8α,9β-Estrone Methyl Ether, the Elusive Boat C-Ring Isomer

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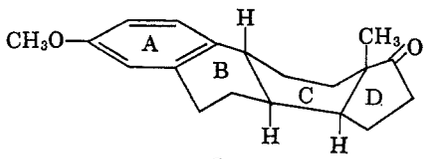
Received August 4, 1967

The title compound has been synthesized from estrone methyl ether as follows. Ring D was opened, by an established method, and the resulting known diester III (R = CH_3) was dehydrogenated with dichlorodicyanobenzoquinone to give the dehydro ester II (R = CH_3). The corresponding diacid II (R = H), on reduction with potassium in ammonia, was converted into a mixture of at least four diastereoisomers which contained some of the desired substance IV (R = H). Selective Dieckmann cyclization of the corresponding diester mixture effected ring closure of most of the isomers except for IV (R = CH_3), which was in this way separated in a fairly pure form. Forcing Dieckmann cyclization conditions effected ring closure of IV (R = CH_3) which, on heating with aqueous triethylene glycol, underwent hydrolysis and decarboxylation to give 8α,9β-estrone methyl ether (I).

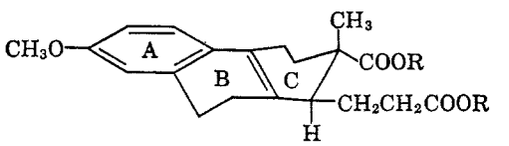
We have previously synthesized and characterized all but one of the eight possible stereoisomeric racemic forms of estrone, including the natural product.[1] One of the stereoisomers described by Anner and Miescher,[2] "estrone e," appeared to differ from any of ours and was tentatively regarded as the "missing" eighth racemate; however some doubt remained as to whether this material may represent another form of *dl*-8-isoestrone. Unfortunately the mode of formation of "estrone e" affords no clue as to its configuration. Now the estrone isomer in question, namely 8-iso-9-isoestrone, is unique in that its *trans,syn,trans* arrangement of rings B/C/D can be accommodated only if ring C is in the energy-rich boat form (see formula I). It is this unusual feature which renders synthesis by usual methods difficult. In the present paper we record an unequivocal synthesis of one enantiomeric form of this substance as its methyl ether, namely 8α,9β-estrone methyl ether (I). Unfortunately it has not been possible to resolve the question of the nature of "estrone e," because this material is not available for comparison purposes.

The plan of attack envisaged opening ring D of estrone methyl ether (V) and introduction of an 8,9 double bond to give a substance such as II. Reduction of the styrene bond of II (R = H) with alkali metal in ammonia would be expected[3] to give a mixture of possibly as many as four B/C-fused stereoisomers containing a preponderance of III (R = H), as well as at least some of the desired *trans,syn,trans* product IV (R = H). It was planned to submit this mixture of reduction products, as their esters, to Dieckmann cyclization with the expectation that the desired 8α,9β ester IV (R = CH_3) would react least rapidly because it can cyclize only if ring C is forced into the boat conformation. It was hoped that this expedient would afford a means of separating the ester IV (R = CH_3) which under forcing cyclization conditions should lead to 8α,9β-estrone methyl ether (I).

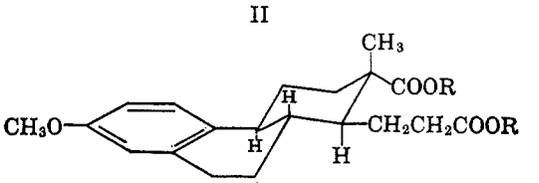
Estrone methyl ether (V) was converted into homomarrianolic acid methyl ether (III, R = H) as previously described.[4] The crystalline dimethyl ester



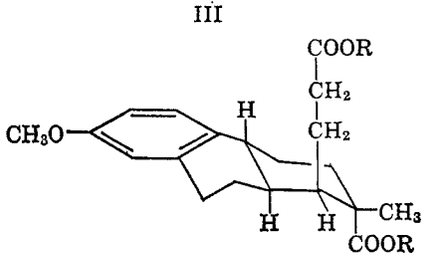
I



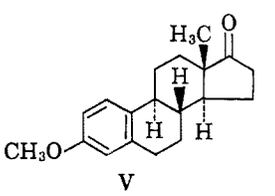
II



III



IV



V

III (R = CH_3), on treatment at 25° with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in acetic acid containing 5% water, was converted into an oily product. Although the retention time on thin layer chromatography was identical with that of the starting material, this product showed a new absorption in the ultraviolet spectrum at 273 mμ, which is characteristic of the methoxystyrene chromophore in systems like II.[5] The extinction coefficient of this band was 13,000 compared with the expected value of 18,000[5] for pure material, indicating that the product was a mixture containing the desired dehydro compound II (R =

(1) W. S. Johnson, I. A. David, H. C. Dehm, R. J. Highet, E. W. Warnhoff, W. D. Wood, and E. T. Jones, *J. Amer. Chem. Soc.*, **80**, 661 (1958).

