Transformations of Eburicoic Acid. V.[1] Cleavage of Ring A by the Fungus *Glomerella fusarioides*

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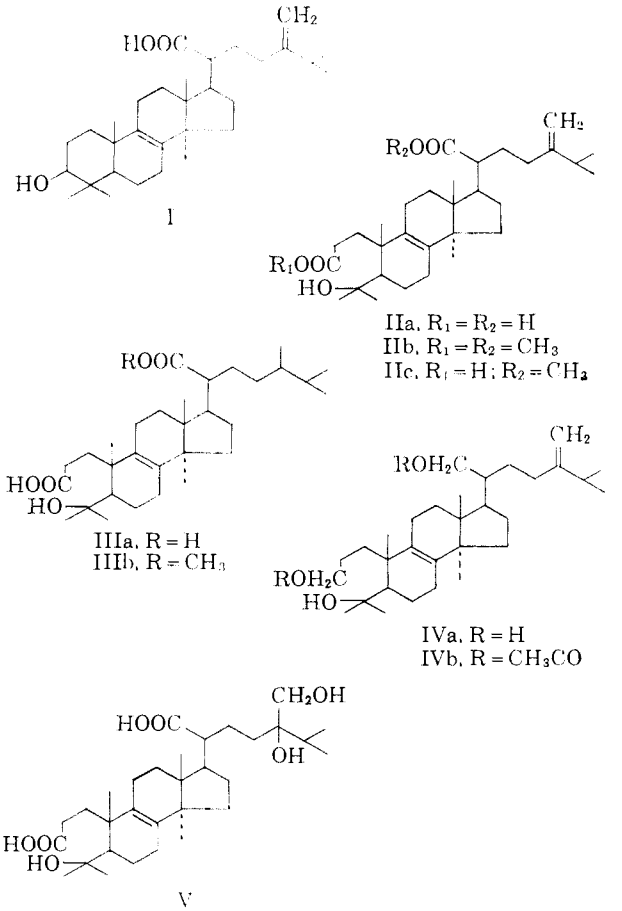
Eburicoic acid (I) has been transformed by *Glomerella fusarioides* into 3,4-seco-$\Delta^{8,24(28)}$-eburicadien-4-ol-3,21-dioic acid (IIa) which possesses antibacterial activity against *Staphylococcus aureus* and *Mycobacterium tuberculosis var. BCG*. The structure of the acid is discussed and the antibacterial activity of several of its derivatives is reported.

In further pursuit of our studies of converting the abundantly available fungal metabolite eburicoic acid (I) into biologically active steroids we were intrigued by the close similarity in structure between this tetracyclic triterpenoid acid and the steroid antibiotics cephalosporin P_1,[2] helvolic acid[3] and fusidic acid.[4] Although the stereochemistry of these antibacterial agents has not as yet been fully established there is no doubt that like eburicoic acid and related acids derived from wood-rotting fungi, they are tetracyclic triterpenoids possessing a carboxyl group in the 21-position. It is also of interest in this connection that the closely related polyporenic acids have been shown to possess antibacterial activity, polyporenic acid A against *Staphylococcus aureus* and polyporenic acid C against *Mycobacterium phlei* and *M. smegmatis*.[5] Minor chemical changes might therefore convert the antibacterially inactive eburicoic acid into an active substance. In the hope that such changes might be brought about by microbial enzymes we have investigated the susceptibility of eburicoic acid to transformation by microorganisms. Among the microorganisms found capable of attacking this substrate with the production of more polar products was the fungus *Glomerella fusarioides* (ATCC 9552). Paper chromatograms of broth samples derived from fermentations using this fungus showed spots causing a clear zone of inhibition when subjected to bioautography on agar plates inoculated with *Staphylococcus aureus* 209P. When larger scale fermentations were carried out with this organism there was obtained after filtration of the broth and acidification to pH 4.0 a flocculent precipitate from which isobutyl methyl ketone extracted a new crystalline acid. This acid (m.p. 236–238°, $[\alpha]D$ +78° (EtOH) was shown to be 3,4-seco-$\Delta^{8,24(28)}$-eburicadien-4-ol-3,21-dioic acid (IIa).

