928. *The Structure and Stereochemistry of Tazettine.*

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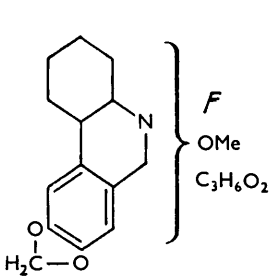
Tazettine, which is shown to contain a hemiketal moiety, can be readily transformed into the ether, deoxytazettine. A study of the Hofmann degradation of this compound showed that the true methine undergoes, in acidic media, rearrangement and loss of methanol to a compound whose structure is proved by synthesis of its degradation products, as well as by elimination to yield 6-phenylpiperonyl alcohol. The products of the Hofmann degradations of tazettine and its derivatives appear to be transformation products of the methines brought about either by the basic conditions of the reaction or by acid introduced during the isolation procedure. Acid treatment of tazettine furnishes two isomeric demethylation products, tazettinol and *iso*-tazettinol, the further study of which enables a preliminary statement to be made concerning the absolute stereochemistry of the parent base.

TAZETTINE, a minor alkaloid of the *Amaryllidaceae*, was first extensively investigated by Späth and Kahovec [1] who arrived at the partial structure (I) for the alkaloid. This base was later shown [2] to be identical with " base VIII " [3] and with ungernine.[4] Kondo and his co-workers [5] accumulated many valuable data which was analyzed by Wenkert,[6] who was able to deduce the structures of two of the five end products of Kondo's Hofmann degradations on tazettine which had been subject to methylation. These results along with the note by Clemo and Felton [7] could be expressed by the partial formula (II) in which the methoxy-group is placed *para* to the piperonyl residue and the presence of a readily esterifiable hydroxyl, an *N*-methyl, and an ether group had been recognized; and further the double bond was isolated. Wenkert [6] proposed a complete stereostructure for the base which, accounting satisfactorily for a few aspects of the chemistry of tazettine, most importantly could not predict or account for tazettine methine, $C_{18}H_{19}O_4N$ (Späth and

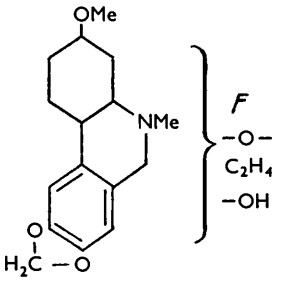
[1] Späth and Kahovec, *Ber.*, 1934, **67**, 1501.
[2] Späth, Kondo, and Kuffner, *Ber.*, 1936, **69**, 1086.
[3] Kondo, Tomimura, and Ishiwata, *J. Pharm. Soc. Japan*, 1932, **52**, 433.
[4] Norkina and Orechoff, *Ber.*, 1936, **69**, 500; Späth, Orechoff, and Kuffner, *ibid.*, p. 2446.
[5] (*a*) Kondo, Ikeda, and Okuda, *Ann. Report ITSUU Lab.*, 1950, **1**, 61; (*b*) Kondo and Ikeda, *ibid.*, 1951, **2**, 55; (*c*) Kondo, Ikeda, and Takeda, *ibid.*, p. 60; Kondo, Ikeda, and Taga, (*d*) *ibid.*, 1952, **3**, 65; (*e*) 1953, **4**, 73; (*f*) 1954, **5**, 72.
[6] Wenkert, *Experientia*, 1954, **10**, 476.
[7] Clemo and Felton, *Chem. and Ind.*, 1952, 801.

Kahovec [1]). Clemo and Hoggarth [8] confirmed this formula but, although they studied the methine in some detail, were unable to determine its structure. It remained for Taylor, Uyeo, and Yajima [9] to recognize in Späth and Clemo's results the structure (IV) for the methine which was confirmed by synthesis.

