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The Synthesis of β-Carboline Derivatives. IX.[1] Syntheses of 2-(1-Hydroxymethyl-propyl)-1,2,3,4,6,7-hexahydro-12*H*, 12*bH*-indolo[2,3-*a*]-quinolizine (10-Desoxy-18,19-dihydro-15-*epi*-hunterburnine)

Tetsuo Kimura[2a] and Yoshio Ban[2]

Faculty of Pharmaceutical Sciences, Hokkaido University[2]

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There have been synthesized *dl*-10-desoxy-18,19-dihydro-15-*epi*-hunterburnine according to the oxidative cyclization reaction with mercuric acetate, and its structure was determined by nuclear magnetic resonance (NMR) and mass-spectra.

There have been published many papers on the isolation and the structural elucidation of Hunteria alkaloids (Apocynaceae), of which the crude extract has been reported to have hypotensive activity.[3,4] These alkaloids are classified into the following four groups.[5]

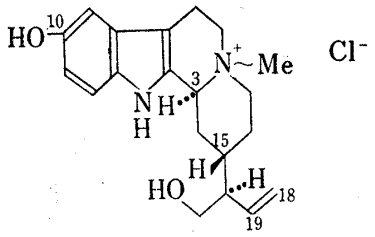
A Eburnamine group
B Seco-corynantheol group
C Tertiary bases of unknown structure
} The tertiary base group
D Quaternary bases

The hypotensive activity is found in the majority of the quaternary bases, and some of the tertiary bases are known to enhance the activity on quaternization.[6a] Thus, attention has been drawn to these quaternary bases, particularly hunterburnine metho-salts. It is interestingly to notice the indication by Taylor and his co-workers who pointed out that none of the quaternary bases so far isolated are the quaternary salts of the known co-occurring tertiary bases, and it is in question whether or not the quaternary compounds are derived from their direct tertiary precursors.[6a,7]

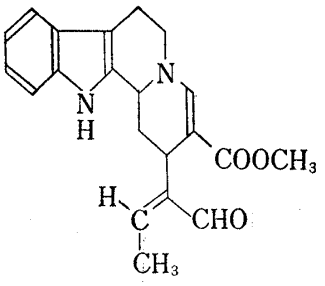
Hunterburnine metho-salts (Ia and Ib) were isolated in 1962 from the bark of *Hunteria eburnea* Pichon by Taylor and his co-workers,[6] who clarified that both of these alkaloids, $C_{20}H_{27}O_2N_2Cl$, contain a 5-hydroxyindole chromophore, an isolated double bond, and an aliphatic hydroxyl group which is readily acetylated, and they occur in the forms of the diastereoisomeric quaternary N(b)-salts. By the X-ray analysis of their methiodides,[6b,c,d] one of them was shown to have β-oriented N(b)-Me being *trans* to C_{15}-substituent, and the other was indicated to have α-oriented N(b)-Me which is *cis* to C_{15}-substituent. Then the former was named as hunterburnine β-methiodide and the latter as hunterburnine α-methiodide, which have been represented by IIb and IIa, respectively. In the NMR-spectra of

1) Part VIII: Y. Ban and T. Kimura, *Chem. Pharm. Bull.* (Tokyo), **16**, 549 (1968).
2) Location: *Kita-12-jo, Nishi-6-chome, Sapporo, Hokkaido*; *a*) Present address: *Governmeni Industtral Development Laboratory, Hokkaido, 41-2 Higashi-tsukisamu, Sapporo, Hokkaido.*
3) M. Raymond-Hamet, *Compt. Rend.*, **244**, 2991 (1957).
4) A. Engelhardt and H. Gelbrecht, *Naturwissenschaften*, **45**, 547 (1959); *Arzneimittel Forsch.*, **11**, 414 (1961).
5) R.H.F. Manske, "The Alkaloids, Vol. VIII. The Indole Alkaloids," Academic Press, New York, N.Y., 1965, Chapter 11.
6) *a*) M.F. Bartlett, B. Korzun, R. Sklar, A.F. Smith and W.I. Taylor, *J. Org. Chem.*, **28**, 1445 (1963); *b*) J.D.M. Asher, J.M. Robertson, G.A. Sim, M.F. Bartlett, R. Sklar and W.I. Taylor, *Proc. Chem. Soc.*, **1962**, 72; *c*) C.C. Scott, G.A. Sim and J.M. Robertson, *ibid.*, **1962**, 355; *d*) J.D.M. Asher, J. M. Robertson and G.A. Sim, *J. Chem. Soc.*, **1965**, 6355.
7) E. Schlittler and W.I. Taylor, *Experientia*, **16**, 244 (1960).

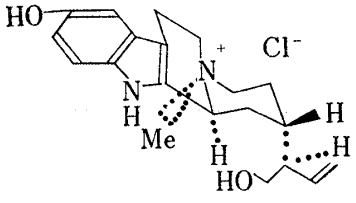
hunterburnine methochlorides, β-isomer involves its N-methyl proton signal at 6.69τ and α-isomer shows it at 6.53τ,[6a] which is well in accord with the known observations[8,9] and the above conclusion that the former has *trans*-fusion at C/D-ring juncture, while the latter has *cis*-fusion at the same position. The absolute stereochemistry shown in (IIa and IIb) is only based on the biogenesis and the assumption that the rule[10] of uniform absolute stereochemistry of the substituent at C-15 of yohimbine and at the corresponding position of emetine[11] should be valid in this case.



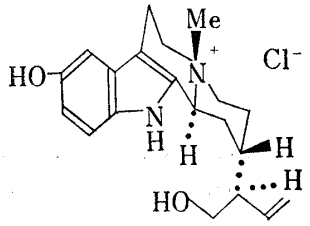
Ia : Me=α (hunterburnine
Ib : Me=β methochloride)



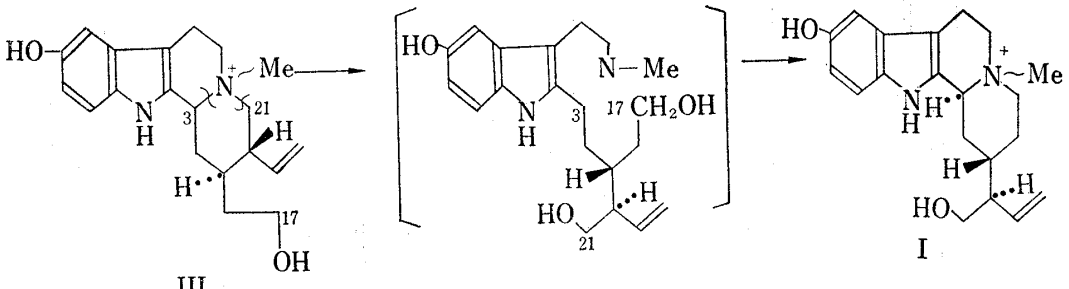
IV (vallesiachotamine)



