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Asymmetric Reductions. IX. The Reduction of Trimethylacetaldehyde-1-*d* by Actively Fermenting Yeast[1]

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Optically active neopentyl alcohol-1-*d* has been prepared by the reduction of trimethylacetaldehyde-1-*d* with actively fermenting yeast. Although the alcohol does not rotate the plane of polarized sodium light appreciably, the acid phthalate has an optical rotation of $[\alpha]^{28}D$ -1.14 ± 0.04. This may correspond to a compound of high optical purity. The probable absolute configuration of this alcohol is considered. The steric requirements of the enzyme system in this instance are compared to those found by Westheimer, Fischer, Conn and Vennesland in the ADH–DPNH reduction of acetaldehyde-1-*d*. The reduction of trimethylacetaldehyde-1-*d* by the isolated enzyme system, ADH–DPNH was too slow to permit its use for studying the stereospecificity of this reaction.

The reduction of aldehydes and ketones to the corresponding alcohols by actively fermenting yeast is well known.[2,3] Furthermore, the reduction of acetaldehyde by reduced diphosphopyridine nucleotide (DPNH) and alcohol dehydrogenase (ADH) to give ethanol involves the transfer of a hydrogen atom from the DPNH to the substrate as shown by the elegant investigations of Westheimer, Vennesland and co-workers.[4–7] They have further demonstrated that with this purified enzyme system the transfer of deuterium from DPND to acetaldehyde is direct, reversible and completely stereospecific leading to a pure isomer (−)ethanol-1-*d*. Although direct proof is lacking, it seems highly probable that this same enzyme system is responsible for the reduction of these related aldehydes and ketones *in vivo* by the actively fermenting yeast.[8] Further evidence is needed on this point, however. It also has been shown[8] during oxidation studies on a series of methylalkylcarbinols by the DPN–ADH system that the reaction was relatively non-selective as to substrate structure but was specific to substrate configuration in the series of methyl-*n*-alkylcarbinols studied.

We have been studying this enzymatic system with the aim of gaining further information concerning the steric requirements for such hydrogen transfer reactions and if possible to correlate these results with those from the chemical asymmetric reductions in general.[9] Trimethylacetaldehyde-1-*d* was chosen for study since we wanted an example that would be reduced both by the enzymatic system and the optically active Grignard reagent which we have studied extensively.[9] A hindered aldehyde was necessary, otherwise the Grignard reagent would undergo addition only. Trimethylacetaldehyde-1-*d* is one of the few aldehydes suitable for study by both systems. It is prepared *via* the lead tetraacetate cleavage of the corresponding glycol, 2,2,5,5-tetramethylhexane-3,4-diol-3,4-d_2, which was obtained by the lithium aluminum deuteride reduction of dipivaloyl.[10,11] A preliminary study of the rate of reduction of trimethylacetaldehyde using purified DPNH and ADH and following the reaction spectrophotometrically[12] showed that the rate was in the order of $^1/_{10,000}$ that of acetaldehyde, much too slow to be employed, according to the scheme of Levy, Loewus and Vennesland,[7] for the production of quantities of neopentyl alcohol-1-*d* sufficient for accurate optical rotation measurements. On the other hand, reduction by actively fermenting yeast[2b] was rapid and the gram quantities of neopentyl alcohol-1-*d* necessary could be isolated with comparative ease in approximately 50% yield. The alcohol was purified by gas–liquid partition chromatography and the purity and identity were checked by infrared spectroscopy. Extreme care was exercised to rule out the possibility that any observed rotation was due to an optically active impurity.[13] The neopentyl alcohol-1-*d*, $[\alpha]^{28}D$ $+ 0.02 \pm 0.02$, was essentially without rotation. However, the acid phthalate derivative[14] was prepared and purified, $[\alpha]^{28}D$ -1.06 ± 0.04. Since this had 93% of the theoretical deuterium content, the calculated rotation for the completely deuterated alcohol would be $[\alpha]^{28}D$ -1.14 ± 0.04. Regeneration of the neopentyl alcohol-1-*d* from its acid phthalate gave a product with the same properties as the original starting material. This was reconverted to the acid phthalate whose specific rotation, melting point and infrared spectrum were un-

(1) This investigation has been supported in part by research grant No. 5248 from the National Institutes of Health of the U. S. Public Health Service.

