2. **Potassium *tert*-Butoxide, Sodium Hydride, Sodium 2,6-Di-*tert*-Butylphenoxide in THF.**—Saturated solutions of the pyridinium salts **6**, **15a**, **15b**, and **17** were prepared by stirring 50 mg of each of the salts in THF (100 ml, freshly distilled from lithium aluminum hydride) for 24 hr. The uv spectra of the three solutions were recorded. The bases (50 mg) were added to 25-ml aliquots of the solutions of the pyridinium salts and the ultraviolet spectra recorded. Table II summarizes the observations.

Acknowledgment.—We wish to thank Professor Jack Vriesenga for assistance in obtaining the 100-MHz nmr spectra. Also, we wish to acknowledge the National Science Foundation for aid in the purchase of the 100-MHz nmr spectrometer and Bristol Laboratories for a gift of 60-MHz nmr spectrometer.

Registry No.—**4**, 40430-00-0; **5a**, 40430-01-1; **5b**, 36612-08-5; **5c**, 40513-85-7; **5d**, 40430-03-3; **6**, 40513-86-8; **7**, 40513-87-9; **8a**, 40430-04-4; **8b**, 40430-05-5; **9a**, 36844-27-6; **9b**, 40430-06-6; **10a**, 36844-26-5; **10b**, 40430-08-8; **11a**, 40513-89-1; **11b**, 40429-16-1; **12a**, 40429-17-2; **12b**, 40429-18-3; **13a**, 36612-07-4; **13b**, 40429-20-7; **14a**, 40429-21-8; **14b**, 40429-22-9; **14c**, 40429-23-0; **15a**, 40429-24-1; **15b**, 40429-25-2; **16a**, 40429-26-3; **16b**, 40429-27-4; **16c**, 40429-28-5; **17**, 40429-29-6; **18**, 40429-30-9; 1,8-diaminooctane, 373-44-4; isophthaloyl chloride, 99-63-8; 3,5-pyridinedicarbonyl chloride, 15074-61-0; 1,7-diaminoheptane, 646-19-5; 1,6-diaminohexane, 124-09-4; 1,5-diaminopentane, 462-94-2; α-bromo-2,6-dichlorotoluene, 20443-98-5; *p*-toluenesulfonyl chloride, 98-59-9; 1,7-heptanediol-4-one ethylene ketal, 5694-96-2; 1,9-nonanediol-5-one ethylene ketal, 5694-92-8; potassium phthalimide, 1074-82-4; 1-(2,6-dichlorobenzyl)-3,5-(*N*,*N*′-dimethyldicarbamoyl)-2(1*H*)-pyridone, 40429-36-5; 3,5-(*N*,*N*′-dimethyldicarbamoyl)pyridine, 40429-35-4.

Model Studies of the Synthesis of Echitamine and Related Indole Alkaloids.[1] II

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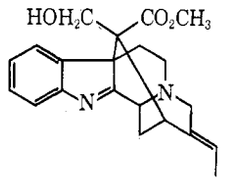
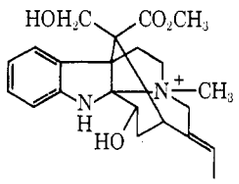
Attempts to synthesize the pentacyclic skeleton of akuammiline are described. The key step in this synthetic approach is the formation of the C-6 to C-7 bond by a nucleophilic substitution reaction. This transformation would complete the akuammiline skeleton from the tetrahydrocarbazole intermediate **16** which bears four of the required five rings. However, all attempts to generate the crucial C-6 to C-7 bond met with failure. The synthesis of several novel tetracyclic tetrahydrocarbazole derivatives is presented along with a sequence leading unexpectedly to indolo[2,3-*c*]norcar-3-en-2-one (**12**) and indolo[2,3-*b*]cyclohepta-2,4-dienone (**13**).

Echitamine and its probable biogenetic precursor deacetylakuammiline are examples of a group of indole alkaloids bearing a C-16–C-7 bond. A number of these alkaloids are now known[2,3] but no representative of this group has been obtained by chemical synthesis.



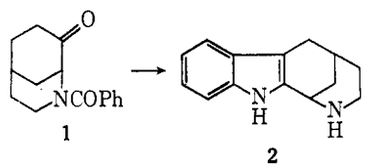
deacetylakuammiline



echitamine

In investigating routes to the pentacyclic framework of these molecules we sought to take advantage of the nucleophilic character of the indole nucleus in forming the final ring from a tetracyclic intermediate possessing the C-7–C-16 bond. Thus, elimination of *p*-toluenesulfonic acid from the tosylate shown in Scheme I would lead to the skeleton of deacetylakuammiline. A similar approach has been successfully employed in the synthesis of minovine,[4] and a previous report from these laboratories[5] describes results of a model system which proved encouraging.

The tetracyclic intermediate required for this scheme was obtained by two independent routes. In one route 2-azaindolo[2,3-*g*]bicyclo[3.3.1]non-7-ene (**2**) arose from a Fischer indole synthesis with 2-

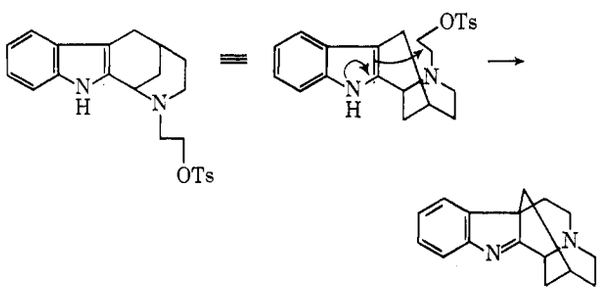


1 **2**

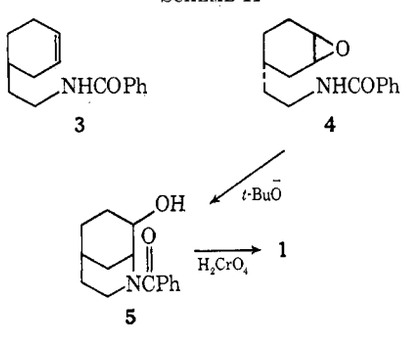
benzoyl-2-azabicyclo[3.3.1]nonan-8-one (**1**) followed by alkaline hydrolysis of the benzoyl moiety.

The ketone utilized in the Fischer indole synthesis was prepared following the route outlined in Scheme II.

