[Contribution from the School of Chemistry, Rutgers, The State University]

Syntheses Related to Etiojervane. II. Synthesis of Some Substituted Fluorenes

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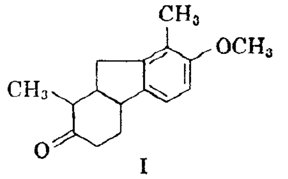
6-Bromo-3-methoxy-2-methylbenzoic acid has been prepared and its methyl ester transformed by the Ullmann reaction to 4,4′-dimethoxy-3,3′-dimethyldiphenic acid (XII). Acid XII could be converted *via* the anhydride to 2,7-dimethoxy-1,8-dimethylfluorenone or by sulfuric acid and subsequent decarboxylation to 2,7-dimethoxy-1,6-dimethylfluorenone. The analogous series of transformations starting from 6-bromo-3-methoxybenzoic acid yielded 2,7-dimethoxyfluorenone (XXII). These fluorenones were reduced to the corresponding fluorenes and the ether linkages of XIV and XXIII were cleaved to the hydroxyfluorenes. Attempts to reduce one benzene ring of 2,7-dihydroxy-1,8-dimethylfluorenone were not successful.

As described in paper I of this series[2] the immediate objective of these synthetic experiments was ketone I, a hexahydrofluorene which by addition of one more ring would yield a substance having the carbon skeleton of etiojervane.

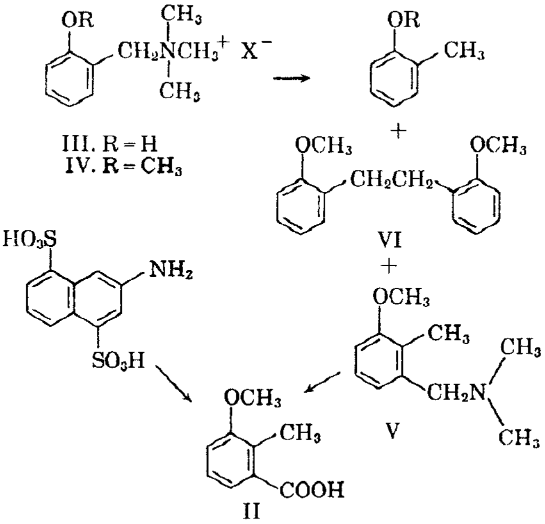


I

Since the methyl groups and oxygen functions of I are symmetrically situated, a logical approach was to attempt to construct the two halves of the molecule from the same starting material. 3-Methoxy-2-methylbenzoic acid II was a substance suitable for this purpose.

An attempt to make use of the interesting reaction of Kantor and Hauser[3] for preparing II was only partly successful. From 2-hydroxybenzyltrimethylammonium iodide (III) only *o*-cresol was isolated. However, 2 - methoxybenzyltrimethylammonium chloride (IV) produced some of the desired amine, 3-methoxy-2-methylbenzyldimethylamine (V) in addition to 2,2′-dimethoxydibenzyl (VI) an unexpected by-product.[4]

The rearranged amine V which was obtained could be oxidized without difficulty to acid II. However, the alkali fusion[5] of 3-amino-1,5-disulfonic acid proved to be the more economical process for its preparation.



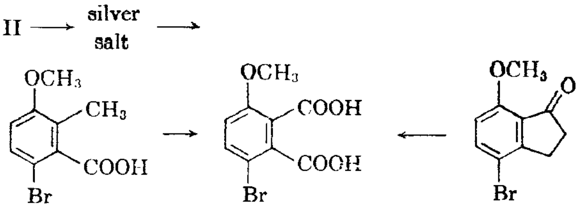
III. R = H
IV. R = CH_3

VI

V

II

The synthetic plan required that two molecules of acid II be linked at the positions *para* to the methoxyl group. The easiest way of accomplishing this appeared to be *via* the Ullmann reaction on the bromo derivative IX. It might be anticipated that direct bromination of II in the usual manner would produce large amounts of the isomer with the bromine *ortho* to the methoxyl group. As expected the silver salt of II reacted, presumably through intramolecular attack of an intermediate acyl hypobromite,[6] to yield mainly the desired brominated product VII. The structure of VII was proved by oxidation to phthalic acid VIII. An authentic sample of VIII was prepared from hydrindone IX of known structure.[7]



VII VIII IX

The use of a small amount of 2,4-dimethylsulfolane as a solvent facilitated the Ullmann reaction with the methyl ester of VII. The product was

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[1] Abstracted from a thesis presented by R. W. Faessinger to the Graduate School for the Ph.D. degree, June 1957.

