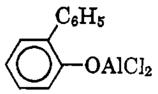
greater than molar amounts of aluminum chloride. The phenolic hydroxyl group reacts initially with aluminum chloride with evolution of hydrogen chloride and it is evidently then the species (I)[3] which isomerizes



I

in the presence of excess aluminum chloride to the more stable *meta* isomer. Water is presumably a promoter in this reaction, as in the previously described cases[1,2]; however, its effect on the present reaction has not been studied. It is interesting to note that no *p*-phenylphenol is detectable in the reaction and furthermore that *p*-phenylphenol under the same conditions, even for extended periods of time, does not appear to be appreciably affected. In the isomerization of terphenyls[1] the same equilibrium mixture of *meta* and *para* isomers is obtained starting with any of the three terphenyls.

Experimental Section

To a 2-l. three-necked round-bottom flask equipped with a stirrer, condenser, and thermometer was added 300 g. (1.77 moles) of *o*-phenylphenol, 500 ml. of chlorobenzene, and 300 g. (2.24 moles) of anhydrous aluminum chloride. The reaction was stirred on the steam bath for 1 hr., then added to dilute hydrochloric acid and ice. The organic layer was separated and washed twice with dilute hydrochloric acid. The solution was then extracted with 10% sodium hydroxide solution and the aqueous alkaline layer was acidified. The oil that separated was taken up in ether; the solution was dried over magnesium sulfate and filtered. The ether was evaporated on the steam bath and the residue distilled at 20 mm. through a short Vigreux column. Two fractions were isolated: (1) 131.7 g., b.p. 144–164°; (2) 120.9 g., b.p. 164–170°; and 17 g. of tarry residue. Fraction 1 was shown to be a mixture of *o*-phenylphenol (73%) and *m*-phenylphenol (27%) by thin layer chromatography and infrared. Fraction 2 was substantially pure *m*-phenylphenol, m.p. 75–77°. One recrystallization (heptane) raised the melting point to 78° (lit. m.p. 74–75°,[4] 75°[5]). The combined yield of *m*-phenylphenol was 156.4 g. (0.92 mole, 77%).

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[3] P. H. Gore in G. A. Olah, "Friedel-Crafts and Related Reactions," Vol. III, Interscience Publishers, Inc., New York, N. Y., 1964, p. 46.

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Photochemical Transformations and Reactions of 3β-Acetoxy-16β-diazoacetylisopregn-5-en-20-one

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Contribution No. 187 from the Instituto de Química de la Universidad Nacional Autónoma de México, México 20, D. F., Mexico

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We recently described the preparation of 3β-hydroxy-16-diazoandrostan-17-one and its conversion by ultraviolet radiation to the corresponding D-nor carboxylic acid.[1] D-Nor-16-carboxyandrost-5-en-3β-ol can be transformed to the diazoketone, which by treatment with acetic acid affords the D-nor-17-desoxycorticosteroid acetate.[2] These results led us to prepare a steroid 16-diazo ketone and to study its chemical and photochemical reactions.

Discussion

By treating 3β-acetoxyisopregn-5-en-20-one 16-carbonyl chloride with diazomethane there was obtained, in good yield, 16β-diazoacetyl-3β-acetoxyisopregn-5-en-20-one (I).[2] Irradiation of I with a Hanau S-700 mercury lamp in tetrahydrofuran gave 16β-hydroxyacetyl-3β-acetoxyisopregn-5-en-20-one (II). Acetylation of II with acetic anhydride–pyridine gave a compound identical with the product previously obtained by treatment of the diazo ketone I with acetic acid.[3] Irradiation of I in methanol led to an Arndt–Eistert rearrangement affording the methyl ester of 3β-acetoxyisopregn-5-en-20-on-16β-ylacetic acid (III) characterized by its infrared absorptions at 1740 (acetate), 1709 (ester), and 1700 cm.$^{-1}$ (20-ketone), and proton magnetic resonance at 2.06 (methyl ketone), 2.20 (acetate), and 3.68 p.p.m. (CH_3O); the elementary analysis was in agreement with $C_{26}H_{38}O_5$. The β orientation of the C-16 group was confirmed by the optical rotatory dispersion curve, which showed a negative Cotton effect.[3] Also in agreement with this assignment is the resonance frequency of the angular methyl protons at 1.02 p.p.m.[4] Alkali hydrolysis of III gave 3β-hydroxyisopregn-5-en-20-on-16β-ylacetic acid (IV) with infrared absorption at 1690 and 3300–3000 cm.$^{-1}$, a negative Cotton effect curve, and elemental analysis in agreement with $C_{23}H_{34}O_4$.