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

(3) Several cases of metal–ammonia reductions to give mixtures containing less stable isomers have been reported; *cf.*, for example, W. S. Johnson, J. Ackerman, J. F. Eastham, and H. A. DeWalt, Jr., *J. Amer. Chem. Soc.*, **78**, 6302 (1956); H. E. Zimmerman, *ibid.*, **78**, 1168 (1956).

(4) W. S. Johnson, D. K. Banerjee, W. P. Schneider, C. D. Gutsche, W. E. Shelberg, and L. J. Chinn, *ibid.*, **74**, 2832 (1952).

(5) J. E. Cole, Jr., W. S. Johnson, P. A. Robins, and J. Walker, *J. Chem. Soc.*, 244 (1962). Note that the alternative 9,11-dehydro isomer would be expected to show absorption at about 263 mμ.

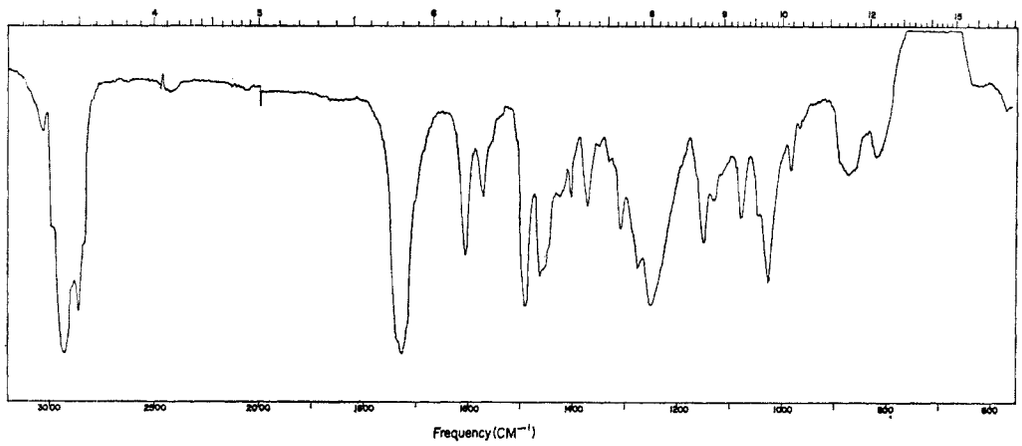


Figure 1.—Infrared spectrum of 8α,9β-estrone methyl ether in chloroform.

CH_3) and starting material III (R = CH_3) in the ratio of about 7:3. The nmr spectrum of the product was very similar to that of pure III (R = CH_3) except for the signal for the C-18 methyl group which appeared as a pair of sharp singlets at δ = 1.22 and 1.16 ppm, accounting for a total of three protons. The latter band corresponded exactly to the signal for the C-18 methyl group in the substance III (R = CH_3). There was no absorption corresponding to the vinyl proton; therefore there was little, if any, of the alternative 9,11-dehydro isomer in the mixture. When anhydrous acetic acid was used for the dehydrogenation reaction, the extinction coefficient at 273 mμ in the ultraviolet spectrum of the product was low, 4800-8000; with commercial glacial acetic acid, it was 10,000. We do not have a satisfactory rationalization of the role of the water in this reaction.

The crude mixture containing the dehydro ester II (R = CH_3) was saponified to give the diacid II (R = H) contaminated with III (R = H). This product was twice submitted to treatment with potassium in ammonia containing anisole. Thus the styrene bond of the diacid was reduced to the exclusion of Birch reduction of ring A. When the anisole was omitted from the reaction mixture there was always considerable reduction of ring A. Chromatography of the product afforded a reduced diacid fraction which was converted, with diazomethane, into a mixture of dimethyl esters, the ultraviolet absorption spectrum of which was comparable with that of III (R = CH_3). The vapor phase chromatogram of this product on an SE-30 column at 270° showed four peaks: A, retention time 8.2 min (relative peak area, 15%); B, 9.2 (6%); C, 9.8 (12%); and D, 10.6 (67%). By coinjection experiments peaks A, C, and D were shown to have retention times identical with those of authentic[1] *dl*-9-iso- (*cis,anti,trans*), *dl*-8-iso- (*cis,syn,-trans*), and natural (*trans,anti,trans*) homomarrianolate methyl ether (III, R = CH_3). Peak B, therefore, was regarded as corresponding to the desired 8α,9β (*trans,-syn,trans*) isomer IV (R = CH_3). This conclusion was confirmed by its chemical behavior (see below).