IIa



IIb



III I

Chart 1

It is worthy to note the fascinating proposal by Taylor, *et al.* on the biogenesis that the skeleton of hunterburnine metho-salts (I) could be derived from that of the quaternary corynantheol type of compound (III). The similar hypothesis was proposed by Djerassi, *et al.* with vallesiachotamine (IV), an alkaloid isolated from Vallesia dichotoma Ruiz et Pav.[12]

Thus, we tried to synthesize 10-desoxy-18,19-dihydro-hunterburnine metho-salt (V) as an approach to the total synthesis of these alkaloids.[13] After many fruitless experiments

8) T.M. Moynehan, K. Schofield, R.A.Y. Jones and A.R. Katritzky, *J. Chem. Soc.*, **1962**, 2637.
9) M. Shamma and J.M. Richey, *J. Am. Chem. Soc.*, **85**, 2507 (1963).
10) E. Wenkert and N.V. Bringi, *J. Am. Chem. Soc.*, **81**, 1474, 6535 (1959).
11) Y. Ban, M. Terashima and O. Yonemitsu, *Chem. Ind.* (London), **1959**, 569; M. Terashima, *Chem. Pharm. Bull.* (Tokyo), **8**, 517 (1960) and references cited therein.
12) C. Djerassi, H.J. Monteiro, A. Walser and L.J. Durham, *J. Am. Chem. Soc.*, **88**, 1792 (1966).
13) In connection with the present synthesis, it should be referred to the syntheses of eburnamine group of alkaloids which were accomplished by Wenkert, *et al.* [E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, **87**, 1580 (1965)] and Harley-Mason, *et al.* [J.E.D. Barton and J. Harley-Mason, *Chem. Commun.*, **1965**, 298], and also seco-corynantheol group of compound was synthesized by Yamada and Shioiri [S. Yamada and T. Shioiri, *Tetrahedron Letters*, **1967**, 351].

including the extensive application of our own method,[1] the oxidative cyclizations developed by Wenkert and his co-workers[14] were adopted with success for this purpose.

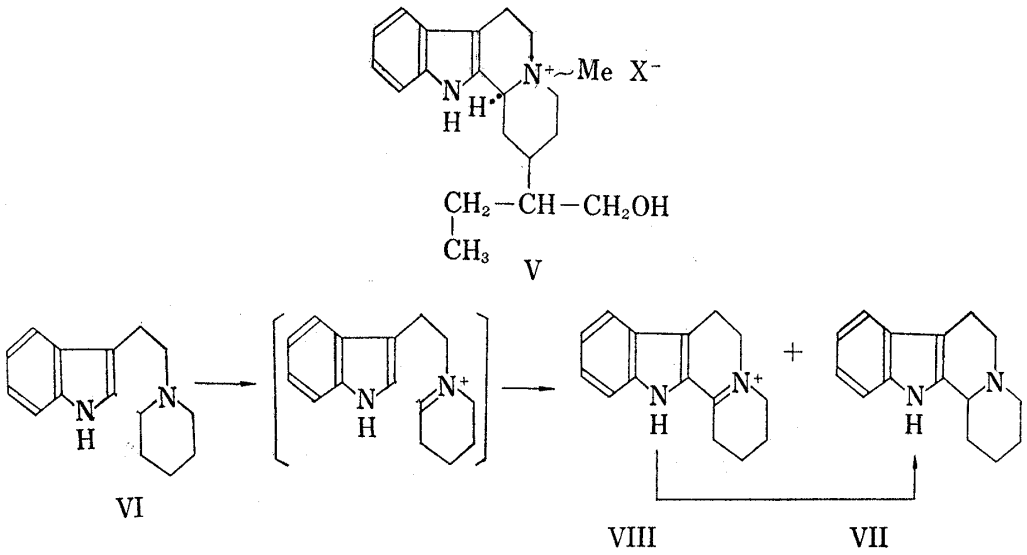


Chart 2

As a preliminary experiment to get an optimum condition of this reaction,[14] the tertiary base (VI) was treated with mercuric acetate under various conditions and the best result

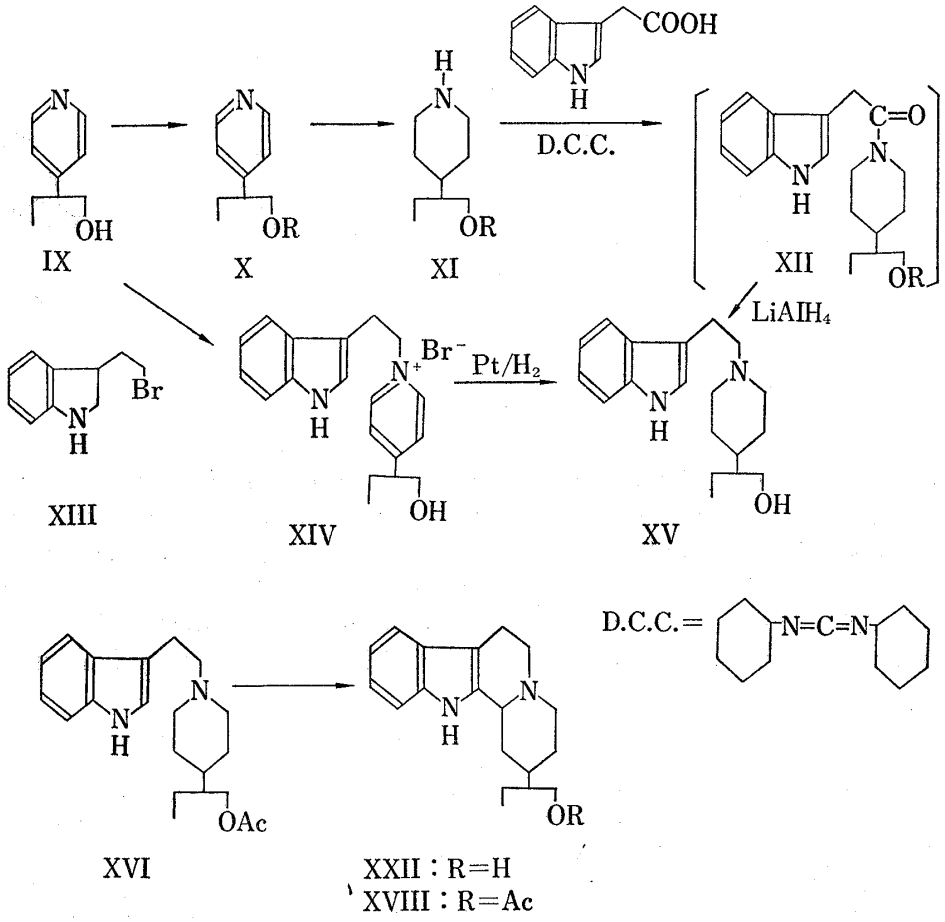


Chart 3

14) E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, **84**, 4914 (1962).

