nate, 28446-76-6; dimethyl α-styrylphosphonate, 1707-07-9; dimethyl α-diazoethylphosphonate, 26584-15-6.

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The Synthesis and Chemistry of 1′,1′,4′(S)-Trimethyl-3β-trityloxyandrost-5-eno[16β,17β-b]azetidinium Tosylate

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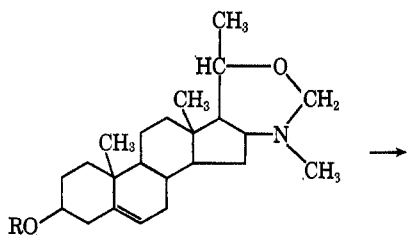
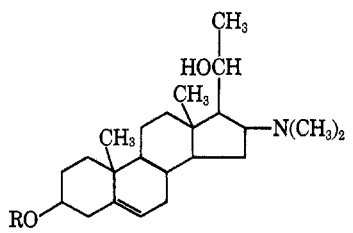
Treatment of 16β-dimethylamino-3β-trityloxypregn-5-en-20β-ol (**2b**) with *p*-toluenesulfonyl chloride in pyridine afforded 1′,1′,4′(*S*)-trimethyl-3β-trityloxyandrost-5-eno[16β,17β-*b*]azetidinium tosylate (**3a**). Reaction of the latter compound with refluxing ethanolamine (or potassium hydroxide in refluxing dioxane) yielded the Hofmann degradation product 16β-dimethylaminopregna-5,20-dien-3β-yl trityl ether (**4a**). The mother liquor of the ethanolamine reaction also contained the *N*-hydroxyethylamino compound **5a**. Reduction of **3a** with lithium aluminum hydride gave 16β-dimethylaminopregn-5-en-3β-yl trityl ether (**6**).

Published literature[1] in the steroid field has indicated that a tertiary amine grouping in a 1,4 relationship to a hydroxyl group may spontaneously cyclize under the influence of *p*-toluenesulfonyl chloride to form a pyrollidine ring. It was of interest, since 16β-dimethylaminopregn-5-ene-3β,20β-diol (**2a**)[2] was available, to know if the same conditions acting on this compound would produce an azetidine ring.[3] Such a transformation would establish a new heterocyclic-fused ring on the steroid system.

Since the 3β-hydroxyl group of the above-mentioned compound could conceivably interfere with a study of the reaction, it was thought best to protect this function preferentially. This was done by tritylation[4] of the *N*-methyloxazine **1a**[2] to form the 3-trityl ether **1b**,

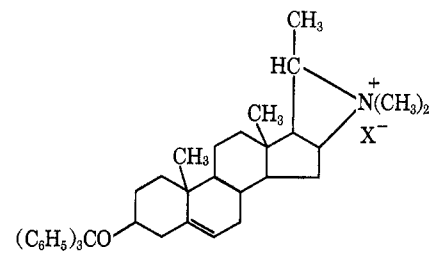


1a, R = H
b, R = $(C_6H_5)_3C$



2a, R = H
b, R = $(C_6H_5)_3C$

which was reduced with lithium aluminum hydride to afford 16β-dimethylamino-3β-trityloxypregn-5-en-20β-ol (**2b**). Reaction of **2b** with *p*-toluenesulfonyl chloride in pyridine at room temperature for 65 hr gave reasonable yields of the azetidine tosylate **3a**. This compound's structure was confirmed by its infrared spectrum, which



3a, X = O_3S—C_6H_4—CH_3
b, X = Br

had the tosylate ion bands previously reported,[1a] by the nmr spectrum confirming the quaternary alkylated nitrogen, and the mass spectrum which showed the expected molecular ion (minus *p*-toluenesulfonic acid) at *m/e* 586, and this ion minus the trityl grouping at *m/e* 343. Assuming a conventional rear-side attack of the nitrogen electrons to displace the C_{20}-β-toysl grouping, the resultant configuration of the steroidal C_{20}-methyl grouping on the azetidine ring would be *S*.

