g. of sodium hydride in 200 ml. of benzene. After the addition was complete and gas evolution had subsided, 132 ml. of methyl iodide was added to the cooled mixture which was then allowed to stand at room temperature for 48 hr. The mixture was stirred and refluxed for 6 hr., about 150 ml. of solvent removed by distillation, the mixture cooled and 30 ml. of acetic acid added. The crude product, isolated as described above, was distilled at reduced pressure giving 47.5 g. of a viscous yellow oil, b.p. 200–210° (0.5 mm.). This oil was crystallized from ether at −70° to give 15.0 g. of colorless solid, m.p. 62–65°. Repeated recrystallization from petroleum ether (60–68°) gave colorless prisms, m.p. 66.8–67.6°.

Anal. Calcd. for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.6, 66.6; H, 7.48, 7.48.

The half-ester was prepared by selective saponification of 1.355 g. of the pure diester in 40 ml. of methanol with 4.1 ml. of 0.969 *N* sodium hydroxide for 23 days at room temperature. The crude acidic material, isolated as in the selective saponification described above, was crystallized from benzene–petroleum ether (60–68°) giving 0.657 g. of colorless prisms, m.p. 138–139°. Repeated recrystallization raised the m.p. to 140–140.8°.

Anal. Calcd. for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94; neut. equiv., 348. Found: C, 65.8; H, 7.10; neut. equiv., 347.

6-*p*-Anisyl-3-carbomethoxy-2-ketocyclohex-6-ene-1-acetic Acid (IX, R = H). (a) **Sodium Hydride Method.**—This reaction was carried out under strictly anhydrous conditions. A solution of 20 g. of methyl γ-anisoylbutyrate, m.p. 52–54°, and 37.2 g. of dimethyl succinate in 100 ml. of anhydrous benzene containing 2 drops of absolute methanol was added all at once to a stirred suspension of 10.56 g. of sodium hydride in 100 ml. of benzene maintained at 40°. The evolution of hydrogen which ensued had stopped after 7 hr. of stirring at 40°. A solution of 25 ml. of acetic acid in 25 ml. of benzene was added to decompose residual sodium hydride; then the benzene solution was extracted thoroughly with 1 *N* ammonium hydroxide. Acidification of the combined alkaline solutions yielded 24 g. of a tan precipitate which on crystallization from ethyl acetate gave a total of 15.8 g. (58% yield) in three crops of the keto half-ester, m.p. 163–165° (reported[7] 163–165°).

A similar run at 48° for 4.5 hr. gave material, m.p. 163–165°, in 52% yield. The starting keto ester was recovered from the neutral benzene layer in 25% yield.

A sample prepared for analysis by three recrystallizations from ethyl acetate was obtained as colorless prisms, m.p. 168–168.6°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 226 mμ (log ε 4.05), 292 (4.10); $\lambda_{\min}$ 256 (3.67); $\lambda_{\max}^{\mathrm{KBr}}$ 6.04 μ (α,β-unsaturated C=O).

Anal. Calcd. for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 64.2; H, 5.81.

(b) **Potassium *t*-Butoxide Method.**—To a solution of 2.17 g. of potassium in 51 ml. of dry *t*-butyl alcohol (nitrogen atmosphere),[37] 11.68 g. of dimethyl succinate was added with stirring at room temperature. After the mixture became homogeneous, 10 g. of methyl γ-anisoylbutyrate, m.p. 52–54°, was added with 10 ml. of dry *t*-butyl alcohol. The mixture was stirred for 20 minutes and then allowed to stand overnight at room temperature. A solution of 6.24 g. of potassium in 150 ml. of dry *t*-butyl alcohol was added with stirring and the mixture allowed to stand at room temperature (nitrogen atmosphere) for 7 days. The yellow solid which had precipitated during this period was separated by filtration and dissolved in 600 ml. of ice-cold water. On acidification of the resulting red solution an oil separated. On standing this oil solidified in the form of yellow crystals amounting to 9.15 g. Crystallization from ethyl acetate gave a total of 6.66 g. (49% yield) of colorless prisms, m.p. 160–163°.

When 35.4 g. of methyl γ-anisoylbutyrate was condensed with 42.4 g. of dimethyl succinate in a refluxing solution of 18 g. of potassium in *t*-butyl alcohol, none of the keto half-ester IX (R = H) was obtained. Instead 18.6 g. (48% yield) of the keto acid IX (R = H, H in place of CO-OCH_3), m.p. 118–121°, was isolated. Repeated recrystallization of a specimen of this material raised the m.p. to 135–137° (reported[7] 137–138.5°). A sample of the methyl ester was prepared with diazomethane. After three recrystallizations from ethyl acetate–petroleum ether (60–68°), it melted at 93–93.5° (reported[7] 91°); $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 226 mμ (log ε 4.11), 289 (4.10); $\lambda_{\min}$ 254 (3.64); $\lambda_{\max}^{\mathrm{Nujol}}$ 5.80 μ (ester C=O), 6.05 (α,β-unsaturated C=O).