was obtained when the base (VI) was heated with 10 moles of mercuric acetate at 110—118° for 2.5 hours under nitrogen. The reaction mixture was deduced to be mostly the quaternary base (VIII) by its UV spectrum. After the reduction with sodium borohydride, the crystalline solids were obtained in about 50% yield from the mixture by chromatographic separation on alumina. This crystal was identified with the tetracyclic amine (VII) by the behavior of the thin-layer chromatography, the mixed melting point test and IR comparison.

As a key intermediate for the present synthesis, N-[β-(3′-indolyl)ethyl]-4-(1-hydroxymethyl-propyl)piperidine (XV) was prepared from 2-(4-pyridyl)butanol (IX)[15] by two methods; one *via* the amide (XII) which was obtained from the piperidine derivative (XI; R =PhCO) by the condensation with indole-3-acetic acid [IX→X→XI→XII→XV] and the other *via* the quaternary salt (XIV) [IX→XIV→XV]. The latter is more favorable in respect of the reaction time, the yield and so on. The alcohol (XV) was obtained as colorless small needles melting at 140.0—140.5° and its structure was confirmed by NMR- (as its acetate in Fig. 5*a*) and mass-spectra (Fig. 2a)

The acetyl derivative (XVI), which was prepared in the usual manner from XV and determined its structure by the thin layer chromatography, NMR- (Fig. 5a) and IR spectra, was submitted to the oxidative cyclization by the above procedure to afford the tetracyclic compound (XVII) as feathery needles melting at 196.8—197.8° along with the recovered starting material as the alcohol (XV, in 44.3%). The corresponding acetate (XVIII) was obtained in the usual manner as small prisms melting at 142.0—143.0°, and characterized by elemental analyses, NMR- (Fig. 5b) and mass-spectra (Fig. 3). The structure of the product was confirmed in the following.

At first, it is significant to point out on the thin layer chromatography[16] that the cyclized

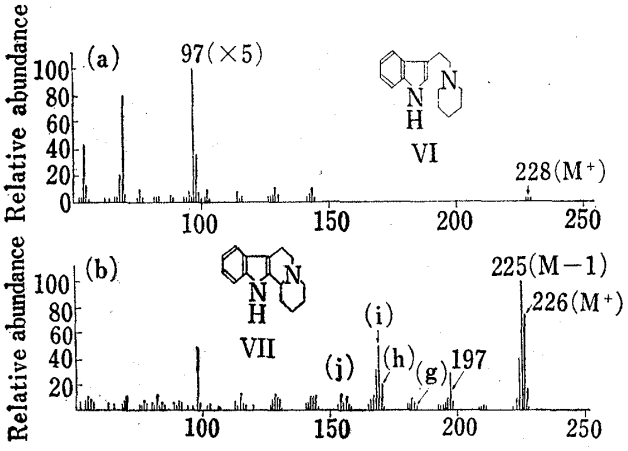


Fig. 1

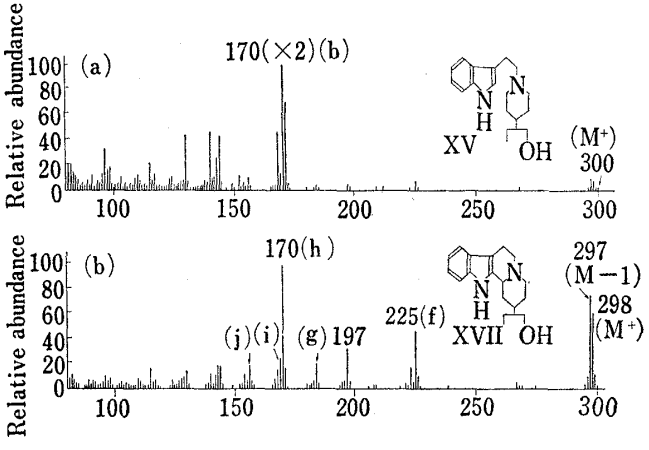


Fig. 2

compounds (VII, XVII and XVIII) in this series show higher *Rf*-values compared with the starting materials (VI, XV and XVI, respectively) without exception.

There is the common difference between the mass-spectra of the starting materials (Fig. 1a and 2a) and those of the tetracyclic products (Fig. 1b, 2b and 3) in

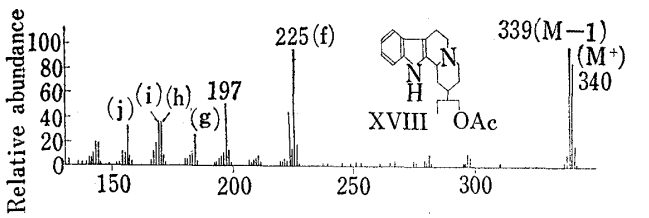


Fig. 3

15) M. Pailer and G. Beier, *Monatsh. Chem.*, **88**, 830 (1957).

16) The adsobent used in this experiment is Merck Alumina-G for Thin-Layer Chromatography. Solvents are:(A) petroleum ether–dichloromethane–ethanol (3 ml: 8 ml: 5 drops) for VI and VII, (B) benzene–acetone (2:1) for XV and XVII, and (C) benzene–acetone (7:3) for XVI and XVIII.

Table I. The Relative Abundance of the Major Ion Peaks over $m/e=156$

	M+	M−1	$m/e=225$	$m/e=197$	$m/e=184$	$m/e=170$	$m/e=169$	$m/e=156$
VI	—	—	—	—	—	—	—	—
XV	—	—	—	—	—	$100\times2^{a)}$	$6^{a)}$	5
VII	76	100		30	6	22	50	12
XVII	63	77	47	32	11	$100^{b)}$	$25^{b)}$	20
XVIII	86	100	95	52	27	37	37	33

a) These ions may be caused to the fragments(b) and (d), respectively
b) These ions may be caused to the fragments (h) and (i), respectively.

