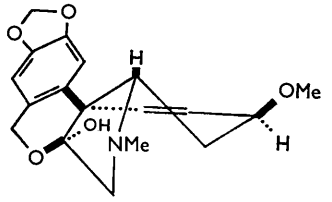
479. *Stereochemistry of the Hemiketal Moiety of Tazettine.*

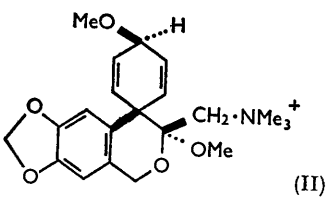
By Yoshisuke Tsuda and Shojiro Uyeo.

Treatment of *O*-methyltazettine methine methiodide with potassium t-butoxide leads, among other products, to two isomeric compounds (VII and VIII). Further examination of these yields results which establish the configuration of the hemiketal moiety of the parent alkaloid. Thus the absolute stereochemistry of tazettine is represented by formula (I).

The structure of tazettine, including its absolute stereochemistry, has been established [1,2] with the exception of the configuration of the hemiketal moiety. Of the two possibilities, the *cis*-fused C/D ring system as in (I) (written in one of the two conformations of ring B) would be reasonable because of its greater stability. In the *trans*-fused case one might have thought that it should have isomerised upon treatment [1] with acid into the *cis*-form. In any event the hemiketal moiety in tazettine is stable, as shown [3] by its failure to react with carbonyl reagents. In the course of a restudy of the Hofmann degradation of *O*-methyltazettine methine methiodide (II) we have obtained compounds the further reactions of which are in complete agreement with the formula (I) for tazettine.



(I)

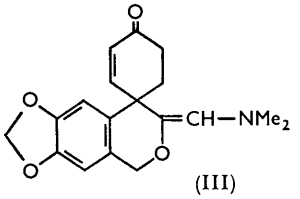


(II)

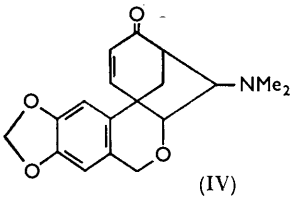
Vigorous treatment of *O*-methyltazettine methine methiodide [4] (II) with potassium t-butoxide in t-butyl alcohol furnished a complex mixture from which 2-*p*-methoxyphenyl-4,5-methylenedioxybenzyl alcohol, its acetate,[1] and five αβ-unsaturated ketones (compounds A—E) were isolated (see Experimental section). Three of these compounds, C, D, and E, have been shown to have the constitutions (III), (IV), and (V), respectively.[5]

[1] Ikeda, Taylor, Tsuda, Uyeo, and Yajima, *J.*, 1956, 4749.
[2] Irie, Tsuda, and Uyeo, *J.*, 1959, 1446.
[3] Ikeda, Taylor, and Uyeo, *Chem. and Ind.*, 1955, 1088.
[4] Kondo, Ikeda, and Okuda, *Ann. Report ITSUU Lab.*, 1950, **1**, 61.
[5] Tsuda and Uyeo, unpublished work.

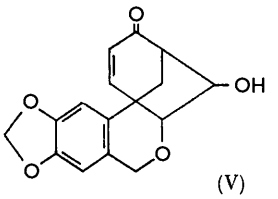
Compound A, $C_{19}H_{23}O_5N$, contained one methoxyl group and exhibited bands at 1660 (six-membered ring, conjugated ketone) and at 1408 cm.$^{-1}$ (methylene group adjacent to carbonyl) in the infrared spectrum and a strong absorption (ε 10,800 at 230 mμ) in the



(III)



(IV)