Since little is known of the chemistry of such azetidine systems, a modest chemical study of **3a** was undertaken. It has been shown that a condensed azetidinium ring structure, when it is nonplanar, will undergo reversal of the quaternization on reaction with nucleophiles.[5] In this case, however, treatment of **3a** with lithium bromide afforded only anion replacement to give the azetidinium bromide **3b**. The analogous iodide could be formed by treatment with sodium iodide, but the product was very labile to air and/or light and could not be characterized satisfactorily. This displacement reaction without ring opening may indicate that the azetidine ring is not distorted in

(1) (a) F. L. Weisenborn and D. Burn, *J. Amer. Chem. Soc.*, **75**, 259 (1953); (b) S. W. Pelletier and W. A. Jacobs, *ibid.*, **75**, 4442 (1953); (c) R. Ledger and J. McKenna, *Chem. Ind. (London)*, 1662 (1963); (d) L. Labler, J. Hora, and V. Cerny, *Collect. Czech. Chem. Commun.*, **28**, 2015 (1963).

(2) M. Heller and S. Bernstein, *J. Org. Chem.*, **32**, 3981 (1967).

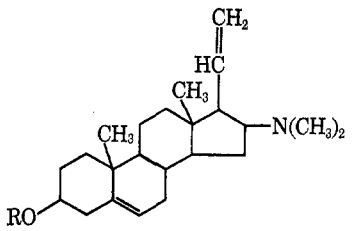
(3) This is similar to the general method of preparing azetidines by ring closure of γ-haloamines: see J. A. Moore in "Heterocyclic Compounds With Three- and Four-Membered Rings," Part Two, A. Weissberger, Ed., Interscience, New York, N. Y., 1964, p 891.

(4) R. T. Blickenstaff, *J. Amer. Chem. Soc.*, **82**, 3673 (1960).

(5) G. Fodor, *ibid.*, **88**, 1040 (1966).

this case, although the proof is by no means unequivocal (*vide infra*).

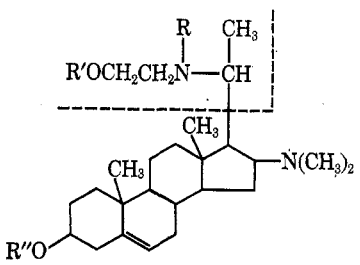
The observation of the variety of cleavages possible by heating a quaternary amine in ethanolamine[1d,6] suggested the application of this reaction to **3a**. The most easily isolated product was identified as the conventional Hoffmann degradation product **4a**[7] which was further heated in acetic acid to give the 3β-ol, **4b**. The nmr spectra of these compounds proved the



4a, R = $(C_6H_5)_3C$
b, R = H

proposed structures conclusively, since a normal basic dimethylamino band was seen at δ 2.18–2.19 ppm and the ABX splitting of the $C_{20,21}$-ethylene system was observed in the δ 4.74–5.15 ppm region. These two spectra also showed conclusively that the C_6-vinyl hydrogen is shielded by at least one of the phenyl rings of the trityl grouping since the trityl ether compounds herein prepared show this band at *ca.* δ 4.9 ppm, while the 3β-hydroxy compound **4b** has this band at the more normal location, δ 5.38 ppm.

Because a considerable amount of material was left in the mother liquor which resulted from the ethanolamine reaction, this mother liquor was subjected to partition chromatography on Celite to give one major component **5a**. Unfortunately, this component could not be crystallized; so it was acetylated in the hopes