[2] R. A. Barnes and N. N. Gerber, *J. Org. Chem.*, **26**, 4540 (1961).

[3] W. Kantor and C. R. Hauser, *J. Am. Chem. Soc.*, **73**, 4122 (1951).

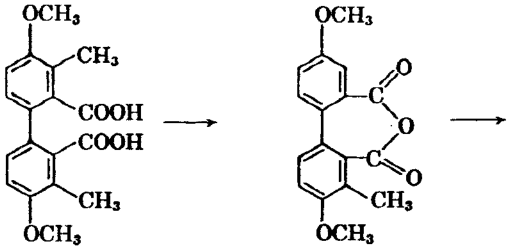
[4] The mechanism for formation of this product is currently being investigated.

[5] This reaction has been described by O. Baudisch and W. H. Perkin, *J. Chem. Soc.*, **95**, 1883 (1909), and L. F. Fieser and W. C. Lothrop, *J. Am. Chem. Soc.*, **58**, 752 (1936).

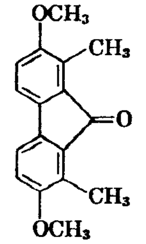
[6] W. G. Dauben and H. Tilles, *J. Am. Chem. Soc.*, **72**, 3185 (1950).

[7] R. A. Barnes, E. R. Kraft, and L. Gordon, *J. Am. Chem. Soc.*, **71**, 3523 (1949).

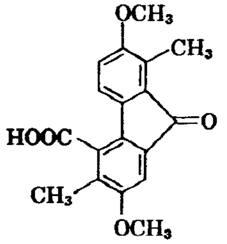
saponified and isolated as the diphenic acid XII. Cyclization of XII to the desired fluorene XIV could be accomplished by first preparing the anhydride XII and then eliminating carbon dioxide by pyrolysis.[8]



XII XIII



XIV

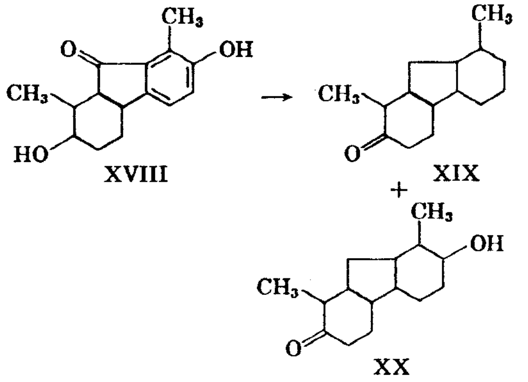


XV

If moisture was not carefully excluded during the heating of the anhydride, some of a Friedel-Crafts type of cyclization took place with formation of acid XV. This acid could also be prepared by reaction of XII with sulfuric acid; decarboxylation of XV produced 2,7-dimethoxy-1,6-dimethylfluorenone XVI, an isomer of the desired fluorenone.

Either sodium and amyl alcohol or sodium amalgam in ethanol reduced the carbonyl group of fluorenone, 2,7-dimethoxyfluorenone, or fluorenone XVI. However, with fluorenone XIV, having two methyl groups adjacent to the carbonyl group, the reduction under these conditions proceeded only to the alcohol stage. Complete reduction was accomplished by catalytic hydrogenolysis over copper–chromium oxide or by the Wolff-Kishner and Clemmensen procedures.

For ultimate conversion to a ketone group, it was necessary that a methoxyl group of XIV (preferably only one)[9] be converted to a hydroxyl group. Partial ether cleavage of XIV was not successful and after complete cleavage, partial methylation with diazomethane was not an effective procedure for obtaining the desired monomethyl ether. Nevertheless, dihydroxyfluorene XVIII was reduced with copper–chromium oxide at 210°. Even under these relatively mild conditions, there was produced a mixture of products apparently resulting from hydrogenolysis and perhydrogenation. This was evident when the crude reaction mixture was oxidized and the mixture of ketones characterized by the preparation of derivatives.