A study was made in order to develop the mildest conditions for essentially complete Dieckmann cyclization of dimethyl homomarrianolate methyl ether (III, R = CH_3) which involved heating the diester with 1.5 mol equiv of sodium *t*-amyloxide in benzene solution for a 15–20-min period. These cyclization conditions were then applied to the aforementioned oily mixture of diesters. The crude product was heated with aqueous triethylene glycol to effect decarbomethoxylation, and the resulting mixture was saponified to afford a neutral ketone and an uncyclized acidic fraction corresponding to 81 and 15%, respectively, of the starting diester mixture. The ketonic material was shown (see Experimental Section) to consist of approximately 9% of 9β-estrone methyl ether, 90% of a mixture of 8α-estrone methyl ether and estrone methyl ether (V), and 1% of new isomer which proved to be 8α,9β-estrone methyl ether (I) (see below).

The uncyclized portion from the Dieckmann treatment, in the form of the dicarboxylic acids, was submitted to chromatography on silica gel, and the chromatographic fractions, as the dimethyl esters, were analyzed by vapor phase chromatography. The early fractions contained the desired dimethyl 8α,9β-homomarrianolate methyl ether (IV, R = CH_3) which was 97% pure by vapor phase chromatography. Analysis of later chromatographic fractions indicated that the original uncyclized portion from the Dieckmann treatment consisted of approximately 50% of the desired 8α,9β isomer IV (R = CH_3) together with roughly equal amounts of the three other isomeric diesters (see above). Thus appreciable separation of the desired diacid II (R = H) was realized. In this separation procedure the preponderant homomarrianolate methyl ether (II, R = H) was transformed almost entirely to the corresponding estrone methyl ether (V), the 9β- and 8α-homomarrianolate methyl ethers were partially converted to the corresponding estrone methyl ether isomer, and the 8α,9β-homomarrianolate methyl ether (IV, R = H) remained almost entirely unaffected. The purest (97%) sample of dimethyl 8α,9β-homomarrianolate methyl ether was subjected to forcing (6-hr) Dieckmann cyclization conditions followed by decarbomethoxylation to afford a neutral ketonic fraction in 84% yield. After further purification by chromatography and evaporative distillation, the product was induced to crystallize. The melting point is extremely sensitive to traces of impurities, and material with mp 62–64° appeared to be indistinguishable by the usual analytical methods from the highest melting material obtained, *i.e.*, 73.5–74°. The solution infrared spectrum, Figure 1, of the new crystalline estrone iso-

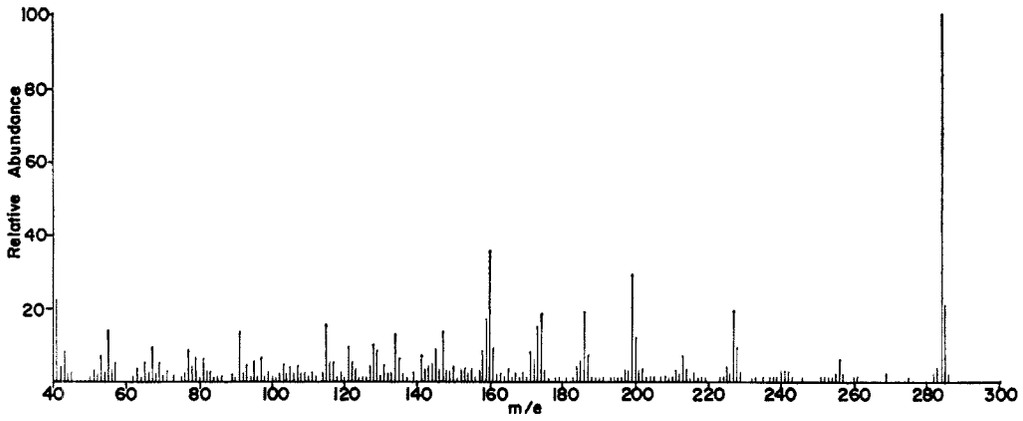


Figure 2.—Mass spectrum of 8α,9β-estrone methyl ether.

mer was different from any of those of the seven other racemic stereoisomers.[1] The mass spectrum fragmentation pattern, Figure 2, also differed from any of those of the other isomers.[6] In particular, the relative intensity of the peak at *m/e* 227 (M-57) for the six previously described isomeric estrone methyl ethers of unnatural configurations was 5–8 (based on 100 for the molecular ion peak). The relative intensities of this peak were 12 for natural estrone methyl ether and 19 for 8α,9β-estrone methyl ether. It has been shown[6] that this peak at *m/e* 227 arises from the loss of ring D with migration of one hydrogen atom. That 8α,9β-estrone methyl ether exhibits the highest relative intensity of this peak is consistent with the fact that loss of ring D would be energetically favored because of relief of strain associated with the boat conformation of the C ring.