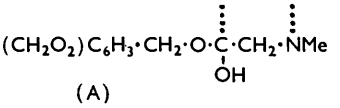
Although the methine has an ester-carbonyl group, the infrared spectrum of tazettine showed no carbonyl absorption so that the carbonyl group was masked or was being formed under Hofmann conditions. In fact, since an ester of dimethylglycine (IV) was being formed, the partial structure (A) appeared possible for tazettine in which under



(I)



(II)



(A)

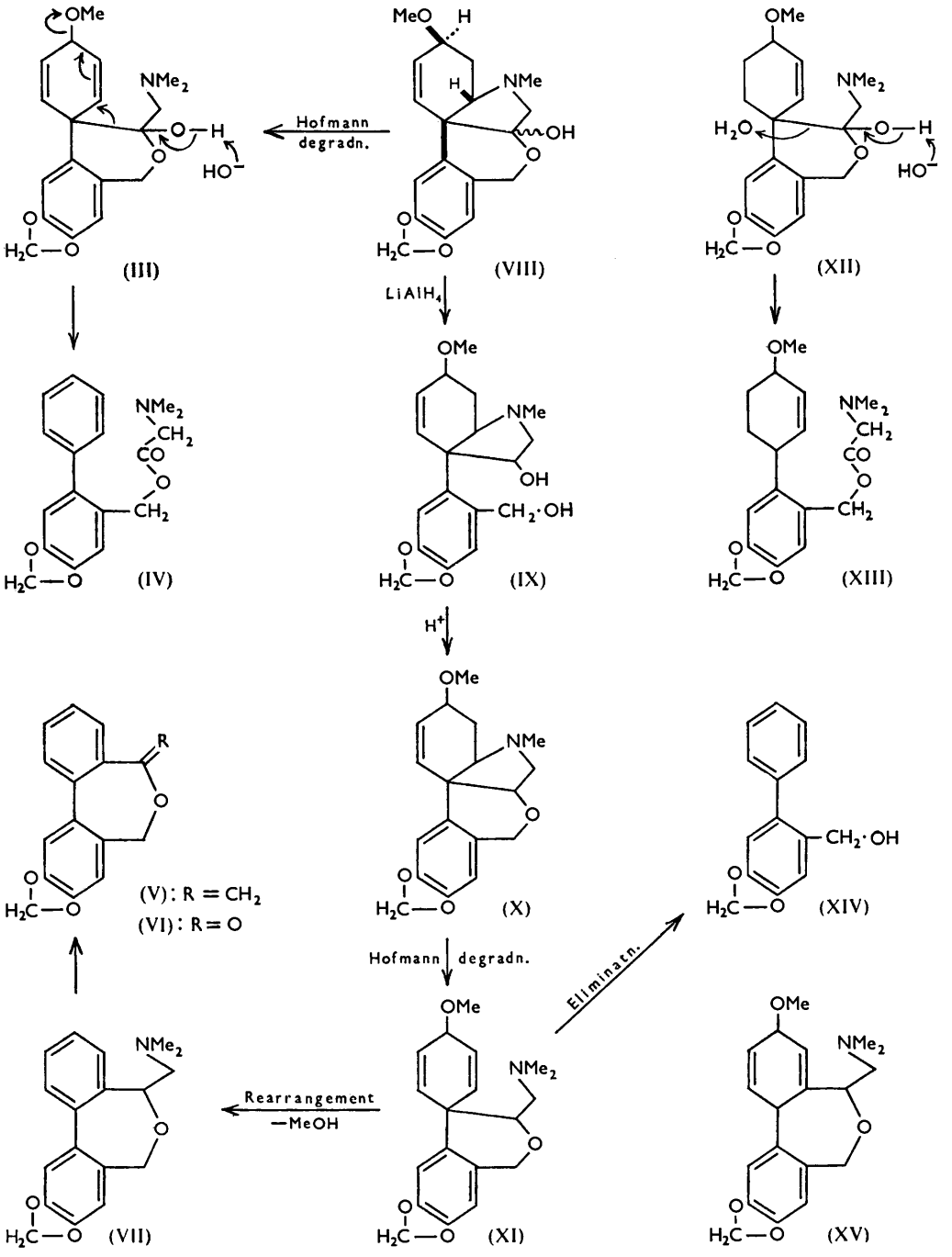
Hofmann condition the dotted bonds were broken. If the partial formula (A) were correct, tazettine might be expected to react with carbonyl reagents under a variety of conditions which it did not, as already stated by Kondo.[5a] However, with lithium aluminium hydride (contrary to Kondo's preliminary experiment [5f]) it was smoothly converted into a dihydro-compound, tazettadiol, which contained two readily acylatable hydroxyl groups and, in addition, in hot dilute acid lost the elements of water to form the ether, deoxytazettine. This behaviour has an exact parallel in the reactions of the hemiacetal moiety present in lycorenine.[10]

