Registry No. 1, 79233-94-6; 2, 79233-95-7; 3, 79233-96-8; 4, 79233-97-9; 5, 79233-98-0; 6, 79233-99-1; 7, 79297-70-4; 8, 79234-00-7; 9, 79234-01-8; 10, 79234-02-9; 11, 79234-03-0; 11·HCl, 79297-71-5; 12, 79297-72-6; 12·HCl, 79355-24-1; 13, 79234-04-1; 14, 79234-05-2; 15, 79234-06-3; 16, 79234-07-4; 17, 79234-08-5; 18, 79234-09-6; 19, 79234-10-9; methyl thioglucolate, 2365-48-2; cyclohexenone, 930-68-7; ethyl urethane, 51-79-6.

Supplementary Material Available: Tables I–IV, listing atomic coordinates, thermal parameters, bond distances, and angles for 19 (3 pages). Ordering information is given on any current masthead page.

3,4,9,9a-Tetrahydro-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazol-2(1*H*)-one Derivatives and N,3-Disubstituted 3,3a,4,4a,10,10a-Hexahydro-3a-hydroxy-2-oxo-1,9b:4,10-diethanoimidazo[4,5-*b*]carbazole-5(2*H*)-carboxamides

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The treatment of 2-[[2-(1*H*-indol-3-yl)ethyl]imino]cyclohexanone (1) with hot concentrated sulfuric acid to give the pentacyclic compound 4 is described. The treatment of 4 with 2 equiv of isocyanate gave N,3-disubstituted 3,3a,4,4a,10,10a-hexahydro-3a-hydroxy-2-oxo-1,9b:4,10-diethanoimidazo[4,5-*b*]carbazole-5(2*H*)-carboxamides 11. When bulky isocyanates were used, the reaction stopped at the diurea stage 10. The latter were irreversibly converted to 11 by heating at 140 °C.

In another paper[1] we have described the acid-catalyzed cyclization of the Schiff base 1 to the spiro ketone 2 by using Pictet–Spengler[2] reaction conditions. However, when 1 was treated under strong acid conditions (Scheme I), an isomeric compound was obtained which still contained the ketone function as shown by infrared absorption at 1721 cm^{-1}. The ultraviolet absorption spectrum [248 nm (ϵ 8580) and 303 (3450); in acid solution, 248 nm (ϵ 610) and 304 (305)] was characteristic of an indoline chromophore[3] rather than of an indole.

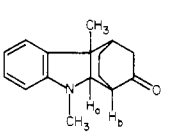
Structure 3 was suggested for this compound on the basis of the strong-acid-catalyzed rearrangement of 1-[(3,4-dihydroxyphenyl)methyl]-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indoles to polycyclic fused indolines as described by Harley-Mason and Waterfield.[4] This structure (3) would arise by cyclization to the indole 3-position followed by electrophilic attack of the indolenium ion on the enol.

Alternatively, another oxoindoline, 4, could have arisen by diprotonation of 1a, cyclization to the indole 3-position, and electrophilic attack of the indolenium ion on the enol.

To decide between these two structures, we turned to nuclear magnetic spectral analysis. The proton magnetic resonance spectrum is in agreement with the structure 4. The aromatic protons exhibit two multiplets centered at δ 6.82 and 6.43. The former multiplet is due to H-5 and H-7 (ortho and para to the aniline nitrogen), while the latter results from H-6 and H-8. The aniline proton as a doublet at δ 5.64 (J = 3.0 Hz) is coupled with H-9a and disappears on exchange with deuterium oxide. The H-12 (NH) as a broad multiplet resonates at δ 2.82 (D_2O exchangeable). The decoupling experiments gave the location of the lone aliphatic protons and their mutual relationships. Thus, the doublet at δ 3.75 (J = 4.2 Hz)[5] corresponds to H-9a being coupled to H-1 at δ 2.33. The doublet at δ 2.96 (J = 3.0 Hz) is due to H-3 which is coupled to H-4 at δ 1.97. The latter split signal, which sits on the top of that for the methylene group, collapses to a sharp spike on decoupling. Four complex envelopes centered at δ 2.45 (2 H, NCH_2, partly burried under Me_2SO-d_6 band), 1.95 (2 H), 1.40 (2 H), and 1.25 (2 H) account for the remaining aliphatic protons. Decoupling without deuterium oxide was also carried out. On irradiating the aniline proton (δ 5.64), the 9a-proton (originally appearing as a triplet) collapsed to a sharp doublet at δ 3.75 (J = 4.2 Hz). Thus, the position of H-9a is unambiguously established. The ^{13}C NMR partially decoupled spectrum ($CDCl_3$) of 4 shows only one aliphatic quaternary carbon at 47.03 ppm which corresponds to C-4a. The resonances of aromatic carbons resemble closely those of indoline. The resonances of tertiary carbons show four distinct lines at δ 61.9, 60.9, 49.1, and 47.0, respectively. There are also four methylene carbon resonances at δ 38.8, 37.4, 20.1, and 15.4. These data give support to structure 4 and eliminate the alternative structure 3 since it would contain two quaternary carbon atoms.