Analysis of the acid and of the derivatives to be described indicated the formula $C_{31}H_{50}O_5$, that is, the composition of eburicoic acid plus two atoms of oxygen. Titration of the new acid with base showed the presence of two acidic groups, both of which could be esterified with diazomethane to form an amorphous dimethyl ester (IIb). In the expectation that the very difficultly hydrolyzable 21-carbomethoxy group would resist saponification the diester was treated with 1 *N* KOH in methanol at room temperature to afford in excellent yield monomethyl ester acid IIc, characterized by titration and by an n.m.r. signal at τ 6.36 indicating a single methoxyl group. A parallel series of experiments was performed with the dihydro acid IIIa obtained by reduction of the 24(28)-double bond in IIa with palladium on charcoal. The presence of this double bond in IIa was further substantiated by the characteristic n.m.r. signal at τ 5.07 (pyridine) and the CH out-of-plane deformation band at 11.25 μ, both of which are absent in the dihydro acid.

There remained to be accounted the fifth oxygen atom, which was shown to be present as a tertiary hydroxyl group by reduction of seco acid IIa with lithium aluminum hydride to form triol IVa, which on acetyla-



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(2) B. M. Baird, T. G. Halsall, E. R. H. Jones, and G. Lowe, *Proc. Chem. Soc.*, 257 (1961); T. G. Halsall, E. R. H. Jones, and G. Lowe, *ibid.*, 16 (1963).

(3) N. L. Allinger and J. L. Coke, *J. Org. Chem.*, **26**, 4552 (1961).

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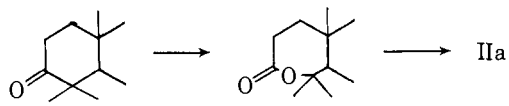
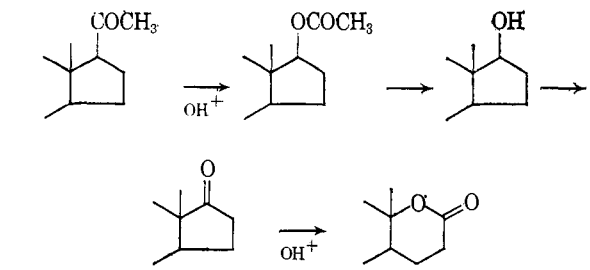
(5) S. Marcus, *Biochem. J.*, **50**, 518 (1952).

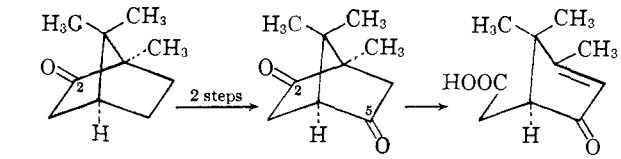
tion afforded diacetate IVb. Convincing evidence for locating this tertiary hydroxyl group at C-4 came from an examination of the n.m.r. spectra of dicarboxylic acid IIa, dihydro-21-monomethyl ester IIIb, and triol IVa. Diacid IIa in pyridine solution possesses a peak at τ 8.52 (six protons), which is absent in eburicoic acid. The latter displays, instead, a signal corresponding to six protons at τ 8.97 characteristic of the 4,4-dimethyl grouping. Similarly, IIIb and IVa in $CDCl_3$ solution possess peaks equivalent to six protons at τ 8.72 and 8.68, respectively, again shifted downfield with respect to the signals at τ 9.04 and 9.20 for the *gem*-dimethyl grouping in methyl eburicoate. This amount of deshielding of the methyl protons of that grouping in acid IIa and its derivatives is most satisfactorily accounted for by attaching a hydroxyl group at C-4 to take the place of one of the carbon–carbon bonds in ring A of eburicoic acid. It is significant, and confirmatory of this assignment, that the signals for the two methyl groups attached to C-4 appear as singlets in seco compounds IIIb and IVa, these methyl groups now being equivalent as a result of freedom to rotate about the C-4–C-5 bond. In summary then, we feel that the above facts provide convincing evidence for the ring A seco structure IIa for the new metabolite. The latter may be visualized to arise by a Baeyer–Villiger type oxidation of the 3-ketone derived from I, followed by hydrolysis of the resulting seven-membered ring lactone.