Ketone XX was isolated as the 2,4-dinitrophenylhydrazone and ketone XIX as the semicarbazone.

The desired partial hydrogenation might have been more successful[10] if the synthesis were modified to yield the monomethyl ether of XVIII.[9] However, other routes[11] have now been developed for the preparation of I.

EXPERIMENTAL[12]

2-Hydroxybenzyltrimethylammonium iodide (III). Phenol (51.7 g.), paraformaldehyde (16.5 g.), and 25% aqueous dimethylamine (100 ml.) were allowed to react by the procedure of Decombe.[13] The fraction (30 g.) which boiled at 104–108° (17 mm.) had n_D^{23} 1.522 and formed a picrate which melted at 154–155°. This material reacted with methyl iodide in ether to yield IV which had a m.p. of 174–175°.

Anal. Calcd. for $C_{10}H_{16}ONI$: C, 40.97; H, 5.50. Found: C, 40.98; H, 5.48.

2-Methoxybenzyltrimethylammonium chloride (IV). 2-Methoxybenzyl alcohol (15.6 g.) in dry benzene (100 ml.) containing calcium chloride (15 g.) was saturated with dry hydrogen chloride and allowed to stand overnight in a stoppered flask. The benzene solution was decanted and warmed *in vacuo* to remove excess hydrogen chloride. This solution was cooled and treated with a solution of trimethylamine (10 g.) in dry benzene (100 g.). The reaction mixture was allowed to stand for 48 hr. and the crystalline mass was filtered and recrystallized from acetone to yield 17 g. (70%) of product which melted at 194.4–195°. This product absorbed atmospheric moisture readily and analysis indicated that it was largely the monohydrate.

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[8] E. H. Huntress and I. S. Cliff, *J. Am. Chem. Soc.*, 55, 2559 (1933) used this procedure for preparing 1,8-dichlorofluorenone.

[9] Musser and Adkins, *J. Am. Chem. Soc.*, 60, 664 (1938) have found that hydroxyl-containing aromatic rings were more readily reduced by copper-chromium oxide than the corresponding aromatic ethers. See also A. L. Wilds and F. McCormack, *J. Am. Chem. Soc.*, 70, 4127 (1948).

[10] Although the partial reduction was not successful, reduction using other catalysts or by chemical means, *i. e.*, lithium and amines, should be successful in converting XVIII to perhydro derivatives which may serve as intermediates for the preparation of nonaromatic jervane derivatives.

[11] To be reported in a future communication.

[12] Microanalyses were by W. Manser, Zurich, Switzerland. Melting points were observed on a Kofler hot stage. Infrared spectra were determined using the Perkin-Elmer Model 21 spectrophotometer.

[13] J. Decombe, *Compt. rend.*, 196, 866 (1933).

Anal. Calcd. for $C_{11}H_{18}ONCl$: C, 61.24; H, 8.41. Calcd. for $C_{11}H_{18}ONCl \cdot H_2O$: C, 56.52; H, 8.63. Found: C, 57.25; H, 8.60.

Attempted rearrangement of III *and* IV. Sodium (23 g.) was converted to sodamide in liquid ammonia (400 ml.). To this solution, compound III (111 g.) was added in portions with continuous stirring. When the addition was complete, the mixture was stirred for an additional 3.5 hr. Ammonium chloride (54 g.) was added to destroy the excess sodamide and then the ammonia was allowed to evaporate. The residual inorganic material was dissolved in water and the product extracted with ether. The residue remaining after evaporation of the ether was distilled to give a main fraction (24.8 g., 60%) whose properties indicated it to be *o*-cresol: b.p. 186–189°, m.p. 30°, n_D^{30} 1.540. This substance formed a picrate which melted at 87–88°. No basic organic product could be detected.

A similar experiment using compound IV (23.7 g.), sodium (3.5 g.) in liquid ammonia (150 ml.) produced a product (7.3 g.) which could be distilled to yield three fractions: fraction 1 (1 g.), b.p. 78–83° (23 mm.), $n_D^{28.5}$ 1.5138; fraction 2 (3 g.), b.p. 76–79° (4 mm.); fraction 3 (3 g.), b.p. 110–115° (4 mm.).