By treatment with diazomethane IV was transformed to the corresponding methyl ester V with infrared absorption at 1700 and 1735 cm.$^{-1}$ (acetyl and acetate groups) and n.m.r. resonances at 2.17 (21H) and 3.62 p.p.m. (OMe). Compound IV was further characterized as the acetate VI. The latter with diazomethane produced compound III, identical with the compound obtained by irradiation of the diazo ketone I in methanol. To obtain further proof of a photoinduced Wolff rearrangement, the diazo ketone I was allowed to react with freshly prepared silver oxide in methanol leading to compound III. When the compound IV was treated with acetic anhydride and *p*-toluenesulfonic acid, the enol lactone (VII) of 3β-acetoxyisopregn-5-en-20-on-16β-ylacetic acid was obtained showing infrared absorption at 1780 and 1750 cm.$^{-1}$ and proton resonance at 0.92–1.0 (angular methyls), 1.89 (olefinic methyl), and 1.98 p.p.m. (acetate). The end absorption in the ultraviolet at 210 mμ (ϵ 5340) was also in agreement with the presence of a tetrasubstituted double bond.

Using the usual procedure of the Arndt–Eistert synthesis it was possible to prepare the amide VIII by treating the diazo ketone with ammonia [infrared absorption at 3480 (NH), 1720 (acetate), 1700 (acetyl), 1680 (C=C), and 1595 cm.$^{-1}$ (amide); n.m.r. at 3.5

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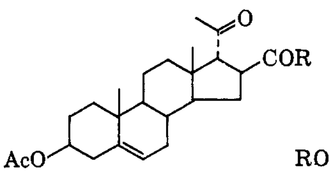
[1] J. L. Mateos, O. Chao, and H. Flores, *Tetrahedron*, **19**, 1051 (1963).

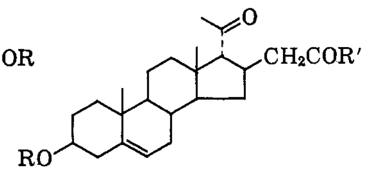
[2] (a) M. Steiger and Reichstein, *Helv. Chim. Acta* **20**, 1164 (1937); (b) H. Reimann, H. Schneider, O. Zagneatoko Sarre, C. Federbush, C. Towne, N. Charney, and E. P. Oliveto, *Chem. Ind.* (London), 334 1963); (c) J. L. Mateos, and R. Pozas, *Steroids*, **2**, 527 (1963).

[3] J. L. Mateos, M. A. Dosal, and R. Cetina, *Bol. inst. quim. univ. nacl. autón Méx.*, **15**, 63 (1963).

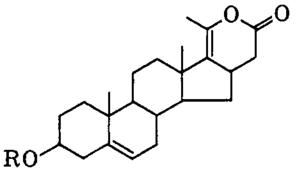
[4] P. Crabbé, *Tetrahedron*, **19**, 51 (1963).