SCHEME I



SCHEME II



3 **4** **5**

(1) The authors gratefully acknowledge financial support from the National Institutes of Health (Grant GM18196) and a Public Health Service Career Program Award (1-K3-NB-28,105) from the National Institute of Neurological Disease and Blindness.

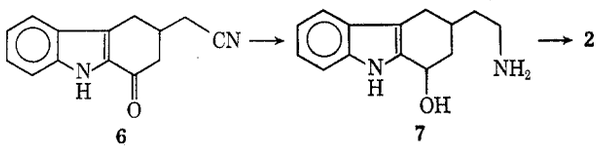
(2) J. E. Saxton, "The Alkaloids," Vol. X, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1968, p 501.

(3) A. I. Scott, *Accounts Chem. Res.*, **3**, 151 (1970).

(4) F. E. Ziegler and F. B. Spitzner, *J. Amer. Chem. Soc.*, **92**, 3493 (1970).

(5) L. J. Dolby and Z. Esfandiary, *J. Org. Chem.*, **37**, 43 (1972).

SCHEME III



Oxidation of *N*-benzoyl-2-(Δ^3-cyclohexenyl)ethylamine (**3**) with *m*-chloroperbenzoic acid gave rise to an amorphous solid from which the trans epoxide **4** was obtained by fractional crystallization. On treatment with potassium *tert*-butoxide the amido epoxide **4** underwent cyclization to give 2-aza-2-benzoylbicyclo-[3.3.1]nonan-8-ol (**5**) in high yield. For preparative purposes the crude epoxide mixture was treated in a similar fashion to give **5** in 40–45% yields. Oxidation of **5** to the ketone **1** proved unexpectedly troublesome; a variety of methods gave rise to intractable mixtures. Ultimately, the ketone **5** was obtained in moderate yields with chromic acid in aqueous acetic acid.

Brief treatment of the crude phenylhydrazone of **1** with hot dilute sulfuric acid gave rise to a dark product which was subjected directly to alkaline hydrolysis. The crystalline tetracyclic amine **2** was obtained from the hydrolysis mixture in 2–5% yields. The ultraviolet spectrum of **2** shows characteristic indole absorption. The pmr, ir, and mass spectra were likewise consistent with the expected structure. Ultimate confirmation of the structure was obtained, however, by an independent synthesis.

The great facility with which 2-hydroxyalkylindoles enter into elimination–addition reactions[6] suggested that the tetracyclic amine **2** could be obtained from 3-(2-aminoethyl)-1-hydroxy-1,2,3,4-tetrahydrocarbazole (**7**) (Scheme III). This proved to be the case. Reduction of 3-cyanomethyl-1-oxo-1,2,3,4-tetrahydrocarbazole (**6**) with lithium aluminum hydride under carefully controlled conditions followed by pyrolysis of the crude reduction product in refluxing *o*-dichlorobenzene gave the tetracyclic amine **2** in yields of 40%. Material obtained by this route was identical with that obtained from the Fischer indole synthesis.

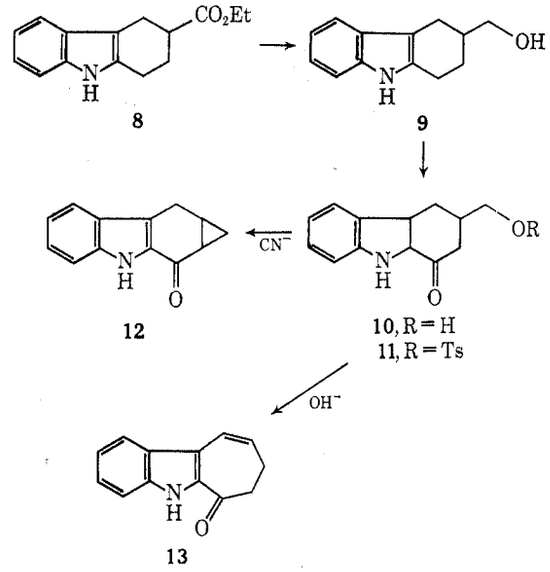
The preparation of the keto nitrile **6** was accompanied by an interesting rearrangement leading to indole[2,3-*b*]cyclohepta-2,4-dienone (**13**) (Scheme IV). Reduction of 3-carboethoxy-1,2,3,4-tetrahydrocarbazole (**8**) with lithium aluminum hydride gave the carbinol **9**. Oxidation of **9** with periodic acid[7] in methanol provided 3-hydroxymethyl-1-oxo-1,2,4,3-tetrahydrocarbazole (**10**), which was converted to the corresponding *p*-toluenesulfonate ester **11**.

On treatment with sodium cyanide in either ethanol or dimethyl sulfoxide, **11** gave rise not to the expected keto nitrile **6** but to indolo[2,3-*c*]norcar-3-en-2-one (**12**). The structure of **12** follows from elemental analysis and one-proton multiplets in the pmr spectrum centered at 0.8 and 1.4 ppm assigned to the methylene protons of the cyclopropane ring. In an effort to duplicate this reaction with sodium hydroxide in ethanol

(6) R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, N. Y., 1970, pp 94–108; for pertinent examples see G. Büchi, R. E. Manning, and S. A. Monti, *J. Amer. Chem. Soc.*, **88**, 2532 (1966); R. J. Sundberg, *J. Org. Chem.*, **33**, 487 (1968); L. J. Dolby and P. D. Lord, *ibid.*, **34**, 2988 (1969).

(7) L. J. Dolby and D. L. Booth, *J. Amer. Chem. Soc.*, **88**, 1049 (1966).

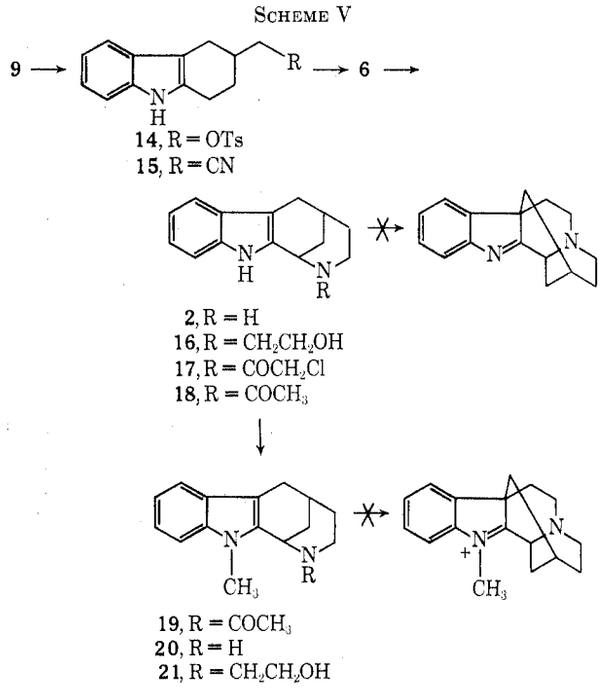
SCHEME IV



an excellent yield of the cycloheptadienone **13** was realized. The norcarenone **12** could be detected in the reaction mixture by tlc and is undoubtedly the precursor of **13**. Although unexpected, these results are not without precedent. Julia and coworkers have prepared benzosuberones in an analogous fashion from 3-hydroxymethyl-α-tetralones.[8]