(2) (a) C. Neuberg and F. F. Nord, *Ber.*, **52**, 2237 (1919). (b) C. Neuberg, "Advances in Carbohydrate Chemistry," Vol. IV, Academic Press, Inc., New York, N. Y., 1949, pp. 75–117.

(3) P. Levene and A. Walti, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 545.

(4) F. H. Westheimer, H. F. Fisher, E. E. Conn and B. Vennesland, THIS JOURNAL, **73**, 2403 (1951).

(5) H. F. Fisher, E. E. Conn, B. Vennesland and F. H. Westheimer, *J. Biol. Chem.*, **202**, 687 (1953).

(6) F. A. Loewus, F. H. Westheimer and B. Vennesland, THIS JOURNAL, **75**, 5018 (1953).

(7) H. R. Levy, F. A. Loewus and B. Vennesland, *ibid.*, **79**, 2949 (1957).

(8) J. van Eys and N. O. Kaplan, *ibid.*, **79**, 2782 (1957).

(9) W. M. Foley, F. J. Welch, E. M. LaCombe and H. S. Mosher, *ibid.*, **81**, 2779 (1959), and other references listed therein.

(10) J. M. Snell and S. M. McElvain, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 115.

(11) N. J. Leonard and P. M. Mader, THIS JOURNAL, **72**, 5388 (1950).

(12) A. P. Nygaard and H. Theorell, *Acta Chem. Scand.*, **9**, 1300 (1955).

(13) The retention times of all the known fusel oil components were determined on the partition column being used. Only isobutyl alcohol overlapped the neopentyl alcohol peak. That any optically active impurity was absent was demonstrated by a control run with non-deuterated trimethylacetaldehyde. The resulting neopentyl alcohol and its acid phthalate, after purification in the same manner, were without measurable optical rotation.

(14) Neopentyl alcohol acid phthalate is nicely crystalline while those of the two most likely optically active impurities, primary active amyl alcohol and *sec*-butyl alcohol are both liquids and thus if not removed by gas partition chromatography would certainly be removed by crystallization of this derivative.

changed within experimental error. The infrared spectra of these two compounds were identical to those of the *dl*-neopentyl alcohol-1-*d* and acid phthalate made by lithium aluminum deuteride reduction of trimethylacetaldehyde. A second independent fermentation gave neopentyl alcohol-1-*d* and acid phthalate with identical properties within experimental error.

Discussion

Although direct evidence is not available at this time, it seems likely that the enzymatically produced neopentyl alcohol-1-*d* represents a compound of substantial optical purity. The (−) ethanol-1-*d* produced by the DPNH–ADH reduction of acetaldehyde-1-*d* has been proven to be optically pure.[4,5] Because of the greater steric requirement in the reduction of trimethylacetaldehyde-1-*d*, one would not anticipate that the stereospecificity would be less. The energy of activation for the reduction would be higher and the reaction therefore much slower but the differences in energies of activations between the two pathways which produce the *d* and *l* forms respectively should be increased if anything. In addition, the high rotation of the acid phthalate in comparison to those of the other two known acid phthalates of 1-deutero alcohols (Table I) is indicative of comparable optical purity. The optical purity of the second[15] and third[16] examples in Table I are not known with certainty but are estimated to be high and are known to be the same.[17] Note that the acid phthalate of the benzyl alcohol-1-*d* is less than that of the neopentyl alcohol-1-*d* acid phthalate by a factor of $^1/_5$. Because of the ultraviolet absorbing phenyl group in the benzyl case one would anticipate that this would have a larger rotation than the neopentyl example, other factors being equal.

