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140. Yoshio Ban and Yasuhiko Sato: Studies on the Structures of Some Cholestanoindoles.*1

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During the course of studies on syntheses of aspidosperma alkaloids, attention was turned to the structures of some cholestanoindoles appeared in the literature,[1~3] in connection with the sterospecific control on direction of the Fischer indole synthesis.

In 1909, Dorée discovered the fact that the Fischer indole synthesis readily proceeds on heating phenylhydrazine with 5β-cholestan-3-one (Ⅳ) in acetic acid.[1] In 1935, this observation was extended to the preparation of the 5α-tetrahydrocarbazole derivative from 5α-chlolestan-3-one (Ⅰ), for which product Dorée and Petrow proposed formulation of a cholest-3-eno[3,4-*b*]indole (Ⅱ).[2]

Although this conclusion was reached by surface film measurements which suggested an angular structure, it was revised by Antaki and Petrow to the linear structure (Ⅲ), based upon the known reactivity of C_2-methylene in the 5α-series.[3] They also preferred the angular structure (Ⅴ) for the product obtained from 5β-cholestan-3-one (Ⅳ).

Thus, the structures of these indole derivatives have been only tentatively assigned but generally accepted ever since then, because their formulation is coincident with the direction of enolisation of the starting ketones,[4] which seems reasonable under consideration of a plausible mechanism of the Fischer indole synthesis.[5]

Recently, Warnhoff and NaNonggai[6] investigated the structure of the Schwenk and Whitman's compound (m.p. 230~232°)[7] being obtained from the reaction of 2α,4α-dibromo-5α-cholestan-3-one (Ⅵ) with N,N-dimethylaniline. They demonstrated this compound by the formula (Ⅷ), which was identified with the product from the Fischer indole synthesis with 1-methyl-1-phenyl-hydrazine and cholest-4-en-3-one (Ⅸ). Furthermore, the compound (Ⅷ) was hydrogenated to the two dihydro-compounds, one of which was identical with the product prepared by the Fischer indole synthesis with 5β-cholestan-3-one (Ⅳ).

Consequently, the establishment of the structures of cholestenoindoles (Ⅲ and Ⅴ), must be significant not only for our synthetic purpose, but also in respect of the above correlation works.

Thus, the product of the Fischer indole synthesis with 5β-cholestan-3-one (Ⅳ) was oxidized with ozone in chloroform according to the procedure of Witkop[8] to afford 42% yield of the lactam ketone (Ⅹ), m.p. 235~236°, $[\alpha]_D$ −40°, IR cm^{-1} : ν 1680 (ketone), 1655

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1) C. Dorée: J. Chem. Soc., **1909**, 638; C. Dorée, J. A. Gardner: *Ibid.*, **1908**, 1625.
2) C. Dorée, V. Petrow: *Ibid.*, **1935**, 1391.
3) H. Antaki, V. Petrow: *Ibid.*, **1951**, 901.
4) L. F. Fieser, M. Fieser: "Steroids," Reinfold Publishing Corporation, New York, 1959, p. 282.
5) R. C. Elderfield: "Heterocyclic Compounds," Vol. 3, p. 13, 1960 (John Wiley & Sons, Inc., New York).
6) E. W. Warnhoff, P. NaNonggai: J. Org. Chem., **27**, 1186 (1962).
7) E. Schwenk, B. Whitman: J. Am. Chem. Soc., **59**, 949 (1937).
8) *a*) B. Witkop, J. B. Patrick: J. Am. Chem. Soc., **72**, 614, 633 (1950); **73**, 2188, 2193 (1951) .*b*) B. Witkop, J. B. Patrick, Rosenblum: *Ibid.*, **73**, 2641 (1951).