To circumvent this difficulty, methylol **9** was converted to the corresponding *p*-toluenesulfonate ester **14**, which reacted smoothly with sodium cyanide in ethanol to give 3-cyanomethyl-1,2,3,4-tetrahydrocarbazole (**15**) (Scheme V). Periodic acid oxidation of

SCHEME V



15 in methanol then gave rise to the desired keto nitrile **6**. With a convenient source of the tetracyclic amine **2** at hand the amino alcohol **16** was readily obtained by treatment of **2** with ethylene oxide

(8) S. Julia, M. Julia, and C. Huynh, *C. R. Acad. Sci.*, **246**, 3464 (1958).

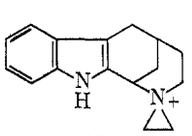
in tetrahydrofuran containing a small amount of methanol.

Treatment of the ethanolamine **16** with *p*-toluenesulfonyl chloride in pyridine resulted in the formation of a polymeric material which displayed typical indole absorption in its ultraviolet spectrum. Similar results were obtained with methanesulfonyl chloride–triethylamine in dimethylformamide or 1,2-dimethoxyethane. In no case was there obtained material having the characteristic indolenine absorption maxima near 260 nm.[4]

The chloroacetamide **17** was prepared in the expectation that generation of the indolic anion would result in the desired cyclization. Reaction of **17** with sodium hydride in tetrahydrofuran resulted in the formation of an amorphous material which retained the indole nucleus and the amide carbonyl by ultraviolet and infrared spectroscopy. The material was insoluble in hot 10% acetic acid and had no distinct melting point.

It was expected that methylation of the indole nitrogen would minimize polymer formation and the desired ring closure would be favored. The acetamide **18** was prepared from **2** by the action of acetic anhydride in pyridine. Reaction of **18** with sodium hydride followed by methyl iodide gave rise to the methylated acetamide **19**, which was directly subjected to hydrazinolysis, giving the methylated tetracyclic amine **20**. Treatment of **20** with ethylene oxide gave rise to the methylated ethanolamine **21**, which was treated with methanesulfonyl chloride or *p*-toluenesulfonyl chloride as described for the demethyl compound. Inasmuch as the product expected from the desired cyclization is an indoleninium salt, the reaction mixtures were treated with sodium borohydride to reduce the immonium moiety and facilitate the isolation of products. If water was added to the reaction mixture before the sodium borohydride a good recovery of starting material resulted. If the order of reagent addition was reversed a complex mixture of products was obtained from which three major components were obtained by preparative tlc. All of the products showed typical indole absorption in their ultraviolet spectra and were not further characterized. No absorption assignable to the expected indoline could be detected in either the reaction mixture or any of the products.

The failure of the cyclization reactions can be rationalized by postulating the aziridinium ion **22** as an



22

intermediate which fails to cyclize under the conditions employed.

Experimental Section[9]

***N*-Benzoyl-2-(Δ³-cyclohexenyl)ethylamine (3).**—A mixture of 2-(Δ³-cyclohexenyl)ethylamine[10] (85 g, 0.67 mol) in 1 *N* sodium hydroxide (500 ml) was treated with benzoyl chloride (127 g, 0.910 mol) over 1 hr at 0°. Additional 1 *N* sodium hydroxide was added as required to maintain a pH above 10. After the addition of the benzoyl chloride the mixture was vigorously stirred for 1 hr. The precipitate was collected and taken up in ether. The organic solution was washed with sodium bicarbonate solution and brine and dried. The ether was removed under reduced pressure and the residue was recrystallized from benzene–hexane to give the benzamide **3** (143 g, 92%): mp 84–85°; ir $\tilde{\nu}_{max}^{CHCl_3}$ 3350 and 1650 cm^{-1}; pmr ($CDCl_3$) δ 0.80–2.91 (m, 9), 3.20–3.72 (m, 2), 5.66 (b s, 2), and 7.10–8.20 (m, 5).

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.44; H, 8.41; N, 5.94.

***N*-Benzoyl-3-(2-aminoethyl)-7-oxabicyclo[4.1.0]heptane (4).**—To a solution of the cyclohexenylbenzamide **3** (95.5 g, 0.420 mol) in chloroform (1 l.) was added 80% *m*-chloroperbenzoic acid (100 g, 0.46 equiv) in portions with cooling to maintain the temperature below 30°. After the addition was complete the mixture was stirred at room temperature for 16 hr. Potassium carbonate (100 g) in water (600 ml) was added and the phases were separated. The aqueous phase was extracted with chloroform and the combined chloroform solutions were washed with bisulfite solution and brine and dried. Removal of the chloroform under reduced pressure left the epoxide mixture **10** as an oil (104 g, 98%) which solidified on standing. Repeated crystallization from ethyl acetate–hexanes provided the trans isomer **4**: mp 113–115°; $\tilde{\nu}_{max}^{CHCl_3}$ 3500, 1660, and 1215 cm^{-1}; pmr ($CDCl_3$) δ 0.65–2.25 (m, 9), 3.08 (b s, 2), 3.38 (q, 2), 7.02 (b s, 1), 7.30 (u d, 3), and 7.72 (u d, 2).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.11; H, 7.69; N, 5.67.

2-Aza-2-benzoylbicyclo[3.3.1]nonan-8-ol (5).—A solution of the crude epoxide mixture **4** (25 g, 0.10 mol) in tetrahydrofuran (60 ml) was added dropwise over 10 min to a solution of potassium (7 g, 0.2 mol) in *tert*-butyl alcohol (200 ml). The solution was refluxed for 12 hr and water (10 ml) was added. The mixture was concentrated under reduced pressure and the dark residue was triturated with methanol (20 ml) to separate the nonanol **5** (10 g, 40%) as a colorless powder. When the pure trans isomer was treated in an identical fashion an 87% yield was realized. Crystallization from ethanol provided an analytical sample: mp 197–198°; ir $\tilde{\nu}_{max}^{Nujol}$ 3365 and 1605 cm^{-1}; pmr δ 1.50–3.20 (m, 9), 3.60–5.05 (m, 5), and 7.25–8.20 (p, 5).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.41; H, 7.88; N, 5.65.