A study of the Hofmann degradation of deoxytazettine threw much light on the constitution of tazettine (cf. two preliminary communications [11]). It was found that in dilute aqueous acid at room temperature the methine readily rearranges with loss of the elements of methanol, to yield optically inactive deoxytazettine *neo*methine * (VII) whose structure was proved as follows. Hofmann degradation of the *neo*methine furnished trimethylamine and the nitrogen-free compound (V) which, although showing no infrared carbonyl absorption, gave, as expected, a 2 : 4-dinitrophenylhydrazone. Oxidation of this compound (V) with potassium permanganate gave the lactone (VI) from which 4 : 5-methylenedioxydiphenyl-2 : 2′-dicarboxylic acid was obtained by further oxidation. The constitutions of the last two compounds and therefore of the *neo*methine (VII) were confirmed by Ullmann syntheses. Methyl 6-bromopiperonylate and methyl *o*-iodobenzoate, heated at 230° for 3·5 hours with copper bronze, gave after fractionation of the products the dicarboxylic acid in 10% yield. Similarly, 6-bromopiperonaldehyde and methyl *o*-iodobenzoate gave methyl 6-formyl-3 : 4-methylenedioxydiphenyl-2′-carboxylate in 7% yield, converted into the lactone (VI) on reduction with sodium borohydride.

Once the structure of the *neo*methine was known, two structures for the true methine presented themselves, namely (XI) and (XV). In both cases, in agreement with ultra-violet and infrared evidence, the double bonds were not conjugated with each other or the piperonyl residue and were not contiguous to the methoxy-group. There were serious criticisms of structure (XV) which eliminate it; it would not be expected to survive the original alkaline Hofmann conditions since by loss of methanol it would aromatize to the

* Since conversion of tazettine methine into this substance is not merely isomerisation but involves elimination of CH_4O, the name "*neo*methine" is now preferred to "*iso*methine."

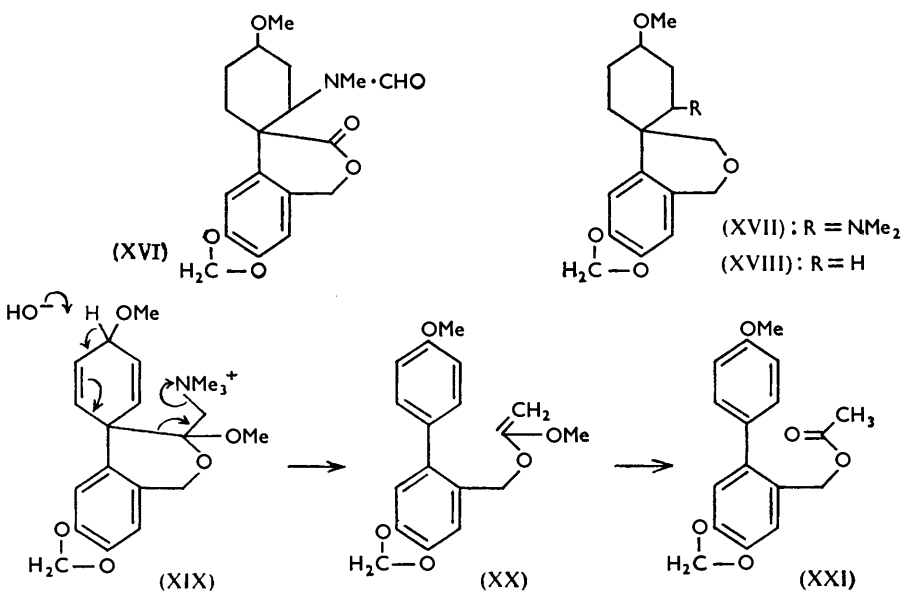
[8] Clemo and Hoggarth, *Chem. and Ind.*, 1954, 1046.
[9] Taylor, Uyeo, and Yajima, *J.*, 1954, 6183.
[10] Kitagawa, Taylor, Uyeo, and Yajima, *J.*, 1955, 1066.
[11] Ikeda, Taylor, and Uyeo, *Chem. and Ind.*, 1955, 1088; Ikeda, Taylor, Tsuda, and Uyeo, *ibid.*, 1956, 411.