The Reformatsky Reaction with VI (R = CH_3).—A mixture of 250 ml. each of dry benzene and dry ether, 13.00 g. of the keto diester, m.p. 95–95.5°, 0.3 g. of iodine, 12 g. of freshly cleaned (with sandpaper) and cut zinc foil and 6 ml. of methyl bromoacetate was heated (bath at 70°) with vigorous stirring (Hershberg wire stirrer) in a dry atmosphere of nitrogen. Within 5 minutes the color of the iodine had disappeared and the solution became cloudy. After 30 minutes a colorless addition product had precipitated. Five 6-g. portions of zinc foil were added at 1 hr. intervals and two 3-ml. portions of methyl bromoacetate at 2 hr. intervals. After a total reaction time of 6 hr., the mixture was cooled in an ice-bath and acetic acid was added to dissolve the crystalline complex. The solution was separated from the zinc, diluted with water and the aqueous layer extracted with ether. The combined organic layers were washed with water, then thoroughly with dilute ammonium hydroxide (until the aqueous layer was colorless) and finally with saturated brine. The solution was dried over anhydrous magnesium sulfate, the solvent evaporated, and the yellow oily residue fractionally crystallized from ether to give a total of 4.29 g. of prisms, m.p. 112.5–113°, and 4.40 g. of needles, m.p. 100–102°. The former compound was the lactone of **6β-*p*-anisyl-3α-carbomethoxy-2β-carbomethoxymethyl-2α-hydroxy-3β-methylcyclohexane-1α-acetic acid (X)** and was obtained from 90–100° petroleum ether as colorless prisms, m.p. 112.5–113°; $\lambda_{\max}^{\mathrm{KBr}}$ 5.65 μ (γ-lactone C=O), 5.82 (ester C=O).

Anal. Calcd. for $C_{21}H_{26}O_7$: C, 64.60; H, 6.71. Found: C, 64.7; H, 6.75.

The lower melting compound was **methyl 6β-*p*-anisyl-3α-carbomethoxy-2α-carbomethoxymethyl-2β-hydroxy-3β-methylcyclohexane-1α-acetate (XI)** and was obtained from 60–68° petroleum ether as colorless needles, m.p. 101.2–101.9°; $\lambda_{\max}^{\mathrm{KBr}}$ 2.9 μ (OH), 5.82 (ester C=O).

Anal. Calcd. for $C_{22}H_{30}O_8$: C, 62.54; H, 7.16. Found: C, 62.6; H, 7.27.

Lactone of 6β-*p*-Anisyl-3α-carbomethoxy-2α-carbomethoxymethyl-2β-hydroxy-3β-methylcyclohexane-1α-acetic Acid (XII).—A solution of 3.49 g. of the hydroxy ester XI, m.p. 101–101.5°, in 10 ml. of 98–100% formic acid was heated for 4 hr. on the steam-bath; then the solvent was removed by distillation under reduced pressure. The residue, on tri-

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[37] *Cf.* technique described in *Org. Syntheses*, **30**, 18 (1950).

turation with 25 ml. of ether, afforded 3.05 g. (94% yield) of fine needles, m.p. 136–136.5°.

A sample of the same material (mixed m.p. determination) isolated directly from a Reformatsky reaction in which the crude product had been distilled at 0.2 mm. was repeatedly recrystallized from 90–100° petroleum ether, to give colorless needles, m.p. 136.5–137°; $\lambda_{\max}^{\text{KBr}}$ 5.65 μ (γ-lactone C=O), 5.81 (ester C=O).

Anal. Calcd. for $C_{21}H_{26}O_7$: C, 64.60; H, 6.71. Found: C, 64.7; H, 6.80.

Methyl 5β-*p*-Anisyl-2-α-carbomethoxy-6α-carboxymethyl-2β-methylcyclohexylidene-1-acetate (XIII). **(a) From the Lactone X.**—A solution of 5.85 g. of the lactone X, m.p. 112.5–113°, in 200 ml. of methanol and 16.0 ml. of 0.969 *N* sodium hydroxide was boiled under reflux for 1 hr. The solvent was removed by distillation at reduced pressure, water was added and the mixture acidified and extracted with ether. The ether solution was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated at reduced pressure. The residue was crystallized from benzene–petroleum ether (60–68°) to give a total of 4.53 g. (77% yield) of colorless material, m.p. 121–122°. Repeated recrystallization from the same solvent pair gave colorless prisms, m.p. 121.1–121.9°; $\lambda_{\max}^{95\%\ \text{EtOH}}$ 223 mμ (log ε 4.29), 278 (3.42), 284 (3.35); $\lambda_{\min}$ 263 (3.32), 283 (3.34).

Anal. Calcd. for $C_{21}H_{26}O_7$: C, 64.60; H, 6.71. Found: C, 64.9; H, 6.78.

Essentially the same yield of product was obtained when the reaction mixture was allowed to stand at room temperature for 1 week.

The methyl ester, prepared by the diazomethane method, was obtained from 60–68° petroleum ether as colorless prisms, m.p. 75.2–75.8°.

Anal. Calcd. for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.2; H, 7.10.

(b) From the Lactone XII.—A solution of 3.09 g. of the lactone XII, m.p. 136–136.5°, in 80 ml. of methanol and 8.50 ml. of 0.969 *N* sodium hydroxide was boiled under reflux for 1.5 hr. The crude product was isolated as described above under part (a). Crystallization gave a total of 1.25 g. (40% yield) of the unsaturated acid XIII, m.p. 121–122°. From the mother liquors there was isolated 0.30 g. (9% yield) of **6β-*p*-anisyl-3α-carbomethoxy-2α-carbomethoxymethyl-2β-hydroxy-3β-methylcyclohexane-1α-acetic acid**, m.p. 181–182°. Repeated recrystallizations from methanol gave colorless prisms, m.p. 181.3–182.8° dec., when immersed at 176° and the rate of heating was 1° per minute; $\lambda_{\max}^{\text{KBr}}$ 2.88 μ (OH), 5.85 (ester and acid C=O).