Fraction 1 was identified as *o*-cresyl methyl ether by oxidation to 2-methoxybenzoic acid, m.p. 100° alone or when mixed with an authentic sample.

Fraction 2 was oxidized with alkaline permanganate solution to yield 3-methoxy-2-methylbenzoic acid. The identity of this acid was established by comparison of the infrared spectrum with an authentic sample and by a mixture melting point (148–149°).

Fraction 3 solidified and was then recrystallized from acetone-hexane to yield 2,2′-dimethoxydibenzyl (VI), m.p. 82–83° (lit.[14] m.p. 86°).

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.48. Found: C, 79.40; H, 7.71.

The structure of VI was verified by oxidation with alkaline permanganate to yield 2,2′-dimethoxybenzil, m.p. 130–131° (lit.[15] m.p. 130°).

A repetition of this experiment on a larger scale (67 g. of compound IV) produced only 1 g. of fraction 2, the rearranged product, and larger amounts of fraction 1 (11 g.) and fraction 3 (19.5 g.).

6-Bromo-3-methoxy-2-methylbenzoic acid (VII). 3-Hydroxy-2-methylbenzoic acid, obtained in *ca.* 30% yield by the alkali fusion of 7-amino-1,5-disulfonic acid,[16] was methylated using dimethyl sulfate in aqueous alcoholic potassium hydroxide solution. The resulting 3-methoxy-2-methylbenzoic acid (16.6 g.), m.p. 148–149° (reported[5] m.p. 141–142°), was converted to the silver salt as previously described.[17] The dry silver salt (24 g.) was suspended in boiling dry carbon tetrachloride (300 ml.), and bromine (14.5 g.) in carbon tetrachloride (12 ml.) was added dropwise with rapid stirring. The mixture was stirred for 30 min. after the addition was complete and filtered while hot. The precipitate of silver bromide was washed with some hot carbon tetrachloride and the filtrate was concentrated to one fourth of its volume. This solution was diluted with petroleum ether and chilled. The precipitated acid was recrystallized from hexane–carbon tetrachloride to yield 11 g. (50%) of acid VII which melted at 104–105°.

Anal. Calcd. for $C_9H_7O_3Br$: C, 44.10; H, 3.70. Found: C, 44.04; H, 3.76.

A benzene solution of this acid deposited crystals which melted at 90°. A further recrystallization from carbon tetrachloride regenerated product with the previous melting point, 105°.

The mother liquors from the recrystallizations were combined and evaporated to yield a red oil. A solution of this oil in ethanol containing sodium hydroxide was hydrogenated using palladium on charcoal and hydrogen (50 p.s.i.). Acidification of the filtered hydrogenation product yielded 6 g. (36%) of recovered acid II.

3-Bromo-6-methoxyphthalic anhydride (X). (*A*) 4-Bromo-7-methoxyhydrindene[7] (1 g.) was refluxed with potassium permanganate (10 g.), 10% potassium hydroxide solution (3 ml.), and water (250 ml.) for 12 hr. The solution was acidified and extracted continuously with ether for 24 hr. The ether extract was evaporated to dryness and the crude acid (X) was converted to the anhydride by sublimation at 130° (1 mm.). This product melted at 211–212°.

Anal. Calcd. for $C_9H_5O_4Br$: C, 42.05; H, 1.96. Found: C, 41.89; H, 2.17.

B. A sample of acid VII was oxidized as described in part *A*. Processing of the reaction mixture yielded the anhydride of acid VIII which melted at 211–212° alone or when mixed with a sample prepared in part *A;* the infrared spectra of the two samples were also identical.

Methyl 4,4′-dimethoxy-3,3′-dimethyldiphenate (XI). Acid VII (24.5 g.) was converted to the methyl ester (18 g., 70%) by reaction with methanol (250 ml.) in the presence of *p*-toluenesulfonic acid (3 g.). The ester was an oil, b.p. 153–155° (3 mm.), n_D^{26} 1.5458. A portion of this material (6 g.) was mixed with powdered copper (5 g.) and anhydrous 2,4-dimethylsulfolane (1 ml.). This mixture was stirred slowly in a metal bath at 250° for 4 hr. The cooled reaction mass was pulverized and extracted in a Soxhlet apparatus with ether. The ether solution was concentrated and the residue recrystallized from aqueous acetone. There was obtained 3.5 g. (85%) of material which melted at 157–158°.