TABLE I

SPECIFIC ROTATIONS OF RCHDOH AND THEIR ACID PHTHALATES

R	RCHDOH $[\alpha]^5D$	RCHDO-$C_8H_6O_3$ $[\alpha]^5D$
CH_3[7]	−0.28 ± 0.03 (28°)[a]	.....[a]
n-$C_3H_{7-15,17}$	− .185 ± .002 (25°)[b]	+0.38 ± 0.05 (25°)
$C_6H_{5-15,17}$	− .715 ± .002 (20°)[b]	+0.219 ± .005 (25°)
$(CH_3)_3C$-	+ .02 ± .02 (28°)[c]	−1.14 ± .04 (28°)

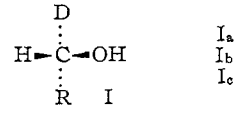
[a] The acid phthalate, which would be a liquid, was not reported; the alcohol is optically pure. [b] The optical purity[17] of these two examples is estimated to approach 100% and both are known to be of the same degree of optical purity and configurationally related. [c] See Experimental section.

Nevertheless this conclusion must be tentative since the unreliability of this type of evidence for predicting optical purity is evident by inspecting the values for the free alcohols in Table I. The molecular rotations for the first three examples, without regard to absolute configuration, agree well enough, but the fourth is completely out of line. Further examples and independent evidence of optical purity are obviously necessary.[18]

One is tempted to generalize from the data in Table I that those deutero alcohols of type R-CHDOH and their acid phthalates have opposite signs of rotation and thus the neopentyl alcohol-1-*d* which gives the (−) acid phthalate should be designated (+) in spite of its dubious positive rotation. If one considers the analogous compounds where CH_3 replaces D, then this conclusion is not in accord with the fact that (+) *sec*-butyl alcohol gives a (+) acid phthalate[19] and that the acid phthalate of methyl-*t*-butylcarbinol has the same sign[19] as the alcohol; thus this analogy is unreliable.

It has been established that the methyl-*n*-alkylcarbinols with the same sign of rotation are configurationally related,[19] but since methyl-*t*-butylcarbinol (as well as other related branched-chain carbinols) is related to methyl-*n*-butylcarbinol of opposite sign,[9] it would appear unwise to attempt to correlate absolute configurations among the four compounds in Table I on this basis. Nevertheless, because of the *relative* rotations of the free carbinols and acid phthalates, it would appear safe to conclude that those examples in which the rotation becomes significantly more negative in going from the free carbinol to the acid phthalate have the same absolute configuration, *i.e.* (+) butyl alcohol 1-*d*, (+) benzyl alcohol-1-*d*, and that neopentyl alcohol-1-*d* which gives the (−) acid phthalate.

On mechanistic grounds the first two have been assigned[17] absolute configurations I_a and I_b which is the S configuration on the basis of the Cahn, Ingold, Prelog[20] designation. The same type of mechanistic arguments[21] as developed in references 17 and 9 and the known absolute configuration of the optically active reducing agent lead to the conclusion that I_c is the correct absolute configuration



I

I_a R = *n*-C_3H_7(+)
I_b R = C_6H_5(+)
I_c R = $C(CH_3)_3$

for this compound. Unfortunately the information on the acid phthalate of (−) ethanol-1-*d* is not available at this time and thus any conclusion based on this generalization concerning its relative configuration must wait.[22]

If we make the reasonable assumption that the steric control of the asymmetric enzymatic reduction is similar to that of the known asymmetric reductions of the Grignard[9] and Meerwein–Ponndorf[17,23,24] types, an assumption whose validity is strengthened by the recent work of Prelog and co-workers[25] on the bacterial reduction of alicyclic

(15) A. Streitwieser, Jr., and J. R. Wolfe, Jr., THIS JOURNAL, **79**, 903 (1957).

(16) A. Streitwieser, Jr., *ibid.*, **77**, 1117 (1955).

(17) A. Streitwieser, Jr., J. R. Wolfe, Jr., and W. D. Schaeffer, *Tetrahedron*, **6**, 340 (1959).

(18) Such is being collected, A. Streitwieser, Jr., private communication. In addition, the investigations reported in the present paper are being extended to other examples of phytochemical reductions.

(19) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911); **101**, 620 (1912); **105**, 1115 (1914).

(20) R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia*, **12**, 81 (1956).

(21) To be reported in a subsequent paper. The neopentyl alcohol-1-*d* produced in the asymmetric reduction of trimethylacetaldehyde-1-*d* by the Grignard reagent from (+)-1-chloro-2-methylbutane gives a (−) acid phthalate.