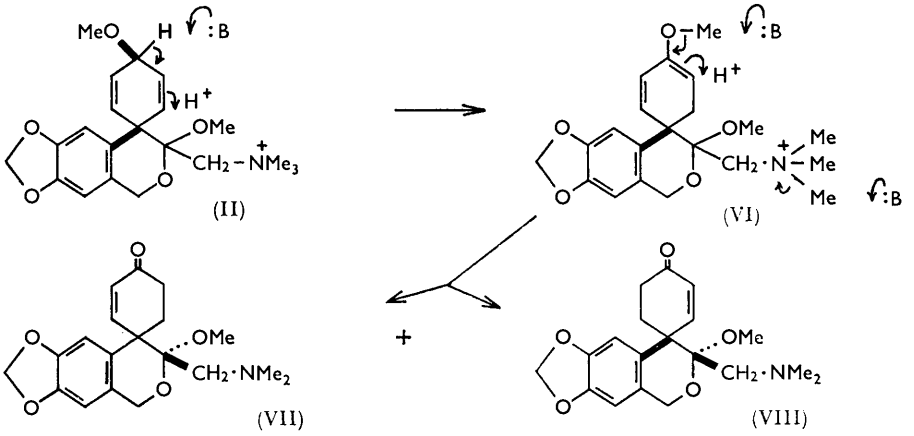


(V)

ultraviolet region which was unaffected by a change in pH. The nuclear magnetic resonance spectrum * exhibited singlets at 2·48, 1·99, 1·30, 0·09, and −1·26 p.p.m. indicative of NMe_2, $N{\cdot}CH_2{\cdot}\overset{|}{C}-$, OMe, $Ar{\cdot}CH_2{\cdot}O$, and methylenedioxy-groups. No peaks corresponding to $-O{\cdot}CH\!<$ were observed. Hydrogenation gave a dihydro-compound in which the double bond only had been saturated.

Compound B, $C_{19}H_{23}O_5N$, was apparently isomeric with compound A and readily distinguishable from it because it could not be obtained crystalline. Its close relation to compound A was established by hydrogenation, which gave the dihydro-derivative of compound A. Thus compounds A and B differed only in the position in the six-membered ring of the double bond conjugated to the carbonyl group.

We felt that compounds A and B should be the two possible products (VII and VIII) which could be formed from (II) as a result of elimination of one *N*-methyl group and prototropic rearrangement in ring B, followed by hydrolysis of the resulting enol ether (II ⟶ VI ⟶ VII and VIII).



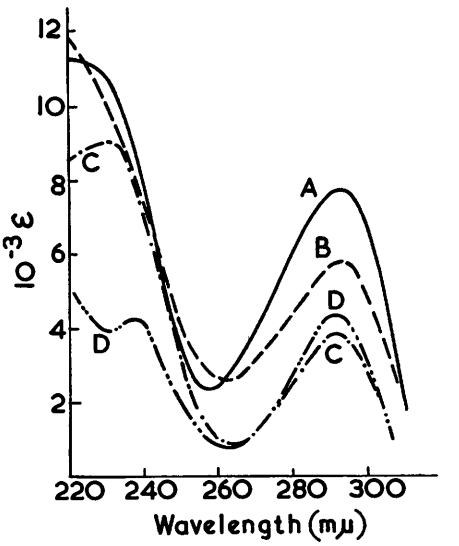
Compound B exhibited an infrared band at 1672 cm.$^{-1}$ (conjugated carbonyl) and also end-absorption (ε ~9900 at 230 mμ) in the ultraviolet spectrum, similar to that of compound A. However, upon acidification, this intensity, in contrast to that of compound A, was greatly diminished ($\lambda_{max.}$ 237 mμ, ε 4300; see Figure). This behaviour closely resembled that of dihydro-oxocrinine methine,[6] suggesting that a Michael type condensation takes place with compound B in acidic solution. In fact, the original isolation of compound B was possible only after its basified solution had been heated. To permit

* The nuclear magnetic resonance spectrum was taken for a 0·5 mol. chloroform solution on a Varian V4300, 40 mc. machine. Chemical shifts were measured relative to water (external standard).

[6] Wildman, *J. Amer. Chem. Soc.*, 1958, **80**, 2567.