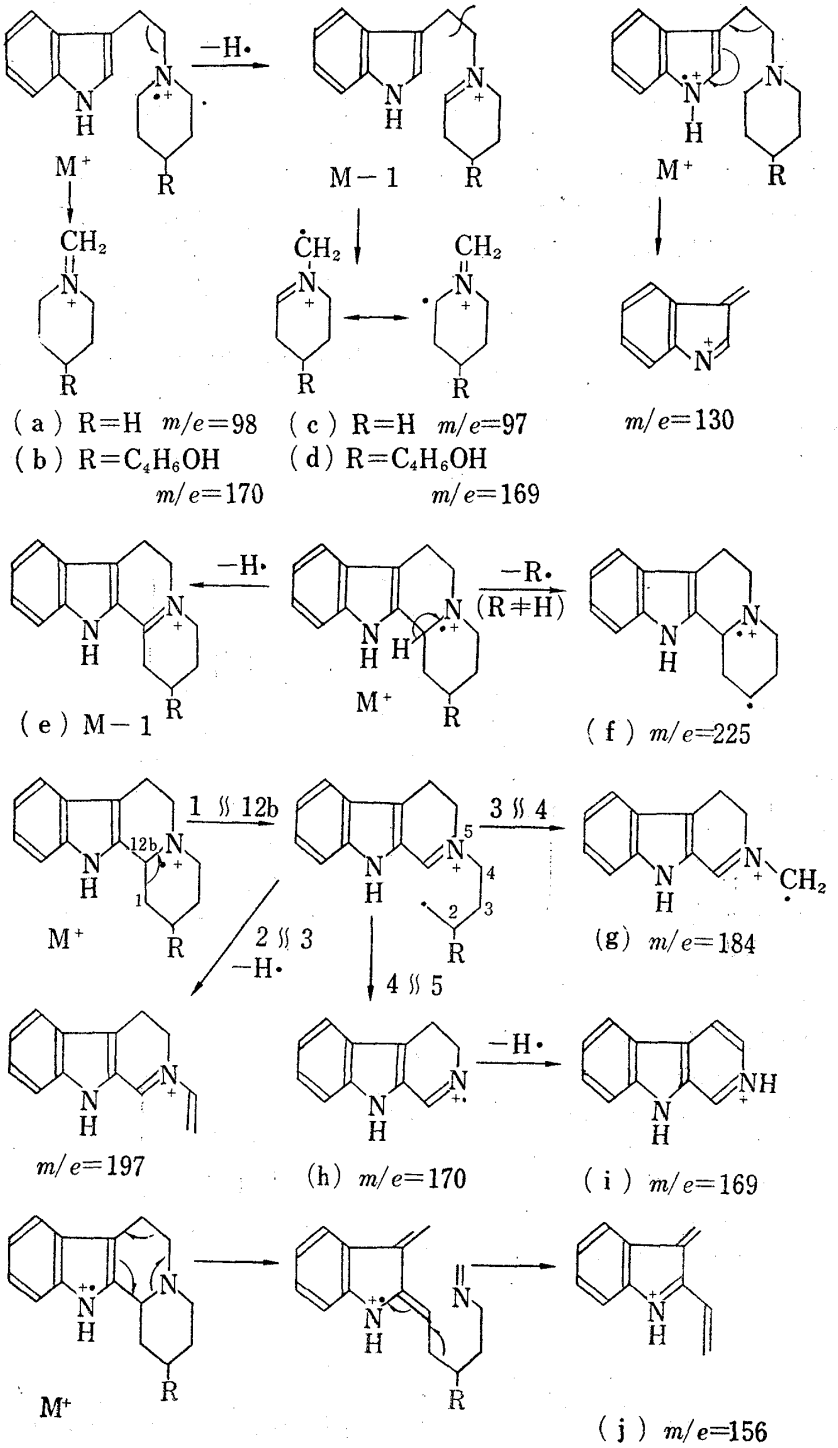


Chart 4

terms of molecular ion peaks and (M–1) ion peaks, as are tabulated in Table I. With the starting materials of the uncyclized series, fragments (b; m/e=170) and (c; m/e=97) (see Chart 4) were most abundant ones, while in the tetracyclic compounds of the cyclized series, the (M–1) ions and the fragment (h; m/e=170) were most intensive peaks. And with the above obtained tetracyclic series there were observed the fragments [(M–1), m/e=184 (g), 170 (h), 169 (i) and 156 (j)] characteristic of the tetrahydro-β-carbolines as Djerassi pointed out[17] for the establishment of the structures of the products (VII, XVII and XVIII).

On comparison of the NMR-spectra[18] of the starting materials (see Fig. 4a and 5a) with the tetracyclic products (see Fig. 4b and 5b), the formers showed the signals at 3.02τ (Fig. 4a) and 3.15τ (Fig. 5a), while these signals disappeared with the latters (Fig. 4b and 5b). As

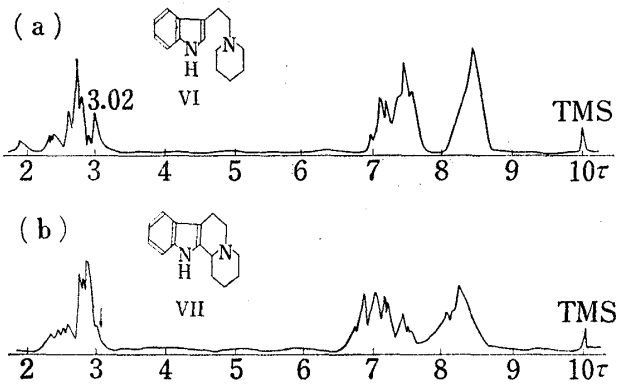


Fig. 4

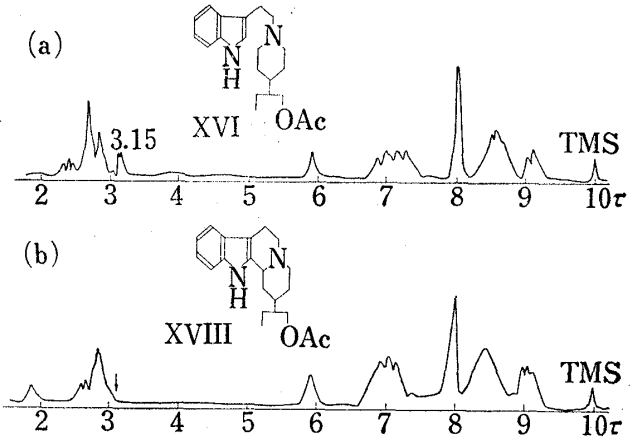
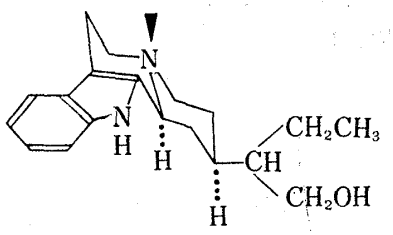


Fig. 5

the indole is known to involve a signal of its α-proton at 3.00—3.30τ,[19a] the present signals at 3.02 τ and 3.15τ in the starting materials may be assigned to the proton at the same position, respectively, and the disappearance of these signals indicates that the compounds (VII and XVIII) were cyclized at the α-position of indole nucleus. Moreover, there was not observed any signal of the angular proton characteristic of *cis*–quinolizidines[19b] pointed out by Brossi, *et al.* which suggests that the present compounds could be of *trans*–quinolizidine type.