*neo*methine (VII); also it cannot account for the fact that the true methine in aqueous acid gives, not only the *neo*methine, but also 6-phenylpiperonyl alcohol (XIV). Both of these facts are consistent with formula (XI) for the methine; there is no way for base-catalyzed aromatization to occur, and, with acid, rearrangement would furnish the *neo*-methine (VII) and by elimination 6-phenylpiperonyl alcohol (and probably dimethylamino-acetaldehyde but no attempt was made to isolate it). The apparent optical inactivity of

the *neo*methine (VII) is, however, not easy to explain since the rearrangement would be expected to be concerted and therefore occur with retention of configuration. It was now possible to write structures (X), (IX), and (VIII) for deoxytazettine, tazettadiol, and tazettine respectively. The pK_a results (see Experimental section) are in agreement with this structure; *i.e.*, the double bond is removed from the nitrogen atom and the hydroxyl group has little or no effect on the basicity. This formula for tazettine also accounts for the formation of phenanthridine on distillation with zinc dust,[1] as well as that of 10-methyl-6 : 7-methylenedioxyphenanthridinium chloride under the milder conditions of the Oppenauer oxidation.

In attempt to rationalize the discrepancy between the Hofmann degradation products of tazettine obtained by the schools of Späth and Kondo, Wenkert [6] suggested that under Kondo's alkaline methylating conditions a hydroxyl group was epimerized so that the decomposition took a different and more complicated route. Wiesner and Valenta [12] later seemed to have concluded that under the Kondo methylating conditions an arrangement took place, though the logic of the proposed prototropic shifts about an enolate anion is difficult to follow. It has been found by us that Kondo had actually prepared and studied *O*-methyltazettine methiodide, and we made *O*-methyltazettine whose stability to reduction by lithium aluminium hydride provided further support for the hemiketal moiety in the parent base. Tazettine reacted slowly with diazomethane to yield oily *O*-methyltazettine (VIII; OH = OMe), which could also be prepared by treating tazettine with thionyl chloride followed by sodium methoxide. The oily base was characterized as styphnate and methiodide. The last compound was identical with the derivative prepared by Kondo and his co-workers [5a] from tazettine by dimethyl sulphate and sodium hydroxide followed by potassium iodide. It was hoped that it would be possible to regenerate tazettine from its *O*-methyl derivative with aqueous acid but only ill-defined products were obtained.

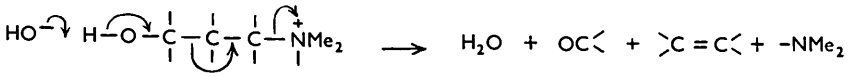


Highet and Wildman [13] obtained results consistent with the partial formula (A) from a study of tazettamide, produced from tazettine by oxidation with manganese dioxide. Further degradation of tazettamide has now provided striking confirmation of the correctness of formula (VIII) for tazettine. Dihydrotazettamide (XVI), on reduction with lithium aluminium hydride followed by digestion with dilute acid, furnished the ether (XVII) which on Emde degradation of its methochloride gave the nitrogen-free compound (XVIII).

[12] Wiesner and Valenta, British Industries Fair Review (April 1956), *Chem. and Ind.*, 1956, R 36.
[13] Highet and Wildman, *ibid.*, 1955, 1159.

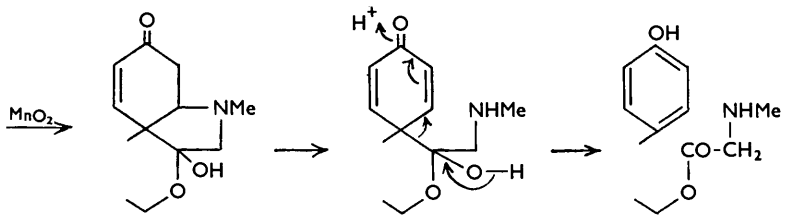
This substance, in agreement with its structure which has a plane of symmetry, was found to be optically inactive. A synthesis of the compound (XVIII) should not only confirm the structure of tazettine but also solve much of its stereochemistry.