Compound 4 forms the diacetyl derivative 5 with cold acetic anhydride. It reacts with carbonyl reagents, forms an oxime 6, and is also reduced to the secondary alcohol 7 by potassium borohydride at room temperature. The treatment of 7 with acetic anhydride at 25 °C gives the

(1) G. Bobowski, in press.
(2) W. M. Whaley and T. R. Govindarchari, *Org. React.*, 6, 151–190 (1951).
(3) (a) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products", Pergamon Press, Oxford, 1964, p 298; (b) J. R. Williams and L. R. Unger, *Chem. Commun.* 1605–1606 (1970); (c) J. E. D. Barton and J. Harley-Mason, *ibid.*, 298–299 (1965).
(4) J. Harley-Mason and W. R. Waterfield, *Tetrahedron*, 19, 65–76 (1963).
(5) P. A. Cranwell and J. E. Saxton, *Tetrahedron*, 20, 877–881 (1964). In a partly similar structure (but lacking aminoethano bridge), the authors report H_a as a doublet at 3.40 ppm (J = 4.5 Hz); obviously, the neighboring *N*-methyl group causes partial shielding.



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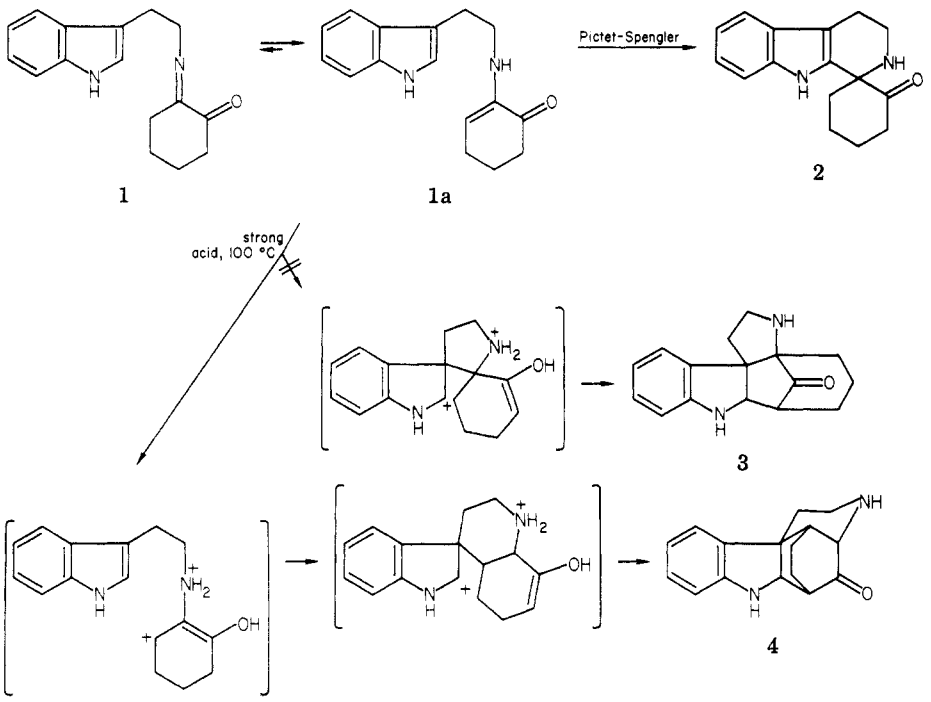
Scheme I



diacetyl alcohol **8**, while on further heating at 100 °C with an excess reagent, the triacetyl derivative **9** is obtained. On treatment of **4** with 2 equiv of alkyl isocyanate (when R is a small alkyl group), the resulting diurea compounds **10** spontaneously cyclized to form the hexacyclic hydroxy derivatives **11**. When the isocyanate contained a large substituent, like cyclohexyl, the diurea ketone derivative **10d** was the sole product isolated in 80% yield. However, **10d** could be transformed irreversibly into the hexacyclic derivative **11d** on heating at 140 °C for 1 h. The treatment of **4** with phenyl isocyanate in tetrahydrofuran resulted in a precipitate which contained the diurea derivative **10e** (50%). The workup of the filtrate gave the hexacyclic product **11e**. In analogy to the cyclohexyl derivative (**10d**), compound **10e** was converted irreversibly into the hexacyclic hydroxy derivative **11e** on heating at 140 °C. The facile spontaneous cyclization of diurea derivatives **10** [when the substituent is small (**10a–c**)] at room temperature gives additional chemical support to structure **4**. The diurea derivatives could be stabilized (when R is phenyl or cyclohexyl) by converting to their oximes or carbinols by potassium borohydride reduction as exemplified by the transformation of **10e** into **12** and **13**. The sequence of reactions is represented in the Scheme II.