I, R = CHN_2
II, R = CH_2OH



III, R = Ac; R' = OMe
IV, R = H; R' = OH
V, R = H; R' = OMe
VI, R = Ac; R' = OH
VIII, R = Ac; R' = NH_2
IX, R = Ac; R' = NHC_6H_5



VII

(NH_2), 2.02 (acetate), and 2.18 p.p.m. (acetyl)]. In the same manner, using aniline in place of ammonia, the anilide was obtained [showing infrared absorption at 3460 (NH) and 1600 cm.$^{-1}$ (amide)]. Nuclear magnetic resonance showed absorption at 7.4–7.2 (aromatic protons) and 2.76 p.p.m. (NH). All of the transformations in the side chain were accomplished without changing the β configuration. This was confirmed by optical rotatory dispersion of the various derivatives. In all cases a negative Cotton effect was observed, in agreement with previous studies.[3] Recently, Cross[5] calculated, using the Karplus equations,[6] spin–spin coupling constant ranges for the C-16 and C-17 protons of all four possible stereoisomers in each of three preferred ring D conformations.[7] Although it was pointed out that coupling constant magnitudes alone do not permit an assignment of stereochemistry,[5] it is interesting to note that in the current work observed values of $J_{16,17}$ for all compounds falling in the range 0–4 c.p.s. This is in good agreement with the calculated values and experimental findings for 16β,17α-disubstituted pregnan-20-ones.[5] The 18- and 19-angular methyl proton resonated consistently in the range 58–60 c.p.s.

Experimental Section

Ultraviolet spectra were determined with a Beckman DK-2 spectrophotometer using ethanol as solvent and infrared spectra with a Perkin-Elmer Model 21 recording spectrophotometer, fitted with a sodium chloride prism. Except where stated otherwise, infrared spectra were measured with chloroform solutions, and n.m.r. spectra were determined with deuteriochloroform solutions using a Varian Associates spectrometer, Model A-60. Chemical shifts are given in parts per million using tetramethylsilane as an internal reference. Microanalyses were performed by Dr. Franz Pascher, Bonn, Germany. Melting points are not corrected.

16β-Diazoacetyl-3β-acetoxyisopregn-5-en-20-one (I).—A solution of 10 g. of 3β-acetoxyisopren-5-en-20-one-16β-carboxylic acid in 360 ml. of anhydrous benzene was treated with 9.28 g. of thionyl chloride by dropwise addition at 0°, with agitation. The mixture was refluxed 2 hr. and the excess of thionyl chloride was removed *in vacuo*. Benzene (100 ml.) was added and the solution once more was evaporated to dryness. This operation was repeated three times to eliminate all of the thionyl chloride. The acid chloride obtained, showing infrared absorption at 1780 (COCl), 1740 (acetate), and 1714 cm.$^{-1}$ ($COCH_3$), was not isolated but was dissolved in 100 ml. of anhydrous benzene and to this solution was slowly added 3.3 g. of diazomethane in ether. After being kept at room temperature for 14 hr., the residual diazomethane was evaporated, and the product was crystallized from acetone–hexane: 9.4 g., m.p. 151–152°. Further crystallizations from the same solvent afforded the analytical sample, m.p. 157–158°, $\nu_{max}^{CCl_4}$ 2110 cm.$^{-1}$ (diazo ketone), $J_{16,17} = 0$ c.p.s.

Anal. Calcd. for $C_{25}H_{34}N_2O_2$: C, 70.39; H, 8.03: N, 6.37; O, 15.00. Found C, 70.31; H, 8.35; N, 6.42; O, 15.29.

16β-Hydroxyacetyl-3β-acetoxyisopregn-5-en-20-one (II).—A solution of 1 g. of the diazoketone I in 325 ml. of distilled tetrahydrofuran was irradiated by immersing into the solution a Hanau S-700 mercury lamp (intensity maxima of irradiation at 260, 313, and 363 mμ) while maintaining the temperature of the solution between 10 and 15°. After 30 min. the reaction was complete and the solution was poured in 950 ml. of water and extracted with ether. The ethereal layer was dried over sodium sulfate, filtered, and evaporated to dryness to give a solid compound, m.p. 125–130°, raised by crystallization from methanol to m.p. 151–153°. Further crystallizations from chloroform–methanol gave the analytical sample: m.p. 156–158°; ν_{max} 3430 (OH), 1710 (C═C), and 1740 cm.$^{-1}$ (acetate); n.m.r. 2.00 (acetate) and 2.20 (CH_3CO) p.p.m.; $J_{16,17} = 3.5$ c.p.s.