For further confirmation of this point, the acetate (XVIII) was oxidized with mercuric acetate at 80° for 6 hours, on which the UV-spectrum of the reaction mixture showed the absorption at 355 mμ instead of 280 mμ at the initial solution. The resulting solution was again reduced with sodium borohydride and saponified to yield the alcohol (XVII) in a yield of 50% and identified with the tetracyclic base (XVII) by the thin layer chromatography, the mixed mleting point test and IR comparison. These results confirm that the acetate (XVIII) should be the tetracyclic compound whose C/D-ring juncture was not changed after and before the oxidation process, and that it should be of *trans*-quinolizidine type. This assignment was supported by the Bohlmann bands[20] observed at 2800 and 2740 cm^{-1}.



XIX

Chart 5

17) H. Budzikiewicz, C. Djerassi and D.H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry, Vol.I, Alkaloids," Holden-Day, Inc., 1964, p. 81.
18) The NMR spectra were obtained with deuteriochloroform solution on a Varian model A-60 spectrometer with tetramethylsilane as internal standard.
19) *a*) L. A. Cohen, J.W. Daly, H. Kny and B. Witkop, *J. Am. Chem. Soc.*, **82**, 2184 (1960); *b*) M. Uskoković, H. Bruderer, C. von Planta, T. Williams and A. Brossi, *ibid.*, **86**, 3364 (1964).
20) F. Bohlmann, *Angew. Chem.*, **69**, 641 (1957); *Ber.*, **91**, 2157 (1958).

Thus, we propose the formula (XIX) to represent the stereochemistry of our synthetic *dl*-10-desoxy-18,19-dihydro-15-*epi*-hunterburnine (XVII), in which the substitutent at C-2 [C-15 of hunterburnine methosalts] occupies the equatorial position because of its stable character being different from that of the natural alkaloids.

Subsequently, for the synthesis of dihydro-hunterburnine (XX), which was reported by Taylor and his co-workers[6b] as its methochloride, 5-benzyloxy-tryptophol (XXI)[21] was converted to the corresponding bromide (XXII). Without purification the bromide (XXII) was submitted to the condensation with 2-(4-pyridyl)butanol (IX) giving the quaternary salt (XXIII) as yellow needles melting at 178—180° (decomp.) in 30% yield, which in turn, was

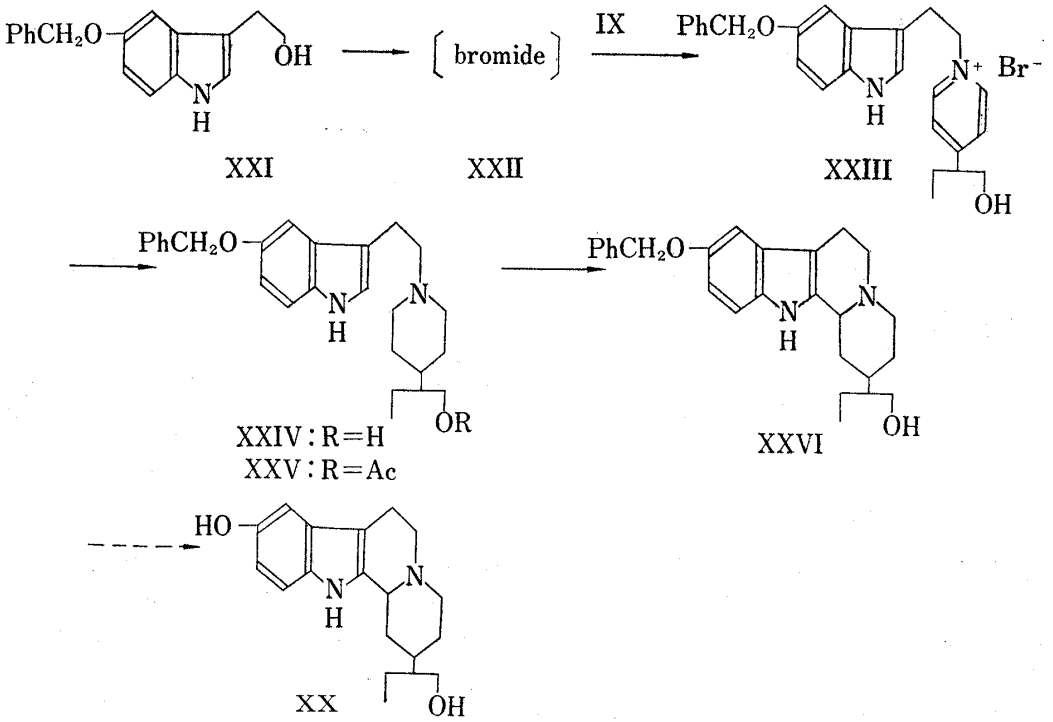


Chart 6

transformed to the piperidine derivative (XXIV), characterized as the hydrochloride, mp 207—210° (decomp.), with sodium borohydride reduction followed by catalytic hydrogenation. A direct hydrogenation of the quaternary salt (XXIII) with Adams' catalyst, which has been effective with the preliminary compound (XIV), afforded the desired product in a very low yield along with others.

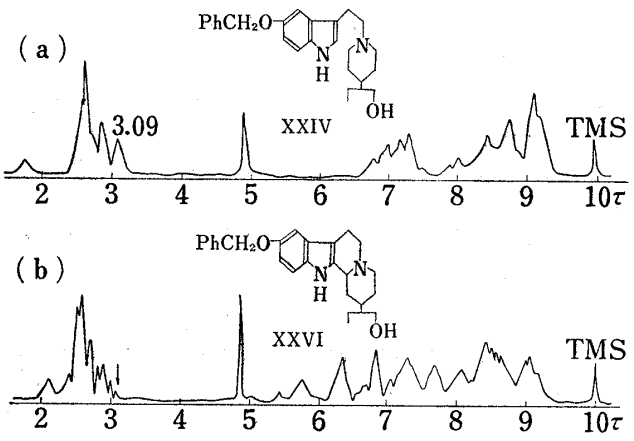


Fig. 6

The tertiary base (XXIV) was converted into the corresponding acetate (XXV) in the usual manner, and the acetate (XXV) so obtained was oxidized with 10 moles of mercuric acetate at 105—110° for 2 hours. After the treatment described before, the products were purified by alumina chromatography to afford the recovered starting material as the alcohol (XXIV) in 47.4% along with the new base as small-needles, mp 156—158°, in 9.3% yield.