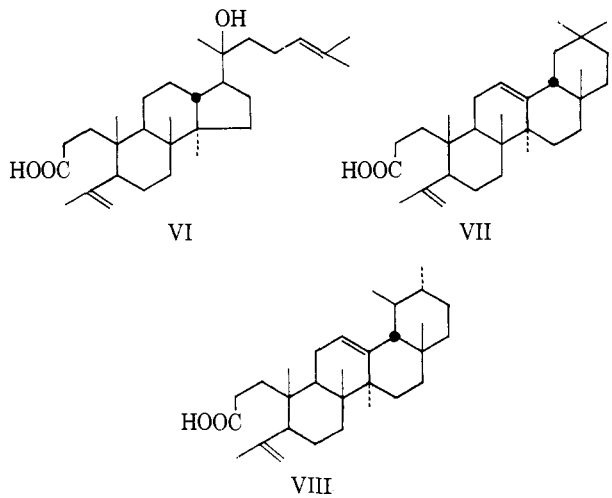
Oxidative ring cleavage reactions of this type are not unknown in the field of microbial transformations. In fact, one of the first microbial oxidations to be discovered was the degradation of progesterone to ring-D lactones,[6,7] which includes among the steps involved two carbon–carbon cleavage reactions analogous to the Baeyer–Villiger reaction.[8] The complete sequence, each step of which has been characterized by isolation and tracer studies,[9] is shown below.

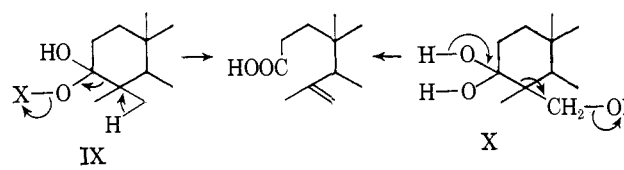
More recently, this reaction has also been found to occur with (+)-camphor, which in an interesting sequence of reactions undergoes hydroxylation and dehydrogenation at C-5, followed by carbon–carbon cleavage between C-1 and C-2 and subsequent β-elimination.[10]





The 3,4-seco structure IIa of our fungal metabolite brings to mind a group of naturally occurring triterpenoid acids in which ring A has likewise been cleaved between carbon atoms 3 and 4, namely, dammarenolic acid (VI),[11,12] nyctanthic acid (VII),[12–14] and roburic acid (VIII).[15] Arigoni, *et al.*,[12] and Whitham[14] have speculated on the biogenesis of these acids from well-known triterpenoid precursors, the former authors postulating a process illustrated in IX, and the latter a fragmentation reaction shown in formula X. In view of the demonstration that Baeyer–Villiger cleavage of ring A in the triterpenoids may occur enzymatically a mechanism involving such a reaction as a first step followed by an elimination reaction on the intermediate ϵ-lactone (or after hydrolysis and conversion of the tertiary hydroxyl group into a suitable leaving group) deserves serious





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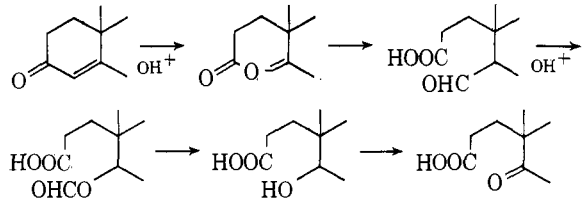
(8) The formation in extremely low yield of Windaus' keto acid (A-nor-3,5-secocholestan-5-on-3-oic acid) by fermentation of cholestenone with *Proactinomyces erythropolis* [G. E. Turfitt, *Biochem. J.*, **42**, 376 (1948)] may also be interpreted to involve as the major oxidative steps two Baeyer–Villiger type reactions, as shown in the following chart, in which the symbol OH^+ stands for the as yet unidentified biochemical equivalent of a peracid.