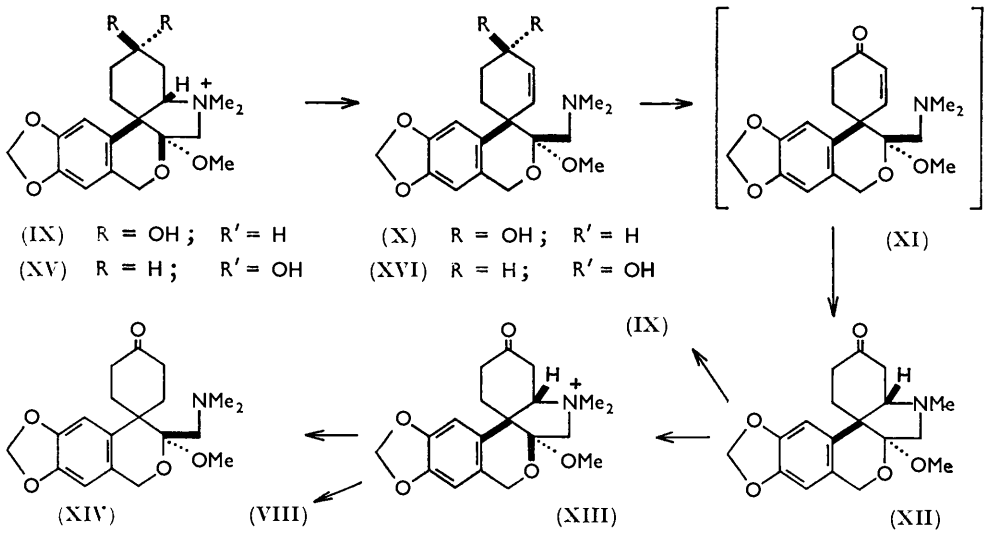
such a ready recyclisation, compound B, on the basis of formula (I) for tazettine, must be represented by (VIII) and thus compound A is (VII).

These structural assignments were proved by preparation of the dihydro-derivative of compound A by another route, and also by recyclisation of one of the intermediates where the position of the double bond (the same as in compound B) was certain. Methylation



Ultraviolet absorption of compound A in (A) EtOH *and* (C) *acidic* EtOH, *and of compound B in* (B) EtOH *and* (D) *acidic* EtOH.

of dihydrotazettinol [7] (or dihydroisotazettinol) [2] with dimethyl sulphate in aqueous potassium hydroxide gave the corresponding *O*-methyl quaternary salt (IX) characterised as the iodide. Hofmann degradation then gave a gummy methine (X) which on oxidation



with manganese dioxide in ether furnished the saturated ketone (XII), whose structure was confirmed by its borohydride reduction and subsequent quaternisation to regenerate the salt (IX). We had expected to get, by manganese dioxide oxidation, the unsaturated

[7] Tsuda and Uyeo, *J.*, 1961, 1055.

ketone (XI) but it had apparently recyclised with oxidative removal [2,8] of one of the *N*-methyl groups. In contrast, compound A (VII) was unaffected by manganese dioxide in ether, so that the ease of cyclisation must be a factor controlling the removal of one of the *N*-methyl groups.

Quaternisation of the ketone (XII ⟶ XIII), followed by hydrogenolysis over palladium–carbon in ethanolic sodium hydroxide, gave a methine (XIV) identical with the dihydro-derivative of compound A. Hofmann degradation of the quaternary ketone (XIII) gave, as expected, compound B (VIII).

The above results show that upon recyclisation the nitrogen goes back to its original point of attachment. Had the C/D ring system been *trans*-fused in tazettine recyclisation would have occurred, for steric reasons, on the side of ring B opposite to that of the parent compound. The validity of the above conclusions is unquestioned provided that we exclude an implausible inversion of the ketal stereochemistry during the *O*-methylation step.

Experimental

Ultraviolet absorption spectra were determined for 95% ethanol solutions, and infrared spectra were taken on Nujol mulls, unless otherwise stated. Light petroleum refers to the fraction of b. p. 50—70°.