Highet and Wildman [13] have suggested that the Hofmann degradation of tazettine and its dihydro-derivative are concerted internal eliminations :



This type of four-centre reaction would only be expected to occur readily if the centres were linearly coplanar.[14] Much later Wiesner and Valenta [12] have applied the same mechanism to our proposal (VIII) for tazettine, without recognizing that such a mechanism must lead in the case of dihydrotazettine to a methine base in which the double bond is conjugated with the piperonyl residue. Highet and Wildman [13] have shown, and we have confirmed, that the double bond in dihydrotazettine methine is not conjugated with the aromatic ring. From our results, given in this paper, it appears that in tazettine and its derivatives a normal Hofmann reaction takes place, subsequent changes being dependent on the methine's stability to base (under Hofmann conditions) or to acid (which may be added in the isolation). We consider then that the Hofmann degradation of tazettine affords initially the true methine (III) which then aromatizes to the base (IV) with concomitant formation of an ester-carbonyl group. In the case of dihydrotazettine there is no possibility of aromatization of the true methine (XII), but a rate-controlled displacement takes place at the benzyl-allylic carbon atom in which the driving force is the formation of the ester-carbonyl group in the product (XIII). It is unlikely that the double bond in the base (XIII) would move into the conjugated position during the Hofmann degradation since Weinstock and Bordwell [15] have demonstrated the stability of 3-phenyl*cyclo*hexene under similar conditions.

Tazettine was smoothly demethylated in refluxing 10% hydrochloric acid to two isomeric alcohols, tazettinol and *iso*tazettinol, the latter predominating. As the names suggest, they were shown to be epimeric allylic alcohols in which the methoxyl group of tazettine is replaced by hydroxyl. Methylation of tazettinol under alkaline conditions furnished *O*-methyltazettine methiodide, and *iso*tazettinol gave *O*-methyl*iso*tazettine methiodide. Two Hofmann degradations on the latter salt affords 2-*p*-methoxyphenyl-4 : 5-methylenedioxybenzyl acetate (XXI), which is also obtained from *O*-methyltazettine methiodide,[16] among other products, by the same procedure. The course of these Hofmann degradations follows the same pattern as for the cases discussed above, the first one giving a methine whose methohydroxide (XIX) decomposed under Hofmann conditions by base-attack on the most acidic proton to yield the enol ether (XX). Since this ether can decompose in two ways, the isolation of the acetate (XXI) as well as of 2-*p*-methoxyphenyl-4 : 5-methylenedioxybenzyl alcohol was not unexpected. Another reaction leading to a diphenyl derivative was the oxidation of tazettinol by manganese dioxide to 2-*p*-hydroxyphenyl-4 : 5-methylenedioxybenzyl alcohol according to the annexed scheme

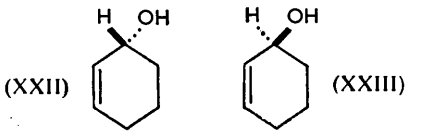


(partial formulæ) in which β-elimination and the dienone–phenol rearrangement are the two most important steps. Reduction of both tazettinol and *iso*tazettinol with lithium

[14] Cf. Barton, *J.*, 1953, 1030.
[15] Weinstock and Bordwell, *J. Amer. Chem. Soc.*, 1955, **77**, 6706.
[16] Ikeda, unpublished observations.

aluminium hydride followed by cyclization with dilute acid gave the corresponding ethers, deoxytazettinol and deoxy*iso*tazettinol. Oxidation of both of these compounds afforded the same αβ-unsaturated ketone, deoxytazettinone. Reduction of deoxytazettinone with sodium borohydride furnished deoxy*iso*tazettinol as the major product. This result implies that the hydroxyl group in the *iso*-series occupies the thermodynamically more stable position, which is in agreement with the much more rapid oxidation of deoxytazettinol than of deoxy*iso*tazettinol by manganese dioxide.