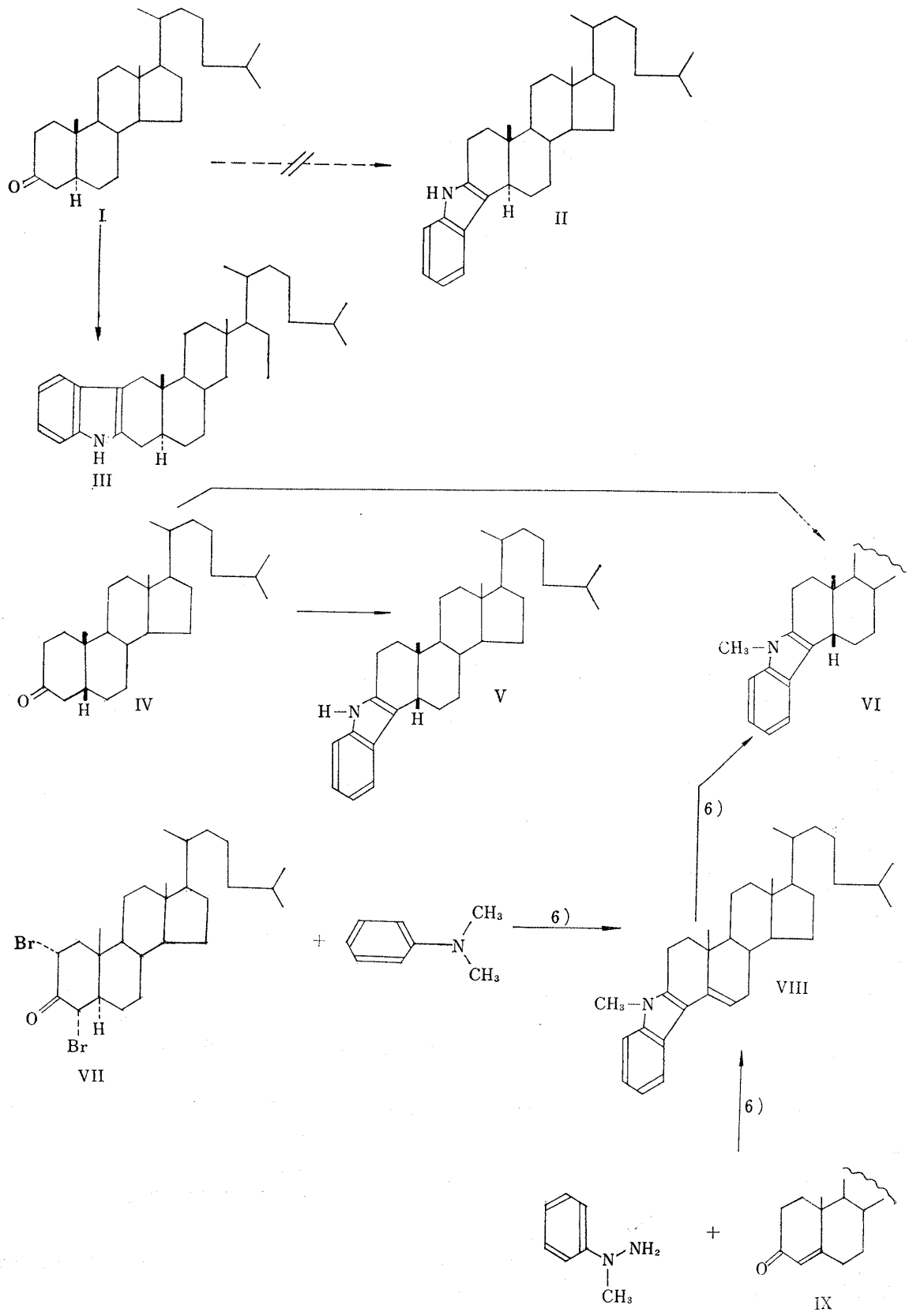

Chart 1.