Reaction of O-Methyltazettine Methine Methiodide with Potassium t-Butoxide.—*O*-Methyltazettine methine methiodide (II) (2 g.) and potassium t-butoxide (1 g.) in t-butyl alcohol (40 ml.) were heated under reflux for 10 hr., during which the methiodide gradually dissolved and potassium iodide separated. The solvent was evaporated under reduced pressure and the residue heated at 120—130°/0·5 mm. for 30 min. Water was added to the cooled mixture, and the whole was saturated with ammonium chloride and extracted with benzene which was washed with 5% hydrochloric acid. The benzene layer was dried (Na_2SO_4) and evaporated to dryness, to give a gum (0·35 g.) which was chromatographed in benzene over acid-washed alumina. Elution with benzene gave 2-*p*-methoxyphenyl-4,5-methylenedioxybenzyl acetate [1] (50 mg.), m. p. and mixed m. p. 87—89°. An ether eluate afforded 2-*p*-methoxy-4,5-methylenedioxybenzyl alcohol [1] (70 mg.), m. p. and mixed m. p. 147—149°. Further elution with chloroform and acetone gave *compound* E (V) (50 mg.) which crystallized as prisms (from chloroform), m. p. 239—240°, $[\alpha]_D$ ±0° (*c* 1·0 in acetone), $\lambda_{max.}$ 235 and 290 mμ (log ε 4·14 and 3·72), $\nu_{max.}$ 3390 (OH) and 1664 cm.$^{-1}$ (conjugated ketone) (Found: C, 66·9; H, 4·9; OMe, 0. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%). The acidic extract was basified with sodium carbonate and repeatedly extracted with ether. Concentration of the ether yielded *compound* C (III) (0·27 g.), m. p. 163—165° (yellow needles from methanol), $[\alpha]_D$ ±0° (*c* 0·5 in $CHCl_3$), $\lambda_{max.}$ 232 and 292 mμ (log ε 4·41 and 3·84), $\nu_{max.}$ 1670 cm.$^{-1}$ (conjugated ketone) (Found: C, 68·9; H, 5·9; N, 4·2; OMe, 0. $C_{18}H_{19}NO_4$ requires C, 69·0; H, 6·1; N, 4·5%). The mother-liquor was evaporated and triturated with methanol, to give *compound* D (IV) (40 mg.), m. p. 204—205° (prisms from methanol), $[\alpha]_D$ ±0° (*c* 0·8 in EtOH), $\lambda_{max.}$ 235 and 290 mμ (log ε 4·05 and 3·74), $\nu_{max.}$ 1672 cm.$^{-1}$ (conjugated ketone) (Found: C, 68·9; H, 6·1; N, 4·8; OMe, 0; *C*-Me, 0. $C_{18}H_{19}NO_4$ requires C, 69·0; H, 6·1; N, 4·5%). Chromatography of the mother-liquor from compounds C and D in benzene over alumina gave *compound* A (0·2 g.), m. p. 101—102° (VII) (prisms from methanol), $[\alpha]_D$ +46° (*c* 3·5 in $CHCl_3$), $\lambda_{max.}$ 292 mμ (log ε 3·89), and end-absorption at 220—230 mμ (log ε 4·05—4·03), $\nu_{max.}$ 2750 (NMe_2), 1660 (conjugated ketone), 1408 ($CO{\cdot}CH_2$) in Nujol mull, and 2786 (NMe_2) and 1669 cm.$^{-1}$ (conjugated ketone) in $CHCl_3$ (Found: C, 66·3; H, 6·5; N, 3·9; OMe, 9·0. $C_{19}H_{23}NO_5$ requires C, 66·1; H, 6·7; N, 4·1; 1OMe, 9·0%). The aqueous solution (*ca.* 200 ml.) from which the basic substances had been removed by extraction with ether was heated, after addition of sodium hydroxide (*ca.* 20 g.), on a water-bath for 5 min. and then extracted again with benzene. The benzene extract was dried (K_2CO_3) and evaporated to give an oil (0·1 g.) which was distilled at about 170° (bath)/0·1 mm. to give the pure *compound* B (VIII) as a colourless gum, $[\alpha]_D$ −238° (*c* 3·6 in $CHCl_3$), $\lambda_{max.}$ 292 mμ (log ε 3·76) and end-absorption at 220—230 mμ (log ε 4·07—4·0), $\nu_{max.}$ 2802 (NMe_2) and 1672 cm.$^{-1}$ (conjugated ketone) in $CHCl_3$. This compound is readily soluble in ether but changed in air into an ether-insoluble material.