Anal. Calcd. for $C_{21}H_{28}O_8$: C, 61.75; H, 6.91. Found: C, 62.0; H, 7.05.

A sample of this hydroxy acid, on treatment with diazomethane, afforded the hydroxy ester, m.p. 100–101°, undepressed on admixture with the substance XI described above.

In another lactone cleavage experiment carried out as described above except that the reflux period was 3 hr., the yield of unsaturated acid, m.p. 121–122°, was 49%. When the heating period was extended to six hr., the yield dropped to 33%, and the product melted at 118–122°.

(c) From the Mixture of Products of the Reformatsky Reaction.—The total crude product from the Reformatsky reaction (carried out as described above) with 6.96 g. of keto ester VI (R = CH_3), m.p. 94–95°, was dissolved in 75 ml. of ether. On standing in the refrigerator for 24 hr., 5.68 g. of a colorless mixture of needles and prisms separated. This product was heated in 25 ml. of 98–100% formic acid on the steam-bath for 3 hr. The crude product, isolated as described in the lactonization experiment above, after treatment with ether amounted to 4.37 g. of crystalline solid, m.p. 106–125°. The filtrate was washed with water, 10% sodium carbonate solution, saturated brine and dried over anhydrous magnesium sulfate. The oily residue (0.60 g.) obtained on evaporation of the solvent was combined with the 4.37-g. crystalline fraction and dissolved in 160 ml. of methanol and 13.0 ml. of 0.983 *N* sodium hydroxide. After heating at reflux for 3 hr., the unsaturated acid was isolated as described above under part a; total yield 3.02 g. (39% over-all), m.p. 121–122°.

Catalytic Hydrogenation of the Unsaturated Acid Diester XIII.—A solution of 4.10 g. of the unsaturated acid XIII, m.p. 121–122°, in a total of 110 ml. of 95% ethanol was hydrogenated over 0.50 g. of (prereduced) 30% palladium-on-strontium carbonate[38] at room temperature and atmospheric pressure. After 48 hr. 1 mole-equivalent of hydrogen was absorbed and the absorption of gas ceased. The oily residue obtained after filtration and evaporation was crystallized from benzene to give a total of 3.27 g. of **6β-*p*-anisyl-3α-carbomethoxy-2α-carbomethoxymethyl-3β-methylcyclohexane-1α-acetic acid (XIV)**, m.p. 172–173°. Repeated recrystallization from benzene gave colorless prisms, m.p. 173.8–174.3°.

Anal. Calcd. for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.2; H, 7.22.

From the mother liquors there was obtained, with the help of added 60–68° petroleum ether, 0.31 g. of colorless solid, m.p. 118–126°. Three recrystallizations from benzene–petroleum ether (60–68°) afforded 0.195 g. of **6β-*p*-anisyl-3α-carbomethoxy-2β-carbomethoxymethyl-3β-methylcyclohexane-1α-acetic acid (XV)** as colorless prisms, m.p. 126–126.4°.

Anal. Calcd. for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.6; H, 7.35.

The methyl ester of XIV, prepared by the diazomethane method, was obtained from methanol as colorless prisms, m.p. 115–115.5°.

Anal. Calcd. for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44. Found: C, 64.9; H, 7.50.

Methyl 2α-Carbomethoxy-9-keto-7-methoxy-2β-methyl-1,2,3,4,4aα,9,10,10aβ-octahydrophenanthrene-1β-acetate (XVI). **(a) By Cyclization of XV.**[14]—A solution of 0.300 g. of the acid diester XV, m.p. 122–124°, 0.5 ml. of purified thionyl chloride and 2 drops of pyridine in 5 ml. of methylene chloride was allowed to stand at room temperature for 2 hr. The solvent was removed by distillation at reduced pressure, and the last traces of thionyl chloride were eliminated in the usual manner by co-distillation several times with 5-ml. portions of methylene chloride. The acid chloride was dissolved in 5 ml. of methylene chloride and added dropwise over a period of 5 minutes to a stirred and cooled (ice-bath) suspension of 0.38 g. of anhydrous aluminum chloride in 10 ml. of methylene chloride. A yellow complex formed immediately. After stirring for 2 hr., the ice-bath was removed and stirring continued for another 2 hr. at room temperature. Ice, concentrated hydrochloric acid and ether were added. The organic layer was washed with water, 5% potassium hydroxide solution, then thoroughly with saturated brine and finally dried over anhydrous magnesium sulfate. Evaporation of the solvent and trituration of the residue with ether–petroleum ether (40–60°) afforded 0.220 g. (77% yield) of material melting at 104–104.5°. Two recrystallizations from methanol gave long colorless needles, m.p. 104.2–104.6°.

Anal. Calcd. for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.4; H, 7.06.

(b) By Oppenauer Oxidation of the Corresponding Hydroxy Compound.—A 0.250-g. sample of the hydroxy diester i,[17] prepared as described below, in 30 ml. of toluene was oxidized with 3 ml. of cyclohexanone and 0.30 g. of aluminum isopropoxide in 10 ml. of toluene according to the method of Wettstein and Meystre.[39] Crystallization of the crude product from methanol gave 0.109 g. (first crop), m.p. 103–104°, and 0.079 g. (second crop), m.p. 101–102°. The m.p. was not depressed on admixture with material prepared as described above under part a.