21) J. Koo, S. Avakian and G.J. Martin, *J. Org. Chem.*, **34**, 496 (1951).

On inspection of the NMR-spectrum of the latter product (Fig. 6b), the patterns near 3.0τ are not clearly distinguishable from the proton signals of benzyloxy group, but the signal of α-proton of indole (3.09τ in Fig. 6a) was hardly observed indicating along with the elemental analyses that the cyclization may be successful. The efforts to obtain the final product, dihydro-hunterburnine (XX), are in progress.

Experimental[22]

Mercuric Acetate Oxidation of N-[β-(3-Indolyl)ethyl]piperidine (VI) to 1,2,3,4,6,7-Hexahydro-12*H*,12*bH*-indolo[2,3-α]quinolizine (VII)——A solution of the base (VI; 251 mg, 1.1 mmoles) and mercuric acetate (3.506 g, 11.0 mmoles) in 5% acetic acid (30 ml) was heated at 110—118° (bath temperature) for 2.5 hr under nitrogen and treated with hydrogen sulfide for 1 hr at the same temperature. After filtration of the mixture through cellulose powder and careful washings of the filter cake with diluted acetic acid, the combined filtrates were concentrated to dryness and the residue was again dissolved in 50% aqueous EtOH (30 ml). The pH was brought to 6—7 with solid $NaHCO_3$, to which was added 200 mg of sodium borohydride and the mixture was left at room temperature overnight. The solution was acidified with HCl and concentrated to a small volume, separating a small amount of the undissolved tar. After removal of the tar, the filtrate was extracted with benzene. The acidic aqueous layer was made alkaline with K_2CO_3 giving a crystalline precipitate (fraction A) which was filtered and washed with a small amount of water. The filtrate and washings were combined, made alkaline with NaOH, and the resulting solution was distilled. The distillate had a strong smell of piperidine. The residue was extracted with $CHCl_3$ and the fraction A was combined with the $CHCl_3$ extract, washed with water and dried over K_2CO_3. The whole extract was filtered through alumina (2 g) and concentrated to yield 155 mg of the crude material as crystals. Recrystallization from *n*-hexane gave 125 mg (50.2%) of pale yellow small prisms, mp 151—152° (lit.[23] mp 152—153°). These crystals were identical with 1,2,3,4,6,7-hexahydro-12*H*,12*bH*-indolo[2,3-*a*]quinolizine (VII) by the mixed melting point test, IR comparison and thin-layer chromatography.

2-(4-Pyridyl)butyl Acetate (X; R=Ac)——2-(4-Pyridyl)butanol (IX; 3.024 g) was acetylated with acetic anhydride (6 ml) and pyridine (15 ml) at room temperature. After decomposition with ice-water, the precipitates were taken up in benzene. The benzene was evaporated and the residue was purified by distillation to give yellow syrup, bp 105—107° (3 mmHg), in 84.2% yield. *Anal.* Calcd. for $C_{11}H_{15}NO_2$: C, 68.36; H, 7.82; N, 7.25. Found: C, 68.59; H, 8.04; N, 7.03. IR ν_{max}^{film} cm^{-1}: 1742, 1602.

2-(4-Pyridyl)butyl Benzoate (X; R=PhCO)——2-(4-Pyridyl)butanol (3.320 g) was benzoylated with benzoyl chloride (3.810 g) and pyridine (30 ml) by Schotten-Baumann method. Worked up in the usual manner, it afforded pale yellow syrup, bp 153—155° (2 mmHg), in 54.6% yield. *Anal.* Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.05; H, 6.95; N, 5.54. IR ν_{max}^{film} cm^{-1}: 1727, 1603.

Catalytic Hydrogenation of the Acetate (X; R=Ac)——A solution of the foregoing acetate (2.88 g) in EtOH (50 ml) containing 2 ml of concentrated HCl was hydrogenated over 100 mg of Adams' catalyst under 40 lbs of hydrogen as the initial pressure at room temperature. After 12 hr, absorption of hydrogen ceased, but the solution was yet yellowish. Then further 200 mg of Adams' catalyst was added, and again hydrogenated at room temperature under atmospheric pressure. After 2 hr the catalyst was filtered off and the filtrate was concentrated to give the crystalline hydrochloride. Recrystallization from acetone-EtOH afforded 2.55 g (88.5%) of the piperidine-alcohol (XI; R=H) hydrochloride as colorless hygroscopic scales, mp 118—119°. The IR spectrum indicated that the ester bond was hydrolysed during the hydrogenation. *Anal.* Calcd. for $C_9H_{19}ON \cdot HCl$: C, 55.80; H, 10.41; N, 7.23. Found: C, 55.90; H, 10.56; N, 7.02.

This hydrochloride was converted to its free base as a colorless oil, bp 113—115° (3 mmHg), with a large amount of residue. *Anal.* Calcd. for $C_9H_{19}O_2N$: C, 68.77; H, 12.13; N, 8.91. Found: C, 69.11; H, 12.41; N, 8.77. IR ν_{max}^{film} cm^{-1}: 3300 (broad), 2760, 2600 (1742 disappeared).

2-(4-Piperidyl)butyl Benzoate (XI; R=PhCO)——A solution of the foregoing benzoate (X; R=PhCO, 2.29 g) in EtOH (60 ml) containing 1 ml of concentrated HCl was hydrogenated over 340 mg of Adams' catalyst under atmospheric pressure of hydrogen at room temperature for 10 hr. After filtration of the catalyst the solvent was removed to give the hydrochloride as an almost colorless solid, but its melting point was not determined because of its hygroscopic character. The hydrochloride was dissolved in water, made alkaline with Na_2CO_3 and extracted with ether. The solvent was removed and the residue was distilled to give 1.75 g (75.0%) of a colorless oil, bp 152—157° (2 mmHg). *Anal.* Calcd. for $C_{16}H_{23}NO_2$: C, 73.50; H, 8.87; N, 5.36. Found: C, 73.37; H, 9.05; N, 5.73. IR ν_{max}^{film} cm^{-1}: 2790, 2720, 1724.