(9) G. S. Fonken, H. C. Murray, and L. M. Reineke, *J. Am. Chem. Soc.*, **82**, 5507 (1960); G. E. Peterson, R. W. Thoma, D. Perlman, and J. Fried, *J. Bacteriol.*, **74**, 684 (1957); R. L. Prairie and P. Talalay, *Biochemistry* **2**, 203 (1963).

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consideration as an alternative for the biogenesis of these naturally occurring seco acids.[16]

Glomerella fusarioides had previously been employed for microbial conversions of steroids and it is interesting to note the different modes of attack by this organism on different substrates. Thus, in contrast to the ring cleavage reaction observed with eburicoic acid, estrone and estradiol are hydroxylated in the 7α- and 15α-positions,[17] and cortexolone has been reported to undergo 11α-hydroxylation.[18]

The antibacterial activity shown by seco acid IIa on bioautography was confirmed by a serial dilution assay using *S. aureus* 209P, in which this substance showed activity at a minimum inhibiting concentration (MIC) of 65 γ/ml. The MIC values of all the derivatives of IIa described in this paper are listed in Table I. According to these data saturation of the side-chain double bond has no effect on activity. The most potent compounds were the 21-methyl ester acids IIc and IIIb. The neutral dimethyl ester IIb and triol IVa showed no activity even at the highest levels tested. It may be concluded from these findings that a carboxyl group in ring A is essential for activity but that a second such highly polar group at a distant part of the molecule is detrimental. This latter conclusion is supported by the finding that glycol V prepared from IIa with osmium tetroxide showed no activity at 100 γ/ml.

TABLE I

MINIMUM INHIBITING CONCENTRATIONS OF SECO ACIDS TOWARD *Staphylococcus aureus* 209P

Compound	MIC, γ/ml.
IIa	65
IIb	>100
IIc	2
IIIa	70
IIIb	2
IVa	>100
V	>100
Fusidic acid	0.02

To obtain a broader picture of their antibiotic activity, dicarboxylic acid IIa and its monomethyl ester IIc were tested in serial dilution assays against the following bacteria and fungi: *Salmonella schottmuelleri, Pseudomonas aeruginosa, Proteus vulgaris, Candida albicans, Trichophyton mentagrophytes, Fusarium bulbigenum,* and *Mycobacterium tuberculosis var. BCG.* Compounds IIa and IIc showed activity against the last-named organism at MIC values of 9 and 2 γ/ml., respectively, but were inactive against all the others at 100 γ/ml.

Experimental

All melting points were taken in a Thomas–Hoover apparatus and are corrected for stem exposure. Ultraviolet spectra were determined on a Cary 11, infrared spectra on a Perkin-Elmer 21, and nuclear magnetic resonance spectra on a Varian A-60 spectrometer in $CDCl_3$ or pyridine solution with tetramethylsilane as internal standard.