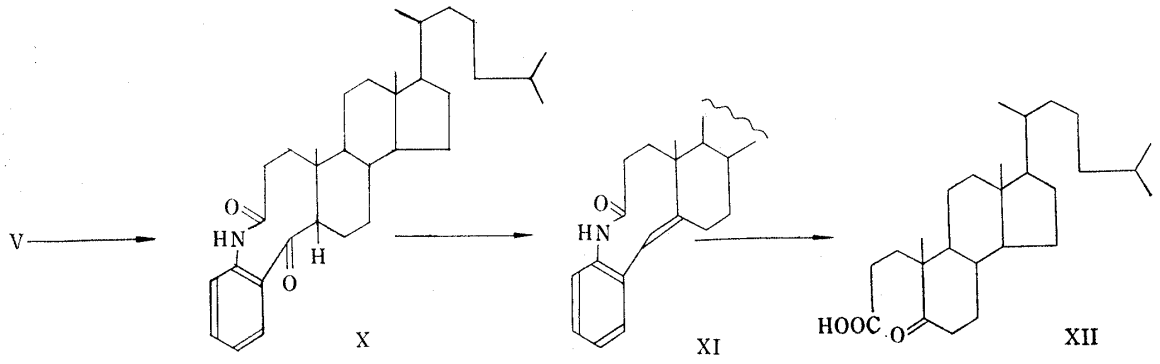

Chart 2.

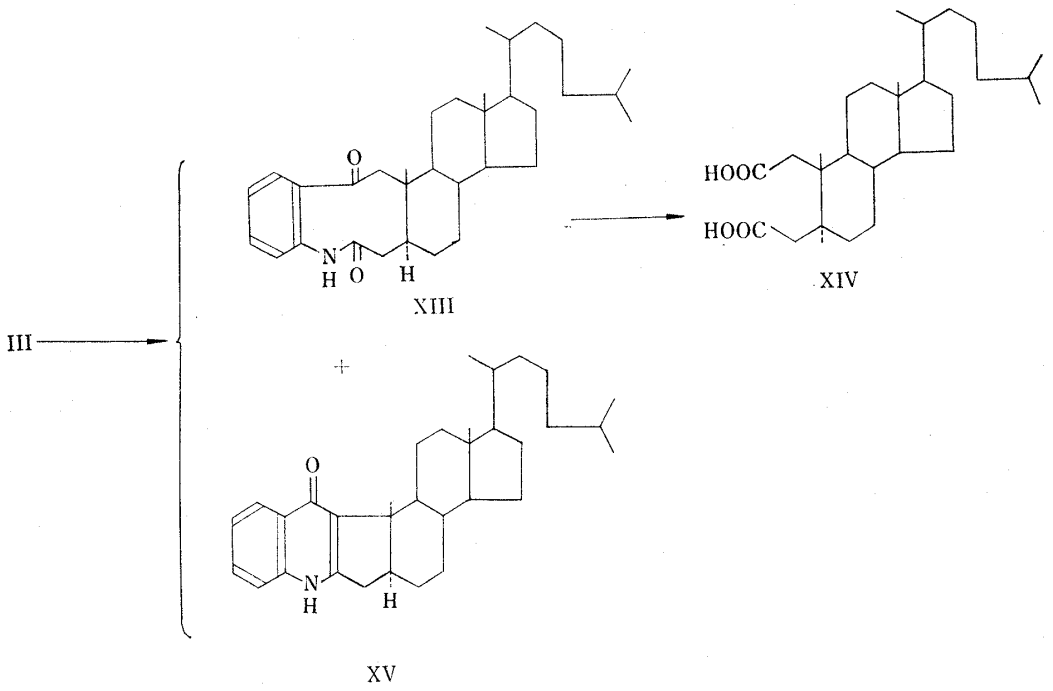

Chart 3.

(lactam), which was reduced with sodium borohydride to afford the unexpected unsaturated lactam (XI), m.p. 205~208°, $[\alpha]_D$ +48°, IR cm^{-1} : ν 1625 (lactam), 1600, 1575 (C=C and phenyl) (the absorption at 1680 cm^{-1} disappeared) in 93.1% yield. The unsaturated lactam (XI) was again oxidized with ozone in acetic acid, and followed by treatment with 20% sodium hydroxide for 20 hr. to afford the seco-norketoacid (XII),[9] m.p. 146~148°, $[\alpha]_D$ +37.1°, which was identified with an authentic sample by mixed melting point determination, infrared spectra and comparison of their specific rotation values.