5a, R = R′ = H; R″ = $(C_6H_5)_3C$
b, R = R′ = Ac; R″ = $(C_6H_5)_3C$
c, R = R′ = Ac; R″ = H
d, R = Ac; R′ = R″ = H

of attaining a crystalline compound. The new compound **5b** was amorphous, but it did show *O*-acetyl and *N*-acetyl absorption in its infrared spectrum. Its nmr spectrum also indicated such groupings, but further revealed a splitting of these signals in the acetyl region. Removal of the trityl group from **5b** with acetic acid finally gave a crystalline compound **5c** after preparative thin layer chromatography. The latter compound again showed ester and amide absorption in its infrared spectrum and revealed the same type of splitting of the acetyl signals in its nmr spectrum. The nmr spectrum also indicated a widening of the signal of the C_{18}-hydrogen atoms. The mass spectrum disclosed molecular weight of 488 for the largest mass ion, which supported an acetoxyethylamide structure for **5c**. This was further corroborated by a signal in the mass spectrum at *m/e* 316 (M − 172) which suggests the molecular ion minus a cleavage fragment consisting of the entire C_{20} and C_{21} moiety as indicated by the dotted line in the structure. Furthermore, a signal at *m/e* 172 for this moiety was noted. The balance of the nmr spectrum also supported this structure, so that the splitting of the acetyl signals and widening of the C_{18}-hydrogen signal in the nmr spectrum could be explained by the presence of rotamers of **5c** due to the interference of the C_{18} hydrogens with the free rotation of the large substituent at C_{20}. This was further borne out by the coalescing of these signals when the nmr spectrum was taken at 90°. The indicated structure for **5c** then permitted the appropriate 3-trityl ether structures to be proposed for **5a** and **5b**.

It is apparent that **5a** was formed by the nucleophilic attack of the ethanolamine on the azetidine **3a** with the opening of the C_{20}-nitrogen bond. Since it appears most likely to be a concerted attack with bond cleavage, the stereochemistry of the hydroxyethylamine grouping about C_{20} in **5a** has been assigned as β. No trace of the isomer of **5a** which would be formed by attack at the C_{16} position with opening of the C_{16}-nitrogen bond was seen. This isomer would not have the *m/e* 316 signal or show rotamers in the nmr. Nucleophilic displacement of this type under very mild conditions has been discussed above.[5] It has also been achieved[8] under more vigorous conditions (heating with 10% sodium hydroxide or benzylamine). It is interesting that no Hoffmann degradation products are reported in this last reference.

A very small amount of more polar material recovered from the above-described preparative thin layer chromatography was assigned the structure of the alcohol-amide **5d** on the basis of its nmr and mass spectra. It is possible that this compound arose during the removal of the trityl group from **5b**.

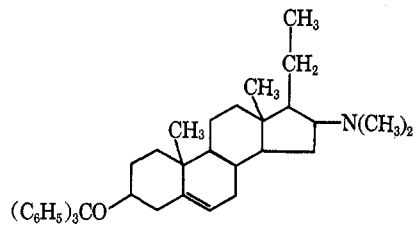
In the hope of achieving a chemical proof of the stereochemistry at C_{20} of **5a**, the azetidinium tosylate **3a** was refluxed with potassium hydroxide in dioxane. For this purpose, the synthesis of **2a** was desired. Unfortunately, only the olefin **4a** was found as a product.

An attempt was made to functionalize **4a** at the C_{21} position by reaction with 9-borabicyclo[3.3.1]nonane[9] as a selective hydroborating agent[10] relative to the Δ^5 double bond. However, no reaction could be made to take place.

It has been observed that treatment of quaternary methylated amines with lithium aluminum hydride served to remove a methyl group from the salt, presumably by SN2 displacement by hydride ion on the *N*-methyl group.[1c,11] In this case, treatment of **3a** with lithium aluminum hydride in refluxing tetrahy-

(6) S. Hünig and W. Baron, *Chem. Ber.*, **90**, 395, 403 (1957).
(7) See ref 3, p 906.
(8) A. Ebnöther and E. Jucker, *Helv. Chim. Acta*, **47**, 745 (1964).
(9) E. F. Knights and H. C. Brown, *J. Amer. Chem. Soc.*, **90**, 5280 (1968).
(10) E. F. Knights and H. C. Brown, *ibid.*, **90**, 5281 (1968).
(11) G. W. Kenner and M. A. Murray, *J. Chem. Soc.*, 406 (1950); A. C. Cope, E. Ciganek, L. J. Fleckenstein, and M. A. P. Meisinger, *J. Amer. Chem. Soc.*, **82**, 4651 (1960).

drofuran opened the azetidine ring to form the pregnene **6**. The structure of the latter was confirmed



6

by reducing the diene **4a** catalytically to afford **6**. In this case, obviously, the hydride ion displacement was at C_{20} followed by cleavage of the C_{20}-nitrogen bond. In general, reaction of the quaternary azetidine ring with nucleophiles may give Hoffmann degradation products and/or substitution products with ring opening besides simple displacement of the anion without ring opening.