Anal. Calcd. for $C_{20}H_{22}O_6$: C, 67.02; H, 6.18. Found: C, 67.08; H, 6.22.

4,4′-Dimethoxy-3,3′-dimethyldiphenic acid XII *and anhydride* XIII. The ester from the preceding experiment (7 g.) was heated at reflux temperature for 24 hr. with a solution of potassium hydroxide (30 g.) in ethanol (100 ml.) and water (50 ml.). At the end of the reflux period additional water was added (50 ml.) and most of the ethanol was distilled. The aqueous solution was treated with decolorizing charcoal and the filtered solution was acidified to Congo Red with hydrochloric acid. The crude acid (XII) was recrystallized from hot water. There was obtained 6 g. (90%) of product which melted at 137–138°.

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.31; H, 5.51.

A mixture of this acid XII (9.9 g.) and acetic anhydride (25 ml.) was refluxed for 45 min. The reaction mixture was chilled to precipitate nearly all the desired anhydride. This material was filtered, slurried for 5 min. with cold sodium bicarbonate solution, and filtered again. The precipitate was washed well with water and dried to yield 8.8 g. (85%) of anhydride XIII which melted at 241–242°.

Anal. Calcd. for $C_{18}H_{16}O_5$: C, 69.21; H, 5.16. Found: C, 69.42; H, 4.81.

2,7-Dimethoxy-1,8-dimethylfluorenone (XIV). Anhydride XIII (15.6 g.) and anhydrous 2,4-dimethylsulfolane (10 ml.) were heated in a metal bath at 300° for 4 hr. The reaction flask was protected from atmospheric moisture by a calcium chloride tube. The solid cake which formed when the reaction mixture was cooled was broken up and dissolved in dioxane. The dioxane solution was added to potassium hydroxide (7 g.) in water (25 ml.) and the combined solution was heated on the steam bath for 6 hr. The hydrolysis mixture was concentrated *in vacuo* to a volume of 50 ml. and diluted with water (200 ml.). The suspension which resulted was allowed to stand for several hours and then filtered to yield 11.4 g. (85%) of crude fluorenone XIV. Recrystallization from dioxane yielded pure XIV (10 g.) which melted at 251–252°.

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(14) A. Schonberg and W. Malchow, *Ber.*, 55, 3751 (1922).

(15) F. B. Garner and S. Sugden, *J. Chem. Soc.*, 2882 (1927).

(16) The authors wish to thank the American Cyanamid Co., Bound Brook, N. J., for carrying out the alkali fusion on a large scale.

(17) R. A. Barnes and R. J. Prochaska, *J. Am. Chem. Soc.*, 72, 3188 (1950).

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 76.09; H, 6.01. Found: C, 76.36; H, 6.28.

Acidification of the alkaline solution remaining after filtration of XIV, yielded 1.1 g. (6%) of acid XII.

2,7-Dimethoxy-1,6-dimethylfluorenone-5-carboxylic acid (XV). When the preparation of fluorenone XIV was carried out as in the preceding experiment, except that anhydrous conditions were not maintained, the yield of XIV decreased to 50–60% and from the alkaline solution there was obtained, not recovered acid XII, but instead acid XV (20–30%) which melted at 283–284°. When this acid was recrystallized from dioxane it was obtained as orange leaflets (a dioxane solvate) which gradually turned red on drying. The analysis indicates that even prolonged drying failed to remove all of the dioxane.

Anal. Calcd. for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Calcd. for $C_{18}H_{16}O_5 \cdot {}^1/_4\ C_4H_8O_2$: C, 68.25; H, 5.43. Found: C, 68.38, 68.76; H, 5.08, 5.14.

2,7-Dimethoxy-1,6-dimethylfluorenone (XVI). (*A*) Acid XV (3 g.) was dissolved in quinoline containing copper powder (1 g.). The reaction mixture was refluxed for 4 hr. and then filtered into ice cold dilute hydrochloric acid. The precipitate which formed was filtered, dried, and recrystallized from benzene-ligroin to yield 2 g. (74%) fluorenone XVI which melted at 199–200°.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.09; H, 6.01. Found: C, 76.31; H, 5.72.

