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°; $\lambda_{max}^{95\%\ EtOH}$ 248 mμ (log ε 4.32); λ_{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°; $\lambda_{max}^{95\%\ EtOH}$ 226 mμ (log ε 4.03), 276 (3.22), 282 (3.17); λ_{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 semi-solid 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°; $\lambda_{max}^{95\%\ EtOH}$ 222 mμ (log ε 4.02), 274 (3.22), 280 (3.15); λ_{max}^{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°; λ_{max}^{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 non-crystalline 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

BY WILLIAM S. JOHNSON AND WILLIAM F. JOHNS[1]

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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]

(1) Wisconsin Alumni Research Foundation Research Assistant, 1953–1954.

(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).

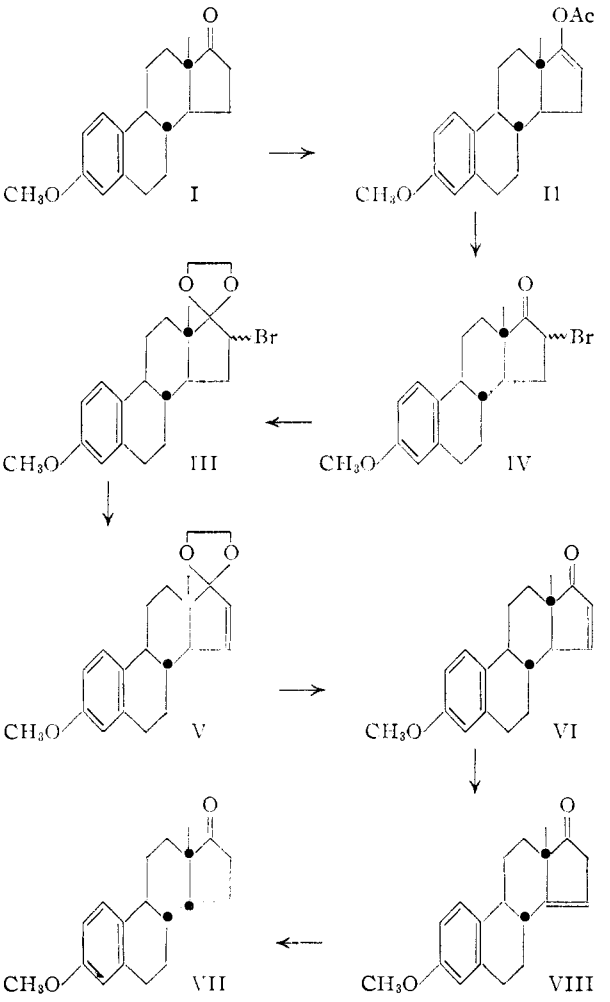
(5) *Cf.* a similar system (ref. 4b) in which there appeared to be no detectable amount of the C/D *trans*-15,16-dehydro compound at equilibrium.

Our initial studies, accordingly, were directed toward the preparation of the 15,16-dehydroketone VI.

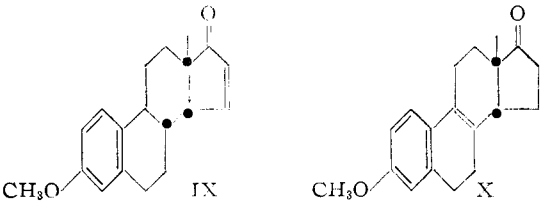
Bromination of estrone methyl ether has been reported to give, in 22% yield, a monobromo derivative presumed to be the 16-bromoketone IV.[6] Further unpublished studies[7] showed that bromination in acetic acid yielded a complex mixture evidently containing significant amounts of a product of nuclear bromination in ring A. The direct bromination approach, therefore, was considered unpromising, and we turned our attention to the bromination of the enol acetate II, following a method that proved so successful in the preparation of 16-bromoepiandrosterone acetate.[8]

Estrone methyl ether (I) was converted readily by the action of isopropenyl acetate[9] into the enol acetate, m.p. 114–115°. Treatment of this substance, as previously described,[8] with 1 mole equivalent of bromine in chloroform at 0°, produced a mixture from which crude 16-bromoketone IV was isolated in 57% yield. Chromatography showed the presence of estrone methyl ether, as well as a dibromo derivative, m.p. 236–238°, which contained bromine in the aromatic nucleus as evidenced by a bathochromic shift of the anisole spectrum, *viz.*, λ_{max} 283, 292 mμ as compared with λ_{max} 278, 286 mμ for the authentic 16-bromoketone IV. On the assumption that the undesired nuclear bromination was promoted by acid, the reaction was tried in the presence of solid potassium carbonate. The bromination was rapid at 0°, and the 16-bromoketone IV was isolated readily in 91% yield. The pure substance melted at 176–177°. The previously reported substance,[6] m.p. 191–193°, may be the epimeric 16-bromoketone, or a product of nuclear bromination.