2-Aza-2-benzoylbicyclo[3.3.1]nonan-8-one (1).—A solution of potassium dichromate (720 mg, 2.94 mmol) in 9 *N* sulfuric acid (5 ml) was added dropwise to a solution of the nonanol **5** (1.80 g, 7.35 mmol) in acetic acid (10 ml) over 30 min. The mixture was then stirred for 30 min at room temperature and diluted with water (50 ml). The mixture was extracted with ethyl acetate and the extracts were washed with dilute sodium hydroxide, water, and brine and dried. Removal of the solvent left an oily mixture which was triturated with ether to separate starting material (525 mg, 29%). The ether solution was filtered through alumina (Woelm neutral, activity I, 5 g) eluting with additional ether. Removal of the solvent under reduced pressure gave the ketone **1** (520 mg, 29%) as an oil, homogeneous by tlc: ir $\tilde{\nu}_{max}^{CHCl_3}$ 1730 and 1635 cm^{-1}; pmr ($CDCl_3$) δ 1.10–2.80 (m, 9), 3.15–3.50 (b m, 2), 4.45 (b s, 1), and 7.10–7.80 (m, 5). The semicarbazone crystallized from acetone to give an analytical sample, mp 196–198°.

Anal. Calcd for $C_{16}H_{20}N_4O_2$: C, 63.98; H, 6.71; N, 18.65. Found: C, 64.04; H, 6.81; N, 18.66.

2-Azaindolo[2,3-*g*]bicyclo[3.3.1]non-7-ene (2).—A mixture of the ketone **1** (4.5 g, 18.5 mmol) and phenylhydrazine (2.2 g, 20

(9) All melting points were determined in a Drechsel stirring oil melting point apparatus and are uncorrected. All boiling points are also uncorrected. All boiling points are also uncorrected. Infrared spectra were measured with either Beckman IR-5A or IR-7 infrared spectrophotometers. Proton magnetic resonance spectra were determined at either 60 or 100 MHz with Varian Models A-60 and HA-100 pmr spectrometers. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane internal standard. In the presentation of the pmr spectra the following notations are used: b, broad; u, unsymmetrical; s, singlet; d, doublet; t, triplet; q, quartet; p, pentuplet; and m, multiplet. Ultraviolet spectra were determined on a Cary Model 15 recording spectrophotometer. The mass spectra were obtained with a Consolidated Electrodynamics Corp. Model 21-110 double focus mass spectrometer equipped with a direct inlet system. Thin layer chromatographic analyses were carried out on Baker-flex silica gel 1B precoated plates obtained from J. T. Baker, Chemical Co., Phillipsburg, N. J. A 3% ceric sulfate–10% sulfuric acid solution or a 5% phosphomolybdic acid was used to visualize the spots.

(10) L. A. Spurlock and R. J. Schultz, *J. Amer. Chem. Soc.*, **92**, 6302 (1970).

mmol) was refluxed in ethanol (30 ml) for 5 hr. The ethanol was removed under reduced pressure and the residue was dissolved in 6 *N* sulfuric acid (20 ml). The mixture was warmed on the steam bath for 10 min. The resultant precipitate was collected, washed with water, and dried. The dark powder was taken up in ethyl acetate and filtered through alumina (Woelm neutral, activity I, 60 g) eluting with ethyl acetate. The eluents were concentrated under reduced pressure to leave a light brown powder (1.62 g). Tlc indicated the presence of a minimum of six compounds. A portion of this crude material (0.49 g) was heated at 160° in ethylene glycol (7 ml) containing sodium hydroxide (850 mg) for 2 hr. The dark mixture was diluted with water (20 ml) and extracted with ethyl acetate. The extracts were washed with water and brine and dried. The solvent was removed under reduced pressure and the residue was sublimed (165°, 0.05 mm) to give crude tetracyclic amine **2** (26 mg, 2.2% based on starting ketone) as a yellow powder. Repeated crystallization from ethyl acetate gave an analytical sample: mp 223–225°; ir $\tilde{\nu}_{max}^{CHCl_3}$ 3470 and 1455 cm^{-1}; nmr ($CDCl_3$) δ 1.50–3.45 (m, 10), 4.45 (b s, 1), and 7.30–7.88 (m, 5); uv λ_{max}^{ETOH} 291 nm (ϵ 6200), 283 (7200), 276 (6900), and 226 (33,000); *m/e* 212 (M^+), 169 (100).

Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 79.17; H, 7.67; N, 13.38.

3-Carbethoxy-1,2,3,4-tetrahydrocarbazole (8).—Freshly distilled phenylhydrazine (43.0 g, 0.40 mol) was added dropwise to a refluxing solution of 4-carbethoxycyclohexanone[11] (68.0 g, 0.40 mol) in glacial acetic acid (600 ml) over 35 min. The mixture was refluxed for 1 hr and cooled in an ice bath with stirring. Water (300 ml) was added to complete precipitation and the product was collected and washed well with water. The product was dried in a vacuum oven overnight, giving **8** as a pale yellow powder (80.3 g, 80%). Crystallization from methanol gave an analytical sample: mp 95–97°; ir $\tilde{\nu}_{max}^{CHCl_3}$ 3510 and 1720 cm^{-1}; pmr ($CDCl_3$) δ 1.25 (t, 3), 1.90–3.20 (m, 7), 4.18 (q, 2), and 6.9–7.8 (m, 5); uv λ_{max}^{ETOH} 289 nm (ϵ 5940), 282 (7180), 274 (6720), and 226 (33,700).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04; N, 5.76. Found: C, 74.7; H, 6.97; N, 5.67.