Experimental Section[12]

3′6′(*R*)-Dimethyl-2′,3′,4′,5′-tetrahydro-3β-trityloxyandrost-5-eno[16β,17β-*d*]-1′,3′-oxazine (1b).—A mixture of the oxazino compound **1a**[2] (0.77 g), trityl chloride (0.7 g), and pyridine (10 ml) was refluxed for 6 hr and poured into ice–water, and the resultant precipitate was collected. The solid was dissolved in methylene chloride and passed through a small pad of Magnesol. The solvent was removed *in vacuo* and the residue crystallized from methylene chloride–acetone to yield **1b** (0.54 g), mp 251–256°. The analytical sample had mp 257.5–258°; $[\alpha]^{25}D$ −31° ($CHCl_3$); ir 704 cm^{-1}; nmr ($CDCl_3$) δ 0.95 (s, 3, 19 H), 1.13 (s, 18 H), 1.35 (d, 3, J = 7 Hz, 21 H), 1.99 (s, 3, NCH_3), 3.49 and 4.32 (pair of doublets, 2′,2′ H), 4.88 (m, 1, 6 H), and 7.18–7.62 ppm (m, 15, aromatic H).

Anal. Calcd for $C_{42}H_{51}NO_2$ (601.84): C, 83.81; H, 8.54; N, 2.33. Found: C, 83.65; H, 8.50; N, 2.30.

16β-Dimethylamino-3β-trityloxypregn-5-en-20β-ol (2b).—A mixture of the trityl ether **1b** (5.04 g), lithium aluminum hydride (5 g), and tetrahydrofuran (250 ml) was stirred and refluxed 22 hr. The mixture was cooled in an ice bath and a saturated solution of potassium sodium tartrate added dropwise until the excess lithium aluminum hydride was consumed. The mixture was filtered, and the residue was stirred with additional hot tetrahydrofuran and filtered. The combined filtrates were evaporated *in vacuo*. Crystallization of the residue in methylene chloride–acetone afforded **2b** (3.29 g), mp 226.5–228°. An additional 0.39 g, mp 221.5–223.5°, was collected from the mother liquor. The analytical sample had mp 227.5–229°; $[\alpha]^{25}D$ −28° ($CHCl_3$); ir 3450 and 708 cm^{-1}; nmr ($CDCl_3$) δ 0.97 (s, 3, 19 H), 1.00 (s, 3, 18 H), 1.28 (d, 3, J = 6.5 Hz, 21 H), 2.30 (s, 6, $N(CH_3)_2$), 2.68–3.28 (m, 2, 16 H and 3 H), 4.40 (m, 1, 20 H), 4.91 (m, 1, 6 H), and 7.12–7.63 ppm (m, 15, aromatic H).

Anal. Calcd for $C_{42}H_{53}NO_2$ (603.85): C, 83.53; H, 8.85; N, 2.32. Found: C, 83.39; H, 8.99; N, 2.29.