Experimental Section

Melting points were determined by using a Thomas-Hoover capillary melting point apparatus which was calibrated against known standards. Infrared (IR) and ultraviolet (UV) spectra were obtained, respectively, with a Beckman DK-1 spectrophotometer and a Baird Model 455 double-beam spectrograph. Proton magnetic resonance (^{1}H NMR) spectra were recorded on a Varian A-60 and a Bruker WH90 spectrometers with tetramethylsilane as an internal reference. Carbon magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker WH90 with a 22.63-MHz operating frequency by using a 6% solution in deuteriochloroform. The mass spectra were recorded on a Finnigan 1015 Qudrupole mass spectrometer. Thin-layer chromatography (TLC) was carried out on silica gel G (Stahl) by using benzene, acetone, heptane or acetonitrile, ethyl acetate, and ethanol in varying proportions. The chromatograms were developed in an iodine chamber.

3,4,9,9a-Tetrahydro-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazol-2(1*H*)-one (4). Method A. 2-[[2-(1*H*-Indol-3-yl)-ethyl]imino]cyclohexanone[1] (Schiff base **1**, 19 g) was added portionwise with stirring to 80 mL of concentrated sulfuric acid, and the resulting, honeylike solution was heated at 100 °C under nitrogen for 45 min. The dark contents were poured onto crushed ice, made basic with sodium hydroxide, and extracted three times with 200 mL of chloroform. The combined extracts were washed, dried (Na_2SO_4), and evaporated, giving 13.2 g of an off-white solid. Crystallization from ethanol gave 10.2 g (54%) of 3,4,9,9a-tetrahydro-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazol-2(1*H*)-one (**4**) as nearly white crystals: mp 205–206 °C, dec; UV (ethanol) λ_{max} 248 nm (ϵ 8580), 303 (3450); UV (ethanolic HCl) 248 nm (ϵ 1220), 268 (610), 304 (305); IR ($CHCl_3$) 3400, 3290 (NH), 1721 (C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 6.82 (m, 2 H, H-5, H-7), 6.43 (m, 2 H, H-6, H-8), 5.64 (d, $J_{NH,H-9a}$ = 3.0 Hz, Ar NH, D_2O exchangeable), 2.82 (br m, NH-12, D_2O exchangeable), 3.75 (apparent t, 1 H; on D_2O exchange collapses to a d, J = 4.2 Hz, H-9a), 2.96 (d, J = 3.0 Hz, H-3); decoupled spectrum (2% Me_2SO-d_6, D_2O exchanged) δ 3.75 (d, $J_{H-9a,H-1}$ = 4.2 Hz, H-9a), 2.96 (d, $J_{H-3,H-4}$ = 3.0 Hz, H-3), 2.33 (m, H-1), 1.97 (m, H-4); ^{13}C NMR (22.63 MHz, $CDCl_3$) δ 133.4 (C_{4b}), 128.2 (C_5), 118.5 (C_6), 123.2 (C_7), 108.7 (C_8), 150.2 (C_{8a}), 47.0 (C_{4a}), 221.7 (C=O); mass spectrum, m/e 254.

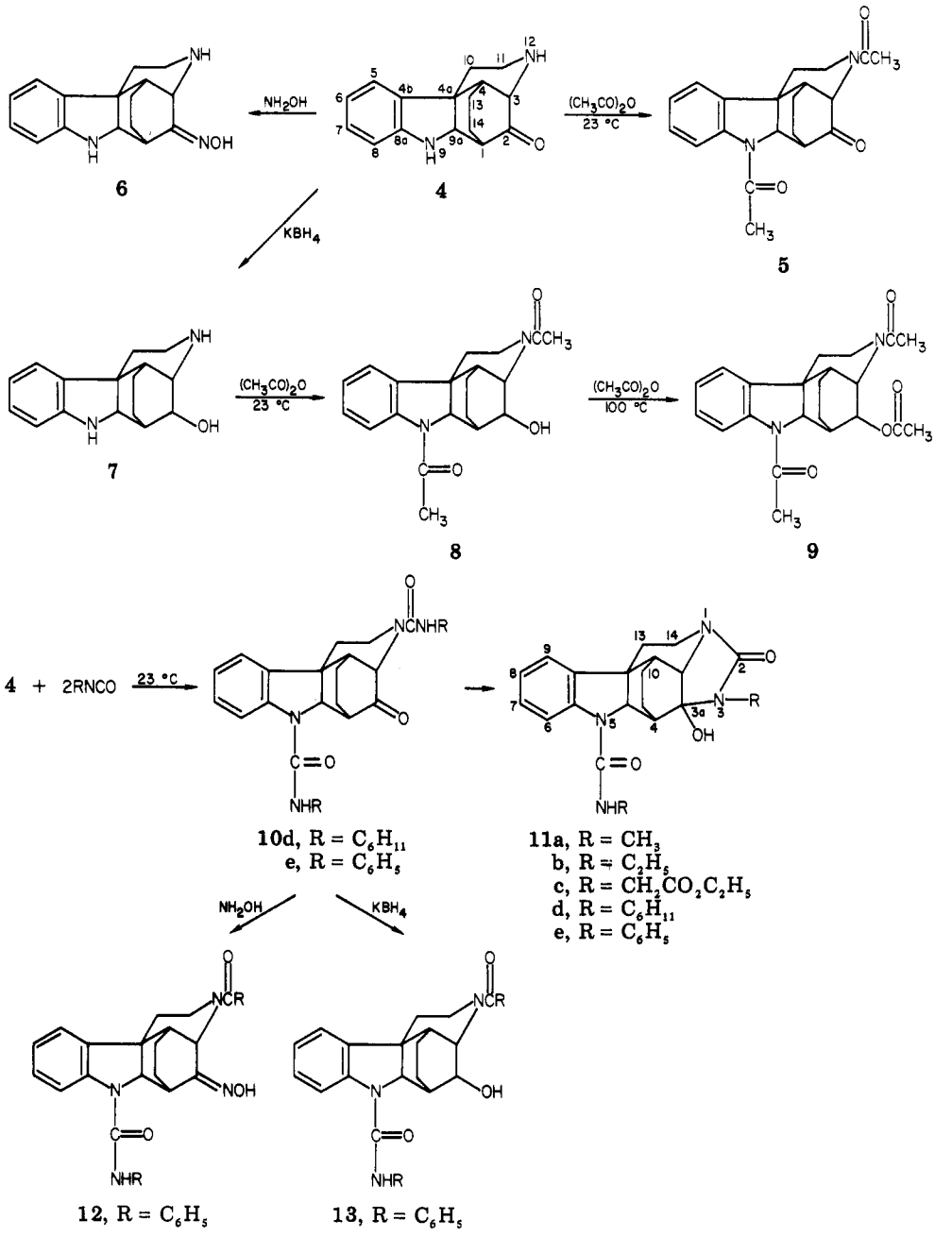
Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.26; H, 7.31; N, 10.89.