3-Hydroxymethyl-1,2,3,4-tetrahydrocarbazole (9).—A solution of the ester **8** (80.0 g, 0.316 mol) in tetrahydrofuran (200 ml) was added to a slurry of lithium aluminum hydride (18.0 g, 0.475 mol) in ether (600 ml) over 1 hr at room temperature. The mixture was stirred for 2 hr and excess lithium aluminum hydride was decomposed with water (50 ml). Hydrochloric acid (400 ml, 6 *N*) was added and the phases were separated. The aqueous phase was extracted with ether and the combined organic solutions were washed with water and brine. Drying and removing the solvent under reduced pressure left the carbinol **9** as a yellow oil (64 g, 100%) which on standing set to a hard glass: ir $\tilde{\nu}_{max}^{CHCl_3}$ 3450 and 1540 cm^{-1}; nmr ($CDCl_3$) δ 1.20–3.00 (m, 7), 3.56 (d, 2), and 6.90–7.80 (m, 5). The acetate crystallized from methanol as needles, mp 97–99°.

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.72; H, 6.96; N, 5.65.

3-Hydroxymethyl-1,2,3,4-tetrahydrocarbazole *p*-Toluenesulfonate (14).—A cooled solution of *p*-toluenesulfonyl chloride (72.5 g, 0.38 mol) in pyridine (150 ml) was added to a cooled solution of the carbinol **9** (64 g, 0.32 mol) in pyridine (150 ml). The solution was allowed to stand in the cold for 16 hr. The mixture was poured into water (600 ml) and after 30 min the precipitate was collected and dissolved in ethyl acetate. The organic solution was washed with 3 *N* sulfuric acid, water, and brine. Drying and removing the solvent under reduced pressure gave the crude tosylate **14** (86.5 g, 77%) as a tan powder. The analytical sample crystallized from acetone: mp 138–140° dec; ir $\tilde{\nu}_{max}^{CHCl_3}$ 4250, 1360, and 1175 cm^{-1}; pmr ($CDCl_3$–DMSO-d_6) δ 1.52–2.81 (m, 7), 2.30 (s, 3), 3.92 (b d, 2 H), 6.71–7.80 (m, 9); uv λ_{max}^{EtOH} 290 nm (ϵ 5100), 283 (6000), 283 (6000), and 226 (39,500)

Anal. Calcd for $C_{20}H_{21}NO_3S$: C, 67.50; H, 5.96; N, 3.94. Found: C, 67.26; H, 5.91; N, 3.81.

3-Cyanomethyl-1,2,3,4-tetrahydrocarbazole (15).—A solution of the tosylate **14** (85.0 g, 0.240 mol) and sodium cyanide (20.0 g, 0.408 mol) in ethanol (500 ml) was refluxed for 14 hr. The mixture was concentrated to 200 ml under reduced pressure and water (600 ml) was added. The dark mixture was extracted with ether and the extracts were washed with water and brine and dried. The solution was concentrated under reduced pressure to give a dark heavy oil which was filtered through alumina (100 g, Alcoa F-20) eluting with benzene. Concentration of the eluent gave the nitrile **15** as a pale yellow oil (44 g, 88%) which solidified on standing to a waxy solid. Crystallization from ether–hexane gave the analytical sample: mp 99–101°; $\tilde{\nu}_{max}^{CHCl_3}$ 3425 and 2260 cm^{-1}; pmr ($CDCl_3$) δ 1.25–3.10 (m, 9) and 6.80–7.62 (m, 5).

Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 80.29; H, 6.78; N, 13.55.

3-Hydroxymethyl-1-oxo-1,2,3,4-tetrahydrocarbazole (10).—To a cooled solution of the carbinol **9** (10 g, 50 mmol) in methanol (50 ml) was added a solution of periodic acid (22.6 g, 100 mmol) in water (50 ml) over 45 min while the temperature was maintained below 5°. The mixture was stirred for 1 hr at 0° and the resultant precipitate was collected. The precipitate was taken up in ethyl acetate and the organic solution was washed with bisulfite solution and brine and dried. Evaporation of the solvent left a dark solid which was filtered through Florisil, eluting first with ether to remove a small amount of dark oil. Elution with ethyl acetate and evaporation of the eluent gave the keto alcohol **10** as a yellow powder (6.6 g, 62%). An analytical sample crystallized from ethyl acetate showed mp 173–175°; ir $\tilde{\nu}_{max}^{Nujol}$ 3300 and 1650 cm^{-1}; pmr (CD_3COOD) δ 2.40–2.90 (m, 4), 3.10 (b d, 1), 3.72 (b s, 2), 6.80–7.62 (m, 5); uv λ_{max}^{EtOH} 304 nm (ϵ 2200) and 237 (1400).

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.72; H, 6.05; N, 6.45.

3-Hydroxymethyl-1-oxo-1,2,3,4-tetrahydrocarbazole *p*-Toluenesulfonate (11).—A cooled solution of *p*-toluenesulfonyl chloride (7.0 g, 36 mmol) in pyridine (15 ml) was added to a cooled solution of the alcohol **10** (6.58 g, 30.6 mmol). The mixture was allowed to stand in the cold overnight and was then poured into water (300 ml). After 15 min the mixture was acidified with concentrated hydrochloric acid and the precipitate was filtered. The precipitate was washed with water and cold methanol and dried to give the tosylate **11** as a yellow powder (9.67 g, 90%). The analytical sample crystallized from butyl acetate as plates: mp 188–190° dec; ir $\tilde{\nu}_{max}^{Nujol}$ 3290, 1645, 1350, and 1175 cm^{-1}; pmr ($CDCl_3$) δ 2.84 (s, 3) 2.90–3.70 (m, 5), 4.52 (d, 2 H), and 7.40–8.27 (m, 9).

Anal. Calcd for $C_{20}H_{19}NO_4S$: C, 64.71; H, 5.24; N, 3.53. Found: C, 65.02; H, 5.18; N, 3.79.

3-Cyanomethyl-1-oxo-1,2,3,4-tetrahydrocarbazole (6).—A solution of 3-cyanomethyl-1,2,3,4-tetrahydrocarbazole (**15**) (2.00 g, 9.50 mmol) in methanol (30 ml) was added dropwise over 30 min to a solution of periodic acid (6.00 g, 26.6 mmol) in methanol (50 ml) at 10–20°. After the addition was complete the mixture was stirred at room temperature for 2 hr and then at 0° for 30 min. The mixture was poured into water (100 ml) and after stirring to coagulate the precipitate the aqueous solution was decanted. The precipitate was taken up in ethyl acetate, washed with sodium thiosulfate solution and brine, and dried. Concentration of the solution under reduced pressure gave the nitrile **6** as a tan powder (1.38 g, 65%). Crystallization from ethyl acetate gave an analytical sample: mp 218–219°; ir $\tilde{\nu}_{max}^{CHCl_3}$ 3350, 2250, and 1645 cm^{-1}; pmr ($CDCl_3$–DMSO-d_6) δ 2.44–2.90 (b d, 7), 6.98–7.83 (m, 5); uv λ_{max}^{EtOH} 308 nm (ϵ 2000) and 236 (1500).