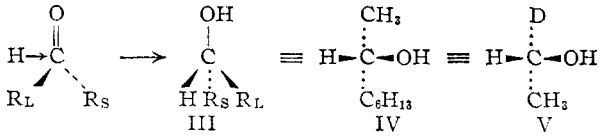
(22) The footnote on page 341 of reference 17 should be noted in this regard.

(23) W. E. Doering and R. W. Young, THIS JOURNAL, **72**, 631 (1950).

(24) K. Wallenfels and H. Sund, *Biochem. Zeit.*, **329**, 59 (1957).

(25) (a) W. R. Feldman and V. Prelog, *Helv. Chim. Acta*, **41**, 2396 (1958); (b) P. Baumann and V. Prelog, *ibid.*, **41**, 2362, 2379 (1958); **42**, 736 (1959); (c) V. Prelog and D. Zach, *ibid.*, **42**, 1862 (1959); (d) W. Acklin and V. Prelog, *ibid.*, **42**, 1239 (1959).

ketones with *Curvularia falcata*, then we can represent the process as follows where R_L is the larger and R_S is the smaller group.[26] If one assumes that the nature of the enzyme is such that the hydrogen transfer occurs from the left as represented, then



III IV V

the configuration of the product will be III. This is the absolute configuration IV proven for (+)-2-octanol,[27] the product from the enzymatic reduction of 2-octanone by actively fermenting yeast.[2] It is also the configuration of the R-neopentyl alcohol (I_e) which has been proposed for the product from the yeast reduction of trimethylacetaldehyde-1-*d*. On the other hand, the configuration of the (−) ethanol-1-*d* (V) predicted on these assumptions is opposite to that proposed by Loewus, Levy and Vennesland[7] for their enzymatically produced product[28] but corresponds to the prediction by Brewster[29] based on the generalities developed for estimating rotations.

The configuration V is that arrived at for (−) ethanol-1-*d* on rather speculative grounds by van Eys and Kaplan. If (−) ethanol-1-*d* proves to be configurationally related to (+) butanol-1-*d*, *i.e.*, has the S configuration instead of the R, as predicted by Brewster[29] and as expected on the basis of previous asymmetric reduction work,[9,29] then theory and the stereochemical nature of these products will be in harmony.

Experimental

Dipivaloyl.—Ethyl pivalate, b.p. 116–118°, $n^{20}D$ 1.3904, prepared in 87.5% yield by the sulfuric acid catalyzed esterification[30] of pivalic acid was converted into a mixture of pivaloin and dipivaloyl by the acyloin condensation.[10] The mixture was oxidized with dichromate[11] to dipivaloyl which was purified by fractionation through a 30-plate helix-packed column, b.p. 77–79° (28–30 mm.), $n^{20}D$ 1.4150–1.4152. The absence of pivaloin was readily ascertained by examination of the infrared spectrum.

2,2,5,5-Tetramethyl-3,4-hexandiol-3,4-d_2.—In a vigorously maintained anhydrous system, 100 g. (0.58 mole), of dipivaloyl in 150 ml. of anhydrous ether was added dropwise with stirring to a suspension of 13.3 g. (0.317 mole) of lithium aluminum deuteride[31] in 400 ml. of ether over a 5-hr. period. After stirring and refluxing for an additional hour the mixture was cooled in an ice bath and decomposed with 300 ml. of 10% sulfuric acid. The ether layer and ether extracts were combined, washed successively with water, 10% sodium carbonate and water, dried over anhydrous sodium sulfate and the ether removed. The residue was crystallized from petroleum ether, m.p. 121–121.5° (sealed tube); on a Kofler hot stage the crystals appeared to change from plates to needles at about 70° and sublimed at about 90°. The total yield after working up mother liquors was 86.1 g. (86.3%). The infrared spectrum showed characteristic C–D absorption at 4.94 μ with a shoulder at 4.74 μ. It lacked a characteristic band at 10.2 μ present in the undeuterated parent compound. A sample was burned and the water converted to hydrogen[32] which was analyzed by mass spectra.[32] The theoretical deuterium content is 2.0 deuterium atoms per molecule, found 2.0 ± 0.05 deuterium atoms per molecule.