Hydrogenation of Compound A.—Compound A (VII) (0·1 g.) in ethanol (10 ml.) was

[8] Henbest and Thomas, *J.*, 1957, 3032.

hydrogenated over 10% palladium–carbon (0·1 g.) for 1·5 hr. The filtered solution was evaporated and the residue crystallized from methanol to give *dihydro-compound* A (XIV) (80 mg.) as prisms, m. p. 97—98°, $[\alpha]_D$ −139° (*c* 0·8 in $CHCl_3$), $\lambda_{max.}$ 235 and 295 mμ (log ε 3·33 and 3·78), $\nu_{max.}$ 2760 (NMe_2), 1700 (C=O), 1403 ($CO{\cdot}CH_2$) in Nujol mull and 2765 (NMe_2) 1701 (C=O), 1404 cm.$^{-1}$ ($CO{\cdot}CH_2$) in $CHCl_3$ (Found: C, 66·0; H, 7·4. $C_{19}H_{25}NO_5$ requires C, 65·7; H, 7·3%).

Hydrogenation of Compound B.—Compound B (VIII) (0·15 g.) in ethanol (10 ml.) containing 10% ethanolic sodium hydroxide (2 ml.) was hydrogenated over 10% palladium–carbon for 1 hr. After removal of the catalyst the filtrate was diluted with water and extracted with ether which was re-extracted with 5% hydrochloric acid. Basification of the acidic solution with sodium carbonate and extraction with ether gave a gum after evaporation which was chromatographed over alumina. A dihydro-compound (XIV) (100 mg.), m. p. 96—97° (from ether–light petroleum), was isolated from benzene–ether eluates. The m. p. was not depressed on admixture with dihydro-compound A and the infrared spectra were identical.

Methylation of Dihydrotazettinol.—10% Aqueous potassium hydroxide (40 ml.) was added at a rate of 4 ml. an hour to a stirred mixture of dihydrotazettinol [7] (0·5 g.) and dimethyl sulphate (5 ml.). After an additional 2 hours' stirring, the mixture was neutralized with 20% sulphuric acid and was evaporated to dryness under reduced pressure after addition of potassium iodide (0·5 g.). The residue was repeatedly extracted with boiling chloroform, and the chloroform was dried (K_2CO_3) and evaporated to give *dihydro-O-methyltazettinol methiodide* (IX) (0·3 g.) as needles (from ethanol), m. p. 253—254° (decomp.) (Found: C, 47·9; H, 5·6. $C_{18}H_{23}NO_5,CH_3I$ requires C, 48·0; H, 5·5%).

Methylation of Dihydroisotazettinol.—Dihydroisotazettinol (0·2 g.) was methylated by the procedure described for dihydrotazettinol, to yield *dihydro-O-methylisotazettinol methiodide* (XV) (0·2 g.) as plates (from ethanol), m. p. 245—247° (decomp.) (Found: C, 48·2; H, 5·7%).

Hofmann Degradation of Dihydro-O-methyltazettinol Methiodide.—The methiodide (IX) (0·28 g.) and an excess of freshly prepared silver oxide in methanol (10 ml.) and water (10 ml.) were stirred for 30 min., then filtered, and the silver salts were washed with methanol and water. The combined filtrates and washings were evaporated to dryness and the residue was heated at 150—160°/0·5 mm. for 20 min. The resulting product was taken up in ether, which was washed with water, then concentrated to dryness to yield the gummy methine (X) (0·18 g.).

Hofmann Degradation of Dihydro-O-methylisotazettinol Methiodide.—The methiodide (XV) (0·5 g.) was subjected to the Hofmann degradation as described above to give the *methine* (XVI) (0·35 g.), m. p. 133—134°, (from ether–light petroleum), $[\alpha]_D$ −402° (*c* 2·9 in EtOH) (Found: C, 65·7; H, 7·2. $C_{19}H_{25}NO_5$ requires C, 65·7; H, 7·3%).