The later fractions from the aforementioned chromatography of the diester mixture were rich in the 8α diester. Dieckmann cyclization, followed by decarbomethoxylation, afforded an oily ketonic product. Vapor phase chromatography of chromatographed material indicated a composition of approximately 2% of 9β- and 98% of 8α-estrone methyl ether. A sample of 8α-estrone methyl ether, mp 91.5–92.5°, was isolated from the oily ketone by recrystallization. The solution infrared spectrum of this substance was identical with that of the previously described *dl*-8-isoestrone methyl ether.

Experimental Section[7]

Dimethyl Homomarrianolate Methyl Ether (III, R = CH_3).—Crude homomarrianolic acid was produced as previously described[4] and converted by treatment with diazomethane into the dimethyl ester, mp 87–88° (lit.[8] mp 83.5–84°). The nmr spectrum[7b] showed absorption for three protons as a multiplet at δ 6.57–7.21 (aromatic protons), three protons as a singlet at 3.73 ($ArOCH_3$), three protons as a singlet at 3.68 (CO_2CH_3), three protons as a singlet at 3.62 (CO_2CH_3), and three protons as a singlet at 1.16 ppm (CCH_3).

Dehydrogenation of Dimethyl Homomarrianolate Methyl Ether.—To a solution of 1.90 g of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 80 ml of glacial acetic acid was added 4 ml of water. The resulting aqueous solution was stirred rapidly at 25–27° for 20 min; then 2.04 g of the aforementioned diester III (R = CH_3), mp 84–86°, was added in one portion. Upon addition of the diester, the initially yellow solution turned to a green color which then gradually faded to pale yellow as the beige hydroquinone precipitated. After 30 min the solution was filtered into 150 ml of a saturated aqueous sodium acetate solution, and the resulting mixture was stirred for 5 min at 25°. The mixture was poured into ether, and the organic layer was washed thoroughly with water and then with 5% potassium bicarbonate solution until the aqueous phase was colorless. The organic layer was finally washed with saturated brine and dried over anhydrous sodium sulfate. The residue obtained on evaporation of the solvent amounted to 1.24 g of a yellow oil: $\lambda_{max}^{CHCl_3}$ 5.78 μ (ester C=O); λ_{max}^{MeOH} 273 mμ (ε 13,000). The nmr spectrum of a similar preparation, λ_{max}^{MeOH} 272 mμ (ε 10,000), in which commercial glacial acetic acid was used as the solvent, showed absorption for three protons as a multiplet at δ 6.59–7.19 (aromatic protons), three protons as a singlet at 3.73 ($ArOCH_3$), six protons as three singlets at 3.67, 3.62, and 3.56 ($COOCH_3$), and three protons as a pair of singlets at 1.22 and 1.16 ppm (CCH_3) in a ratio of 3:2 as determined by peak heights.

A solution of 1.12 g of the aforementioned oily diester mixture in 35 ml of methanol and 70 ml of water containing 10 g of (85%) potassium hydroxide pellets was stirred at reflux for 4 hr. The mixture was cooled, ethyl acetate and water were added, and the aqueous phase was cooled to 0° and then acidified to pH 2 with ice-cold 5% hydrochloric acid. Particular caution was taken in this acidification step in order to minimize the possibility of lactonization. The acidic material which separated from the solution was isolated with ice-cold ethyl acetate[7f] and amounted to 0.93 g of cream-colored solid, λ_{max}^{MeOH} 273 mμ (ε 11,400). Three preparations, identical with that described above, were combined to afford 3.25 g of the white semicrystalline dicarboxylic acid mixture, λ_{max}^{MeOH} 273 mμ (ε 11,700).

Potassium in Ammonia Reduction.—A solution of 3.25 g (9.4 mmol) of the aforementioned diacid mixture, λ_{max}^{MeOH} 273 mμ (ε 11,700), in 60 ml of hexamethylphosphoramide (bp 68° (0.5 mm)) containing 15 ml of anisole and 10 drops of water was added with vigorous stirring to a solution of 4.5 g of potassium in 1.5 l. of distilled liquid ammonia. The blue reaction mixture was stirred rapidly at reflux (−33°) for 20 min; sufficient ammonium chloride was then added to discharge the blue color.