On the other hand, the indole obtained from 5α-cholestan-3-one (I) was similarly subjected to ozonolysis in chloroform and the crude product was chromatographed on alumina to give two substances, one of which was assigned the linear keto-lactam (XIII), m.p. 234~235°, $[\alpha]_D$ +34°, IR cm^{-1}: ν 1695 (Ar-CO-), 1630(-NHCO-), and the other was deduced to be a quinolone derivative (XV), m.p. 180~183°, $[\alpha]_D$ +66.6°, IR cm^{-1} : ν 1630, UV λ_{max} mμ : 330, 317, which had been produced by intramolecular condensation of XIII with alkaline alumina during chromatography. Each compound was produced in 19% yield, respectively. The former (XIII) was oxidized with 30% hydrogen

9) *a*) R. B. Turner : J. Am. Chem. Soc., **72**, 579 (1950). *b*) W. G. Dauben, H. G. Wight, G. A. Boswell: J. Org. Chem., **23**, 1787 (1958). *c*) R. Tscheshe, Ann., **489**, 185 (1932).

peroxide in acetic acid and followed by hydrolysis to afford the crude acid which was purified by chromatography over silica-gel. This compound (m.p. 188~191°, $[\alpha]_D$ +43.3°) was identified with an authentic sample of Windaus-Uibrig acid (XIV)[10] which was obtained by direct oxidation of 5α-cholestan-3-ol, by mixed melting point test, and by direct comparisons of infrared spectra and specific rotation values.

Thus, the present degradation work has established the structures of cholestanoindoles derived from 5β- (IV) and 5α-cholestan-3-ones (I) as V and III, respectively, which confirms that the orientation of the Fischer indole synthesis with these compounds is in accordance with the direction of enolisation of the starting ketones.

Experimental*3

5β-Cholest-3-eno[3,4-*b*]indole (V)[1,7]——This compound was prepared in 84.6% yield from phenylhydrazine and 5β-cholestan-3-one according to the known procedure.[1,7] The substance was recrystallized from benzene-methanol (1:3) to afford colorless needles, m.p. 193~194.5° (lit., m.p. 192°,[1] m.p. 192~193°[7]); $[\alpha]_D^{17}$ +160.3° (c=1.0, $CHCl_3$); *Anal.* Calcd. for $C_{33}H_{49}N$: C, 86.21; H, 10.74; N, 3.05. Found: C, 86.49; H, 10.87; N, 3.03.

2,3-Dioxo-2,3-seco-5β-cholestano[3,4-*b*]indole (X)——Through a solution of 5β-cholest-3-eno[3,4-*b*]-indole (V, 2.500 g.) in 50 ml. of $CHCl_3$ was passed 3~4% ozone at −15° under an ice-salt cooling for 30 min. After the excess of ozone was expelled by nitrogen, the solvent ($CHCl_3$) was thoroughly evaporated *in vacuo* under a stream of N_2 on a water bath kept at 35~40°. To the residue, ether was added, washed with sodium bicarbonate solution, then with water, and dried over $MgSO_4$, from which the solvent was removed *in vacuo* to leave a yellow brownish caramel. This substance was chromatographed over alumina (50 g.). A main fraction eluted by ethyl acetate afforded a viscous oil, to which was added petr. ether and the whole solution was allowed to stand overnight, depositing 1.152 g. of crystals, m.p. 228~229.5°. These crystals were recrystallized from dioxane-water (5:1) to yield 1.059 g. (42.3%) of colorless scales, m.p. 235~236°, $[\alpha]_D^{22}$ −40.0° (c=1, dioxane). *Anal.* Calcd. for $C_{33}H_{49}O_2N$: C, 80.60; H, 10.04; N, 2.85. Found: C, 80.50; H, 10.19; N, 3.05. IR cm^{-1}: ν 3280 (-NH-); 1680 (C=O), 1655 (-NHCO-), 1600 (arom.).