1′,1′,4′(*S*)-Trimethyl-3β-trityloxyandrost-5-eno[16β,17β-*b*]-azetidinium Tosylate (3a).—A solution of the dimethylaminopregnene **2b** (0.177 g) and *p*-toluenesulfonyl chloride (0.2 g) in pyridine (5 ml) was allowed to stand at room temperature for 20 hr. The mixture was then poured into ice–water and extracted exhaustively with methylene chloride. The extract was dried (Na_2SO_4) and the solvent removed *in vacuo*. Crystallization from methanol–acetone afforded the tosylate **3a** (0.04 g): mp 245–246° dec; $[\alpha]^{25}D$ −6.5° (CH_3OH); ir 1200, 1125, 1040, 1016, 708, and 683 cm^{-1}; nmr (DMSO-d_6) δ 0.91 (s, 6, 18 H and 19 H), 1.38 (d, 3, J = Hz, 21 H), 2.28 (s, 3, CH_3 ar), 2.89, 2.98 (two s, 6, $N(CH_3)_2^+$), 4.83 (m, 1, 6 H), and 7.11–7.57 ppm (m, 19, aromatic H); mass spectrum (70 eV) m/e 586, 571, 343, 172.

Anal. Calcd for $C_{49}H_{59}NO_4S$ (757.97): C, 77.64; H, 7.85; N, 1.85; S, 4.23. Found: C, 77.72; H, 8.14; N, 1.95; S, 4.21.

In later runs it was found that increasing the reaction time to 65 hr increased the yield to 65–68%.

1′,1′,4′(*S*)-Trimethyl-3β-trityloxyandrost-5-eno[16β,17β-*b*]-azetidinium Bromide (3b).—To a solution of the tosylate **3a** (0.5 g) in methylene chloride (100 ml) was added a solution of lithium bromide (5 g) in acetone (50 ml). After standing 5 min at room temperature, the solution was concentrated *in vacuo* at room temperature to *ca.* 10 ml. Methylene chloride (150 ml) was added and the resultant precipitate collected. The filtrate was taken to dryness *in vacuo* and the residue crystallized from acetone to give **3b**: mp 175.5–176.5°; $[\alpha]^{25}D$ −7.6° (CH_3OH); ir 1050, 775, 765, 748, and 705 cm^{-1}; nmr (DMSO-d_6) δ 0.93 (s, 6, 18 H and 19 H), 1.42 (d, 3, J = 7 Hz, 21 H), 2.93 and 3.02 (two s, 6, $N(CH_3)_2^+$), 4.87 (m, 1, 6 H), and 7.19–7.52 ppm (m, 15, aromatic H).

Anal. Calcd for $C_{42}H_{52}BrNO$ (666.76): C, 75.65; H, 7.86; Br, 11.99; N, 2.10. Found: C, 75.46; H, 7.84; Br, 11.63; N, 2.01.

16β-Dimethylaminopregna-5,20-dien-3β-yl Trityl Ether (4a). A.—A mixture of the tosylate **3a** (0.31 g) and ethanolamine (12 ml) was refluxed 4 hr and then poured into ice–water. The resultant crude precipitate (0.24 g) was collected and crystallized from acetone–methanol to afford **4a** (0.088 g), mp 190–192°. The analytical sample had mp 196.5–197.5°; $[\alpha]^{25}D$ −43° ($CHCl_3$); ir 1048, 773, 760, and 704 cm^{-1}; nmr ($CDCl_3$) δ 0.72 (s, 3, 18 H), 0.96 (s, 3, 19 H), 2.18 (s, 6, $N(CH_3)_2$), 2.50 (m, 1, 16 H), 3.33 (m, 1, 3 H), 4.72–5.14 (m, 3, 6 H and 21 H), 6.0 (m, 1, 20 H), and 7.14–7.62 ppm (m, 15, aromatic H).

Anal. Calcd for $C_{42}H_{51}NO$ (585.84): C, 86.10; H, 8.78; N, 2.39. Found: C, 86.02; H, 8.93; N, 2.37.

B.—A mixture of the tosylate **3a** (0.95 g), potassium hydroxide (5 g), water (15 ml), and dioxane (50 ml) (two phase system) was stirred and refluxed for 19 hr. The mixture was poured into ice–water and the resultant precipitate (0.75 g) collected, mp 185–190°. A tlc showed essentially only **4a** as the product. This was crystallized to give 0.57 g of **4a**, mp 198–200°. A further 0.045 g, mp 195.5–197°, was isolated from the mother liquor. Each fraction had an identical ir spectrum with that of the sample characterized above.