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.70; H, 5.27; N, 12.65.

Indolo[2,3-*c*]-2-oxobicyclo[4.1.0]-3-heptene (12).—A solution of the tosylate **11** (0191 g, 2.5 mmol) and sodium cyanide (1.0 g, 20 mmol) in 90% ethanol (50 ml) was refluxed for 2.5 hr. Water (30 ml) was added and the mixture was concentrated under reduced pressure to remove the ethanol. The aqueous mixture was extracted with ethyl acetate and the extract was washed with water and brine and dried. Evaporation under reduced pressure left the norcaranone **12** as a yellow solid (0.45 g, 93%). Crystallization from ethyl acetate gave an analytical sample: mp 156–157°; ir $\tilde{\nu}_{max}^{CHCl_3}$ 3460, 3300, and 1640 cm^{-1}; pmr ($CDCl_3$) δ 0.81 (q, 1 H), 1.25–1.60 (m, 1), 2.10 (m, 2), 3.42 (m, 2), and 7.02–7.70 (m, 5); uv λ_{max}^{EtOH} 307 nm (ϵ 1900) and 235 (1500); *m/e* 197 (M^+), 168 (100).

Anal. Calcd for $C_{13}H_{11}NO$: C, 79.17; H, 5.62; N, 7.10. Found: C, 78.65; H, 5.69; N, 7.16.

Indolo[2,3-*b*]cyclohepta-2,4-dienone (13).—A solution of the tosylate **11** (1.0 g, 2.7 mmol) and sodium hydroxide (0.32 g, 8.0 mmol) in ethanol (20 ml) was refluxed for 3.5 hr. After 1 hr tlc indicated the presence of the norcaranone **24**. The mixture was concentrated under reduced pressure and the residue was diluted with water and extracted with ethyl acetate. The extract was washed with water and brine and dried. Removal of the solvent

(11) R. A. Finnegan and P. L. Bachman, *J. Org. Chem.*, **30**, 4145 (1965).

under reduced pressure left the cycloheptadienone **13** (505 mg, 95%) as a yellow powder. Sublimation (130°, 0.05 mm) and crystallization from benzene–hexanes gave the analytical sample as long yellow needles: mp 145–146°; ir $\nu_{max}^{CHCl_3}$ 3460, 1640, and 1330 cm^{-1}; pmr ($CDCl_3$) δ 2.40 (q, 2), 2.75 (m, 2), 6.20 (m, 2), and 6.80–7.75 (m, 5); uv λ_{max}^{EtOH} 360 nm (ϵ 6400), 322 (13,300), 247 (25,300), and 232 (24,400).

Anal. Calcd for $C_{13}H_{11}NO$: C, 79.17; H, 5.62; N, 7.10. Found: C, 79.49; H, 5.68; N, 6.91.

Indoloazabicyclononene 2 from 6.—A warm solution of the nitrile **6** (6.1 g, 27 mmol) in dry tetrahydrofuran (200 ml) was added rapidly to a refluxing slurry of lithium aluminum hydride (5.0 g, 0.13 mol) in glyme (200 ml). After the addition was complete the mixture was refluxed for 20 min and cooled. Excess hydride was decomposed with water (5 ml); 4 *N* sodium hydroxide (5 ml) was added followed by additional water (15 ml). The salts were filtered and washed with tetrahydrofuran. Evaporation of the filtrate under reduced pressure left a colorless foam (5.8 g, 95% weight recovery). The foam was refluxed in *o*-dichlorobenzene (450 ml) for 1.5 hr. The solvent was evaporated under reduced pressure and the residue was taken up in 15% acetic acid and extracted with ether. The acidic solution was made alkaline with 50% sodium hydroxide and extracted with ethyl acetate. The extract was washed with water and brine and dried. Evaporation of the solvent under reduced pressure followed by sublimation of the residue (165°, 0.05 mm) gave **2** (2.5 g, 44%) as a pale yellow powder. Crystallization from ethyl acetate gave small, colorless blocks, mp 220–222° dec. Admixture with material obtained from the Fischer indole synthesis gave mp 220–222° dec. The infrared spectrum of material obtained from this synthesis was identical with the infrared spectrum of material obtained previously.

2-Aza-2-(2-hydroxyethyl)indolo[2,3-*g*]bicyclo[3.3.1]non-7-ene (16).—A solution of the tetracyclic amine **2** (2.53 g, 12 mmol) and ethylene oxide (2.5 g, 56 mmol) in 10% methanolic tetrahydrofuran (50 ml) was heated in a stainless steel bomb on the steam bath for 5 hr. The solvent was removed under reduced pressure and the residue was triturated with a small amount of ethyl acetate to give the ethanolamine **16** (2.47 g, 81%). Crystallization from ethyl acetate gave an analytical sample: mp 194–196°; ir $\nu_{max}^{CHCl_3}$ 3390 and 1450 cm^{-1}; pmr ($CDCl_3$) δ 1.80–4.00 (m, 10), 4.05–4.40 (m, 4), 4.55 (b, s, 1), 7.25–7.98 (m, 4), and 8.50 (b s, 1); *m/e* 256 (M^+), 225, 194, and 169 (100).

Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 75.26; H, 7.66; N, 10.76.

Reaction of Ethanolamine 16 with Methanesulfonyl Chloride.—A solution of the ethanolamine **16** (258 mg, 1.01 mmol) in dry dimethylformamide (5 ml) was cooled to −20°. Triethylamine (152 mg, 1.51 mmol) was added followed by dropwise addition of methanesulfonyl chloride (127 mg, 1.11 mmol) over 3 min. The mixture was stirred at −20° for 2 hr and allowed to stand at room temperature for 44 hr. Water (30 ml) was added and the mixture was extracted with chloroform. The organic solution was washed with water and brine and dried. Concentration under reduced pressure gave a brown gum (153 mg). The gum was taken up in methylene chloride (3 ml). Addition of a small amount of ether precipitated an amorphous white powder (148 mg, 58% weight recovery). The material was insoluble in hot 3 *N* hydrochloric acid. The uv spectrum showed absorption at λ_{max}^{EtOH} 291, 283, 276, and 227 nm. Tlc indicated that there was no starting material and showed a single spot at the origin with 6:3:1 ethyl acetate–methanol–triethylamine as eluent.