N-[β-(3'-Indolyl)ethyl]-4-(1-hydroxymethyl-propyl)pyridinium Bromide (XIV)——A solution of 3-(2-bromoethyl)indole (XIII; 2.24 g, 10 mmoles) and 2-(4-pyridyl)butanol (IX; 1.51 g, 10 mmoles) in absolute

22) All melting points are not corrected.
23) Y. Ban and M. Seo, *Tetrahedron*, 16, 5, 11 (1961).

benzene (10 ml) was heated at 90±2° for 7 hr under nitrogen atmosphere. On cooling, absolute ether was added to the reaction mixture, and the separated quaternary salt was washed with ether and dried *in vacuo*. The quaternary bromide (3.63 g, 96.8%) was obtained as a brown viscous oil and was not crystallized from any solvents, but the crude quaternary bromide was used directly in the next step.

N-[β-(3′-Indolyl)ethyl]-4-(1-hydroxymethyl-propyl)piperidine (XV)——a) *Via* the Amide (XII) resulted from the Condensation of Indole-3-acetic Acid with the Benzoyl-Ester (XI; R=PhCO): To a solution of indole-3-acetic acid (930 mg, 5.36 mmoles) and N,N′-dicyclohexylcarbodiimide (1.238 g, 6.0 mmoles) in absolute benzene (80 ml) was added a solution of the above obtained benzoyl-ester (XI; R=PhCO, 1.352 g, 5.17 mmoles) in the same solvent (10 ml), and the mixture was allowed to stand at room temperature for 45 hr. The resultant N,N′-dicyclohexylurea was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in EtOAc, and the solution was treated with 5% AcOH to remove more of the urea. The solution was washed successively with 10% HCl, saturated $NaHCO_3$, and water and dried over Na_2SO_4. Removal of the solvent afforded 2.695 g of a brown residue which was reduced in the next step without purification.

To a suspension of $LiAlH_4$ (2.00 g) in absolute ether (125 ml) and tetrahydrofuran (75 ml) was slowly added a solution of the above amide (XII, 2.695 g) in absolute tetrahydrofuran (60 ml) under ice-cooling with stirring. The mixture was stirred for further 1 hr and allowed to stand at room temperature overnight. The mixture was refluxed gently for 14 hr, and moist Na_2SO_4 was added to the mixture to decompose the excess $LiAlH_4$ and Li-complex. After filtration and evaporation of the solvent, the residue was dissolved in EtOAc and extracted with 10% HCl. The aqueous layer was made alkaline with K_2CO_3, the separated oil was extracted with EtOAc, and worked up in a usual manner. The solvent was removed and the remaining solids were recrystallized from benzene to give 984 mg (63.3%) of small needles, mp 140.0—140.5°. *Anal.* Calcd. for $C_{19}H_{28}ON_2$: C, 75.95; H, 9.39; N, 9.33. Found: C, 75.80; H, 9.20; N, 9.11. IR ν_{max}^{KBr} cm^{-1}: 3200 (broad), 2800—2700 (broad); $\nu_{max}^{CHCl_3}$ cm^{-1}: 3490, 2800, 2760. NMR (in $CDCl_3$)τ: 3.08 (1H, α-proton of indole). Mass spectrum: Fig. 2a.

b) *Via* the Quaternary Bromide (XIV): A solution of the quaternary bromide (XIV; 3.93 g) in EtOH (60 ml) was hydrogenated over Adams' catalyst (300 mg) at room temperature under 45 lbs pressure of hydrogen. After 4 hr the absorption of hydrogen ceased, the catalyst was filtered off and the solution was evaporated. The residue was dissolved in water and the solution was made alkaline with K_2CO_3. The separated oil was taken up in EtOAc, and washed with water and dried. Removal of the solvent left 2.85 g of semi-solids, which were recrystallized from absolute benzene to give 2.14 g [74.6% yield based on 3-(2-bromoethyl)indole] of colorless small needles, mp 139.0—140.0°. These needles were identical with the compound obtained *via* the (*a*) method by mixed melting point test, thin layer chromatography and IR comparison.

10-Desoxy-18,19-dihydro-15-*epi*-hunterburnine (XVII) by Mercuric Acetate Oxidation Method[14]——N-[β-(3′-Indolyl)ethyl]-4-(1-hydroxymethyl-propyl)piperidine (XV; 2.43 g) was acetylated with acetic anhydride (14 ml) and pyridine (28 ml) at room temperature. The obtained acetate (XVI) was purified through neutral alumina column to afford 2.36 g (85.8%) of a pale brown viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520, 3470, 2780, 2740, 1730. NMR (in $CDCl_3$)τ: 3.15 (1H, α-proton of indole), Fig. 5a. This acetate was submitted to the following reaction without further purification because of difficulties in its crystallization.

A solution of the above acetate (XVI, 1.31 g, 3.83 mmoles) and mercuric acetate (12.19 g, 38.3 mmoles) in 10% AcOH (20 ml) and EtOH (8 ml) was heated with stirring at 105—110° (bath temperature) for 2 hr in a current of nitrogen, and treated with hydrogen sulfide for 2 hr at the same temperature. After filtration of the mixture through cellulose powder and careful washing of the filter cake with a mixture of aqueous AcOH–EtOH (1:1) the combined filtrates were evaporated to dryness. The residue was dissolved in aqueous EtOH, the pH was brought to about 7 with $NaHCO_3$, sodium borohydride (500 mg) was added, and the mixture was allowed to stand at room temperature overnight. The reaction mixture was made alkaline with KOH, heated at 80° for 3 hr and EtOH was removed *in vacuo*. The precipitates were extracted with EtOAc, washed with water and dried over Na_2SO_4. Evaporation of the solvent gave 1.15 g of the brown residue, which was mixed with alumina (10 g) and was settled on the top of alumina column (50 g) for the chromatographic separation. Elution with 1% EtOH–benzene yielded 151 mg of crystals melting at 195.0—197.0° (fraction A), while continued elution with the same solvent yielded 510 mg of crystals melting at 138—140° (fraction B).

The fraction B gave colorless small needles, mp 139.0—140.0°, after recrystallization from benzene and was identical with the starting alcohol (XV) by the mixed melting point test, thin layer chromatography and IR comparison.

The fraction A was recrystallized from absolute benzene to give colorless needles, mp 196.8—197.8°, in 12.5% yield (143 mg). *Anal.* Calcd. for $C_{19}H_{26}ON_2$: C, 76.50; H, 8.78; N, 9.39. Found: C, 76.26; H, 8.64; N, 9.04. IR ν_{max}^{KBr} cm^{-1}: 3400, 3230 (broad), 2800, 2740; $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 3300 (broad), 2800, 2750. Mass spectrum: Fig. 2b.