Methyl 2α-Carbomethoxy-9-keto-7-methoxy-2β-methyl-1,2,3,4,4aα,9,10,10aβ-octahydrophenanthrylidene-1-acetate (XVII).—The cyclization was carried out as described above for XV. The acid chloride from 1.59 g. of the unsaturated acid diester XIII, m.p. 121–122°, was dissolved in 10 ml. of methylene chloride and added to a suspension of 2.03 g. of aluminum chloride in 30 ml. of methylene chloride. The mixture was stirred for 75 minutes in the cold, then for 75 minutes at room temperature before treatment with ice and hydrochloric acid. The crude semi-crystalline product,

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(38) W. S. Johnson, E. R. Rogier, J. Szmuszkovicz, H. I. Hadler, J. Ackerman, B. K. Bhattacharyya, B. M. Bloom, L. Stalmann, R. A. Clement, B. Bannister and H. Wynberg, THIS JOURNAL, **78**, 6289 (1956), footnote 39.

(39) As described by C. Djerassi in Adams, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 235.

isolated as described above, was crystallized from methanol giving a total of 1.33 g. (88% yield) of ketone, m.p. 147.8–148.4°. Further recrystallizations gave colorless prisms of the same m.p.

Anal. Calcd. for $C_{21}H_{24}O_6$: C, 67.72; H, 6.50. Found: C, 68.0, 68.2; H, 6.94, 6.46.

The **2,4-dinitrophenylhydrazone** was obtained as small red needles from chloroform–ethyl acetate. The m.p. was 270.4–271.2° dec. when introduced at 263° with the temperature rising at a rate of 1° per minute.

Anal. Calcd. for $C_{27}H_{28}N_4O_9$: C, 58.69; H, 5.11. Found: C, 58.35; H, 5.24.

Methyl 2α-Carbomethoxy-7-methoxy-2β-methyl-1,2,3,4,-4aα,9,10,10aβ-octahydrophenanthrylidene-1-acetate (XVIII).—Hydrogenation[15] of 0.913 g. of the unsaturated keto diester XVII, m.p. 147.8–148.4°, was carried out in 30 ml. of glacial acetic acid containing 0.2 ml. of 60% perchloric acid over 0.20 g. of 30% palladium-on-carbon[40] at room temperature and atmospheric pressure. Within 80 minutes 2 mole-equivalents of hydrogen was absorbed and the reaction, which had slowed down appreciably, was interrupted. The mixture was filtered, ether and water were added and the organic layer washed thoroughly with water, then with 10% sodium carbonate solution. The combined ether solutions were washed with saturated brine and dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the solvent was crystallized from methanol which gave 0.667 g. (76% yield) of colorless prisms, m.p. 111.4–111.8°. Repeated recrystallization from methanol raised the m.p. to 112–112.2°; λ_{max}^{EtOH} 221.5 mμ (log ϵ 4.43), 277.5 (3.41), 285.5 (3.34); λ_{min} 265 (3.29), 284 (3.33); $\lambda_{max}^{CHCl_3}$ 5.79 μ (ester C=O), 6.11 (conjugated C=C), 6.19 (aromatic nucleus).

Anal. Calcd. for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.2; H, 7.39.

The unsaturated diester of Anner and Miescher,[16] m.p. 113–115°, exhibited λ_{max}^{EtOH} 221 mμ (log ϵ 4.32), 277 (3.40), 286 (3.34); λ_{min} 263 (3.21), 283 (3.32); $\lambda_{max}^{CHCl_3}$ 5.79 μ (ester C=O), 6.10 (conjugated C=C), 6.19 (aromatic nucleus). On admixture with the 112° unsaturated diester the m.p. was 93–112°.

Methyl 2α-Carbomethoxy-9-hydroxy-7-methoxy-2β-methyl-1,2,3,4,4aα,9,10,10aβ-octahydrophenanthrene-1β-acetate (i[17]).—A solution of 0.800 g. of the unsaturated keto diester XVII, m.p. 147.8–148.4°, in a total of 60 ml. of ethyl acetate was hydrogenated over 0.20 g. of (prereduced) 30% palladium-on-strontium carbonate[38] at room temperature and atmospheric pressure. After 22 hr. 2 mole-equivalents of hydrogen was absorbed and the reaction had ceased. The mixture was filtered, evaporated and the residue crystallized from a small volume of ether. After 24 hr. at 0°, 0.452 g. (56% yield) of colorless prisms separated, m.p. 113.5–115°. Repeated recrystallization from dilute methanol gave material melting at 112–115°.

Anal. Calcd. for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50. Found: C, 66.9; H, 7.38.

The **benzoate** was obtained from methanol as colorless needles, m.p. 133.2–133.8°.

Anal. Calcd. for $C_{28}H_{32}O_7$: C, 69.98; H, 6.71. Found: C, 69.7; H, 6.54.

Methyl 2α-Carbomethoxy-7-methoxy-2β-methyl-1,2,3,4,-4aα-9,10,10aβ-octahydrophenanthrene-1β-acetate (XIX). (a) **By Hydrogenolysis[15] of the 9-Keto Compound XVI.**—A solution of 0.125 g. of the keto diester XVI, m.p. 103.2–104.6°, in 20 ml. of acetic acid containing 0.1 ml. of 60% perchloric acid was hydrogenated over 0.10 g. of 30% palladium-on-carbon[40] at room temperature and atmospheric pressure. After 1 hr. 2 mole-equivalents of hydrogen was absorbed. The crude product, isolated as described above for the unsaturated diester XVIII, was crystallized from methanol, which afforded 0.112 (93% yield) of colorless needles, m.p. 98.6–99°. Repeated recrystallization from methanol raised the m.p. to 99.6–99.9° (reported[16] 95–96°), λ_{max}^{EtOH} 218 mμ (log ϵ 3.97), 277.5 (3.31), 285.5 (3.25); λ_{min} 247.5 (2.06), 263.5 (3.25).