Measurement of the dissociation constants of suitable derivatives has supplied a clue as to the configuration of the alkaloid. Deoxy*iso*tazettinol is a stronger base than deoxytazettinol by 1·6 pK_a units, which suggests that the proton of conjugate acid derived from deoxy*iso*tazettinol is hydrogen-bonded to the hydroxyl group, and this requirement is met only if the groups are *cis* in ring B. It follows therefore that in tazettine the methoxyl group is *trans* to the nitrogen atom. The five-membered nitrogen-containing ring must be *cis*-fused to the *cyclo*hexene ring B because the nitrogen must be able to take up a pseudo-axial configuration which facilitates the various elimination reactions of tazettine and its derivatives involving this heteroatom. Finally Mills [17] has shown in the terpenes and steroids that the structural unit (XXII) always has a molecular rotation more positive



(XXII) (XXIII)

than its epimer (XXIII). Comparison of the epimeric allylic alcoholic derivatives derived from tazettine and the theoretical *iso*tazettine (Table 1) shows that if such considerations are valid in this substituted cyclic allylic alcohol then the configuration of the hydroxyl group in tazettine corresponds to that in (XXIII).

TABLE 1. *Optical rotations of some derivatives of tazettine.*

Normal series		*iso*-Series	
Tazettinol	+119°	*iso*Tazettinol	+261°
Deoxytazettinol	+210°	Deoxy*iso*tazettinol	+328°
Acetyldeoxytazettinol	+54°	Acetyldeoxy*iso*tazettinol	+198°
O-Methyltazettine methiodide	+66°	*O*-Methyl*iso*tazettine methiodide	+142°

The main features of the stereochemistry of tazettine have now been elucidated with the exception of the stereochemistry of the hemiketal moiety for which no evidence is yet available, and the suggested structure for further consideration is (VIII).

The opportunity is taken here to discuss the possibility that both sekisanine and sekisanoline are in reality tazettine. In 1897 Morishima [18] isolated from the bulbs of *Lycoris radiata*, together with lycorine, a second alkaloid, m. p. 200°, sekisanine (sekisan is the Chinese name for the plant). Kondo and Tomimura [19] in a re-investigation of this work found that sekisanine had m. p. 207—208°, but despite a close similarity between the physical constants of this base and " base VIII " [3] (later shown to be tazettine [2]) they were not considered identical.[3] A direct comparison of the sekisanine samples with tazettine is no longer possible since the former have been lost. However, since sekisanine was isolated without difficulty, it must have been one of the principal bases which we know today to be lycorenine, tazettine, and lycoramine besides lycorine, and, of these, only the first two can be crystallized directly from the mixture of alkaloids. Comparison of the physical constants of sekisanine with tazettine and lycorenine (Table 2) suggests the identity of the first two. Some discrepancies, for example, the sekisanine methiodide, m. p. 287°, may be due to a misprint in the original publication, and the low melting point of the acetate, is probably due to the difficulty of obtaining a pure sample.

Kondo and Tomimura [20] have also reported the isolation of an amorphous phenolic

[17] Mills, *J.*, 1952, 4976.
[18] Morishima, *Arch. Exp. Path. Pharm.*, 1897, **40**, 221.
[19] Kondo and Tomimura, *J. Pharm. Soc. Japan*, 1927, **47**, 545.
[20] Kondo and Tomimura, *ibid.*, 1928, **48**, 438.

alkaloid named sekisanoline, $C_{18}H_{23}O_5N$, from *Lycoris radiata* Herb. Repetition of this work led to the isolation of a base, m. p. 208°, from the phenolic fraction which was shown to be identical with tazettine by direct comparison. The weak acidity is probably due to the hydroxyl group since *O*-methyltazettine was found to be insoluble in alkali. That

TABLE 2.