2-Aza-2-chloroacetylindolo[2,3-*g*]bicyclo[3.3.1]non-7-ene (17).—A solution of chloroacetyl chloride (520 mg, 4.65 mmol) in dry methylene chloride (10 ml) was added to a cold mixture of the tetracyclic amine **2** (677 mg, 3.19 mmol), potassium carbonate (880 mg, 6.31 mmol), methylene chloride (30 ml), and water (15 ml) over 15 min. The mixture was allowed to warm to room temperature and stirred for 3 hr. The phases were separated and the aqueous phase was extracted with methylene chloride. The combined organic phases were washed with bicarbonate solution, water, and brine. Drying and removal of the solvent left the crude chloroacetamide (923 mg, 97%) as a yellow oil. Crystallization from ethanol gave an analytical sample: mp 170–171°; ir $\nu_{max}^{CHCl_3}$ 3500, 1640, and 1455 cm^{-1}; pmr ($CDCl_3$) δ 1.15–3.45 (m, 9), 3.92 (s, 2), 5.75 (b s, 1), 6.90–7.52 (m, 4), and 8.92 (b s, 1).

Anal. Calcd for $C_{16}H_{17}N_2OCl$: C, 66.55; H, 5.93; N, 9.70. Found: C, 66.38; H, 6.00; N, 9.59.

Reaction of the Chloroacetamide 17 with Sodium Hydride.—The mineral oil of a 57% dispersion of sodium hydride (24.2 mg, 0.578 mmol) was removed by washing with dry 1,2-dimethoxyethane. A solution of the chloroacetamide **17** (111 mg, 0.385 mmol) in dry 1,2-dimethoxyethane (5 ml) was added to a slurry of the washed sodium hydride in dry 1,2-dimethoxyethane (8 ml) over 10 min. The mixture was stirred at room temperature for 2.5 hr. Water (1 ml) was added and the mixture was concentrated under reduced pressure. The aqueous residue was extracted with chloroform and the extracts were washed with water and brine and dried. Removal of the solvent under reduced pressure left a brown, amorphous powder (76.5 mg). The material was taken up in boiling chloroform and cooled to give a white, amorphous powder (25 mg). The material was insoluble in hot acetic acid or 2 *N* hydrochloric acid. The ultraviolet spectrum showed typical indole absorption (λ_{max}^{EtOH} 291, 285, 272, and 225 nm). The infrared spectrum showed amide carbonyl at 1645 cm^{-1}. The compound slowly charred at 315–330°. Concentration of the mother liquors under reduced pressure left a brown residue which had similar solubility and spectral properties.

2-Acetyl-1-azaindolo[2,3-*g*]bicyclo[3.3.1]non-7-ene (18).—To a cooled solution of the tetracyclic amine **2** (2.5 g, 12 mmol) in pyridine (20 ml) was added acetic anhydride (5.4 g, 53 mmol) over 2 min. The mixture was allowed to warm to room temperature and stirred for 4 hr. The mixture was poured into water (100 ml) and after 15 min was extracted with ethyl acetate. The extracts were washed with bicarbonate solution, water, and brine. Drying and removal of the solvent under reduced pressure left a brown solid which was filtered through alumina (Woelm neutral, activity I, 10 g) eluting with chloroform. Concentration of the eluent left the amide **18** (2.6 g, 87%) as a colorless solid. An analytical sample crystallized from ethyl acetate: mp 208–209°; ir $\nu_{max}^{CHCl_3}$ 3500 and 1625 cm^{-1}; pmr ($CDCl_3$) δ 1.50–3.78 (m, 9), 2.01 (s, 3), 5.70 (b s, 1), and 6.90–7.60 (m, 5).

Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.05; H, 7.06; N, 10.76.

2-Azaindolo[2,3-*g*]-1′-methylbicyclo[3.3.1]non-7-ene (20).—The mineral oil of a 57% sodium hydride dispersion (0.80 g, 20 mmol) was removed by washing with dry tetrahydrofuran. The sodium hydride was slurried in tetrahydrofuran (20 ml) and a solution of the acetamide **18** (2.04 g, 8.05 mmol) in tetrahydrofuran (10 ml) was added. The mixture was brought to reflux for 15 min and then cooled in an ice bath. Methyl iodide (1.3 g, 9.2 mmol) was added and the mixture was stirred at room temperature for 5 hr. Water (20 ml) was added and the mixture was concentrated under reduced pressure to remove the tetrahydrofuran. The aqueous concentrate was extracted with chloroform and the organic phase was washed with water and brine and dried. Removal of the solvent under reduced pressure left a yellow oil (2.05 g) which was refluxed in hydrazine (50 ml) for 28 hr. Removal of the hydrazine under reduced pressure left a dark oil which was filtered through Florisil. Benzene eluted a dark oil (330 mg) which was discarded. Ethyl acetate eluted the methylated tetracyclic amine **20** (955 mg, 53%) obtained as a colorless solid. Sublimation (95°, 0.05 mm) and crystallization from benzene–hexanes gave an analytical sample: mp 105–107°; ir $\nu_{max}^{CHCl_3}$ 3300 and 1400 cm^{-1}; pmr ($CDCl_3$) δ 1.05–3.02 (m, 9), 3.55 (s, 3), 4.18 (b s, 1), and 6.92–7.65 (m, 4).

Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.50; H, 8.11; N, 12.09.

2-Aza-2-(2-hydroxyethyl)indolo[2,3-*g*]-1′-methylbicyclo[3.3.1]-non-7-ene (21).—A solution of the methylated tetracyclic amine **20** (430 mg, 1.59 mmol) and ethylene oxide (500 mg, 11.4 mmol) in 5% methanolic tetrahydrofuran was heated in a sealed tube for 8 hr on the steam bath. The solvent was removed under reduced pressure and the residue was filtered through alumina (Woelm neutral, activity I, 5 g) eluting with chloroform. Concentration of the eluents under reduced pressure gave the ethanolamine **21** (474 mg, 92%) as a yellow oil: ir $\nu_{max}^{CHCl_3}$ 3440 (b) and 1480 cm^{-1}; pmr ($CDCl_3$) δ 1.02–3.25 (m, 9), 3.51 (s, 3), 3.52–3.80 (m, 4), 3.90 (b s, 1), and 6.90–7.65 (m, 4). A picrate salt was prepared by the addition of a saturated solution of picric acid in ethanol to an ethanolic solution of the amine. Recrystallization from acetonitrile gave an analytical sample, mp 200–201°.