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 70.2; H, 7.84.

(b) **From the Unsaturated Diester XVIII.**—A suspension of 0.500 g. of 30% palladium-on-strontium carbonate[38] in 25 ml. of ethyl acetate was reduced and equilibrated with hydrogen at room temperature and atmospheric pressure. A solution of 0.699 g. of the unsaturated diester XVIII, m.p. 111.4–111.8; in 25 ml. of ethyl–acetate was then added. After 24 hr. 1 mole-equivalent of hydrogen was absorbed and the gas uptake had ceased. The mixture was filtered, evaporated and the oily residue crystallized from methanol, which gave 0.429 g. (first crop), m.p. 98.2–99.2°, and 0.157 g. (second crop), m.p. 97.2–98.6°, of colorless prisms. The m.p. of the first crop material was not depressed on admixture with the specimen obtained as described above under part a.

***dl*-Estrone Methyl Ether.**—Selective saponification of 0.596 g. of the diester XIX, m.p. 99.6–99.9°, according to the procedure described below for the 14-iso series gave after crystallization from methanol a total of 0.430 g. (75% yield) of half-ester, m.p. 174–175.6°. Two recrystallizations from methanol raised the m.p. to 175.8–176.6° (reported[16] 172–173°). A 0.328-g. sample of this half-ester, m.p. 174.8–175.6°, was submitted to the Arndt–Eistert reaction as described below for the epimer XXI (R = H), followed by saponification. Crystallization of the product from ethyl acetate afforded 0.113 g. (first crop), m.p. 219–220.5°, and 0.081 g. (second crop), m.p. 214.5–217.5°, of *dl*-homomarrianolic acid methyl ether. Three recrystallizations gave colorless prisms, m.p. 224.2–226.8°, undepressed on admixture with an authentic specimen (m.p. 225–226.5°[24]). A specimen of the crude dibasic acid was pyrolyzed with lead carbonate as previously described.[16,24] Crystallization of the evaporatively distilled product from methanol gave colorless prisms, m.p. 143.2–144.2°, undepressed on admixture with authentic *dl*-estrone methyl ether (m.p. 141.8–143.2°).[24]

Methyl 2α-Carbomethoxy-9-keto-7-methoxy-2β-methyl-1,2,3,4,4aα,9,10,10aβ-octahydrophenanthrene-1α-acetate (XX).—The cyclization was carried out as described above for XV. The acid chloride from 1.50 g. of the acid diester XIV, m.p. 172–173°, was dissolved in 10 ml. of methylene chloride and added over a 15-minute period to a cold, stirred suspension of 1.90 g. of aluminum chloride in 30 ml. of methylene chloride. The mixture was stirred for 1.5 hr. in the cold, then for 1.5 hr. at room temperature before treatment with ice and hydrochloric acid. The crude product amounted to 1.35 g. (94% yield) of colorless crystals, m.p. 149–151°. A single crystallization from methanol afforded 1.19 g. of colorless needles, m.p. 153.6–154°.

In earlier experiments in which the cyclization was conducted in benzene solution (yield 57%) or with anhydrous hydrogen fluoride (yield 30%), a lower melting polymorph was encountered. Such material was obtained as colorless, diamond-shaped plates, m.p. 145.4–145.8°, from methanol. On admixture with the higher-melting form, the material melted at 153.6–154°. The lower-melting modification was analyzed.

Anal. Calcd. for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.1; H, 7.10.

The **oxime** was obtained from methanol as colorless needles, m.p. 158–158.6°.

Anal. Calcd. for $C_{21}H_{27}O_6N$: C, 64.76; H, 6.99. Found: C, 65.0; H, 7.09.

Methyl 2α-Carbomethoxy-7-methoxy-2β-methyl-1,2,3,4,-4aα,9,10,10aβ-octahydrophenanthrene-1α-acetate (XXI, R = CH_3).—A solution of 0.648 g. of the keto diester XX, m.p. 153.5–154°, in 25 ml. of acetic acid containing 0.2 ml. of perchloric acid was hydrogenated[15] over 0.2 g. of 30% palladium-on-carbon,[40] at room temperature and atmospheric pressure as described above for the hydrogenolysis of XVI. After 1 hr. 2 mole-equivalents of hydrogen was absorbed, and the gas uptake had become slow. The crude product, isolated as described above, was crystallized from methanol, which afforded 0.523 g. (84% yield) of colorless needles, m.p. 89.5–90°. Further recrystallizations did not improve the m.p.

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 70.1; H, 7.98.

2α-Carbomethoxy-7-methoxy-2β-methyl-1,2,3,4,4aα,9,-10,10aβ-octahydrophenanthrene-1α-acetic Acid (XXI, R = H).—Partial saponification of 0.810 g. of the aforementioned diester XXI (R = CH_3), m.p. 89.5–90°, was carried out as previously described,[16] by treatment with 20 ml. of methanol and 2.55 ml. of 0.969 *N* sodium hydroxide solution. After heating under reflux for 16 hr., the solvent was

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[40] R. P. Linstead and S. Thomas, *J. Chem. Soc.*, 1127 (1940).

removed by distillation at reduced pressure, water added and the acidic material isolated in the conventional manner. Crystallization of the crude product from methanol afforded 0.525 g. (first crop) of colorless needles, m.p. 167–167.8°, and 0.050 g. (second crop), m.p. 166–167.8°. Further recrystallization of the first crop material did not raise the m.p.