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71; O, 19.21. Found: C, 71.81; H, 8.70; O, 19.47.

3β-Acetoxyisopregn-5-en-20-on-16β-ylacetic Acid Methyl Ester (III). A.—A solution of 200 mg. of I in 300 ml. of distilled methanol was irradiated 10 min. with a Hanau S-700 mercury lamp as described above. After elimination of the solvent, the crude product showed m.p. 120–126°, raised to 152–154° on recrystallization from ether–hexane; ν_{max} (KBr) 1700 (CH_3CO), 1709 (methyl ester), and 1740 cm.$^{-1}$ (acetate); n.m.r. 3.68 (CH_3O), 2.06 (acetate), 2.20 (CH_3CO), and 1.02 p.p.m. (CH_3). Optical rotatory dispersion showed a trough at 305 mμ with $[\alpha]$ −1624°.

Anal. Calcd. for $C_{26}H_{38}O_5$: C, 72.52; H, 8.90; O, 18.58. Found: C, 72.39; H, 8.64; O, 18.79.

B.—A solution of 100 mg. of VI in 10 ml. of ether was mixed with an excess of ethereal diazomethane and after 6 hr. at room temperature the product was isolated and crystallized from ether–hexane; m.p. 151–153°. This ester III was identical by melting point, mixture melting point, infrared, and n.m.r. with the sample described above.

C. **By Wolff Rearrangement.**—To a solution of 100 mg. of the diazoketone I in 3 ml. of methanol a suspension of silver oxide (from 100 mg. of silver nitrate and sodium hydroxide) in 1 ml. of methanol was added. The mixture was refluxed 1 hr. and filtered, and the filtrate then was decolorated with activated charcoal and evaporated. The residue was dissolved in benzene and filtered through alumina. After evaporation to dryness the product III had m.p. 124–127°, raised to 149–151° by recrystallization from methanol. The product was identical by infrared, n.m.r., and mixture melting point with the samples described above.

3β-Hydroxyisopregn-5-en-20-on-16β-ylacetic Acid (IV).—A solution of 80 mg. of the methanol irradiation product III in 20 ml. of ethanol was refluxed with a solution of 80 mg. of potassium hydroxide in 3 ml. of water for 1 hr., then poured into water, acidified with 1% hydrochloric acid, and extracted with ether. The ethereal layer was washed and dried, and the solvent was evaporated to give a solid, m.p. 195–198°, raised by crystallization from methanol–water to m.p. 209–211°. A comparative chromatoplate with 3β-hydroxyisopregn-5-en-20-one-16β- and -16α-carboxylic acids gave different R_f values for the three compounds. The analytical specimen of IV showed ν_{max} 1690 (C═O) and broad absorption at 3300–3100 cm.$^{-1}$ for the associated carboxyl group; n.m.r. at 1.02 (18H), 0.94 (19H), and 2.24 p.p.m. (CH_3CO); $J_{16,17} = 0$ c.p.s. The optical rotatory dispersion curve showed a trough at 306 mμ with $[\alpha]$ −1912°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; O, 17.09. Found: C, 73.81; H, 9.03; O, 16.94.

3β-Hydroxyisopregn-5-en-20-on-16β-ylacetic Acid Methyl Ester (V).—To 100 mg. of the acid IV in 5 ml. of ether an excess of diazomethane in ether was added. After 24 hr. at room temperature, the residual diazomethane and ether were evaporated to

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(5) A. D. Cross and P. Crabbé, *J. Am. Chem. Soc.*, **86**, 1221 (1964); see also H. Flores, Thesis, Universidad Nacional Autónoma de México, 1962.