16β-Dimethylaminopregna-5,20-dien-3β-ol (4b).—A solution of the trityl ether **4a** (0.64 g) in acetic acid (50 ml) was heated at 56° for 7.5 hr. Dilution of the solution with water precipitated triphenylcarbinol (0.28 g) which was removed. The solution was made basic with 30% potassium hydroxide and the resultant precipitate collected. Crystallization from acetone afforded **4b** (0.198 g), mp 209.5–211.5°. The analytical sample had mp 210–212°; $[\alpha]^{25}D$ −70° ($CHCl_3$); ir 3250 and 910 cm^{-1}; nmr ($CDCl_3$) δ 0.78 (s, 3, 18 H), 1.01 (s, 3, 19 H), 2.19 (s, 6, $N(CH_3)_2$), 3.47 (m, 1, 3 H), 4.75–5.15 (m, 2, 21 H), 5.38 (m, 1, 6 H), and 5.99 ppm (m, 1, 20 H).

Anal. Calcd for $C_{23}H_{37}NO$ (343.53): C, 80.41; H, 10.86; N, 4.08. Found: C, 80.22; H, 10.73; N, 4.01.

16β-Dimethylamino-20β-(*N*-2′-acetoxyethylacetamido)pregn-5-en-3β-ol (5c).—The mother liquors (*ca.* 3.25 g) from the reaction of the tosylate **3a** (4.6 g) and ethanolamine (150 ml) as in the preparation of **4a** by method A (1.45 g, of **4a** was recovered) was submitted to partition chromatography on Celite with the system heptane–Methyl Cellosolve. From the first half of a hold-back volume was isolated an additional 0.3 g of **4a**. An amorphous solid (1.45 g) was isolated from the fourth hold-back volume, but this could not be crystallized. Analysis by tlc suggested it was still a mixture. A repeated partition chromatography on Celite as above again gave a noncrystallizable amorphous solid **5a** (0.8 g). Its nmr spectrum ($CDCl_3$) had δ 0.82 (s, 3, 18 H), 0.96 (s, 3, 19 H), 1.23 (d, 3, J = 7 Hz, 21 H), 2.25 (s, 6, $N(CH_3)_2$), 2.42–3.68 (m, 6, 3 H, 16 H, and OCH_2CH_2N), 4.92 (m, 1, 6 H), and 7.14–7.64 ppm (m, 15, aromatic H).

Compound **5a** (0.5 g) was acylated in the usual fashion with acetic anhydride (2 ml) in pyridine (4 ml) at room temperature. The mixture was poured into ice–water and the resultant amorphous solid **5b** (0.56 g) was collected. This solid also could not

(12) All melting points are uncorrected. The infrared spectra were determined in a potassium bromide disk. The nmr spectra were obtained in a Varian A-60 spectrometer with tetramethylsilane as internal reference. The mass spectra were determined on an AEI MS-9 spectrometer (Associated Electrical Industries, Ltd.). Celite (Johns-Manville Co.) is a diatomaceous silica product. Magnesol (Food Machinery Chemical Corp.) is a hydrous magnesium silicate. All the analytical samples were shown to be homogeneous by tlc (silica gel G) analysis. The elemental analyses were performed by L. M. Brancone and associates. The partition chromatography was done by C. Pidacks and associates. Spectral analyses and the optical rotational data were obtained from W. Fulmor and associates. We thank George O. Morton for discussions concerning some nmr spectra, Dr. George Van Lear for interpretation of the mass spectra, and Joseph Nocera for preparative assistance.

be crystallized but was essentially one component by tlc analysis: nmr ($CDCl_3$) δ 0.73 (s, 3, 18 H), 0.92 (s, 3, 19 H), 1.38 (d, 3, J = 7 Hz, 21 H), 2.01, 2.03, 2.04, and 2.13 (4 s, 6, $OC(=O)CH_3$ and $NC(=O)CH_3$), 2.29 (s, 6, $N(CH_3)_2$), 2.58–3.88 (m, 5, 3 H, 16 H, 20 H, NCH_2), 4.18 (m, 2, OCH_2), 4.90 (m, 1, 6 H), and 7.14–7.68 ppm (m, 15, aromatic H).