Dihydro-O-methyltazettinone (XII).—(*a*) The methine (X) (0·1 g.) in ether (10 ml.) was stirred with manganese dioxide (1 g.) for 1 hr. at room temperature. Manganese dioxide was removed and washed with ether, and the combined filtrates and washings were evaporated to give *dihydro-O-methyltazettinone* (XII) (90 mg.), m. p. 164—165° (needles from ethanol), $[\alpha]_D$ −131° (*c* 1·8 in $CHCl_3$), $\lambda_{max.}$ 237 and 294 mμ (log ε 3·66 and 3·71), $\nu_{max.}$ 1712 cm.$^{-1}$ (CO) (Found: C, 64·9; H, 6·2. $C_{18}H_{21}NO_5$ requires C, 65·2; H, 6·4%).

(*b*) The methine (XVI) (0·14 g.) in ether (14 ml.) was stirred with manganese dioxide (1·4 g.) for 18 hr. Chromatography of the resulting product in benzene over alumina furnished from a benzene eluate the starting material (50 mg.), m. p. and mixed m. p. 130—132°, and from benzene–chloroform eluate dihydro-*O*-methyltazettinone (XII) (40 mg.), m. p. 161—163°. No depression of m. p. was observed on admixture with the sample obtained as in (*a*). The infrared spectra of the two samples were identical.

Dihydro-O-methyltazettinol Methiodide (IX) *from Dihydro-O-methyltazettinone* (XII).—Dihydro-*O*-methyltazettinone (XII) (25 mg.) and sodium borohydride (50 mg.) in ethanol (5 ml.) were kept at room temperature for 12 hr. After removal of the ethanol, water was added and the mixture extracted with chloroform which was concentrated to dryness. The residue in methanol was heated under reflux with an excess of methyl iodide for 3 hr., the solvent was then removed, and the residue crystallized from ethanol to give dihydro-*O*-methyltazettinol methiodide (IX), m. p. and mixed m. p. 249—252° (decomp.). The infrared spectrum was identical with that of the specimen obtained as above.

Dihydro-O-methyltazettinone Methiodide (XIII).—Dihydro-*O*-methyltazettinone (XII) (200 mg.) and methyl iodide (2 ml.) in methanol (10 ml.) were refluxed for 6 hr. After removal of methanol, water was added, and the whole basified with a few drops of aqueous ammonia and

extracted with ether which removed some unchanged starting material (90 mg.). The water layer was concentrated to dryness *in vacuo*, to yield the methiodide (XIII) as a gum.

Dihydro-compound A (XIV).—The above methiodide (XIII) (70 mg.) in 5% ethanolic sodium hydroxide (10 ml.) was hydrogenated over 10% palladium–carbon (100 mg.) at room temperature for 3 hr. After removal of the catalyst and concentration of the filtrate to dryness, water was added and the whole extracted with ether which was re-extracted with 2% hydrochloric acid. Basification of the acidic solution with sodium carbonate and extraction with ether afforded an oil which was chromatographed in benzene over alumina. Benzene and benzene–chloroform eluates were combined and rechromatographed in chloroform over silica gel. Elution with methanol–chloroform (1 : 99) gave dihydro-compound A (XIV) (30 mg.) as prisms, m. p. 96—98° after crystallization from ether–light petroleum. The m. p. was not depressed on admixture with the sample derived from compound A and the infrared spectra of the two samples were identical.

Compound B.—Dihydro-*O*-methyltazettinone methiodide (XIII) (50 mg.) and 20% aqueous sodium hydroxide (5 ml.) in water (5 ml.) and benzene (10 ml.) were heated on a water-bath for 5 min. The benzene layer was separated, dried (K_2CO_3), and evaporated to dryness, yielding compound B (VIII) as a gum whose infrared spectrum in chloroform was identical with that of compound B.

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