2-Oxo-2,3-seco-cholest-4-eno[3,4-*b*]indole (XI)——The foregoing keto-lactam (X, 300 mg.) was dissolved in tetrahydrofuran-ethanol (1:1) on warming, to which solution after cooling was added $NaBH_4$ (500 mg.). The resulting mixture was kept at room temperature for 1 hr. and then warmed in a water bath kept at 70° for 3 hr. The solvent was removed *in vacuo* and to the residue 25 ml. of water was added to separate colorless crystals which were collected by filtration. The crude product was recrystallized from benzene to afford 270 mg. (93.1%) of colorless needles, m.p. 205~208°, $[\alpha]_D^{22}$ +48.0° (c=0.5, $CHCl_3$). *Anal.* Calcd. for $C_{33}H_{49}ON \cdot 2H_2O$: C, 77.44; H, 10.44; N, 2.74. Found: C, 76.97; H, 10.89; N, 2.95. IR cm^{-1}: ν 1625 (-NHCO-), 1600, 1575 (conjugated double bond and aromatic bond). UV λ_{max}^{EtOH} mμ (log ε): 241 (3.82), 290 (3.31); λ_{min}^{EtOH} mμ (log ε): 222 (3.57), 266 (2.76).

5-Oxo-3,4-seco-A-norcholestan-3-oic Acid (XII)——Through a solution of the foregoing lactam (XI, 225 mg.) in 15 ml. of glacial acetic acid was passed 3~4% ozone at −15° under an ice-salt cooling for 20 min., during which time the color of the reaction mixture changed into purple, then to orange and to yellow. After ozonolysis, a large excess of ether was added, the ether layer was washed with water to remove the acetic acid, then the acidic substance in ether was transferred into saturated sodium bicarbonate solution. The aqueous layer was acidified, extracted with ether, dried over Na_2SO_4 and the solvent was removed to afford 118 mg. of an acidic substance. This product was refluxed in 8 ml. of 20% NaOH for 20 hr. On cooling, 10 ml. of water was added, acidified with 10% HCl to deposit crystals, which were collected. The crude product (83 mg.) was recrystallized from hexane to yield 41 mg. of colorless needles, m.p. 146~148° (lit. m.p. 152~153°,[9a] m.p. 150~152°,[9b] m.p. 154~154.5°.[9c]), $[\alpha]_D^{17.5}$ +37.1° (c=0.7, $CHCl_3$), which was identified by mixed melting point test, and by direct comparisons of IR and rotation values with an authentic sample obtained from 5α-cholestan-3-one in the usual manner. *Anal.* Calcd. for $C_{26}H_{44}O_3$: C, 77.17; H, 10.96. Found: C, 76.95; H, 11.00.

5α-Cholest-2-eno[3,2-*b*]indole (III)[1,7]——This compound was prepared by the Fischer indole synthesis with phenylhydrazine and 5α-cholestan-3-one (I) in 91.1% yield according to the known procedure.[1,7] $[\alpha]_D^{17}$ +68.0° (c=1, $CHCl_3$). *Anal.* Calcd. for $C_{33}H_{49}N$: C, 86.21; H, 10.74; N, 3.05. Found: C, 86.08; H, 10.70; N, 3.22.

*3 All melting points are uncorrected.

10) *a*) A. Windaus, C. L. Uibrig: Ber., **47**, 2387 (1914); A. Windaus, O. Dalmer: *Ibid.*, 52, 162 (1919); *b*) W. R. Nes, H. Lettée: Ann., **598**, 65 (1956); *c*) R. E. Marker, E. Rohrmann: J. Am. Chem. Soc., **62**, 516 (1940); *d*) S. Hara, N. Matsumoto, M. Takeuchi: Chem. & Ind. (London), **1962**, 2086.