(*B*) Acid XII (3 g.) was cyclized according to the procedure of Huntress and Cliff.[8] The crude keto acid (XV) was decarboxylated with quinoline and copper as in part *A*. The crude fluorenone which resulted melted at 170–190° and was purified by chromatography on alumina (40 g.). Elution with 25% benzene in petroleum ether removed the desired fluorenone XVI, which melted at 198–199° alone or when mixed with a sample obtained in part *A*.

4,4'-Dimethoxydiphenic anhydride (XXI). 6-Bromo-3-methoxybenzoic acid[6] was converted to 4,4'-dimethoxydiphenic acid by the same procedure used to prepare acid XII from acid IX. There was obtained about 40% of a product which melted at 242–245°. This substance was converted to the anhydride as in the preparation of XIII. There was obtained 89% of material which melted at 200–203° dec.

Anal. Calcd. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.26. Found: C, 67.38; H, 4.39.

2,7-Dimethoxyfluorene (XXII). 4,4'-Dimethoxydiphenic anhydride (7.5 g.) was heated at 310–320° until the evolution of gas was no longer apparent. From time to time the material which sublimed was dislodged and returned to the melt. The cold reaction product was dissolved in acetone, filtered, and diluted with water. The resulting precipitate was hydrolyzed by boiling with 50% aqueous alcohol (100 ml.) containing potassium hydroxide (10 g.). The reaction mixture was heated on the steam bath until the alcohol had distilled. The residual suspension was cooled and filtered. The precipitate was recrystallized from acetone-hexane to yield 1.5 g. (24%) of *2,7-dimethoxyfluorenone* which melted at 123–125°. This product was characterized by means of its infrared spectrum.[18]

From the alkaline solution there was obtained, by acidification, 5.8 g. of recovered 4,4'-dimethoxydiphenic acid.

2,7-Dimethoxyfluorenone (1 g.) was dissolved in ethylene glycol (20 ml.) and heated with 85% hydrazine hydrate at 120° for 10 min. to remove water. Potassium hydroxide (0.7 g.) was added and the temperature was raised to 190° for 90 min. The reaction mixture was poured into cold water and the precipitate which formed was filtered. Recrystallization from ethanol and water afforded 0.7 g. (74%) of 2,7-dimethoxyfluorene which melted at 170–171°.

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.61; H, 6.24.

This same substance was also obtained when 2,7-dimethoxyfluorenone (1 g.) in hot ethanol (100 ml.) was treated with 2% sodium amalgam (25 g.) until the orange coloration disappeared. The product (0.8 g.) was isolated by dilution of the reaction mixture with water and filtration.

2,7-Dihydroxyfluorene (XXIII). 2,7-Dimethoxyfluorene (1 g.) was refluxed with a mixture of glacial acetic acid (20 ml.) and 48% hydrobromic acid (20 ml.) for 6 hr. The resulting solution was poured into cold water (150 ml.) and the precipitate filtered and washed well with water. Recrystallization from aqueous ethanol furnished 0.6 g. (68%) of 2,7-dihydroxyfluorene which melted at 249–250°.[19]

Anal. Calcd. for $C_{13}H_{10}O_2$: C, 78.77; H, 5.08. Found: C, 78.68; H, 5.06.

2,7-Dimethoxy-1,6-dimethylfluorene. Fluorenone XVI (1 g.) was dissolved in amyl alcohol and the solution heated to 90°, when sodium (5 g.) was added. The mixture was stirred vigorously until the orange color disappeared and then for an additional hour. The excess sodium was dissolved by adding ethanol and then the mixture was poured into water. The precipitate was recrystallized from ethanol to yield 0.8 g. (84%) of the fluorene which melted at 217–218°.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 79.99; H, 7.16.

2,7-Dimethoxy-1,8-dimethyl-9-fluorenol. Fluorenone XIV (3 g.) was dissolved in a mixture of ethanol (70 ml.) and benzene (25 ml.) and treated with sodium amalgam (50 g.). The reaction mixture was stirred at 60° until the red color vanished and then for another hour. The solution was filtered and the ethanol removed *in vacuo*. The residue was suspended in water and the product extracted with benzene. The benzene was evaporated and the residue recrystallized from ethanol to yield 2.4 g. (79%) of the fluorenol which melted at 224–225°.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.55; H, 6.69. Found: C, 75.68; H, 6.66.