(6) C. Djerassi, J. M. Wilson, H. Budzikiewicz, and J. W. Chamberlin, *J. Amer. Chem. Soc.*, **84**, 4544 (1962); private communication from H. Budzikiewicz.

(7) (a) Melting points were determined on a Kofler hot-stage microscope calibrated against totally immersed Anschutz thermometers. (b) Nmr spectra were determined on a Varian Associates A-60 nmr spectrometer under the supervision of Dr. L. J. Durham. Deuteriochloroform was employed as the solvent with tetramethylsilane as the internal reference. The chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane = 0. (c) Mass spectra were determined on a C.E.C. 103C spectrometer equipped with an all-glass heated (200°) inlet system under the supervision of Dr. H. Budzikiewicz. (d) Vapor phase chromatographic analyses were performed on an Aerograph Hy-Fi vapor chromatographic apparatus (Model 600C) fitted with a 5 ft × 0.125 in. column packed with 5% SE-30 on a 60–80 Chromosorb W base. Prepurified nitrogen was employed as the carrier gas and, unless otherwise noted, a flow rate of 25 cc/min (at 25°) was used for the analyses. (e) The elution order used in column chromatography was petroleum ether (bp 60–68°), benzene, ether, ethyl acetate, and acetone. (f) The isolation procedure normally followed consisted of extraction of the product with the solvent indicated. The combined organic layers were washed thoroughly with water, followed by saturated salt solution, and then dried over anhydrous sodium sulfate. The solvent was then removed by rotary evaporation under reduced pressure (water aspirator) at about 50°.

(8) M. W. Goldberg and S. Studer, *Helv. Chim. Acta*, **25**, 1553 (1942).

The ammonia was allowed to evaporate overnight at room temperature; ether (500 ml) and water (500 ml) were then added. The organic phase was washed with two 100-ml portions of an aqueous 5% potassium hydroxide solution. The combined aqueous basic extracts were washed with ether, then chilled to 0°, and acidified to pH 2 with ice-cold concentrated hydrochloric acid. The aqueous mixture was extracted with ice-cold ethyl acetate, and the combined organic extracts were washed thoroughly with ice-cold water. Isolation of the product in the customary manner[7f] gave 3.22 g of a cream-colored amorphous solid, λ_{max}^{MeOH} 275 mμ (ε 4100). This material was subjected for a second time to the reaction conditions described directly above to afford 3.21 g of solid, λ_{max}^{MeOH} 285 mμ (ε 2500) and 277 (3400), having a slight odor of phenol. This product was chromatographed on 180 g of silica gel. Elution with 7.5–10% ether in benzene gave 2.04 g (a 62% yield based on starting diester mixture) of a white amorphous solid, λ_{max}^{MeOH} 286 mμ (ε 2240) and 277 (1950). This material on treatment with an ethereal solution of diazomethane gave 2.23 g of an oily diester mixture. Vapor phase chromatographic analysis[7d] at 268° showed four peaks: A, retention time 8.2 min (relative area about 15%); B, 9.2 (6%); C, 9.8 (12%); and D, 10.6 (67%). Although resolution of the peaks was poor, an additional estimate of the composition of the diester mixture was provided by subsequent analysis of transformation products. Each of the above percentages may therefore be regarded as representing approximate absolute yields. Coinjection of this mixture with authentic specimens of *dl*-9-iso-,[1] *dl*-8-iso-,[1] and natural homomarrianolate methyl ether resulted in enhancement of peaks A, C, and D, respectively.

Dieckmann Cyclization. A. Of Dimethyl Homomarrianolate Methyl Ether.—To a colorless solution of 0.187 g (0.50 mmol) of the naturally derived diester III (R = CH_3), mp 85.8–87.0°, in 8.3 ml of anhydrous benzene was added 0.63 ml (1.5 mol-equiv) of a 1.2 *N* solution of sodium *t*-amyloxide in benzene.[9] The mixture was heated at reflux for 0.5 hr and was then poured into an ice-cold solution of 50% acetic acid. The product, isolated by extraction with benzene,[7f] amounted to 0.170 g of crude β-keto ester which gave a blue coloration with an alcoholic solution of ferric chloride. The infrared spectrum showed no absorption at 8.91 μ which is a band characteristic of dimethyl homomarrianolate methyl ether. In another similar cyclization, aliquots of the reaction mixture were removed at 2-min intervals. Analysis of the relative peak intensities of the infrared bands at 5.70 and 8.70 μ (characteristic of only the β-keto ester) with respect to the 8.91-μ absorption indicated that the reaction was 75–85% complete after 1 min and essentially complete after 15 min.