2,3-Dioxo-2,3-seco-5α-cholestano[3,2-*b*]indole (XIII) and A-Nor-5α-cholest-1-eno[2,1-*b*]quinolin-4′(1′*H*)-one (XV)——Through a solution of 5α-cholest-2-eno[3,2-*b*]indole (III, 2.50 g.) in 40 ml. of $CHCl_3$ was passed 3～4% ozone at −15° under an ice-salt cooling for 9 min. After the excess of ozone was substituted for nitrogen gas, the solvent ($CHCl_3$) was thoroughly removed under a stream of N_2 on a water bath kept at 35～40°. To the residue, ether was added, washed with 2% sodium bicarbonate, saturated NaCl solution and dried over $MgSO_4$. The ether was removed *in vacuo* to afford a red brownish caramel (2.60 g.), which was chromatographed over alumina (75 g.). A fraction eluted by ethyl acetate was concentrated to give a hard oil, to which was added several drops of ethyl acetate, and the whole was allowed to stand overnight. There deposited 550 mg. of crystals which were recrystallized from dioxane-water (3:1) to afford XIII (510 mg. (19.1%)) as colorless sandy crystals, m.p. 234～235°, $[\alpha]_D^{22}$ +34.0° (c=1, dioxane). *Anal.* Calcd. for $C_{33}H_{49}O_2N$: C, 80.60; H, 10.04; N, 2.85. Found: C, 80.49; H, 10.15; N, 2.87. IR cm^{-1}: ν 3330 (NH), 1695 (Ar-CO-), 1630 (-NHCO-), 1605 (arom.).

Further, the mother liquor, from which the crude product (XIII) had been isolated, was concentrated to dryness and ethyl acetate was added and allowed to stand at room temperature. The quinolone (XV) deposited as 512 mg. (19.1%) of pale yellow crystals, m.p. 180～183°. $[\alpha]_D^{21}$ +66.6° (c=1.05, dioxane). IR cm^{-1}: ν 1630 (Nujol). UV λ_{max}^{EtOH} mμ (log ε): 242 (4.48), 247.5 (4.45), 317 (4.02), 330 (4.04); λ_{min}^{EtOH} mμ (log ε): 223.5 (4.16), 270 (3.14), 323 (3.94). *Anal.* Calcd. for $C_{33}H_{47}ON$: C, 83.63; H, 10.00; N, 2.96. Found: C, 83.55; H, 10.07; N, 2.75.

2,3-Seco-5α-cholestane-2,3-dioic Acid (XIV, Windaus-Uibrig Acid)——To a solution of the foregoing keto-lactam (XIII, 270 mg.) in 30 ml. of glacial acetic acid was added 3 ml. of 30% H_2O_2 and the whole solution was allowed to stand at room temperature for 30 min., and heated on a water bath for 3 hr. The solvent was removed *in vacuo*, ether was added, and an acidic substance dissolved in ether was transferred into 10% sodium carbonate solution. After a small amount of insoluble material was filtered off, the aqueous solution was acidified with 10% HCl under cooling to separate colorless crystals which were collected by filtration, washed with water and dried. The crude product (171 mg., m.p. 150～160°) was subjected to chromatography over silica gel (12 g.). A fraction eluted by benzene-ether (1:1, 200 ml.) afforded 86 mg. of caramel-like substance, which formed crystals (48 mg.) on adding petr. ether. Recrystallized from hydrous acetic acid, there were obtained 13 mg. (6.1%) of XIV as colorless needles, m.p. 188～191° (lit. m.p. 196°,[10a] m.p. 189～190°,[10b] m.p. 193～195°[10c]), $[\alpha]_D^{18}$ +43.3° (c=0.6, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{46}O_4$: C, 74.61; H, 10.66. Found: C, 74.69; H, 10.82.

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Summary

The structures of indolocholestanes derived from 5α- (I) and 5β-cholestan-3-ones (IV) have been established as V and III, respectively, by chemical degradations.

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