Trimethylacetaldehyde-1-D.—The above deuterated glycol, 86.0 g. (0.49 mole), in 1400 ml. of dry toluene, was cooled to 15° and treated in an inert atmosphere with stirring with lead tetraacetate, 260 g. (0.54 mole), in one portion. The temperature was allowed to rise to 25° and the suspension stirred for 7 hr. After settling for 2 hr. the liquid was decanted and the solid washed with a little toluene and centrifuged. Fractionation under nitrogen through a 30-plate, helix-packed column gave 46.2 g. (55%), b.p. 74–76°, $n^{20}D$ 1.3790. Characteristic peaks at 12.5 and 13.7 μ for the non-deuterated aldehyde were absent in this product and a moderately strong C–D band at 4.95 μ with a shoulder at 4.75 μ was present. Because of its ease of autoxidation, it was used immediately in the next step or sealed under nitrogen.

Neopentyl Alcohol-1-*d*, (I_e).—A solution of (+) glucose, 910 g. (5.05 mole) in 2.8 l. of water and a paste of 0.9 kg. of fresh Fleishmann's Bakers yeast in 1.08 l. of water, was charged to a 12-l. stirred fermenter[3] maintained at 32–34°. After fifteen minutes, when the fermentation was going vigorously, trimethylacetaldehyde-1-*d* (20.15 g., 0.23 mole) in 10 ml. of ethanol was added over a thirty-minute period. When gas evolution had ceased after 5 hr., the mixture was allowed to stand overnight and then steam distilled. The distillate was fractionated through a 60-plate column and the steam distillate which followed the removal of ethanol was extracted with ether, the ether extracts dried over barium oxide and most of the ether removed under a column. The residue was purified by gas partition chromatography on a $^3/_8'' \times 5'$ Ucon-polar column[33] in 50-mg. portions, m.p. 53–54° (sealed tube), $[\alpha]^{28}D$ 0.02 ± 0.02 (l = 2, c = 62, acetone). Under the conditions of the separation (temp., 103°, flow rate 60 ml./mm.) the retention time was 5.9 min. Under identical conditions the retention times for possible impurities were: water, 3.0 min.; *sec*-butyl alcohol, 3.4 min.; primary active amyl alcohol, 10.4 min.; isoamyl alcohol, 10.4 min.; isobutyl alcohol, 5.4 min.; *n*-amyl alcohol, 13.8 min.; *sec*-amyl alcohol, 6.8 min. The infrared spectrum of the deuterated compound showed a C-D band at 4.65 μ with a shoulder at 4.75 μ. Small bands at 10.3 μ and 13.4 μ, which were present in the non-deuterated compound, were absent.

Acid Phthalate of Neopentyl Alcohol-1-*d*.—The acid phthalate was prepared in 85% yield using phthalic anhydride and pyridine in the usual method[34] with the exception that the neopentyl alcohol was dissolved in the acetone used in taking its rotation. The acid phthalate was crystallized from petroleum ether (b.p. 77–110°), m.p. 68.5–69.5°, $[\alpha]^{31}D$ −1.10 ± 0.03 (l = 2, c = 34, acetone). A second sample of the above neopentyl alcohol-1-*d*-purified by gas partition chromatography was converted to the acid phthalate and gave after 2, 3 and 4 recrystallizations the following melting points and rotations: m.p. 69.2–70.1°, $[\alpha]^{28}D$ −1.08 ± 0.03 (l = 2, c = 18, acetone); m.p. 68–69°, $[\alpha]^{27}D$ −1.04 ± 0.04 (l = 2, c = 13, acetone); m.p. 68.9–69.5°, $[\alpha]^{28}D$

(26) For this discussion the R groups are assumed to be alkyl or aryl and hydrogen or deuterium of the type that are primarily inert. Thus forces involved would be essentially steric and not electronic as would be expected with oxygen or nitrogen containing groups in which factors other than size might take precedent.

(27) See J. A. Mills and W. Klyne, "Progress in Stereochemistry," Vol. I, Butterworths Scientific Publications, London, 1957, pp. 187.