Anal. Calcd. for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.0; H, 7.33.

2-[2α-Carboxy-7-methoxy-2β-methyl-1,2,3,4,4aα,9,10,10aβ-octahydrophenanthrene-1α]-propionic Acid (XXII).—The Arndt–Eistert reaction was carried out by a slight modification of previously described procedures.[16,41] The acid chloride was prepared from 0.250 g. of the aforementioned half-ester XXI (R = H), m.p. 167–167.8°, utilizing 1 ml. of benzene, 2 drops of pyridine and 0.5 ml. of purified thionyl chloride. After 2 hr. at room temperature, the solvent was removed by distillation at reduced pressure, and most of the residual thionyl chloride was eliminated by co-distillation with an added 1 ml. of benzene. The acid chloride in 2 ml. of benzene was treated with ethereal diazomethane (from 2 g. of N-nitrosomethylurea) for 16 hr. at 0°. The crude oily diazo ketone obtained upon evaporation of the solvent was dissolved in 15 ml. of methanol, heated to 55°, and 0.35 g. of freshly prepared, dry silver oxide was added in portions over a period of 1 hr. The mixture was then boiled under reflux for 1 hr., 0.15 g. of silver oxide added and the mixture boiled for 2 hr. more. The residue obtained after filtration and evaporation was refluxed in a steel flask with 5 ml. each of methanol and 50% potassium hydroxide solution. The acidic fraction, isolated in the conventional manner, consisted of an oil which on trituration with ether afforded 0.107 g. of tan solid, m.p. 230–232°. Concentration of the ether solution yielded an additional 0.035 g. of less pure material, m.p. 225–227°.

A sample of the first crop material was recrystallized twice from ethyl acetate, then sublimed at 220° (0.02 mm.) to give colorless prisms, m.p. 233.5–234.5°.

Anal. Calcd. for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.3; H, 7.45.

14-Isoestrone Methyl Ether (XXIII, R = CH_3).—A mixture of 0.077 g. of the aforementioned dibasic acid XXII, m.p. 231–233°, and 0.08 g. of lead carbonate was pyrolyzed at 300° (0.05 mm.) for 20 minutes according to described procedures.[16,24] The oily distillate was evaporatively distilled at 200° (0.05 mm.) giving 0.050 g. (79% yield) of colorless solid, m.p. 114.5–117°. Three recrystallizations from methanol afforded colorless needles, m.p. 120.6–121°.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.9; H, 8.39.

The 2,4-dinitrophenylhydrazone was obtained from chloroform–ethyl acetate as yellow needles, m.p. 267.5–268.5° dec., when introduced at 263°.

Anal. Calcd. for $C_{25}H_{28}O_5N_4$: C, 64.64; H, 6.08. Found: C, 64.8; H, 6.22.

***dl*-14-Isoestrone.**—The procedure of Wilds and McCormack[42] was employed for the demethylation. A mixture of 0.070 g. of 14-isoestrone methyl ether, m.p. 114.5–117.5°, and 1.5 g. of pyridine hydrochloride was heated at 205–210° for 40 minutes in an atmosphere of nitrogen. The potassium hydroxide-soluble fraction amounted to 0.060 g. (90% yield) of micro-crystalline material, m.p. 211–214°. Two recrystallizations from methanol followed by sublimation at 190° (0.05 mm.) gave colorless micro crystals, m.p. 215.8–216.8°.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.1; H, 8.42.

6-*p*-Anisyl-3-carbomethoxy-2-keto-3-methylcyclohex-6-ene-1-acetic Acid (XXIV).—The esterification was carried out by the procedure of Bowman and Fordham.[30] A mixture of 25.44 g. of the keto acid IX (R = H), m.p. 164–165.5°, 33.6 g. of dihydropyran (freshly distilled from sodium), 160 ml. of benzene and 25 mg. of *p*-toluenesulfonic acid monohydrate was stirred at room temperature for 4.5 hr. during which period the solid dissolved. Pyridine (1 ml.) and ether were added; the mixture was extracted with 10% potassium bicarbonate solution, then washed with water followed by saturated brine and finally dried over anhydrous magnesium sulfate. The crude oily ester obtained upon evaporation of the solvent at 30–35° (reduced pressure), was used directly in the methylation step described directly below.

A solution of the crude tetrahydropyranyl ester in 100 ml. of benzene was added to a suspension of 1.92 g. of sodium hydride in 100 ml. of benzene. After 30 minutes the evolution of hydrogen ceased; 114 g. of methyl iodide was added and the mixture allowed to stand at room temperature for 4 hr. with stirring, then overnight. A solution of 25 mg. of *p*-toluenesulfonic acid monohydrate in 25 ml. of acetic acid was added and the mixture refluxed for 30 minutes in order to cleave the tetrahydropyranyl ester. About 100 ml. of solvent was removed by distillation, water was added and the aqueous layer extracted with ether. The combined organic layers were washed with water, then extracted exhaustively with 10% potassium bicarbonate. The bicarbonate solutions were acidified and extracted with ether. These combined ether solutions were washed with water, then with saturated brine, and dried over anhydrous sodium sulfate. The glassy residue obtained on evaporation of the solvent was crystallized from ether which afforded a total of 19.56 g. (73% yield) of colorless prisms, m.p. 126–128.5°. Two recrystallizations from benzene–petroleum ether (60–68°) raised the m.p. to 129.5–130.5°; $\lambda_{max}^{95\%\ EtOH}$ 226 mμ (log ε 4.03), 292 (4.08); λ_{min} 257 (3.65).