Attempts to effect direct dehydrobromination of 16-bromoepiandrosterone acetate gave very poor results, due apparently to extensive polymerization of the resulting highly reactive cyclopentenone system. In the present series, therefore, we decided against this approach, particularly since preliminary attempts had shown no promise.[7] We turned our attention, instead, to the ingenious device discovered by Dauben, Ben and Chiang[10] of protecting the ketone group as the ketal, prior to dehydrohalogenation. The cyclic ethylene ketal III, m.p. 198–200°, was prepared easily by interaction of ethylene glycol and the bromo ketone IV.[11] When the ketal was heated for 22 hr. with potassium *t*-butoxide in benzene, there was no significant reaction, but with xylene as the solvent, after heating for 16 hr., the unsaturated ketal V, m.p. 125–126° (pure), was produced in 75% yield. Mild hydrolysis of this substance with *p*-toluenesulfonic acid in aqueous acetone at room temperature afforded 15,16-dehydroestrone methyl ether (VI), m.p. 180–181° (pure), in 68% yield. The absorption at 223 mμ (log ε 4.15) and at 5.88 μ established the position of the olefinic bond as conjugated with the keto group. That this substance retained the natural configuration was established by catalytic hydrogenation to produce estrone methyl ether.



When the 15,16-dehydroketone VI was heated for 15 minutes with *p*-toluenesulfonic acid in benzene solution, a mixture was produced from which two isomers of VI were isolated, m.p. 103–104° and 101–102°, in 52 and 20% yield, respectively. The ultraviolet spectrum of the former isomer,



λ_{max} 276 mμ (log ε 3.35), 286 (3.32), was characteristic of the anisole chromophore showing that the olefinic bond was isolated, *i.e.*, not in conjugation with the carbonyl group or with the aromatic

(6) G. F. Marrian and G. A. D. Haslewood, *J. Soc. Ch. Ind. Trans.*, **51**, 277 (1932).

(7) Private communication from A. L. Wilds and R. Doban.

(8) (a) P. Z. Bedoukian, THIS JOURNAL, **67**, 1430 (1945); (b) R. Pappo, B. M. Bloom and W. S. Johnson, *ibid.*, **78**, 6347 (1956).

(9) The procedure of R. B. Moffett and D. I. Weisblat, *ibid.*, **74**, 2183 (1952), was used.

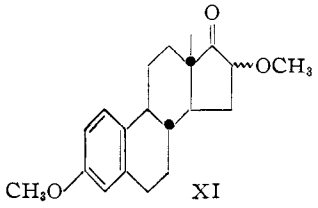
(10) H. J. Dauben, Jr., V. R. Ben and S. H. K. Chiang, Abstracts of the 123rd Meeting of the Am. Chem. Soc., Los Angeles, Calif., 1953, p. 9M.

(11) A modification of the procedure of G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953), was employed.

nucleus.[12] The only unconjugated position into which the olefinic bond of VI would be expected to migrate readily under such mild conditions would be at 14,15. That the 104° isomer is correctly represented by this structure (formula VIII) was supported by the fact that the olefinic bond was hydrogenated easily.[13] The product was different from estrone methyl ether and hence is undoubtedly 14-isoestrone methyl ether. The pure substance melted at 114–115° and the infrared spectrum, which contained no less than 25 distinct bands in the region beyond 8 μ, was indistinguishable from that of the totally synthetic *dl*-isomer, m.p. 120.6–121°,[2] in question.