B. Of the Diester Mixture.—A 2.22-g sample of the aforementioned oily mixture of diesters from the potassium reduction (see above) in 100 ml of anhydrous benzene was treated as described above with 7.5 ml of a 1.2 *N* solution of sodium *t*-amyloxide in benzene. The mixture was heated at reflux for 20 min, then cooled in an ice bath, and added with vigorous stirring to 50 ml of ice-cold 50% aqueous acetic acid. The resulting yellow mixture was extracted with 1:1 benzene–ether. The combined organic layers were washed thoroughly with water followed by 5% sodium bicarbonate solution. Isolation[7f] of the neutral product in the organic solution afforded 2.12 g of an orange viscous oil which gave an intense blue-black coloration with a dry ethanolic solution of ferric chloride, $\lambda_{max}^{CHCl_3}$ 5.70 and 5.80 μ (ketone and ester C=O). This product was treated[10] by heating for 25 min at 185° with 70 ml of triethylene glycol containing 3.5 ml of water. The cooled mixture was poured into water, and the product was isolated with ethyl acetate[7f] to afford 1.71 g of an oily mixture, $\lambda_{max}^{CHCl_3}$ 5.78 (ketone and ester C=O) and 5.87 μ (shoulder, acid C=O). A solution of this material in 50 ml of methanol and 80 ml of water containing 11 g of (85%) potassium hydroxide pellets was stirred at reflux for 4 hr. The mixture was cooled, poured into water, and extracted with 1:1 benzene–ether. The product isolated[7f] from the combined organic layers amounted to 1.36 g (81% based on the diester mixture) of a purple amorphous solid, $\lambda_{max}^{CHCl_3}$ 5.75 μ (ketone C=O). Vapor phase chromatographic analysis[7d] of this product at 255° showed the following peaks which were enhanced on coinjection with the indicated substances: E, retention time 7.2 min (relative area 9%), enhanced by *dl*-9-isoestrone methyl ether; F, 8.2 (90%), enhanced by both estrone methyl ether and *dl*-8-isoestrone methyl ether; and G, 9.4 (shoulder on F), enhanced by 8α,9β-estrone methyl ether (see below).

Acidification of the aqueous basic extracts from the saponification reaction described above with ice-cold 50% hydrochloric acid and isolation by extraction with ethyl acetate[7f] afforded 0.216 g (15% yield based on the diester mixture submitted to the Dieckmann cyclization) of a yellow amorphous solid dicarboxylic acid mixture which was chromatographed on 20 g of silica gel. Elution with 2% ether in benzene gave 0.007 g of a colorless semisolid fraction which was discarded. Elution with 10% ether in benzene gave 0.033 g of a colorless amorphous solid which was esterified with diazomethane. Vpc analysis[7d] at 268° gave mainly one peak (B) which was 97% of the total area, at a retention time of 6.7 min. Coinjection experiments showed this product to be different from the known isomers (see above). Elution of the chromatographic column with 15–25% ether in benzene gave 0.143 g of a white amorphous solid which was treated with diazomethane. Vpc analysis[7d] at 268° of the resulting diester mixture gave the aforementioned peaks: A, at retention time 5.8 min (18%); B, 6.7 (38%); C, 7.4 (24%); and D, 8.7 (20%).

A similar preparation of 0.15 g of diester, which was resistant to Dieckmann cyclization, was purified by chromatography on 30 g of silica gel. The column was developed with two 100-ml portions of petroleum ether, two 100-ml portions of 5% benzene in petroleum ether, and two 100-ml portions of 20% benzene in petroleum ether; a total of 17 mg of material was eluted. The major product was then eluted with twelve 50-ml portions of 50% benzene in petroleum ether. Vapor phase chromatographic analysis[7d] at 283° and a flow rate of 30 ml/min indicated that fractions 4 (13 mg) and 5 (15 mg) consisted of a single substance, retention time 4.5 min, which was shown by coinjection experiments to be different from the hitherto known isomers and therefore corresponded to the desired 8α,9β diester. Fraction 6 was similarly shown to contain mainly this diester along with small amounts of the 9β diester, retention time 9.8 min; the 8α diester, 11.2; and the natural diester, 12.4. Fraction 12 was similarly shown to contain only the 8α diester. Fraction 5, although not crystalline, was regarded as **dimethyl 8α,9β-homomarrianolate methyl ether**: $\lambda_{max}^{CHCl_3}$ 5.78 μ (ester C=O); $\lambda_{max}^{95\%\ EtOH}$ 286 mμ (ε 2150) and 278 (2380); $[\alpha]^{27}D$ −47° (in $CHCl_3$).