Method B. A solution of **1** (0.5 g) in 10 mL of 48% hydrobromic acid was heated on a steam bath under nitrogen for 45 min. The dark brown solution was poured onto ice, made basic with sodium hydroxide, and extracted twice with 20 mL of chloroform. The combined extracts were washed, dried (Na_2SO_4), and evaporated. The brown solid residue was crystallized from ethanol, giving 0.2 g of **4**, mp 205–206 °C dec. This product is identical in all respects with that obtained by method A. The mother liquor contained some 1*H*-indole-3-ethanamine and 1,2-cyclohexanedione resulting from partial hydrolysis of **1**.

Method C. Polyphosphoric acid (10 g) was preheated to 110 °C. The Schiff base **1** (0.5 g) was added, and the syrupy solution was heated at 120 °C with stirring for 1 h and subsequently poured onto ice. The aqueous solution was made basic with sodium hydroxide and extracted twice with 25 mL of chloroform. Drying (Na_2SO_4) and evaporation gave an off-white solid which on recrystallization from ethanol gave 0.3 g of **4**, mp 205–206 °C dec. The product **4** is identical with that obtained by methods A and B.

9,12-Diacetyl-3,4,9,9a-tetrahydro-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazol-2(1*H*)-one (5). To a solution of 1.0 g of 3,4,9,9a-tetrahydro-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazol-2(1*H*)-one (**4**) in 30 mL of ethyl acetate was added 5 mL of

Scheme II



acetic anhydride, and the mixture was allowed to stand at 25 °C for 20 h. Ice and NH_4OH were added to pH 8.0; the organic phase was washed, dried (Na_2SO_4), and concentrated to a low volume, giving 1.1 g of **5** as white crystals, mp 233–237 °C dec. Recrystallization from ethanol gave pure product **5**, mp 238–239 °C dec; UV (ethanol) λ_{max} 250 nm (ϵ 14 920), 280 (3800), 287 (3400); IR (Nujol) 1735 (ketone C=O), 1658 (anilide C=O), 1630 (*N*-$COCH_3$, aliphatic) cm^{-1}.

Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28. Found: C, 70.80; H, 6.51; N, 8.17.

3,4,9,9a-Tetrahydro-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazol-2(1*H*)-one Oxime (6). A stirred mixture of 0.75 g of **4**, 0.5 g of hydroxylamine hydrochloride, and 20 mL of pyridine in 20 mL of ethanol was refluxed for 1 h. The infrared spectrum showed absence of the carbonyl function. The solvent and excess pyridine were evaporated in vacuo. The residue was taken up with cold aqueous sodium bicarbonate, and the nearly white crystalline precipitate (0.8 g) was collected by filtration; mp 219–220 °C dec. Two recrystallizations from ethanol gave the oxime **6** as white crystals: mp 222–224 °C dec; UV (ethanol) λ_{max} 249 nm (ϵ 8680), 303 (3350); IR (KBr) 3390, 3300 (OH, NH), 1606, 1488, 1468 (NH and aromatic) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 10.50 (OH), 6.75 (m, 2 H, H-5, H-7), 6.35 (m, 2 H, H-6, H-8), 5.58 (d, 1 H, $J_{NH,9a}$ = 3.0 Hz, Ar NH, D_2O exchangeable), 3.64 (m, 1 H, H-9a), 3.30 (d, 1 H, $J_{H\text{-}3,H\text{-}4}$ = 3.0 Hz, H-3), 2.60 (m, 1 H, NH-12, D_2O exchangeable).