2,7-Dimethoxy-1,8-dimethylfluorene (XVII). Fluorenone XIV was dissolved in dioxane (45 ml.) and hydrogenated at 200° in a bomb with an initial hydrogen pressure of 1450 p.s.i. and using copper-chromium oxide (0.4 g.) as the catalyst. The product was washed out with ethanol, the mixture was filtered, and the filtrate concentrated. The crude solid product was recrystallized from ethanol to yield 0.3 g. (63%) of fluorene XVII which melted at 235–238°.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.16; H, 7.00.

This substance could also be prepared by the Wolff-Kishner reduction as in the preparation of 2,7-dimethoxyfluorene or by the Clemmensen procedure.[20]

2,7-Dihydroxy-1,8-dimethylfluorenone (XVIII). Fluorenone XIV (1 g.) was heated with hydrobromic acid as in the preparation of 2,7-dihydroxyfluorene. The crude product from this reaction (0.9 g.) was obtained as red needles which began to decompose when heated above 200°. Attempted purification by sublimation or chromatography was not successful. However, recrystallization from methanol-benzene finally produced red-orange plates which melted at 262–265° and which still contained methanol after the usual drying procedure.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 75.57; H, 5.54. Calcd. for $C_{15}H_{12}O_3 \cdot {}^1/_2\ CH_3OH$: C, 72.64 H, 5.51. Found: C, 72.86; H, 5.57.

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[18] M. H. Giunti, *Rev. centro estud. farm. bioquim.*, **34**, 23 (1945) [*Chem. Abstr.*, **40**, 3169 (1946)], has reported the preparation of this fluorenone by methylation of 2,7-dihydroxyfluorenone, but no properties of the product are given in the abstract.

[19] C. D. Nenitzescu and M. Avram, *Acad. rep. populare Romine, Studii cercetari chim.*, **4**, No. 1–2, 57 (1956) [*Chem. Abstr.*, **51**, 3535 (1957)], have also prepared this substance but report a melting point of 233°.

[20] Method II described by E. L. Martin, *Org. Reactions*, I, 164 (1942).

Hydrogenation of fluorenone XVIII. Fluorenone XVIII (1.0 g.) was dissolved in dioxane (40 ml.), copper-chromium oxide (0.5 g.) was added, and the reduction was carried out in a rocking bomb at an initial pressure of 1500 p.s.i. (at 25°). The hydrogenation was allowed to proceed for 8 hr. at 210–215°. The crude product, obtained after filtering the catalyst and concentrating the solution, was a viscous oil. This material was dissolved in benzene (5 ml.) and *t*-butyl alcohol (4 ml.) and oxidized with *t*-butyl chromate[21] solution (10 ml.). The mixture was stirred at 25–30° for 24 hr. and then with benzene and hydrochloric acid (75 ml., 6*N*) until all the solid material was in solution. The organic layer was separated and washed with dilute hydrochloric acid, water, and sodium carbonate solution. The solvent was evaporated and the residue chromatographed on alumina (30 g.) to yield 0.6 g. of a yellow oil. This oil had strong bands in the infrared spectrum at 5.82, 6.27, 6.35, and 6.88 μ indicating the presence of the desired ketone function and an unreduced aromatic ring. However, the derivatives prepared from the oil indicated that complete reduction and some hydrogenolysis[22] had occurred.

Treatment of the crude ketonic material with semicarbazide acetate yielded a crystalline material which melted at 261–262°.

Anal. Calcd. for $C_{16}H_{27}ON_3$: C, 69.27; H, 9.81. Found: C, 69.59; H, 9.63.

The infrared spectrum was that expected for a semicarbazone; λ_{max}^{KBr} 2.91, 3.18, 5.92, 6.33, 6.90, and 7.30 μ, *etc.*

A second small crop of the semicarbazone melted at 189–194°; this substance may be largely the derivative of a stereoisomeric form of ketone XIX.

Anal. Calcd. for $C_{16}H_{27}ON_3$: C, 69.27; H, 9.81. Found: C, 68.75; H, 9.70.

The ketonic product obtained from another run of the hydrogenation under similar conditions was characterized as the 2,4-dinitrophenylhydrazone, m.p. 114–115°. The derivative in this experiment must have resulted from a ketone (XX) in which hydrogenation was complete and in which hydrogenolysis was not as extensive.