Fermentation of Eburicoic Acid with *Glomerella fusarioides* (ATCC 9552).—*Glomerella fusarioides* (ATCC 9552) was grown on a medium containing glucose (10 g.), Difco yeast extract (2.5 g.), K_2HPO_4 (1 g.), agar (20 g.), and distilled water to 1 l. Surface growth from slant cultures was suspended in 2.5 ml. of an aqueous 0.01% sodium lauryl sulfate solution and 1-ml. portions of the suspension were used to inoculate ten 250-ml. conical flasks, each containing 50 ml. of the following sterilized nutrient medium: dextrose (10 g.), cornsteep liquor (6 g.), $NH_4H_2PO_4$ (3 g.), Difco yeast extract (2.5 g.), $CaCO_3$ (2.5 g.), and distilled water to 1 l. After 72 hr. of incubation at 25° with continuous rotary agitation (280 cycles/min., 5.1-cm. radius), 10% (v./v.) transfers were made to seventy 250-ml. conical flasks each containing 50 ml. of fresh sterilized medium B. The eburicoic acid was added to each flask in 0.25 ml. of a sterile solution of the steroid in N,N-dimethylformamide (60 mg./ml.) so that the medium was supplemented with 300 γ/ml. of steroid. After 1 week of further incubation as described above, the contents of the flasks were pooled and filtered through a Seitz K-5 clarifying pad. Disappearance of substrate was followed using the paper chromatographic system III of Pan, *et al.*[19] (hexane–*t*-butyl alcohol–4 *N* NH_4OH, 10:3:10), and products were separated using a modification of the butanol–ammonia system of Ried and Lederer[20] in which the concentration of the NH_4OH was 4 *N* and the ratio of butanol–NH_4OH was 4:1. The filtrate was acidified to pH 4.0 with glacial acetic acid and the resulting flocculent precipitate collected by filtration. The filter cake was dissolved in methyl isobutyl ketone, the solution filtered, and the filtrate evaporated to dryness *in vacuo*. The residual material was triturated with ether and the resulting crystals (349 mg.) recrystallized from acetone. This furnished pure 3,4-seco-$\Delta^{5,24(28)}$-eburicadien-4-ol-3,21-dioic acid (IIa): m.p. 236–238°; $[\alpha]^{23}D$ +78° (*c* 0.54, alcohol); λ_{max}^{KBr} 3.00, 5.87, 6.10, and 11.25 μ; n.m.r. (pyridine): τ 5.07 (28-CH_2), 8.52 (4,4-dimethyl), 8.65 (19-CH_3); neut. equiv. 250 (calcd. 251).

Anal. Calcd. for $C_{31}H_{50}O_5$: C, 74.06; H, 10.03. Found (after drying at 140° to constant weight): C, 73.61, 73.67; H, 10.59, 10.59.

The above conditions when applied to 40-l. fermentors yielded from 18 g. of eburicoic acid (two fermentors: 300 γ of I/ml., 122 hr.) 3.62 g. of methyl isobutyl ketone-soluble material, which after trituration with chloroform afforded 2.22 g. of crystalline material. Recrystallization from acetone gave a total of 1.64 g. of IIa.

The dimethyl ester (IIb) of the above acid (300 mg.) was prepared from acid IIa with ethereal diazomethane in methanol (6 ml.). It could not be crystallized.

3,4-Seco-$\Delta^{5,24(28)}$-eburicadien-4-ol-3,21-dioic Acid 21-Methyl Ester (IIc).—A solution of 300 mg. of the dimethyl ester of 3,4-seco-$\Delta^{5,24(28)}$-eburicadien-4-ol-3,21-dioic acid (IIb) in 30 ml. of 6% KOH in methanol was allowed to stand at room temperature for 6 hr. The mixture was acidified with hydrochloric acid, the methanol was removed *in vacuo*, and the suspension extracted with chloroform. The chloroform extract was dried over sodium sulfate, filtered, and the solvent was removed *in vacuo*. The residue (316 mg.) on recrystallization from hexane afforded 255 mg. of pure monomethyl ester IIc, m.p. 148–150°; $[\alpha]^{24}D$ +100° (*c* 0.41, $CHCl_3$); λ_{max}^{KBr} 3.00, 5.76, 5.84, 6.09, and 11.23 μ.

Anal. Calcd. for $C_{32}H_{52}O_5$: C, 74.37; H, 10.14. Found: C, 74.33; H, 10.05.

3,4-Seco-Δ^{5}-eburicen-4-ol-3,21-dioic Acid (IIIa).—To a prereduced suspension of 25 mg. of 10% Pd-on-charcoal catalyst in 95% alcohol (uptake 1.6 ml.) was added 25 mg. of 3,4-seco-$^{5,24(28)}$-eburicadien-4-ol-3,21-dioic acid (IIa) in 2 ml. of alcohol. Reduction was complete after 1.4 ml. of hydrogen had been taken up (theory 1.3 ml.). The solution was filtered and evaporated to dryness *in vacuo*. The crystalline residue upon recrystallization from methanol gave pure dihydro acid IIIa, m.p. 242–243°; $[\alpha]^{23}D$ +93° (*c* 0.4, alcohol); λ_{max}^{KBr} 3.00 and 5.88 μ.