Anal. Calcd for $C_{16}H_{19}N_3O$: C, 71.34; H, 7.11; N, 15.60. Found: C, 71.21; H, 7.14; N, 15.38.

1,2,3,4,9,9a-Hexahydro-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazol-2-ol (7). To a stirred solution of 0.75 g of **4** in 20 mL of methanol was added 0.5 g of KBH_4, and the resulting clear solution was allowed to stand at 25 °C for 3 days. After the solvent was removed in vacuo, the residue was taken up with cold water and extracted with 40 mL of chloroform. The extract was dried (Na_2SO_4) and evaporated to dryness. The resulting cake was crystallized from ethyl acetate to give 0.4 g of **7** as off-white crystals of analytical purity: mp 180–181 °C dec; UV (ethanol) λ_{max} 249 nm (ϵ 7550), 304 (2900); IR (Nujol) 3310 (NH, OH), 1608 (NH) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 5.45 (d, J = 2.5 Hz, D_2O exchangeable, Ar NH), 4.50 (br m, D_2O exchangeable, OH), 3.96 (m, 1 H, H-2), 3.75 (m, 1 H, H-9a), 3.15 (m, H-3).

Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 74.95; H, 7.85; N, 10.67.

9,12-Diacetyl-1,2,3,4,9,9a-hexahydro-1,4-ethano-3,4a-(imi-

noethano)-4a*H*-carbazol-2-ol (8). A solution of 1.25 g (0.005 mol) of 1,2,3,4,9,9a-hexahydro-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazol-2-ol (**7**) and 2 mL of acetic anhydride in 50 mL of ethyl acetate was allowed to stand for 2 days at room temperature. Cold water and NH_4OH were added to pH 8.0, and the two phases were separated. The aqueous phase was washed, dried (Na_2SO_4), and evaporated. The residual cake was crystallized from acetonitrile, giving 0.9 g of pure 9,12-diacetyl-1,2,3,4,9,9a-hexahydro-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazol-2-ol (**8**): mp 283–283 °C dec; UV (ethanol) λ_{max} 252 nm (ϵ 14070), 279 (4040), 289 (3470); IR (KBr) 3380 (OH), 1660 (anilide $COCH_3$), 1662 (aliphatic $NCOCH_3$) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.02 (d, J = 8.0 Hz, H-8), 7.25–6.90 (m, three aromatic protons), 5.13 (br m, 1 H, OH, D_2O exchangeable), 4.56 (m, 1 H, H-2), 4.12 (d, $J_{H\text{-}9a,H\text{-}1}$ = 4.5 Hz, H-9a), 2.16 (s, 3 H, aromatic $NCOCH_3$), 2.04 (s, 3 H aliphatic $NCOCH_3$).

Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.35; H, 7.17; N, 7.97.

9,12-Diacetyl-1,2,3,4,9,9a-hexahydro-1,4-ethano-3,4a-(iminoethano)-2-acetoxy-4a*H*-carbazole (9). A solution of 0.5 g of diacetyl derivative **8** in 25 mL of acetic anhydride was heated on a steam bath for 2 h, and the excess reagent was evaporated in vacuo. The residue was triturated with hot acetonitrile, giving 0.3 g of **9**, mp 183–184 °C dec. Recrystallization from ethanol gave pure 9,12-diacetyl-1,2,3,4,9,9a-hexahydro-1,4-ethano-3,4a-(iminoethano)-2-acetoxy-4a*H*-carbazole (**9**): mp 184–185 °C dec; UV (ethanol) λ_{max} 250 nm (ϵ 14300), 279 (3790), 288 (3330); IR (KBr) 1736 (ester C=O), 1658 (br, both amido carbonyls) cm^{-1}.

Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.83; H, 6.93; N, 7.18.