Treatment of the acetate **5b** (0.295 g) in acetic acid (25 ml) for 7.5 hr at 56° and then pouring the mixture into ice-water afforded a precipitate which was collected. This was triphenylcarbinol (0.05 g). The filtrate was made basic with 30% potassium hydroxide. The resultant precipitate (0.156 g) was collected and put on two preparative thin layer chromatography plates (200 × 200 × 1 mm) (silica gel G) and developed in the system 85% of benzene–acetone–water (2:1:2) (upper phase) and 15% of methanol. The less polar band (0.127 g) (*ca.* 9–9.5 cm from the origin) was collected and crystallized from acetone–hexane to give **5c** (0.030 g): mp 203–203.5° dec; $[\alpha]^{25}D$ −9.6° ($CHCl_3$); ir 3410, 1750, 1642, 1630, and 1230 cm^{-1}; nmr ($CDCl_3$) δ 0.78, 0.79 (d, 3, 18 H), 0.99 (s, 3, 19 H), 1.41 (d, 3, J = 6 Hz, 21 H), 2.03, 2.04 (d, 3, $NC(=O)CH_3$), 2.11, 2.17 (d, 3, $OC(=O)CH_3$), 2.31 (s, 6, $N(CH_3)_2$), 3.05–3.90 (m, 5, 3 H, 16 H, 20 H, NCH_2), 4.18 (m, 2, OCH_2), and 5.34 ppm (m, 1, 6 H); nmr at 90° ($CDCl_3$ + CD_3OD) δ 0.80 (s, 3, 18 H), 1.00 (s, 3, 19 H), 1.41 (d, 3, J = 7 Hz, 21 H), 2.03 (s, 3, $NC(=O)CH_3$), 2.12 (s, 3, $OC(=O)CH_3$), and 2.32 ppm (s, 6, $N(CH_3)_2$); mass spectrum (70 eV) m/e 488, 316, 172.

Anal. Calcd for $C_{29}H_{48}N_2O_4$ (488.69): C, 71.27; H, 9.90; N, 5.73. Found: C, 71.54; H, 9.86; N, 5.72.

The more polar band from the preparative plate (6.0 mm from the origin) gave a crude compound (0.03 g) which had physical measurement suggesting **5d** as its structure: nmr (DMSO-d_6) δ 0.68, 0.70 (d, 3, 18 H), 0.92 (s, 3, 19 H), 1.98 2.01 (d, 3, $NC(=O)CH_3$), 2.22 (s, 6, $N(CH_3)_2$), 4.50 (d, 1, CHOH), 4.75 (m, 1, CH_2OH), and 5.28 ppm (m, 1, 6 H); mass spectrum (70 eV) m/e 446, 316, 130.

16β-Dimethylaminopregn-5-en-3β-yl Trityl Ether (6). A.—A mixture of the tosylate **3a** (0.5 g) and lithium aluminum hydride (1.0 g) in tetrahydrofuran (250 ml) (the steroid was not in solution) was stirred at room temperature for 15 min and then stirred and refluxed for 5 hr. The resultant mixture was worked up as in the preparation of **2b**. Removal of the solvent *in vacuo* afforded a glass which was crystallized from acetone–methanol to give **6** (0.26 g): mp 159–160° (recrystallization did not change the melting point); $[\alpha]^{25}D$ −27°; ir 765, 760, 747, 705, and 696 cm^{-1}; nmr ($CDCl_3$) δ 0.68 (s, 3, 18 H), 0.96 (s, 3, 19 H), 2.23 (s, 6, $N(CH_3)_2$), 4.91 (m, 1, 6 H), and 7.16–7.67 ppm (m, 15, aromatic H).

Anal. Calcd for $C_{42}H_{53}NO$ (587.85): C, 85.81; H, 9.09; N, 2.38. Found: C, 86.17; H, 9.25; N, 2.17.