(6) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(7) F. U. Brutcher and W. Bauer, *J. Am. Chem. Soc.*, **84**, 2236 (1962).

give a solid of m.p. 182–185°, further crystallized from methanol to m.p. 189–191°, ν_{max} (KBr) at 1700 (CH_3CO) and 1735 cm.$^{-1}$ ($COOCH_3$), n.m.r. 3.62 (CH_3O) and 2.17 p.p.m. (CH_3CO), O.R.D. trough at 305 mμ with [α] −1960°.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34; O, 16.47. Found: C, 74.26; H, 9.96; O, 16.54.

3β-Acetoxyisopregn-5-en-20-on-16β-ylacetic Acid (VI).—To 180 mg. of IV in 2 ml. of pyridine, 4 ml. of acetic anhydride was added, and the mixture was allowed to stand for 16 hr. at room temperature. After work-up in the usual manner there was obtained a product: m.p. 158–160°; ν_{max} 1700 (CH_3CO), 1720 (acetate), and 3350 cm.$^{-1}$ (associated acid); n.m.r. 2.12 (CH_3-CO) and 2.02 p.p.m. (acetate); O.R.D. trough at 305 mμ with [α] −1613°.

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08: H, 8.71: O, 19.21. Found: C, 71.79: H, 8.54; O, 19.70.

Enol Lactone of 3β-Acetoxyisopregn-5-en-20-on-16β-ylacetic Acid (VII).—To a solution of 140 mg. of the acid IV in 1 ml. of acetic anhydride, 1 mg. of *p*-toluenesulfonic acid was added. The mixture was refluxed 4 hr., then poured into water and extracted three times with ether. The ethereal layer was washed with aqueous sodium bicarbonate and water, dried over sodium sulfate, filtered, and evaporated. Thereby was obtained a crystalline solid which on recrystallization from methanol showed m.p. 165–167°, ν_{max} (KBr) 1780 (enol lactone) and 1750 cm.$^{-1}$ (acetate), n.m.r. 1.89 p.p.m. ($CH_3C{=}$), λ_{max} 210 mμ (ϵ 5340).

3β-Acetoxyisopregn-5-en-20-on-16β-ylacetamide (VIII).—To a solution of 200 mg. of diazo ketone I in 1 ml. of dioxane, 0.66 ml. of ammonia (*d* 0.9) and 0.2 ml. of 10% aqueous silver nitrate solution were added. The mixture was refluxed for 60 min. and, after cooling, filtered through a short column of 2 g. of neutral alumina. The solid obtained on evaporation was crystallized from methanol–water: m.p. 220–222°; ν_{max} 3480 (NH), 1720 (acetate), 1700 (CH_3CO), 1680 (C=C), and 1595 cm.$^{-1}$ (amide); n.m.r. 3.50 (NH_2), 2.18 (CH_3CO), and 2.02 p.p.m. (acetate).

Anal. Calcd. for $C_{25}H_{37}NO_4$: C, 72.05; H, 8.98; N, 3.37; O, 15.40. Found: C, 72.09; H, 9.08; N, 3.54; O, 15.63.

Anilide of 3β-Acetoxyisopregn-5-en-20-on-16β-ylacetic Acid (IX).—To a suspension of 200 mg. of diazo ketone I in 0.2 ml. of aniline, 0.2 ml. of 10% aqueous silver nitrate solution was added. The mixture was heated in the steam bath for 10 min., water was added, and the product was extracted with chloroform. After washing with water, the product was dried and the solvent was evaporated. The resultant product was further purified by filtration through 2 g. of neutral alumina using chloroform as eluent to yield the anilide X which was recrystallized from methanol: m.p. 255–256°; ν_{max} 3460 (NH), 1720 (acetate), 1700 (CH_3CO), and 1600 cm.$^{-1}$ (amide); n.m.r. 7.42, 7.30, and 7.20 (aromatic protons), 2.76 (NH), 2.18 (CH_3CO), and 2.08 p.p.m. (acetate).