The companion (102°) dehydro compound, isolated from the isomerization experiment described above, exhibited strong absorption at 221 mμ and at 5.90 μ showing that the olefinic bond was conjugated with the keto group. This substance thus was clearly 15,16-dehydro-14-isoestrone methyl ether (IX), an expected component of the 3-carbon tautomeric system discussed above. It was not surprising to find that catalytic hydrogenation afforded material identical with that obtained by hydrogenation of the 14,15-dehydro compound (see above), namely, 14-isoestrone methyl ether (VII). This fact affords further support for the configuration of VIII.

When the unsaturated ketal V was submitted to relatively vigorous hydrolytic conditions (heating for 2 hr. with *p*-toluenesulfonic acid in acetone), the reaction was accompanied by more extensive isomerization. From the mixture there was isolated in 11% yield a product, m.p. 107–109°, λ_{max} 273 mμ (log ϵ 4.13), which probably was mainly 8,9-dehydro-14-isoestrone methyl ether (X), a previously known product of the isomerization of equilin.[12]



XI

An attempt to effect a base-catalyzed isomerization of VI with methanolic potassium hydroxide gave a compound, $C_{20}H_{26}O_3$, m.p. 132–133°, in 50% yield. This substance was undoubtedly 15-methoxyestrone methyl ether (XI) formed by conjugate addition of methanol to the 15,16-dehydro compound VI. It is possible, but less likely, that epimerization at C_{14} occurred prior to addition of methanol, in which event the 133° compound should be represented as 14-iso XI.

Before the work reported above was undertaken, preliminary experiments were performed in the series with an acetoxy instead of methoxy group at the 3-position. When treated directly with isopropenyl acetate[9] estrone was converted into the enol diacetate, m.p. 149–151°.[14] Our hope that the acetoxy group at the 3-position would render the aromatic nucleus less susceptible to substitution was realized. Bromination, without added potassium carbonate (compare the case of the methyl ether described above), gave the 16-bromoacetoxyketone, m.p. 168–170° (pure), in 76% yield. Further preliminary experiments on ketal formation were complicated by partial solvolysis of the acetoxy group, and this series was not studied further.

Acknowledgment.—We wish to thank Drs. G. Rosenkranz, C. Djerassi and the Syntex Company for providing us with a generous supply of exceedingly pure estrone which was employed in this study.

Experimental[15]

Enol Acetate II of Estrone Methyl Ether.[9]—A solution of 5.96 g. of estrone methyl ether[16] in 90 ml. of isopropenyl acetate containing 1.0 g. of *p*-toluenesulfonic acid monohydrate was distilled slowly (high reflux ratio) through a 5-in. Vigreux column to a volume of about 50 ml. over a 14 hr. period. The solution was cooled, diluted with ether, washed with saturated sodium bicarbonate solution and with water and dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the solvent was adsorbed on a column of 90 g. of Florex. Elution with petroleum ether (65–68°) gave 5.80 g. of crude enol acetate which on crystallization from petroleum ether (65–68°) afforded 4.98 g. (first crop), m.p. 113–114°, and 0.53 g. (second crop), m.p. 114–115°. Recrystallization from petroleum ether (65–68°) and again from methanol gave colorless plates, m.p. 114.5–115°.

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.1; H, 8.09.

A later 1.15-g. fraction was eluted from the chromatographic column with benzene and yielded, on crystallization from methanol, 0.70 g. of estrone methyl ether, m.p. 163–166°.

16-Bromoestrone Methyl Ether (IV).—A suspension of 0.5 g. of anhydrous potassium carbonate in a solution of 0.770 g. of the aforementioned enol acetate, m.p. 110–113°, in 35 ml. of carbon tetrachloride was stirred at 0°, while 0.427 g. of bromine in 10 ml. of carbon tetrachloride was added over a 5-minute period. The colorless mixture was poured into water containing a little sodium bisulfite, the aqueous layer was extracted with chloroform, and the combined organic layers dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the solvent at reduced pressure was crystallized from methanol to give 0.765 g. (first crop), m.p. 173–175°, and 0.025 g. (second crop), m.p. 170–173°. A specimen, m.p. 173–176°, produced in another run was repeatedly recrystallized from methanol to give colorless rods, m.p. 176–177°, $\lambda_{max}^{95\%\ EtOH}$ 278 mμ (log ϵ 3.29), 286 (3.26), 313 (2.10); λ_{min} 248 (2.50), 284 (3.22), 299 (2.02).