3,3a,4,4a,10,10a-Hexahydro-3a-hydroxy-*N*,3-dimethyl-2-oxo-1,9b:4,10-diethanoimidazo[4,5-*b*]carbazole-5(2*H*)-carboxamide (11a). A solution of 0.5 g of 3,4,9,9a-tetrahydro-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazol-2(1*H*)-one (**4**) and 1 mL of methyl isocyanate in 25 mL of dichloromethane was allowed to stand for 20 h at 25 °C. The resulting white precipitate (0.3 g) of **11a** was collected; mp 279–280 °C dec. The solvent and excess isocyanate were evaporated, and the residue was triturated with acetonitrile, giving 0.2 g of additional product **11a**, mp 279–280 °C dec. Recrystallization of the combined crops from ethanol gave 0.35 g of analytically pure 3,3a,4,4a,10,10a-hexahydro-3a-hydroxy-*N*,3-dimethyl-2-oxo-1,9b:4,10-diethanoimidazo[4,5-*b*]carbazole-5(2*H*)-carboxamide (**11a**): mp 280–281 °C dec; UV (ethanol) λ_{max} 250 nm (ϵ 15000), 290 (2760); IR (KBr), 3400, 3320 (OH, NH), 1682 (2-C=O), 1654, 1520 (NHCO) cm^{-1}; IR ($CHCl_3$) 3480 (OH), 3460 (NH), 1692 (2-C=O), 1665, 1615 (NHCO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.38 (d, 1 H, J = 8.0 Hz, H-6), 6.72–7.20 (m, 3 H, aromatic protons), 6.30 (q, 1 H, $J_{CH_3,NH}$ = 4.0 Hz, D_2O exchangeable), 6.16 (s, sharp, 1 H, OH, D_2O exchangeable), 3.78 (d, 1 H, $J_{H\text{-}4,H\text{-}4a}$ = 3.0 Hz, H-4a), 3.43 (d, 1 H, $J_{H\text{-}1a,H\text{-}10}$ = 5.0 Hz, H-1a), 2.67 (s, 3 H, 3-CH_3), 2.58 (d, 3 H, $J_{CH_3,NH}$ = 4.0 Hz, CH_3NH).

Anal. Calcd for $C_{20}H_{24}N_4O_3$: C, 65.20; H, 6.57; N, 15.21. Found: C, 64.92; H, 6.57; N, 15.05.

***N*,3-Diethyl-3,3a,4,4a,10,10a-hexahydro-3a-hydroxy-2-oxo-1,9b:4,10-diethanoimidazo[4,5-*b*]carbazole-5(2*H*)-carboxamide (11b).** To a solution of 3.82 g (0.015 mol) of **4** in 75 mL of dry tetrahydrofuran was added 2.3 g (0.033 mol) of ethyl isocyanate, and the mixture was allowed to stand at 25 °C for 20 h. A few drops of ethanol were added to destroy excess isocyanate, and the solvent was removed in vacuo. Crystallization of the residue from acetonitrile gave 4.9 g (82%) of product **11b** as off-white crystals: mp 232–233 °C dec; UV (ethanol) λ_{max} 209 nm (ϵ 27220), 249.5 (14320), 290 (2650); IR (Nujol) 3300, 3150 (NH, OH), 1676 (2-C=O), 1632, 1520 (NHCO) cm^{-1}.

Anal. Calcd for $C_{22}H_{28}N_4O_3$: C, 66.65; H, 7.12; N, 14.13. Found: C, 66.83; H, 7.24; N, 14.12.

Ethyl 5-[[(2-Ethoxy-2-oxoethyl)amino]carbonyl]-3a,4,4a,5,10,10a-hexahydro-3a-hydroxy-2-oxo-1,9b:4,10-diethanoimidazo[4,5-*b*]carbazole-3(2*H*)-acetate (11c). To a cooled solution of 3.8 g (0.015 mol) of **4** in 50 mL of tetrahydrofuran was added 4.3 g (0.0165 mol) of ethyl isocyanatoacetate, and the mixture was allowed to stand at 23 °C for 3 days. Ethanol (0.5 mL) was added, and the solution was evaporated in vacuo. Crystallization of the residue from ether–ethyl acetate gave 3.8 g (49%) of white crystals of **11c**: mp 187–188 °C dec; UV (ethanol) λ_{max} 207.5 nm (ϵ 36500), 246 (18400), 285 (3020), 293 (2800); IR (Nujol) 3320 (NH, OH), 1726 ($CO_2C_2H_5$), 1680 (2-C=O), 1656, 1520 (NHCO) cm^{-1}.

Anal. Calcd for $C_{26}H_{32}N_4O_7$: C, 60.93; H, 6.29; N, 10.93. Found: C, 60.68; H, 6.33; N, 10.76.

***N*,*N'*-Dicyclohexyl-1,3,4,9a-tetrahydro-2-oxo-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazole-9,12(2*H*)-dicarboxamide (10d).** To a solution of 3.81 g (0.015 mol) of **4** in 100 mL of dry tetrahydrofuran was added 3.92 g (0.0165 mol) of cyclohexyl isocyanate, and the mixture was allowed to stand for 4 days at 25 °C. A few drops of ethanol were added, and the solution was evaporated to dryness in vacuo. Crystallization of the solid residue from ethyl acetate gave 3.9 g of analytically pure, white crystals of **10d**, mp 200–201 °C dec. Concentration of the mother liquor to a low volume gave 2.2 g (total yield 81%) of additional product **10d**: mp 199–200 °C dec; UV (ethanol) λ_{max} 208 nm (infl; ϵ 30520), 248.5 (17120), 286 (2880), 295 (sh, 2520); IR (Nujol) 3400, 3330, 3240 (NH), 1728 (ketone C=O), 1635–1627 (urea C=O), 1527 (NHCO) cm^{-1}; IR ($CHCl_3$) 1724 (ketone C=O), 1650, 1640 (urea C=O), 1525 (NHCO) cm^{-1}.