(28) Their prediction is based on apparently sound assumptions, namely: (1) The mechanism of the reaction which produces (−) butanol-1-*d* and (2) that (−) butanol-1-*d* and (−) ethanol-1-*d* with the same sign have the same configuration. Although there has been no serious question of the first assumption, the second is not above suspicion.[22,29]

(29) Evidence in support of the idea that (−) ethanol-1-*d* and (+) butanol-1-*d* have the same configuration can be found in a recent paper by J. H. Brewster, *Tetrahedron Letters*, **20**, 23 (1959). Based on his rules of atomic and conformational asymmetry and on the molecular rotation and configuration of (+) butane-2-*d* (G. K. Helmkamp, C. D. Joel and H. S. Sharman, *J. Org. Chem.*, **21**, 844 (1956), Brewster calculates that the molecular rotation of butanol-1-*d* should be 0.33° more dextrorotatory that ethanol-1-*d* with the same configuration. Since the molecular rotation of (−) ethanol-1-*d* is −0.13 ± 0.02,[7] an additional 0.33° would give a value for butanol-1-*d* of $[M]D = +0.20°$. This agrees fairly well with Streitwieser's value[17] for (+) butanol-1-*d* ($[M]D = +0.139$) and very well with some preliminary data from fermentation work which indicate that $[M]D$ for butanol-1-*d* should be at least 0.21°.

(30) A. Richard, *Ann. chim. phys.*, [8] **21**, 335 (1910).

(31) Metal Hydrides Corp., reported to be 95.2% pure.

(32) J. Graff and D. Rittenberg, *Anal. Chem.*, **24**, 878 (1952); R. B. Alfin-Slater, S. M. Rock and M. Swislocki, *ibid.*, **22**, 421 (1950).

(33) Wilkins Aerograph, Model A-90.

(34) A. W. Ingersoll, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 376.

-1.04 (1 = 2, c = 12, acetone). The infrared spectrum showed bands at 4.60 μ and 9.94 μ which were not present in the non-deuterated compound.

Anal. Calcd:[35] $C_{13}H_{15}DO_4$: C, 65.81; H, 6.79; D, 0.84. Found: C, 65.62; H, 7.02; D, 0.78.

(35) The carbon hydrogen values are regular combustion analyses; the theoretical hydrogen value is adjusted by assuming that one atom of deuterium per acid phthalate is present.

The combined acid phthalate fractions were hydrolyzed to neopentyl alcohol-1-*d*, which was purified as before to a product of unchanged properties. It was reconverted to the acid phthalate, $[\alpha]^{27}D$ -1.07 ± 0.03 (1 = 2, c = 15, acetone), m.p. 70. The average of all these acid phthalate rotations was $[\alpha]D$ -1.06 ± 0.04. Based on the deuterium analysis indicating 93% labelling, this corresponds to a rotation of $[\alpha]$ -1.14 for the product which would be 100% labelled.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC., SUMMIT, N. J.]

The Alkaloids of *Hunteria eburnea*. I. The Structures of Eburnamine, Isoburnamine, Eburnamenine and Eburnamonine and a Synthesis of *rac*-Eburnamonine[1]

BY M. F. BARTLETT AND W. I. TAYLOR

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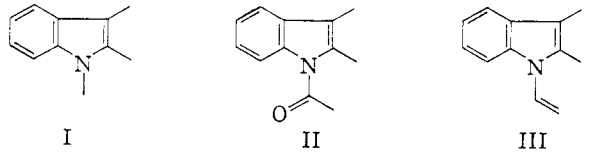
Eburnamine (XII) and its iso compound XII are shown to be interconvertible diastereoisomeric carbinolamines which upon oxidation afford the N-acylindole, eburnamonine (IV). Eburnamenine (XV), an N-vinyleneindole, is produced from the above alcohols by a mild acid-catalyzed dehydration. Reduction of eburnamonine yields the two alcohols as well as dihydroeburnamenine. Selenium dehydrogenation of eburnamonine furnishes 4-ethyl-4-propyl-4,5-dihydrocanthin-6-one, and 4-ethyl- and 4-propyl-canthin-6-ones. A general method is developed for the synthesis of these canthin-6-ones. Wolff-Kishner reduction of eburnamine furnishes *d*-1,1-diethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3a]quinolizine which after racemization proves to be identical with a synthetic sample. From these and other results the structures and stereochemistry of the alkaloids are derived. A simple efficient seven-step synthesis of *dl*-eburnamonine is described.