Anal. Calcd. for $C_{19}H_{23}O_2Br$: C, 62.81; H, 6.38. Found: C, 63.0; H, 6.23.

A run carried out as described above, except that the potassium carbonate was omitted, gave the following results. From 3.57 g. of enol acetate, m.p. 114–115°, and 1.75 g. of bromine there was obtained 2.27 g. (first crop) of the bromoketone, m.p. 172–175°. Later crops melted over a broad range. In another run, the total crude product from 1.59 g. of the enol acetate and 0.664 g. of bromine was chromatographed on 60 g. of Florisil. The fraction (1.1 g.) eluted with 10% benzene in petroleum ether (65–68°) afforded, on crystallization from methanol, 0.71 g. of bromoketone, m.p. 169–172°. Later (benzene) eluates yielded complex

(12) The 8,9-dehydro (m.p. 107–109°) and 9,11-dehydro-14-iso compounds are known to absorb at 275 mμ (log ϵ 4.2) and 263.5 mμ (log ϵ 4.4), respectively; D. Banes, J. Carol and E. O. Haenni, *J. Biol. Chem.*, **187**, 557 (1950).

(13) An olefinic bond in the 8,14-position is known to be resistant to hydrogenation; see for example Fr. Schenck, K. Buchholz and O. Wiese, *Ber.*, **69**, 2696 (1936).

(14) N. S. Leeds, D. K. Fukushima and T. F. Gallagher, THIS JOURNAL, **76**, 2943 (1954).

(15) Melting points are corrected for stem exposure unless otherwise specified.

(16) Prepared from estrone by the procedure of Butenandt as modified by W. S. Johnson, D. K. Banerjee, W. P. Schneider, C. D. Gutsche, W. E. Shelberg and L. J. Chinn, THIS JOURNAL, **74**, 2832 (1952).

mixtures from which there were separated by fractional crystallization from methanol, 0.085 g. of estrone methyl ether, m.p. 164–166°, and 0.010 g. of 2(?),16-dibromoestrone methyl ether as colorless rods, m.p. 236–238° (uncor.), $\lambda_{max}^{95\%\ EtOH}$ 283 mμ (log ε 3.57), 292 (3.54); λ_{min} 256 (2.89), 289 (3.51).

Anal. Calcd. for $C_{19}H_{22}O_2Br_2$: C, 51.60; H, 5.01. Found: C, 51.8; H, 5.12.

3-Methoxy-16-bromo-17-ethylenedioxyestra-1,3,5(10)-triene (III).—A solution of 0.690 g. of the aforementioned bromoketone, m.p. 173–175°, 0.12 g. of *p*-toluenesulfonic acid monohydrate and 6 ml. of ethylene glycol in 30 ml. of toluene was distilled slowly (at a high reflux ratio) through a 5-in. Vigreux column for 30 hr. The solution was cooled, washed with saturated sodium bicarbonate solution and with water and dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the solvent at reduced pressure was crystallized from isopropyl alcohol to give 0.505 g. of the bromoketal, m.p. 182–191°, showing no carbonyl absorption in the infrared region. Repeated recrystallization from methanol gave colorless rods, m.p. 198–200°.

Anal. Calcd. for $C_{21}H_{27}O_3Br$: C, 61.92; H, 6.68. Found: C, 62.3; H, 6.80.

In another run starting with 1.17 g. of bromoketone, the crude product was chromatographed on 20 g. of Florex. The fractions (0.84 g.) eluted with petroleum ether (65–68°) yielded, on crystallization from methanol, 0.630 g. of bromoketal, m.p. 188–190°.

3-Methoxy-17-ethylenedioxyestra-1,3,5(10),15-tetraene (V).—A solution of 0.40 g. of potassium in 20 ml. of dry *t*-butyl alcohol was distilled to dryness under reduced pressure. Xylene (20 ml.) was added, then removed by distillation, and this process was repeated twice more to ensure complete removal of the *t*-butyl alcohol. A solution of 0.635 g. of the aforementioned bromoketal, m.p. 187–190°, in 40 ml. of xylene was added to the potassium *t*-butoxide and the mixture heated under reflux in an atmosphere of nitrogen for 16 hr. The solution was cooled, diluted with ice-water, and the aqueous layer was extracted with ether. The combined organic layers were washed with water and dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the solvent at reduced pressure yielded, on crystallization from methanol, 0.200 g. (first crop), m.p. 124–125°, and 0.180 g. (second crop), m.p. 122–124°. Repeated recrystallization from methanol afforded large colorless plates, m.p. 125–126°.