Anal. Calcd. for $C_{31}H_{41}NO_4$: C, 75.73; H, 8.41; N, 2.85; O, 13.02. Found: C, 75.50; H, 8.64; N, 2.74; O, 13.19.

Nuclear Magnetic Resonance Spectrum of the Methiodide of 1-Methylimidazole

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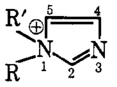
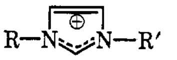
There has been a question in the literature[1] as to the structure of the product resulting from the alkylation of a 1-alkylimidazole. The two possible modes of addition could lead to 1,1-dialkyl- (I), or 1,3-dialkylimidazolium (II) salts.



I

II



III

Chemical degradation supports structures such as II.[2] However, the structure could unambiguously be demonstrated by means of n.m.r. spectrum. The simplest representative of the series was studied, *viz.*, dimethylimidazolium iodide. This iodide was prepared by several investigators,[2,3] but none reported its melting point, owing to its hygroscopic nature. Formation of the iodide in ethyl acetate and recrystallization from the same solvent led, after vacuum drying, to a compound of melting point 86.5–88°.

The n.m.r. spectrum of dimethylimidazolium iodide in D_2O exhibits three singlets centered at τ 5.99, 5.19 and 2.52 with the respective areas 6:2:1, corresponding to six methyl protons, two equivalent 4- and 5-protons, and one 2-proton. Conversely, the n.m.r. spectrum of 1-methylimidazole in chloroform-*d* revealed the magnetic nonequivalence of the 4- and 5-protons, the latter being shifted to higher field.[4] Presumably, for structures such as I a larger difference between these protons would be expected. Indeed, the methyl groups in dimethylimidazolium iodide exert a very strong shielding effect on the adjacent 4- and 5-hydrogens ($\Delta\tau = +2.32$) relative to imidazole.[4]

The symmetry of structure as revealed by n.m.r. confirms that the quaternization of 1-alkylimidazoles results in the formation of 1,3-dialkylimidazolium salts. It also rules out stabilization of the positive charge on one nitrogen such as II, but shows equal distribution between the two nitrogens such as in III. The fact that analogous observations were made for protonated imidazoles and benzimidazoles in H_2SO_4[5] suggests that the pyridine-like double-bonded nitrogen is more basic than the pyrrole-like single-bonded nitrogen. This could be expected if retention of the "aromatic sextet" is kept in consideration.

Experimental Section

1,3-Dimethylimidazolium Iodide.—To a solution of 10.2 g. (0.12 mole) of 1-methylimidazole in 60 ml. of ethyl acetate was added 43.4 g. (0.306 mole) of methyl iodide. The mixture was refluxed overnight and a yellow oil separated during the course of the reaction. After cooling, the oil solidified giving 26.9 g. (96.8% yield) of a hygroscopic solid. Two recrystallizations from ethyl acetate afforded colorless prisms, which after drying *in vacuo* at 75° had a melting point of 86.5–88°.

Anal. Calcd. for $C_5H_9IN_2$: C, 26.80; H, 4.05; I, 56.64; N, 12.50. Found: C, 26.94; H, 4.12; I, 56.89; N, 12.37.

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(2) F. Rung and M. Behrend, *Ann.*, **271**, 28 (1892); A. Pinner and R. Schwarz, *Ber.*, **35**, 2441 (1902); O. Wallach, *Ann.*, **214**, 257 (1882); K. von Auwers and W. Mauss, *Ber.*, **61**, 2411 (1928).

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(4) G. S. Reddy, R. T. Hobgood, Jr., and J. H. Goldstein, *J. Am. Chem. Soc.*, **84**, 336 (1962).

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