Anal. Calcd. for $C_{21}H_{28}O_5N_4$: C, 60.42; H, 6.76. Found: C, 60.26; H, 6.63.

The infrared spectrum for this derivative had bands in agreement with the structure suggested; λ_{max}^{KBr} 2.95, 3.04, 6.17, 6.28, 6.60, 6.66, 7.08 μ, *etc.*

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(21) H. H. Inhoffen, *Ber.*, 84, 90 (1951).

(22) A similar hydrogenolysis of a hydroxyl group has also been found to take place with a palladium catalyst at 175°; see R. A. Barnes and A. H. Sherman, *J. Am. Chem. Soc.*, 75, 3013 (1953).

[CONTRIBUTION OF THE PHARMACEUTICAL CHEMISTRY DEPARTMENT, SCHOOL OF PHARMACY, UNIVERSITY OF MARYLAND]

Steroids. IV. Synthesis of Some 4-Azacholestanes[1–4]

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Reaction of 5-oxo-3,5-seco-4-norcholestan-3-oic acid with ammonia, benzylamine, methylamine, and ethanolamine at elevated temperatures yielded the enamine lactams, 4-aza-5-cholesten-3-one, 4-aza-4-benzyl-5-cholesten-3-one, 4-aza-4-methyl-5-cholesten-3-one, and 4-aza-4-(β-hydroxyethyl)-5-cholesten-3-one. The reduction of these lactams with lithium aluminum hydride gave 4-aza-4-cholestene, 4-aza-4-benzyl-5-cholestene, 4-aza-4-methyl-5-cholestene, and 4-aza-4-(β-hydroxyethyl)-5-cholestene, respectively, as products.

In recent years considerable attention has been given to the synthesis of aza steroids.[1,6] The nitrogen in nearly all of the reported aza steroids is unsubstituted. In the hope of finding new types of structures with useful pharmacodynamic or cancer chemotherapeutic properties, a program directed to the synthesis of a series of 4-substituted aza steroids was initiated. This paper describes the synthesis of some derivatives of 4-azacholestane.

The first substituted 4-aza steroid to be described was 4-aza-4-benzyl-5-cholesten-3-one (III).[7] It was prepared by refluxing 5-oxo-3,5-seco-4-norcholestan-3-oic acid (I) in excess benzylamine, the reaction temperature being about 185°. The related unsubstituted lactam, 4-aza-5-cholesten-3-one (II), has been prepared by the reaction of ammonia with I at temperatures of 140–200°[2,8,9] or with 4-oxa-5-cholesten-3-one at room temperature.[10] In this investigation II was prepared from I and ammonia at 200° and III was prepared by Woodward's procedure.

4-Aza-4-methyl-5-cholesten-3-one (IV) was synthesized (a) by heating the methylamine salt of I at 180° and (b) by heating a solution of I in ethanol, which had been previously saturated with methylamine, in a pressure vessel at 180°. The first of these methods gave poorer yields as the result of the

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(1) For paper III see N. J. Doorenbos and M. T. Wu, *J. Org. Chem.*, 26, 2548 (1961).

(2) Presented, in part, at the 136th meeting of the American Chemical Society in Atlantic City, Fall, 1959.

(3) Abstracted from a thesis submitted by Chien Li Huang to the graduate faculty of the University of Maryland in partial fulfillment of the requirements for the Ph.D. in Pharmaceutical Chemistry, June 1960.

(4) This paper was awarded second prize for the Southern District in the 1960 Lunsford-Richardson Awards sponsored by Vick Chemical Co.

(5) Sterling-Winthrop Research Fellow 1958–1959.

(6) T. L. Jacobs and R. B. Brownfield, *J. Am. Chem. Soc.*, 82, 4033 (1960).

(7) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, 74, 4223 (1952).

(8) N. J. Doorenbos, C. L. Huang, C. R. Tamorria, and M. T. Wu, *J. Org. Chem.*, 26, 2546 (1961).

(9) R. S. Wildi, U. S. Patent 2,897,202 (July 28, 1959).

(10) M. Uskoković and M. Gut, *Helv. Chim. Acta*, 42, 2258 (1959).