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.2; H, 8.12.

When 0.500 g. of the crude bromoketal, m.p. 182–191°, was similarly treated, there were obtained 0.240 g. (first crop), m.p. 120–122°, and 0.042 g. (second crop), m.p. 120–122°, of satisfactory unsaturated ketal.

15,16-Dehydroestrone Methyl Ether (VI).—A solution of 0.080 g. of the aforementioned unsaturated ketal, m.p. 120–122°, and 0.004 g. of *p*-toluenesulfonic acid monohydrate in 6 ml. of acetone and 1 ml. of water was allowed to stand at room temperature for 1 hr. Ether was added, and the solution was washed with saturated sodium bicarbonate solution, then dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the solvent yielded, on crystallization from ether–petroleum ether (65–68°), 0.042 g. (first crop), m.p. 169–173°, and 0.005 g. (second crop), m.p. 165–172°. Comparable material from another run was recrystallized repeatedly from ether and from isopropyl alcohol to give pure material as colorless prisms, m.p. 180–181°, $\lambda_{max}^{95\%\ EtOH}$ 223 mμ (log ε 4.15), 277 (3.30), 286 (3.24); λ_{min} 215 (4.10), 266 (2.34), 284 (2.33); $\lambda_{max}^{CHCl_3}$ 5.88 μ (C=C—C=O).

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 81.0; H, 7.98.

Isomerization of 15,16-Dehydroestrone Methyl Ether. (a) Under Mild Conditions.—A solution of 0.061 g. of the 15,16-dehydro compound, m.p. 173–177° (obtained by one recrystallization from ether of material, m.p. 169–173°, described above), and 0.04 g. of *p*-toluenesulfonic acid monohydrate in 3 ml. of benzene was heated under reflux for 15 minutes, then cooled and adsorbed on a column of 6 g. of Florex. The fraction (0.039 g.) eluted with 70% petroleum ether (32–35°) in benzene yielded, on crystallization from aqueous methanol, 0.032 g. of crude **14,15-dehydroestrone methyl ether (VIII)**, m.p. 95–100°. A comparable sample from another run was recrystallized repeatedly from aqueous methanol and from petroleum ether (32–35°) to give colorless plates, m.p. 103–104°, $\lambda_{max}^{95\%\ EtOH}$ 276 mμ (log ε 3.35), 286 (3.32); λ_{min} 248 (2.59), 283 (3.28); λ_{max}^{Nujol} 5.77 μ (C=O). The analysis of this material (see below) suggested that it crystallized as a hemihydrate.

Anal. Calcd. for $C_{19}H_{22}O_2 \cdot {}^1/_2H_2O$: C, 78.31; H, 7.96. Found: C, 78.5; H, 7.91.

The fraction (0.016 g.), eluted with 40% petroleum ether (32–35°) in benzene through to pure ether, yielded on crystallization from petroleum ether (65–68°), 0.012 g. of **15,16-dehydro-14-isoestrone methyl ether (IX)**, m.p. 100–102°. Repeated recrystallization from aqueous methanol gave colorless plates, m.p. 101–102°, $\lambda_{max}^{95\%\ EtOH}$ 221 mμ (log ε 4.23), 277 (3.43), 286 (3.37); λ_{min} 214 (4.19), 264 (3.32), 284 (3.34); λ_{max}^{Nujol} 5.90 μ (C=C—C=O).

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.5; H, 7.75.