During the course of an examination of the African apocynaceous plant *Hunteria eburnea* Pichon for substances of possible therapeutic value[2] several new alkaloids were isolated. Two of them, eburnamine and isoeburnamine, appeared analytically and spectrophotometrically to be trisubstituted pentacyclic indoles of type I, whereas eburnamenine

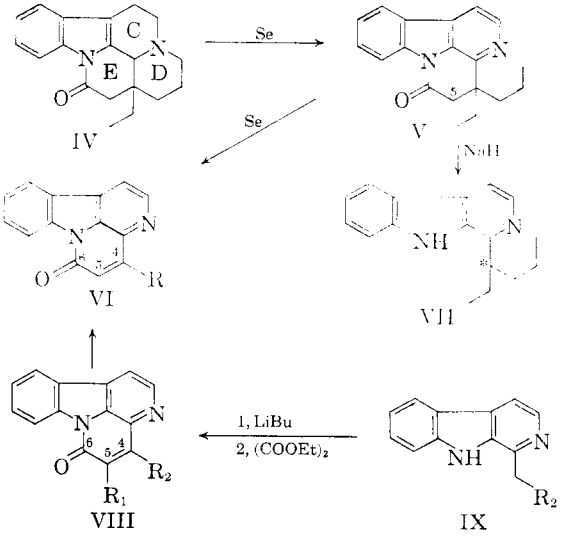


I II III

was an N_a-acylindole of type II, and eburnamenine had a spectrum which was not immediately recognized as being due to the chromophore (III). Since N_a-substituted indoles[3] were of rare occurrence and since this was the first occasion that an N-acylindole had been isolated it seemed that a more detailed investigation would yield some interesting results. It will be shown that these bases represent four representatives of a new class of pentacyclic indole alkaloid.

The position and hydroxylic nature of the oxygen in both eburnamine and its epimer was established by oxidation of the bases with chromic oxide in pyridine to eburnamonine in very high yield. Characterization of the chromophoric moiety of eburnamenine as III was made easily since it could be derived from the alcohols *via* mild acid-catalyzed dehydration; for example, it was sufficient to heat them in acetic acid on a steam-bath. The interrelationship was rounded off by the lithium aluminum hydride reduction of eburnamonine which gave a mixture of eburnamine, isoeburnamine and dihydro-eburnamenine.

Eburnamonine (IV) was chosen for further experimentation because of its stability and the potential usefulness of its N-acyl group not only for degradative purposes but also for the assistance it would provide in giving rise to chromophoric systems with characteristic spectral properties. Dehydrogenation of the base with selenium (5 minutes, 360°) gave an almost quantitative yield of the N-acyl-β-carboline[4] (V) in which ring C has been aromatized and ring D opened. This primary dehydrogenation product (V) after prolonged heating



(1) Part of this work has been the subject of two notes: (a) M. F. Bartlett, W. I. Taylor and Raymond-Hamet, *Compt. rend.*, **249**, 1259 (1959); (b) M. F. Bartlett and W. I. Taylor, *Tetrahedron Letters*, **20**, 20 (1959).

(2) Some pharmacology of crude materials is already in the literature; Raymond-Hamet, *Compt. rend.*, **240**, 1470 (1955); A. E. Gelhardt and H. Gilbrecht, *Naturwiss.*, **45**, 547 (1958).

(3) On the contrary N_a-substitution of indolines is common; probably because of the greater electron density at the nitrogen, they can act as more efficient "traps" for activated alkyl and acyl groups.

(4) The extensive work of Price and co-workers on the constitution of the canthin-6-ones from *Pentaceras australis* was very useful to us for the recognition of this and related systems and provided the basis also for the synthetic work; (a) H. F. Haynes, E. R. Nelson and J. R. Price, *Austral. J. Sci. Res.*, **5**, 387 (1952); (b) E. R. Nelson and J. R. Price, *ibid.*, **5**, 563 (1952); (c) **5**, 768 (1952).