Anal. Calcd for $C_{30}H_{40}N_4O_3$: C, 71.40; H, 7.99; N, 11.10. Found: C, 71.52; H, 8.09; N, 10.84.

***N*,3-Dicyclohexyl-3,3a,4,4a,10,10a-hexahydro-3a-hydroxy-2-oxo-1,9b:4,10-diethanoimidazo[4,5-*b*]carbazole-5(2*H*)-carboxamide (11d).** A solution of 1.2 g of *N*,*N'*-dicyclohexyl-1,3,4,9a-tetrahydro-2-oxo-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazole-9,12(1*H*)-dicarboxamide (**10d**) in 75 mL of xylene and 25 mL of tetrahydrofuran was refluxed for 1 h. When the mixture was cooled to 25 °C, 0.9 g (75%) of **11d** as off-white crystals separated; mp 203–204 °C dec. An analytical sample of **11d** as a 2-propanolate (2:1) was obtained by recrystallization from 2-propanol: mp 203–204 °C dec; UV (ethanol) λ_{max} 210 nm (infl; ϵ 25200), 251 (16880), 290 (5600); IR (Nujol) 3320 (br, NH, OH), 1680 (2-C=O), 1630, 1509 (NHCO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.05 (0.5(CH_3)$_2$CHOH, d, J = 7.0 Hz), 3.33 (OH).

Anal. Calcd for $C_{30}H_{40}N_4O_3$·0.5$(CH_3)_2CHOH$: C, 70.98; H, 8.30; N, 10.50. Found: C, 71.01; H, 8.48; N, 10.58.

1,3,4,9a-Tetrahydro-2-oxo-*N*,*N'*-diphenyl-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazole-9,12(2*H*)-dicarboxamide (10e). To a solution of 2.0 g (0.0079 mol) of **4** in 80 mL of dry tetrahydrofuran was added 2.1 g (0.0174 mol) of phenyl isocyanate, and the mixture was allowed to stand at 25 °C overnight. The resulting white crystals of **10e** (1.8 g) were filtered off; mp 252–253 °C dec. An analytical sample, also melting at 252–253 °C dec, was obtained by recrystallization from acetonitrile: UV (ethanol) λ_{max} 259.5 nm (ϵ 28400), 293 (sh, 4800); IR (Nujol) 3220 (NH), 1733 (ketone C=O), 1650 (sh), 1639, 1530 (NHCO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.60, 8.80 (2 H, NH).

Anal. Calcd for $C_{30}H_{28}N_4O_3$: C, 73.15; H, 5.73; N, 11.38. Found: C, 73.00; H, 5.88; N, 11.49.

3,3a,4,4a,10,10a-Hexahydro-3a-hydroxy-2-oxo-*N*,3-diphenyl-1,9b:4,10-diethanoimidazo[4,5-*b*]carbazole-5(2*H*)-carboxamide (11e). Method A. The original filtrate from the preceeding experiment (formation of **10e**) was evaporated to dryness, and the white residue was crystallized from acetonitrile, giving 1.1 g of pure **11e**: mp 242–243 °C dec; UV (ethanol) λ_{max} 262 nm (ϵ 25750), 295 (infl; 5850); IR (Nujol) 3270, 3200 (NH, OH), 1676 (2-C=O), 1650, 1528 (NHCO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.62 (OH), 8.49 (NH).

Anal. Calcd for $C_{30}H_{28}N_4O_3$: C, 73.15; H, 5.73; N, 11.38. Found: C, 73.25; H, 5.76; N, 11.36.

Method B. A solution of diurea derivative **10e** (1.7 g) in 100 mL of xylene was refluxed for 1 h. After the solution was allowed to cool to 25 °C, 1.4 g (82%) of pure hexacyclic derivative **11e** was obtained; mp 242–243 °C dec. A mixture melting point with analytical sample of **11e** was not depressed, and the spectral data are identical.

1,3,4,9a-Tetrahydro-2-oxo-*N*,*N'*-diphenyl-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazole-9,12(2*H*)-dicarboxamide Oxime (12). A solution of 0.5 g of **10e**, 0.5 g of hydroxylamine hydrochloride, and 2 mL of pyridine in 25 mL of ethanol was refluxed for 3 h. The infrared absorption spectrum showed absence of the ketone function at 1733 cm^{-1}. The solution was evaporated to dryness. The residue was taken up with cold water and the resulting white crystalline product collected; mp 192–194 °C dec. Crystallization from ethanol gave 0.3 g of the oxime **12** as white crystals: mp 195–196 °C dec; UV (ethanol) λ_{max} 260 nm

(ε 28 400), 293 (sh, 4800); IR (Nujol) 3350, 3220 (OH, NH), 1648 (br, C=O), 1530 (NHCO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 10.95 (1 H, OH), 8.70, 8.50 (2 H, NH).

Anal. Calcd for $C_{30}H_{29}N_5O_3$: C, 70.99; H, 5.76; H, 13.80. Found: C, 70.71; H, 5.66; N, 13.61.