Anal. Calcd for $C_{22}H_{30}O_5$: mol wt, 374. Found by mass spectrometry:[7c] mol wt, 374.

C. Of the Mixture Containing Predominantly Dimethyl 8α-Homomarrianolate Methyl Ether.—A solution of 0.013 g of the diester mixture (fractions 9–11 from the chromatogram described directly above) and 0.036 g of (98%) potassium *t*-butoxide in 2 ml of benzene was heated at reflux under nitrogen for 2 hr. The mixture was cooled and poured into cold 5% potassium hydroxide solution, and the product was isolated[7f] by extraction with ethyl acetate. The crude oily β-keto ester obtained in this way, amounting to 9 mg, was treated for 15 min at 191° with with 4 ml of triethylene glycol containing 0.2 ml of water. The product, which was isolated as described above, amounted to 7 mg of a yellow oil, $\lambda_{max}^{CHCl_3}$ 5.76 μ (ketone C=O). Chromatography on 5 g of basic alumina afforded 3 mg of a colorless oil, the infrared spectrum of which was identical with that of the previously described *dl*-8-isoestrone methyl ether.[1] Vapor phase chromatographic analysis[7d] at 260° and a flow rate of 30 ml/min indicated that this product consisted of about 2% of 9β-estrone methyl ether (retention time 10.2 min) and 98% of 8α-estrone methyl ether (11.2). Crystallization from ether–petroleum ether afforded 1 mg, mp 89–92°. Recrystallization from the same solvent pair raised the melting point to 91.5–92.5°.

8α,9β-Estrone Methyl Ether.—A 0.033-g sample of the aforementioned oily dimethyl 8α,9β-homomarrianolate (97% pure by vapor phase chromatography) was dissolved in 10 ml of anhydrous benzene and treated with 0.40 ml of 1.2 *N* sodium *t*-amylate in benzene. The mixture was heated at reflux under nitrogen for 6 hr and then cooled to 0°; 1.0 ml of glacial acetic acid was added with stirring, and the mixture was diluted with water. Isolation by extraction with ethyl acetate[7f] afforded 0.030 g of yellow oily β-keto ester, $\lambda_{max}^{CHCl_3}$ 5.70 (ketone C=O) and 5.80 μ (ester C=O), which gave a blue coloration with an alcoholic solution of ferric chloride. This material was treated for 15 min at 196° with 15 ml of triethylene glycol containing 0.75 ml of water. The yellow solution was allowed to cool to room temperature and was then added to ether and water. The organic layer was washed thoroughly with 5% sodium hydroxide solution

(9) J.-M. Conia, *Rec. Chem. Prog.*, **24**, 43 (1963).

(10) K. V. Yorka, W. L. Truett, and W. S. Johnson, *J. Org. Chem.*, **27**, 4580 (1963).

and then with water followed by saturated brine and dried over anhydrous sodium sulfate. The residue obtained on removal of the solvent at reduced pressure amounted to 0.021 g of yellow oily material, $\lambda_{max}^{CHCl_3}$ 5.77 μ (ketone C=O). This material was chromatographed on 7.5 g of basic alumina. The major fraction, eluted with 20% ether in petroleum ether, amounted to 0.013 g of an oil which was evaporatively distilled at 155–160° (10^{-5} mm) to afford 0.012 g of a colorless oil which crystallized on standing. This material was rinsed with a few drops of ether–petroleum ether to give a sample, mp 65–68°, $[\alpha]D$ +342° (*c* 0.075, MeOH). This material was recrystallized from the same solvent pair to give 0.004 g (17% yield) of colorless prisms: mp 71.8–74°; $\lambda_{max}^{CHCl_3}$ 5.79 μ (C=O); λ_{max}^{EtOH} 286 mμ (shoulder, ϵ 2000) and 278 (2280). Vapor phase chromatographic analysis at 255° and coinjection studies demonstrated the presence of a single component which differed from the hitherto known isomers of estrone methyl ether.

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.1; H, 8.5.

A similar preparation of 8α,9β-isoestrone methyl ether, in which potassium *t*-butoxide was employed for the Dieckmann cyclization, gave a sample, mp 62–64°. The mass spectrum of this substance is reproduced in Figure 2. Recrystallization of this material from ether–petroleum ether afforded a sample melting at 73.5–74°. The infrared spectrum of this specimen is reproduced in Figure 1.

Registry No.—I, 15983-67-2; IV (R = CH_3), 15983-68-3.

Acknowledgment.—Acknowledgment is made to the U. S. Public Health Service and to the National Science Foundation for support of this research. We also wish to thank Dr. George Rosenkranz of Syntex S.A. for a generous supply of extremely pure estrone methyl ether.