Anal. Calcd for $C_{23}H_{25}N_5O_8$: C, 55.31; H, 5.05; N, 14.02. Found: C, 55.18; H, 4.96; N, 13.65.

Reaction of the Methylated Ethanolamine 21 with *p*-Toluenesulfonyl Chloride.—To an ice-cold solution of the ethanolamine **21** (174 mg, 0.654 mmol) in dry pyridine (4 ml) was added freshly sublimed *p*-toluenesulfonyl chloride (150 mg, 0.785 mmol) in dry pyridine (1 ml). The mixture was allowed to warm to room temperature and was stirred under nitrogen for 49 hr. Water

(1 ml) was added and after 15 min sodium borohydride (100 mg) was added. The mixture was stirred for 30 min and then diluted with water (20 ml). The mixture was extracted with ethyl acetate and the extracts were washed with water and brine and dried. Removal of the solvent under reduced pressure left a brown oil (160 mg, 92%) which was identical with the starting material by tlc and pmr spectroscopy.

Reaction of the Methylated Ethanolamine 21 with Methanesulfonyl Chloride.—A solution of the ethanolamine **21** (300 mg, 1.07 mmol) in dry 1,2-dimethoxyethane (5 ml) was cooled to −10° in an ice–salt bath. Freshly distilled triethylamine (360 mg, 3.60 mmol) was added followed by methanesulfonyl chloride (160 mg, 1.40 mmol) over 5 min. The mixture was allowed to warm to room temperature and was stirred for 3.5 hr under nitrogen. Excess sodium borohydride was added and the mixture was stirred at room temperature for 3 hr. Water (30 ml) was added and the mixture was extracted with chloroform. The extracts were washed with water and brine and dried. Removal of the solvent under reduced pressure left a brown gum (330 mg). Tlc indicated the material to be a mixture of at least three components. The mixture was separated by preparative tlc (Merck silica gel PF-254, ethyl acetate as eluent) to give three compounds of R_f 0.05, 0.5, and 0.8. The ultraviolet spectrum of all the components showed typical indole absorption (λ_{max}^{EtOH} 290, 283, 273, and 226 nm).

Registry No.—**1**, 40525-24-4; **1** semicarbazone, 40496-45-5; **2**, 40496-46-6; **3**, 40496-47-7; **4**, 40488-34-4; **5**, 40496-48-8; **6**, 40496-49-9; **8**, 26088-68-6; **9**, 26072-19-5; **9** acetate, 40496-52-4; **10**, 40496-53-5; **11**, 40496-54-6; **12**, 40496-55-7; **13**, 40496-56-8; **14**, 40496-57-9; **15**, 40496-58-0; **16**, 40496-59-1; **17**, 40496-60-4; **18**, 40496-61-5; **20**, 40496-62-6; **21**, 40496-63-7; **21** picrate, 40496-64-8; 2-(Δ³-cyclohexenyl)ethylamine, 40496-65-9; benzoyl chloride, 98-88-4; *m*-chloroperbenzoic acid, 937-14-4; phenylhydrazine, 100-63-0; 4-carbethoxycyclohexanone, 17159-79-4; *p*-toluenesulfonyl chloride, 98-59-9; sodium cyanide, 917-61-3; sodium hydroxide, 1310-73-2; methanesulfonyl chloride, 124-63-0; chloroacetyl chloride, 79-04-9; sodium hydride, 7646-69-7; ethylene oxide, 75-21-8.

Studies on the Oxidation of "Reversed Nucleosides" in Oxygen. I. Synthesis of Eritadenine and Its Derivatives[1]

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Reaction of methyl-5-*O*-tosyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (I) or 5-*O*-tosyl-1,2-*O*-isopropylidene-3-*O*-alkyl-β-D-arabofuranoses (IV) with the sodium salt of adenine in DMF afforded the corresponding "reversed nucleosides" in good yields. After removal of the protective groups of the sugar moiety by treatment with hydrochloric acid, the demasked reversed nucleosides were oxidized by air or oxygen in a dilute alkali solution at room temperature to give eritadenine and its α-*O*-alkyl derivatives. The yields of the acids were generally good. To confirm the structures and evaluate the biological activities, syntheses of their esters were also performed.

Several synthetic routes to eritadenine, one of the significant hypocholesterolemic components of *Lentinus edodes* Sing, have been reported employing D-erythrono lactone as the starting material.[2]

Although various synthetic pathways might be conceivable, a large-scale synthesis of eritadenine using this lactone appears to be somewhat uneconomical[3] because of the rather poor yield of the lactone in the preparations described in the literature.[4] The necessity for a large amount of eritadenine and its derivatives for biological studies required development of a more simplified method of preparation.

Since the low yield of the lactone by the literature method appears to be due to the complicated purification process during which a part of the lactone might have decomposed, it was conceivable that the derived product might be more easily separated from the oxidation mixture after prior condensation of the sugar moiety with a fairly insoluble material such as a purine, thus preventing decomposition. From this point of view, adoption of the procedure for the synthesis of a reversed nucleoside by Leonard[5] proved to be extremely useful.

Reaction of methyl-5-*O*-tosyl-2,3,-*O*-isopropylidene-β-D-ribofuranoside (I)[6] with the sodium salt of adenine in DMF gave the corresponding 9-substituted reversed nucleoside II in excellent yield. The attachment of the substituent was based on the characteristic uv absorption band at λ_{max} (H_2O) 258 nm at pH 2, 260 nm at pH 7, and 262 nm at pH 11. None of the other position isomers could be detected in the reaction mixture. Hydrolysis of II with dilute hydrochloric acid to remove the protective groups at 60–80° afforded the pure demasked reversed nucleoside III in 86.5% yield.

In a test reaction the air oxidation of III in dilute sodium hydroxide solution at room temperature proceeded as expected. Tlc of the reaction mixture showed a spot the R_f value of which was identical with that of an authentic sample of eritadenine. Hence III in 0.5% NaOH solution was stirred in an atmosphere of oxygen at room temperature. After 17 hr, the spot of III had completely disappeared and a single spot was observed at R_f 0.35 on tlc (silica gel GF 254;

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(3) The situation has changed to some degree now, since a simple method for the preparation of the D-erythronolactone from D-glucose was explored in our laboratory and the method described in *J. Org. Chem.*, **36**, 1573 (1971), was also useful for a large-scale synthesis of eritadenine.

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