B.—A mixture of the diene **4a** (0.29 g) and 10% palladium on charcoal (0.03 g) in tetrahydrofuran (20 ml) was stirred and treated with hydrogen at room temperature and atmospheric pressure for 1 hr when approximately 1 mol equiv of hydrogen was absorbed. After filtration of the catalyst, the tetrahydrofuran was removed from the filtrate *in vacuo* to give an amorphous solid. Crystallization from acetone–methanol afforded **6** (0.25 g), mp 160–161°. The infrared spectrum was identical with that of the sample prepared in A.

Registry No.—**1b**, 28463-69-6; **2b**, 28463-70-9; **3a**, 28463-71-0; **3b**, 28463-72-1; **4a**, 28463-73-2; **4b**, 28463-74-3; **5a**, 28463-75-4; **5b**, 28463-76-5; **5c**, 28463-77-6; **6**, 28463-78-7.

The Reduction of Aromatic Nitro and Related Compounds by Dihydroflavins

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The reduction of nitrobenzene by dihydroflavins (or dihydroisoalloxazines) in organic solvents leads to *N*-phenylhydroxylamine and flavins (or isoalloxazines). Nitrosobenzene is very rapidly reduced to *N*-phenylhydroxylamine, and azobenzene leads to hydrazobenzene. Azoxybenzene is sluggishly reduced to hydrazobenzene and aniline. *N*-phenylhydroxylamine also slowly oxidizes reduced flavins, likely *via* disproportionation (to nitrosobenzene and aniline) followed by reaction of the product with dihydroflavin. The reactions of nitrobenzene and six para-substituted nitrobenzenes with dihydro-3-methyllumiflavin in DMF over a range of concentrations follow good second-order kinetics (first order in each reactant). The second-order rate constants fit a Hammett relationship using σ^- substituent constants, ρ^- = +3.6. On the basis of these data along with their relationship to electrochemical and other aromatic nitro reduction methods, a tentative initial step involving electron transfer is proposed. The azobenzene reaction also displays first-order behavior in each reactant (second order overall). No intermediates were observed spectrophotometrically in any of these systems. Aliphatic nitro compounds are unreactive to dihydroflavins.

As part of our studies of the redox chemistry of flavins with organic molecules related to substrates for flavoenzymes,[2] we have investigated reactions between oxidized and reduced flavins (see Scheme I) and the redox states between (and including) nitrobenzene and aniline. The flavoenzymes involved in nitrate reduction and in various metabolic pathways may perform reactions related to those described in this paper.[3] None of the compounds reported in this study reduced flavin, but as reported below several of the oxidation states of nitrobenzene oxidized reduced flavins. Aliphatic nitro compounds were unreactive.

Results

Nitrobenzene and Substituted Nitrobenzenes.—Aromatic, but not aliphatic, nitro compounds oxidize reduced flavins to the normal oxidized flavins in organic solution (isolated chromatographically and identified by thin layer chromatography and spectrally). In the case of nitrobenzene itself the reaction is rather sluggish, requiring approximately 2 days for complete reoxidation of 10^{-4} M dihydroflavin with 10^{-2} M nitrobenzene in dimethylformamide (DMF), dimethyl sulfoxide (DMSO), or acetonitrile.

Thin layer chromatography of the reaction mixture showed major spots for *N*-phenylhydroxylamine and aniline plus unreacted starting material. Every work-up procedure that we have used in preparative experiments has, however, led to destruction of the phenylhydroxylamine with production of aniline. There is evidence as well that phenylhydroxylamine is reduced (by a circuitous route discussed below) to aniline by dihydroflavin. Ultimately in the nitrobenzene reaction

(1) NSF Undergraduate Research Participant, Summer 1969.

(2) M. J. Gibian and D. V. Winkelman, *Tetrahedron Lett.*, **44**, 3901 (1969).

(3) A leading reference is K. Yagi, Ed., "Flavins and Flavoproteins," University Park Press, Baltimore, Md., 1968.