1,3,4,9a-Tetrahydro-2-hydroxy-*N*,*N*'-diphenyl-1,4-ethano-3,4a-(iminoethano)-4a*H*-carbazole-9,12-(2*H*)-dicarboxamide (13). To a solution of 3.0 g of **10** in 150 mL of absolute methanol was added 1.0 g of potassium borohydride with stirring at 23 °C, and the mixture was allowed to stir overnight. The infrared spectrum showed the absence of the ketone function. The solution was neutralized with acetic acid, and the solvent was removed in vacuo. The residue was taken up with cold water, and the white crystalline material (2.7 g, 90% crude yield) was collected by filtration; mp 253-255 °C dec. Crystallization from acetonitrile-tetrahydrofuran (2:1) gave 2.2 g of the diurea alcohol **13**: mp 256-257 °C dec; UV (ethanol) λ_{max} 249 nm (ε 32 800), 257 (32 280); IR (Nujol) 3420, 3320 (OH, NH), 1679 (C=O, anilide), 1633 (aliphatic NCOAr), 1528 (NHCO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.42 [2 H, $(NH)_2$, D_2O exchangeable], 5.10 (d, $J_{H\text{-}2,OH}$ = 5.0 Hz, OH-3, D_2O exchangeable), 4.92 (m, 1 H, H-2).

Anal. Calcd for $C_{30}H_{30}N_4O_3$: C, 72.85; H, 6.11; N, 11.33. Found: C, 73.15; H, 6.13; N, 11.60.

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Registry No. 1, 79234-11-0; 4, 79234-12-1; 5, 79234-13-2; 6, 79234-14-3; 7, 79234-15-4; 8, 79234-16-5; 9, 79234-17-6; 10d, 79234-18-7; 10e, 79234-19-8; 11a, 79234-20-1; 11b, 79234-21-2; 11c, 79234-22-3; 11d, 79234-23-4; 11e, 79234-24-5; 12, 79234-25-6; 13, 79234-26-7; methyl isocyanate, 624-83-9; ethyl isocyanate, 109-90-0; ethyl isocyanatoacetate, 2949-22-6; cyclohexyl isocyanate, 3173-53-3; phenyl isocyanate, 103-71-9.

Pictet-Spengler Reactions of Epinephrine with Formaldehdye and Acetaldehyde

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Formaldehyde reacts with epinephrine (1) in neutral solution to produce tetrahydroisoquinolines **2** and **3**. Analogously, the reaction between acetaldehyde and epinephrine affords **4a**, **4b**, **5a**, and **5b**. At low pH, cyclization para to the activating hydroxy substituents affords only **2** or **4a** and **4b** regiospecifically. The effect of pH on the rate and products of these reactions was studied.

In 1970, a theory was advanced suggesting that some of the physiological effects of ethanol intoxication, dependence, tolerance, and withdrawal might be caused by tetrahydroisoquinoline derivatives formed in vivo by condensation between endogenous catecholamines and acetaldehyde, the primary metabolite of ethanol.[1] Perfusion of isolated adrenal glands, which contain epinephrine (1), with acetaldehyde produced a mixture of compounds which was thought to consist mainly of 1,2,3,4-tetrahydro-1,2-dimethyl-4,6,7-isoquinolinetriols **4a** or **4b**. The same compounds are formed by the adrenal glands of rats exposed to ethanol and pyrogallol[1f] and also by the simple condensation of acetaldehyde with epinephrine or norepinephrine in the absence of biological material. Low concentrations of these crude condensates cause profound physiological and behavioral changes including complete depletion of guinea pig hypothalamic norepinephrine[1d,1g] and selective degeneration of adrenergic nerves[1h] in laboratory animals. This activity of the mixture suggests that its constituents may indeed be responsible for some of the physiological effects of ethanol. Thus we thought it important to define the precise structure of the compounds present in the mixture.

Structures **4a** and **4b** had never been rigorously proven but merely assumed[1,2] as resulting from a Pictet-Spengler condensation between epinephrine and acetaldehyde. Despite several previous attempts, the preparation of these compounds had not been achieved. Partial purification of the epinephrine-acetaldehyde condensation mixture has been attempted by utilizing preparative TLC, but a pure compound was not isolated.[1d] Synthesis of *N*-demethyl-**4** by an independent route was attempted but afforded only a dark-colored mixture which could not be purified or induced to crystallize.[3]

In this report, we describe isolation and complete characterization of the compounds which result from the reaction between epinephrine and formaldehyde (**2** and **3**) and the reaction between epinephrine and acetaldehyde (**4a**, **4b**, **5a**, and **5b**). In addition, we describe the effect of pH on the rate and product distribution of these reactions.

Results

Since the products resulting from the reaction between epinephrine (1) and acetaldehyde were expected to be mixtures of cis and trans isomers, we turned our attention initially to the reaction between epinephrine and formaldehyde. Previous biological studies[1] utilized low substrate concentrations; however, we found that the same products were formed at the more practical higher concentrations which we employ. The pH at which the reaction was conducted profoundly influenced both the rate

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