(b) Under More Vigorous Conditions. Isolation of the 8,9-Dehydro Compound.—A solution of 0.080 g. of the unsaturated ketal V, m.p. 126–127°, and 0.05 g. of *p*-toluenesulfonic acid monohydrate in 20 ml. of acetone was heated under reflux for 2 hr., then cooled and poured into aqueous sodium bicarbonate solution. The aqueous layer was extracted with ether, and the combined organic layers were washed with saturated sodium bicarbonate solution, then dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the solvent under reduced pressure was chromatographed on a column of 3 g. of Florisil. The fraction (0.040 g.) eluted with 50% petroleum ether (65–68°) in benzene gave, on crystallization from aqueous methanol, 0.036 g. of crude 8,9-dehydro-14-isoestrone methyl ether, m.p. 95–102°. Recrystallization from a small volume of methanol gave 0.009 g. of material, m.p. 107–109°, $\lambda_{max}^{95\%\ EtOH}$ 273 mμ (log ε 4.13); λ_{max}^{Nujol} 5.77 μ (C=O). These properties are in close agreement with those reported for this substance.[12]

Hydrogenation of 15,16-Dehydroestrone Methyl Ether.—A 0.025-g. sample of the 15,16-dehydroketone, m.p. 170–177°, was hydrogenated at atmospheric pressure and room temperature over 0.07 g. of 10% palladium-on-carbon (American Platinum Works) in a total of 70 ml. of 95% ethanol. Within 15 minutes 1 mole-equivalent of hydrogen was absorbed and the reaction had ceased. The residue obtained after filtration and evaporation was crystallized from methanol to give 0.022 g. of estrone methyl ether, m.p. 165–168°, undepressed on admixture with authentic material.

14-Isoestrone Methyl Ether (VII). (a) From 14,15-Dehydroestrone Methyl Ether.—A 0.026-g. sample of the 14,15-dehydroketone, m.p. 101–103°, was hydrogenated at atmospheric pressure and room temperature over 0.15 g. of 10% palladium-on-carbon in 15 ml. of 95% ethanol. Within 5 minutes 1 mole-equivalent of hydrogen was absorbed and the reaction had ceased. Crystallization of the crude product, obtained after filtration and evaporation, from methanol gave 0.012 g. (first crop), of colorless plates, m.p. 114–115°, $[\alpha]^{26}D$ +156° (*c* 1.02 in $CHCl_3$), and 0.006 g. (second crop), m.p. 108–112°. The purest specimen, obtained after further recrystallizations of the first crop material, still melted at 114–115°, $\lambda_{max}^{95\%\ EtOH}$ 277 mμ (log ε 3.33), 286 (3.29); λ_{min} 244 (2.48), 284 (3.25).

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.4; H, 8.42.

This analytical specimen was employed in the infrared comparison with the totally synthetic *dl*-compound, m.p. 120.6–121°.[2]

(b) From 15,16-Dehydro-14-isoestrone Methyl Ether.—A solution of 0.009 g. of the unsaturated ketone, m.p. 100–102°, in 15 ml. of 95% ethanol was hydrogenated as described above (part a) over 0.08 g. of catalyst. After 10 minutes, reaction was complete. Crystallization of the crude product from aqueous methanol gave 0.007 g. of material, m.p. 111–113°, undepressed on admixture with the analytical specimen of 14-isoestrone methyl ether described above.

15-Methoxyestrone Methyl Ether (XI).—A slurry of 0.040 g. of 15,16-dehydroestrone methyl ether, m.p. 164–174°, in 2 ml. of methanol containing 2 drops of 5% aqueous sodium hydroxide solution was stirred at room temperature

until the crystals dissolved (10 minutes). After an additional 5 minutes the solution was acidified with dilute hydrochloric acid and extracted with ether. The combined ether layers were washed with saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the solvent at reduced pressure was chromatographed on 4 g. of Florex. The fraction (0.034 g.) eluted with benzene was crystallized from ether to give 0.022 g. of colorless platelets, m.p. 132–133°. Repeated recrystallization from ether and from petroleum ether (65–68°) did not alter the m.p.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.3; H, 8.27.

Enol Acetate of Estrone Acetate.—A solution of 1.00 g. of estrone, m.p. 253–257°, and 0.5 g. of *p*-toluenesulfonic acid in 50 ml. of isopropenyl acetate was distilled slowly (high reflux ratio) through a 5-in. Vigreux column for 17 hr. The crude product, isolated as described above for the preparation of II, was adsorbed on a column of 30 g. of Florex. The early fraction (0.99 g.) eluted with 10% benzene in petroleum ether (65–68°) gave, on crystallization from methanol, 0.87 g. of colorless elongated flat prisms, m.p. 149–151°. Further recrystallization did not raise this m.p.

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.3; H, 7.52.