Anal. Calcd. for $C_{31}H_{52}O_5$: C, 73.76; H, 10.38. Found: C, 73.50; H, 10.18.

3,4-Seco-Δ^{5}-eburicen-4-ol-3,21-dioic Acid 21-Methyl Ester (IIIb).—The dihydro acid IIIa (50 mg.) was suspended in 1 ml. of methanol and methylated with ethereal diazomethane. The amorphous dimethyl ester recovered upon removal of the solvents *in vacuo* was dissolved in 5 ml. of 6% KOH in methanol and allowed to remain at room temperature for 6 hr. The mixture was then acidified with hydrochloric acid, the methanol removed *in vacuo*, and the suspension extracted with chloroform. The chloroform extract was dried over sodium sulfate, filtered, and

(16) *Cf.* also the elegant synthesis of nyctanthic and roburic acids by oxidative photolysis [Quinkert and Heine, *Tetrahedron Letters*, 1659 (1963)].

(17) A. I. Laskin, P. Grabowich, B. Junta, C. de L. Meyers, and J. Fried, *J. Org. Chem.*, **29**, 1333 (1964).

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(19) S. C. Pan, A. I. Laskin, and P. Principe, *J. Chromatog.*, **8**, 32 (1962).

(20) R. L. Reid and M. Lederer, *Biochem. J.*, **50**, 60 (1961).

evaporated to dryness *in vacuo*. The dihydromonomethyl ester (IIIb) was recrystallized from acetone–hexane and furnished 37 mg. of pure product, m.p. 170–172°; $[\alpha]^{23}D$ +76° (*c* 0.34, alcohol); λ_{max}^{KBr} 3.05, 5.78, and 5.85 μ; n.m.r. ($CDCl_3$) τ 6.36 (OCH_3), 8.72 (4,4-dimethyl), 8.84 (19-methyl); neut. equiv. 513.

Anal. Calcd. for $C_{32}H_{54}O_5$: C, 74.09; H, 10.49; OCH_3, 5.98. Found: C, 73.93; H, 10.49; OCH_3, 6.28.

The above dihydromonomethyl ester IIIb was also obtained when the monomethyl ester IIc (50 mg.) was hydrogenated in ethanol (5 ml.) with 50 mg. of 10% Pd-on-charcoal catalyst.

3,4-Seco-$\Delta^{8,24(28)}$-eburicadien-3,4,21-triol (IVa).—A solution of 200 mg. of the 3,4-seco-$\Delta^{8,24(28)}$-eburicadien-4-ol-3,21-dioic acid (IIa) in 20 ml. of freshly distilled tetrahydrofuran was added dropwise over a 15-min. period to a suspension of 200 mg. of lithium aluminum hydride in 30 ml. of tetrahydrofuran. The mixture was refluxed for 3 hr. and, after cooling, 0.5 ml. of a saturated sodium sulfate solution was added. The suspension was filtered, the precipitate washed three times with hot chloroform, and the solution evaporated to dryness *in vacuo*. The residue (197 mg.) on recrystallization from acetone gave 160 mg. of pure triol IVa, m.p. 148–149°; $[\alpha]^{23}D$ +89° (*c* 0.59, $CHCl_3$); λ_{max}^{Nujol} 3.08, 6.10, and 11.28 μ; n.m.r. ($CDCl_3$) τ 5.26 (28-CH_2), 6.33 (m 3- and 21-CH_2), 8.67 (4,4-dimethyl), 8.83 (19-CH_3).

Anal. Calcd. for $C_{31}H_{54}O_3$: C, 78.42; H, 11.47. Found: C, 78.18; H, 11.81.

The diacetate IVb was prepared in pyridine solution with acetic anhydride.