3-Aryl-2-methylserines. I. A New Synthesis

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Received October 13, 1967

The controlled addition of an aryl Grignard reagent to a 4-carboalkoxy-2,4-dimethyloxazol-5-one **6** provides alkyl 2-acetamido-2-aroylpropionates **7** which can be reduced to give derivatives of the title class of compounds. The dominant reduction product is the *erythro* isomer. The synthesis of both isomers of 3-(3,4-dihydroxyphenyl)-2-methylserine is reported.

While β-arylserines have been much studied, in particular over the past 20 years,[1] the corresponding α-methyl derivatives have received scant attention. In 1959, the Japanese workers Kameda and Kimura[2] described the synthesis of two isomeric α-methyl-β-(*p*-nitrophenyl)serines by Bergmann's[3] modification of the Erlenmeyer reaction. The stereochemistry of the isomers was not defined. More recently, Tristram and coworkers[4] have accomplished a stereoselective synthesis of two of the optically active isomers of 3-(3-hydroxyphenyl)-2-methylserine. They were able to assign the absolute stereochemistry to each by virtue of having started with an optically active acyloin of known absolute configuration. Tristram's serines have since been inverted[5] at the 3 position to provide the other two enantiomers.

In this paper, we report a new synthesis which we believe is more generally suited for the preparation of various substituted 3-aryl-2-methylserines. This route is shown schematically in Scheme I. The requisite azlactone **6** can be synthesized from readily attainable starting materials.

Condensation of phenylmagnesium bromide with **6a** at −70° provided the α-acylamino-β-keto ester **7a** in over-all yields above 30%. Others[6,7] have reported reactions of organometallics with oxazolones. Excess reagent was invariably used, however, and a carbinol was usually isolated. Our procedure appears to be the first example of a selective Grignard addition to an oxazolone **6** to provide α-acylamino-β-keto esters.

Reduction of **7a** with buffered sodium borohydride produced two isomeric alcohols, **8a** and **9a**, in a ratio of *ca.* 2–3:1. The major product was assigned the *erythro*[8] configuration on the basis of Cram's rule[9] and other more demonstrable evidence presented later.[10]

A variety of other reductions (diborane, disiamylborane, diisopropylaluminum chloride–isopropyl alcohol, calcium borohydride, and catalytic methods) were examined in order to achieve a higher proportion of **9a**. Only in the case of calcium borohydride was a significant change noted; an approximate 1:1 ratio prevailed, albeit with some sacrifice in the over-all yield.[11]

Hydrolysis of both **8a** and **9a** with hydrochloric acid provided two different amino acids, **10a** and **11a**, respectively. The former, *erythro*, possessed the lower decomposition point and exhibited a strong band in

(1) For a leading reference, see J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," John Wiley and Sons, Inc., New York, N. Y., 1961, Chapter 49.

(2) Y. Kameda and Y. Kimura, *Kanazawa Daigaku Yakugakubu Kenkyu Nempo*, **9**, 23 (1959); *Chem. Abstr.*, **54**, 3237 (1960).

(3) E. D. Bergmann, H. Bendas, and W. Taub, *J. Chem. Soc.*, 2673 (1951).

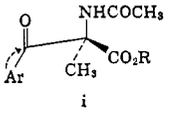
(4) E. W. Tristram, B. F. Powell, D. E. Williams, R. J. Tull, and J. M. Chemerda, presented at the meeting of the New York–New Jersey Section of the American Chemical Society, Jan 1962.

(5) S. H. Pines, S. Karady, M. A. Kozlowski, and M. Sletzinger, *J. Org. Chem.*, **33**, 1762 (1968).

(6) J. W. Cornforth, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, pp 738, 792.

(7) W. I. Awad and M. S. Hafez, *J. Org. Chem.*, **25**, 1180 (1960).

(8) For the sake of clarity, we are defining the *erythro* isomers of this system as those in which the disposition of the heteroatoms and "aliphatic" (CH_3 and C_3–H) portions are similar (ii).



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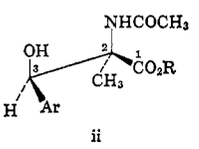

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(9) D. J. Cram and F. A. A. Elhafez, *J. Amer. Chem. Soc.*, **74**, 5828 (1952); D. J. Cram and K. R. Kopecky, *ibid.*, **81**, 2748 (1959).

(10) For characterization *via* nmr spectroscopy, see ref 5.

(11) Benzaldehyde was noted as a by-product in this reduction. It could have been produced by retroaldolization of the *erythro* product.