After the completion of this preparation, Leeds, Fukushima and Gallagher[14] published the preparation of this substance, m.p. 149–150°, by an improved procedure.

16-Bromoestrone Acetate.—A solution of 0.045 g. of the aforementioned enol diacetate, m.p. 149–151°, in 1 ml. of carbon tetrachloride was treated at 0° with 0.0184 g. of bromine in 1.2 ml. of carbon tetrachloride. Within 3 minutes the solution was colorless, and the solvent was evaporated at reduced pressure. Trituration of the residue with ether gave 0.038 g. of crystals, m.p. 163–168°. Repeated recrystallization from methanol gave colorless rods, m.p. 168–170°.

Anal. Calcd. for $C_{20}H_{23}O_3Br$: C, 61.38; H, 5.92. Found: C, 61.0; H, 5.87.

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[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, THE UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE]

A New Synthesis of DL-Lysine-1-C^{14}

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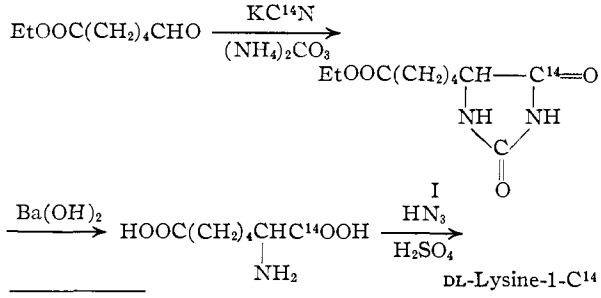
DL-Lysine-1-C^{14} has been synthesized in an over-all yield of 66.5% based on KC^{14}N. An 86% yield of the intermediate DL-α-aminopimelic acid-1-C^{14} was obtained.

DL-Lysine-1-C^{14} has previously been synthesized in two ways. Borsook, *et al.*,[2] using the method of Gaudry,[3] prepared 5-δ-bromobutylhydantoin-4-C^{14} from KC^{14}N. Treatment with ammonia followed by hydrolysis of the resulting amino hydantoin yielded lysine-1-C^{14} in 10–15% yield. Barry[4] reports a simplified procedure with an increased yield. Arnstein, *et al.*,[5] utilized the carboxylation of cyclohexanone with $C^{14}O_2$ in liquid ammonia to form 2-oxocyclohexanecarboxylic acid. Esterification of the product, followed by treatment with hydrazoic acid, led to lysine-1-C^{14} in an over-all yield of 12%. Both methods suffer from low over-all yields and rather long procedures. For this reason, an entirely new synthesis was undertaken which would provide a simple method for the preparation of DL-lysine-1-C^{14} in good yield. The following equations show the synthetic route selected



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In two cold runs, using equimolar amounts of aldehyde and potassium cyanide, the yields of the hydantoin I were 51 and 53%, respectively. A large excess of aldehyde does not improve the yield based on cyanide but complicates the isolation of pure hydantoin. Freshly prepared aldehyde should be used, since use of material several days old reduced the yield of I to 39%. Matched runs using sodium cyanide and potassium cyanide gave only 46% of I in the former case, compared to 53% in the latter. Preparation and isolation of the cyanohydrin of ethyl 5-formylvalerate, followed by treatment of the product with ammonium carbonate, gave the same yield of I as the one-step procedure.

In the "hot run," only 18.6% of I could be isolated from the reaction mixture. However, hydrolysis of the mother liquors with barium hydroxide yielded an additional 67.5% of DL-α-aminopimelic acid-1-C^{14}, making the over-all yield of this compound 86%, based on KC^{14}N. Apparently, an α-aminopimelic acid precursor existed in the mother liquors, possibly the hydantoin amide or potassium salt derived from I. The only apparent difference between the radioactive run and the cold runs was the presence of an excess of potassium hydroxide in the KC^{14}N solution. The excess alkali was partly neutralized with hydrochloric acid before proceeding with the reaction. Thus, it would seem likely that even in the "cold runs," where a 53% yield of hydantoin was obtained, a considerable amount of this α-aminopimelic acid precursor was present.

The isolation of α-aminopimelic acid-1-C^{14} after hydrolysis of the mother liquors of the Bucherer reaction was complicated by the presence of inorganic salts from the original reactants. The acid