Acetyl Derivative (XVIII)——A mixture of the above obtained alcohol (XVII, 80 mg), acetic anhydride (1 ml) and pyridine (2 ml) was left at room temperature for 48 hr and worked up in a usual manner. Re-

crystallization from *n*-hexane gave pale yellow small prisms, mp 142—143° (decomp.), in 80% (73 mg) yield. *Anal.* Calcd. for $C_{21}H_{28}O_2N_2$: C, 74.07; H, 8.29; N, 8.23. Found: C, 73.97; H, 7.97; N, 8.02. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 2800, 2740, 1730. NMR (in $CDCl_3$) τ: Fig. 5b. Mass spectrum : Fig. 3.

3-(2-Bromoethyl)-5-benzyloxy-indole (XXII)——To a solution of (5-benzyloxy-3-indolyl)ethanol (XXI; 1.6 g) in absolute ether (200 ml) was added dropwise 0.6 g of PBr_3 under ice cooling with stirring and the mixture was stirred at −5° for additional 1 hr, and kept in a refrigerator overnight. The ether layer was decanted from the residue and washed successively with $NaHCO_3$, water and dried over Na_2SO_4. Removal of the solvent under reduced pressure below 20° in a current of nitrogen gave pale-pink semi-solids which were darkened and resinified on a short storage. This bromide (XXII) was used in the next step immediately after removal of the solvent.

N-[β-(5′-Benzyloxy-3′-indolyl)ethyl]-4-(1-hydroxymethyl-propyl)-pyridinium Bromide (XXIII)——A solution of the above obtained crude bromide (XXII; 1.6 g) and 2-(4-pyridyl)-butanol (IX; 1.6 g) in absolute benzene (10 ml) was gently refluxed in a current of nitrogen for 10 hr. After removal of the solvent the resultant was dissolved in EtOH, and the solids were separated by addition of EtOAc. The yellow precipitates were collected and recrystallized from EtOH–EtOAc to afford 902 mg (38.7%) of yellow prisms, mp 178—180° (decomp.). *Anal.* Calcd. for $C_{26}H_{29}O_2N_2Br$: C, 64.86; H, 6.07; N, 5.82. Found: C, 65.03; H, 5.91; N, 5.76. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520, 3300 (broad), 1640, 1623, 1583.

N-[β-(5′-Benzyloxy-3′-indolyl)ethyl]-4-(1-hydroxymethyl-propyl)-piperidine (XXIV)——To a solution of the foregoing quaternary bromide (XXIII; 800 mg) in MeOH (50 ml) was added a solution of sodium borohydride (630 mg) in MeOH (25 ml) under ice cooling with stirring in a period of 15 min. The mixture was stirred for further 2 hr, allowed to stand at room temperature overnight, and worked up in a usual manner. The basic components were taken up in ether, the solvent was removed *in vacuo*, and the residue was hydrogenated over 200 mg of Adams' catalyst in EtOH at room temperature and at atmospheric pressure of hydrogen. After 2 hr the catalyst was filtered off and the filtrate was concentrated. The residue was purified through alumina column to give 595 mg (88.0%) of a yellow viscous oil. Recrystallization from any solvents was unsuccessful, but it was identified with the desired compound (XXIV) by their IR- and NMR-spectra. IR ν_{max}^{film} cm^{1}: 3450, 3160, 2800, 2770, 1623, 1585. NMR (in $CDCl_3$) τ: Fig. 6a, 3.09 (1H, α-proton of indole), 4.94 (2H, Ph-CH_2-O-).

Hydrochloride of the base (XXIV) was obtained by the introduction of dry HCl into the ethereal solution of the base (XXIV). Recrystallization from acetone–EtOAc afforded pale-brown small prisms, mp 207—208° (decomp.). *Anal.* Calcd. for $C_{26}H_{34}O_2N_2 \cdot HCl$: C, 70.49; H, 7.96; N, 6.32. Found: C, 70.13; H, 8.29; N, 6.65.

Dihydro-hunterburnine Benzyl Ether (XXVI) by the Mercuric Acetate Oxidation——The above obtained base (XXIV; 900 mg) was acetylated with acetic anhydride (9 ml) and pyridine (9 ml) at room temperature for 40 hr, and worked up in a usual manner the corresponding acetate was obtained as a pale-brown viscous oil in 88% (874 mg) yield. The acetate (XXV) was purified through alumina column, but only obtained as an oil. IR ν_{max}^{film} cm^{-1}: 3440, 2800, 2760, 1745, 1625, 1588.

A mixture of the above acetate (XXV; 791 mg, 1.76 mmoles) and mercuric acetate (5.61 g, 17.6 mmoles) in 10% AcOH (5 ml) and EtOH (5 ml) was heated at 105—110° (bath temperature) for 2 hr in a current of nitrogen, and treated with hydrogen sulfide at the same temperature for 2 hr. After filtration of the mixture through cellulose powder and careful washing of the filter cake with a mixture of 5% AcOH and EtOH (1:1) the combined filtrates were concentrated to dryness and again dissolved in aqueous EtOH (70 ml). The pH was brought to about 7 with $NaHCO_3$,400 mg of sodium borohydride was added and the mixture was allowed to stand at room temperature overnight. To this solution 2.5 g of KOH was added and the whole was heated on a water-bath for 2 hr. After evaporation of EtOH under reduced pressure the separated oil was taken up in EtOAc, on which the extract had a little fluorescence. Worked up as described above, the brown residue was mixed with alumina (7 g) and settled on the top of an alumina column (42 g) for chromatographic separation. Elution with benzene gave 339 mg of a pale brown viscous oil (fraction A), while elution with EtOAc afforded 98 mg of a brown viscous oil (fraction B).

The fraction A was identical with the starting material (XXIV) by its IR spectrum and the thin layer chromatography.

The fraction B was further purified through alumina to give micro needles, mp 156—158°, and recrystallization from benzene did not raise its melting point but rather partly resinified with coloring. This crystalline product (66 mg, 9.3%) wes supposed to be a desired dihydro-hunterburnine benzyl-ether (XXVI) from its IR- and NMR- spectra. *Anal.* Calcd. for $C_{26}H_{32}O_2N_2$: C, 77.19; H, 7.97; N, 6.93. Found: C, 76.80; H, 7.94; N, 6.81. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3490, 3300 (broad), Bohlmann region (weak), 1625, 1586. NMR (in $CDCl_3$) τ: Fig. 6b.

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