Anal. Calcd. for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 65.2; H, 6.33.

Catalytic Hydrogenation of the Unsaturated Methylated Keto Acid XXIV.—A solution of 0.225 g. of this acid, m.p. 126.5–127.5°, in 20 ml. of 95% ethanol was hydrogenated over 0.158 g. of commercial 10% palladium-on-carbon at room temperature and atmospheric pressure. Within 15 minutes 1 mole-equivalent of hydrogen was absorbed and the gas uptake was very slow. The residue obtained upon filtration and evaporation was chromatographed on 12 g. of Florex. The fraction eluted with 10–75% ether in benzene amounted to 0.104 g. (49% yield) of crystalline γ-lactone **of 6-*p*-anisyl-3-carbomethoxy-2-hydroxy-3-methylcyclohex-6-ene-1-acetic acid (XXV)**, m.p. 108–110°. Two recrystallizations from ether–petroleum ether (60–68°) raised the m.p. to 109–110.5°; $\lambda_{max}^{95\%\ EtOH}$ 256 mμ (log ε 4.20); λ_{min} 225 (3.75); $\lambda_{max}^{CS_2}$ 5.60 μ (γ-lactone C═O) and 5.79 (ester C═O).

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.55; H, 6.56.

The fraction eluted from the chromatographic column with 10–25% ethanol in ether amounted to 0.060 g. (27% yield) of crude half-ester VII (R = H), m.p. 115–135°. Recrystallization from benzene–petroleum ether (60–68°) gave 0.051 g. of material, m.p. 138–139°, undepressed on admixture with authentic VII (R = H) described above.

Catalytic Hydrogenation of the Methyl Ester of XXIV.—Reaction of the unsaturated methylated keto acid XXIV, m.p. 126.5–127.5°, with excess ethereal diazomethane afforded a liquid methyl ester which could not be rendered crystalline even after chromatography. A solution of 0.200 g. of such material in 25 ml. of absolute methanol (containing 3 drops of 10% aqueous potassium hydroxide) was hydrogenated over 0.04 g. of commercial 10% palladium-on-carbon at room temperature and atmospheric pressure. Within 30 minutes 1 mole-equivalent of hydrogen was absorbed and the gas uptake had ceased. The residue obtained upon filtration and evaporation amounted to 0.200 g. of colorless oil which could not be crystallized. It was selectively saponified in methanol with 0.6 ml. of 1 *N* sodium hydroxide according to the procedure described in detail above for the preparation of the Ar/CH_3 *trans*-half-ester VII (R = H). This same substance was isolated in the present case; yield 0.162 g. (85%), m.p. 138–140°, undepressed on admixture with the authentic specimen described above.

It should be noted that esterification of the pure half-ester VII (R = H), m.p. 139–140°, with diazomethane, yielded a sample of the methyl ester which was also an oil that resisted crystallization.

The Dienol-lactone XXVI.—A solution of 1.60 g. of the methylated unsaturated keto acid XXIV, m.p. 126–127.5°, in 20 ml. of acetic anhydride and 8 ml. of acetyl chloride was refluxed for 3.5 hr. The solvent was removed at reduced pressure and the residue taken up in benzene. The solution

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[41] W. E. Bachmann, W. Cole and A. L. Wilds, THIS JOURNAL, **62**, 824 (1940).

[42] A. L. Wilds and W. McCormack, *ibid.*, **70**, 4127 (1948).

was extracted with 10% potassium bicarbonate solution, washed with water and dried over anhydrous sodium sulfate. The residue obtained on evaporation of the benzene at reduced pressure was triturated with ether which afforded 0.90 g. of colorless solid, m.p. 124–128°. A second crop amounting to 0.20 g., m.p. 123–126°, was obtained on concentration of the ether solution. Recrystallization of the combined crops from benzene–petroleum ether (60–68°) gave 1.05 g., m.p. 132–134.5°. Sublimation at 110° (0.01 mm.) afforded colorless needles, m.p. 132–134.5°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 248 mμ (log ε 4.32); $\lambda_{\min}$ 217 (3.93).

Anal. Calcd. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.9; H, 5.80.

Catalytic Hydrogenation of the Dienol-lactone XXVI.—A solution of 0.360 g. of the aforementioned enol-lactone, m.p. 132–134.5°, in 20 ml. of benzene was hydrogenated over 0.036 g. of commercial 10% palladium-on-carbon at room temperature and atmospheric pressure. Within 30 minutes 1 mole-equivalent of hydrogen was absorbed. The mixture was filtered and chromatographed on 14 g. of Florisil. The fraction eluted with 2–5% ether in benzene amounted to 0.350 g., m.p. 124–125°. Crystallization from benzene–petroleum ether (60–68°) afforded 0.340 g. (94% yield) of the **enol-lactone (XXVII) of 6β-*p*-anisyl-3β-carbomethoxy-3α-methyl-2-ketocyclohexane-1-acetic acid**, m.p. 127–128°. Two recrystallizations from the same solvent pair gave colorless blades, m.p. 127.6–128.5°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 226 mμ (log ε 4.03), 276 (3.22), 282 (3.17); $\lambda_{\min}$ 256 (3.13).

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.1; H, 6.41.