3,4-Seco-Δ^8-eburicene-4,24,28-triol-3,21-dioic Acid (V).—To a solution of 47 mg. of 3,4-seco-$\Delta^{8,24(28)}$-eburicadien-4-ol-3,21-dioic acid (IIa) in 3 ml. of dioxane and 0.2 ml. of pyridine was added dropwise over a 30 min. period a solution of 26 mg. of OsO_4 in 3 ml. of dioxane. The solution was allowed to remain at room temperature for an additional hour and then decomposed with H_2S. The mixture was filtered over a Celite pad and the filtrate was evaporated to dryness *in vacuo*. The residue (58 mg.) was recrystallized from ethyl acetate with the aid of Darco G-60 affording glycol acid V, m.p. 233–235°; $[\alpha]D$ +68° (*c* 0.47, alcohol); λ_{max}^{KBr} 2.95, and 5.85 μ; neut. equiv. 269 (calcd. 268).

Anal. Calcd. for $C_{31}H_{52}O_7$: C, 69.37; H, 9.77. Found: C, 69.45; H, 9.65.

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Structures Related to Morphine. XXVII.[1] α- and β-5,9-Diethyl-2-methyl-6,7-benzomorphans

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Sodium borohydride reduction of the dihydropyridine base II obtained in the reaction of benzylmagnesium chloride and 3,4-diethylpyridine methiodide has given 2-benzyl-3,4-diethyl-1-methyl-1,2,5,6-tetrahydropyridine (III). This is cyclized by hot hydrobromic acid mainly to α-5,9-diethyl-2-methyl-6,7-benzomorphan (VI) and (as the hydrochloride) by aluminum bromide to a mixture of VI and the β isomer IX as shown by thin film chromatography. Base IX, essentially to the exclusion of VI, resulted from aluminum bromide cyclization of *trans*-2-benzyl-3,4-diethyl-1-methyl-1,2,3,6-tetrahydropyridine hydrobromide (VIII) also synthesized from II *via* V, IV, and VII. The structure and stereochemistry of IX were proved by converting it to the known β-5,9-diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan (X). The stereochemistry of both VI and IX was also confirmed by methiodide rate studies. Compounds VI and IX are relatively potent analgesics and VI has no addiction-sustaining capacity in morphine-addicted monkeys.

The analgesically favorable effect of a properly positioned phenolic hydroxyl in structures with a heterocyclic nitrogen (*e.g.*, the morphinans and benzomorphans)[2] has been known for some time. However, the role of this substituent in tolerance and physical dependence has not been studied, perhaps because deoxy compounds of the order of potency of morphine have not been available.[3] The high activity displayed by various 2′-hydroxy-5,9-dialkyl-6,7-benzomorphans, particularly the β-diastereomers,[4] provided hope that nonphenolic compounds[5] of morphine-like potency are not implausible. Furthermore, any such deoxy compound of possibly negligible addiction liability would not be readily convertible to a product of greater addiction potential, a hazard generally attending hydroxy compounds (*viz.*, conversion of morphine to heroin[2a] and β-*dl*-methadol to β-*dl*-acetylmethadol[2a,6]). Consequently, we have synthesized α- and β-5,9-diethyl-2-methyl-6,7-benzomorphans (VI, IX), deoxy compounds selected for study principally on the basis of comparative results reported earlier[4] in the 2′-hydroxy series.

The synthesis of the α-compound VI was achieved, as usual, by the Grewe method,[7,8] except that sodium borohydride[9] was used instead of palladium-catalyzed hydrogen in the reduction of the dihydro base II to 2-benzyl-3,4-diethyl-1-methyl-1,2,5,6-tetrahydropyridine (III). Cyclization of III with hot hydrobromic acid gave VI in 76% yield. No β-isomer IX could be iso-

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(3) N-Methylmorphinan (ref. 2a), although one-fifth as potent as morphine and comparable to pethidine in animal screening tests, has not been further examined.

(4) J. H. Ager, S. E. Fullerton, and E. L. May, *J. Med. Chem.*, **6**, 322 (1963).

(5) Otherwise close congeners of morphine and the morphinans.

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(8) E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957).

(9) S. E. Fullerton, J. H. Ager, and E. L. May, *ibid.*, **27**, 2554 (1962).