Selective saponification of a specimen of 0.280 g. of the enol-lactone, m.p. 127–128°, under the conditions described above for the preparation of the Ar/CH_3 *trans*-half-ester VII (R = H) afforded, after recrystallization, 0.240 g. of this same substance, m.p. 138–139°. Two recrystallizations gave material m.p. 140–142°, alone or on admixture with authentic half-ester VII (R = H).

Enol-lactone XXVIII of 6-*p*-Anisyl-3-carbomethoxy-5,6-dihydroxy-2-keto-3-methylcyclohexane-1-acetic Acid.—A mixture of 0.500 g. of the aforementioned dienol-lactone, m.p. 125–126°, 2 ml. of 100% formic acid and 0.16 ml. of 37.5% hydrogen peroxide solution was agitated at room temperature for 7 hr. The mixture was then added to excess 10% potassium bicarbonate and ether. The organic layer was washed thoroughly with additional 10% potassium bicarbonate, then with water followed by saturated brine and finally dried over anhydrous sodium sulfate. The residue obtained on evaporation of the ether was dissolved in 7 ml. of methanol, 1.5 ml. of 10% methanolic *p*-toluenesulfonic acid monohydrate was added and the mixture allowed to stand at room temperature for 24 hr. The solvent was evaporated at reduced pressure and the residue treated with potassium bicarbonate and ether, washed and dried as described above. Crystallization of the crude semisolid product from ethyl acetate afforded 0.184 g. (33% yield), of diol, m.p. 167–171°. Three recrystallizations from ethyl acetate gave clusters of small colorless blades, m.p. 172.4–173.3°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 222 mμ (log ε 4.02), 274 (3.22), 280 (3.15); $\lambda_{\max}^{\mathrm{Nujol}}$ 2.80 μ (OH), 5.71 (γ-lactone C=O), 5.80 (ester C=O).

Anal. Calcd. for $C_{18}H_{20}O_7$: C, 62.06; H, 5.79. Found: C, 61.9; H, 5.75.

The residue obtained on evaporation of the mother liquors was chromatographed on 20 g. of Florisil. The fraction eluted with 25% ether in benzene amounted to 0.035 g. of starting dienol-lactone, m.p. 124–126°. The fraction eluted with 1% ethyl acetate in ether amounted to 0.046 g. of an oil. The fraction eluted with 5% ethyl acetate in ether amounted to 0.016 g. of crystalline solid, m.p. 148–150°; $\lambda_{\max}^{\mathrm{Nujol}}$ 2.71 μ (OH), 3.02 (associated OH), 5.71 (γ-lactone C=O), 5.80 (ester C=O). Further work on this product has been postponed until additional material has been prepared. The remaining eluates contained noncrystalline material.

Attempts to dehydrate the high-melting glycol by heating with oxalic acid in toluene or with methanolic *p*-toluenesulfonic acid resulted in recovery of significant amounts of unchanged glycol.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

14-Isoestrone Methyl Ether and its Identity with Totally Synthetic Material

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Bromination of the enol acetate II of estrone methyl ether afforded the 16-bromo derivative IV which was converted to the ethylene ketal III. Dehydrohalogenation with potassium *t*-butoxide converted III into the unsaturated ketal V, which on mild acid hydrolysis was transformed into the 15,16-dehydro ketone VI. This last substance, on treatment with acid, could be isomerized to a mixture of the 14,15-dehydro tautomer VIII and the 15,16-dehydro-14-isoketone IX. Both of these isomerization products gave 14-isoestrone methyl ether VII on catalytic hydrogenation. The infrared spectrum of this substance was identical with that of a totally synthetic *dl*-compound obtained in another study.

In one of our studies of the total synthesis of estrone,[2] a stereoisomer was also produced which, by virtue of its mode of formation, was presumed to be *dl*-14-isoestrone. Our substance was evidently identical with a stereoisomer that had been previously prepared in a different synthesis by Anner and Miescher[3] who, on similar grounds, also postulated its correspondence to 14-isoestrone. The objective of the present study was to prepare authentic 14-isoestrone methyl ether by partial synthesis from estrone for the purpose of comparison with the methyl ether of the *dl*-compound. An account of this study is given herewith.

Since catalytic hydrogenation of a 14,15-dehydro 17-keto steroid generally has given at least some of the 14-iso compound,[4] we elected to explore the possibility of preparing 14-isoestrone methyl ether *via* the 14,15-dehydro compound VIII. It seemed probable that this latter substance, or the equally useful 15,16-dehydro-14-iso compound IX, could be produced from the 15,16-dehydro isomer VI because, at equilibrium, the 3-carbon tautomeric system VI ⇄ VIII ⇄ IX was expected to contain little, if any, of the form VI due to the relative instability of the C/D *trans* ring fusion.[5]

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[2] W. S. Johnson, R. G. Christiansen and R. E. Ireland, THIS JOURNAL, **79**, 1995 (1957).

[3] G. Anner and K. Miescher, *Helv. Chim. Acta*, **32**, 1957 (1949).

[4] See for example (a) A. F. St. André, H. B. MacPhillamy, J. A. Nelson, A. C. Shabica and C. R. Scholz, THIS JOURNAL, **74**, 5506 (1952); (b) W. S. Johnson, J. W. Peterson and C. D. Gutsche, *ibid.*, **69**, 2942 (1947).

[5] *Cf.* a similar system (ref. 4b) in which there appeared to be no detectable amount of the C/D *trans*-15,16-dehydro compound at equilibrium.