	Sekisanine	Tazettine $C_{18}H_{21}O_5N$	Lycorenine $C_{18}H_{23}O_4N$
Analysis	C, 66·5, 66·4	65·3	68·2
	H, 6·7, 5·8	6·4	7·3
	N, 5·06, 4·6	4·2	4·4
M. p.	207—209°	207—209°	199—200°
$[\alpha]_D$ (EtOH)	+114·6°	+121·6°	+126·5°
Picrate, m. p.	212°	211°	Not readily cryst.
Hydrochloride, m. p.	211°	206°	,,
Methiodide, m. p.	287°	228°	260°
Acetate	72°	125°	180°
Methoxyl	None	One	One
Methylenedioxy	Present	Present	Absent
N-Methyl	Present	Present	Present

sekisanoline was impure tazettine is further supported by its empirical formula and a positive test for a methylenedioxy-group, although the reported optical rotation of sekisanoline was quite different from that of tazettine.

EXPERIMENTAL

Ultraviolet spectra were measured in ethanol.

Tazettadiol.—Lithium aluminium hydride (0·5 g.) was added portionwise with stirring to tazettine (1·5 g.) in tetrahydrofuran (50 ml). Twelve hours later, after addition of chloroform and a little water, the inorganic salts were filtered off, and the solution was dried (K_2CO_3), then evaporated to dryness. On trituration with ether the resulting oil crystallized, yielding *tazettadiol* (1·15 g.), m. p. 118—119° (after crystallization from acetone or ethanol–ether), $[\alpha]_D^{25}$ +65° (*c* 1·7 in EtOH) (Found, in a sample dried over P_2O_5 at room temperature : C, 61·6, 61·3; H, 7·1, 7·1; N, 3·9. Found, in a sample dried *in vacuo* for 5 hr. : C, 65·0; H, 6·6. $C_{18}H_{23}O_5N,H_2O$ requires C, 61·5; H, 7·2; N, 4·0. $C_{18}H_{23}O_5N$ requires C, 64·9; H, 7·0%).

Tazettadiol (0·1 g.), *p*-nitrobenzoyl chloride (0·3 g.), and dry pyridine (3 ml.) were heated on a water-bath for 20 min., the pyridine was removed *in vacuo*, and water was added to the residue. The chloroform extract was washed with 5% potassium carbonate solution, dried ($MgSO_4$), and distilled, yielding the pale yellow *di*-p-*nitrobenzoate* (90 mg.), m. p. 184—185° (from chloroform–ethanol) (Found : C, 60·5; H, 4·7; N, 6·6. $C_{32}H_{29}O_{11}N_3$ requires C, 60·8; H, 4·6; N, 6·7%).

Deoxytazettine.—Tazettadiol (0·25 g.) was heated on a water-bath for 1·5 hr. with 3% sulphuric acid (35 ml.). The base (0·21 g.), isolated after basification and extraction with ether, furnished *deoxytazettine*, m. p. 135—136° (from ether), $[\alpha]_D^{19}$ +225° (*c* 1·8 in EtOH) (Found : C, 68·5, 68·4; H, 6·6, 6·7; N, 4·3. $C_{18}H_{21}O_4N$ requires C, 68·6; H, 6·7; N, 4·4%).

Deoxydihydrotazettine.—Deoxytazettine (0·1 g.) in ethanol (10 ml.) was shaken with 30% palladised charcoal (0·1 g.) in an atmosphere of hydrogen for 5 hr. The crude product was chromatographed in benzene over activated alumina (2 g.). The benzene eluate gave the dihydro-compound (50 mg.), m. p. and mixed m. p. 82—84°, $[\alpha]_D^{26}$ +14·8° (*c* 0·68 in MeOH), identical with a sample of deoxydihydrotazettine (Kondo *et al.*,[5d,f]) (Found : C, 67·9; H, 7·2; N, 4·2. Calc. for $C_{18}H_{23}O_4N$: C, 68·1; H, 7·3; N, 4·4%). The *picrate*, crystallized from acetone, had m. p. 191° (decomp.) (Found : C, 52·7; H, 4·9; N, 10·2. $C_{18}H_{23}O_4N,C_6H_3O_7N_3$ requires C, 52·8; H, 4·8; N, 10·3%).

Deoxytazettine Methiodide.—Tazettadiol (1·15 g.) was refluxed for 5 hr. with methyl iodide in methanol. After concentration the residue yielded from acetone (2 ml.) the *methiodide* (0·57 g.), m. p. 231—233° (decomp.), $[\alpha]_D^{12}$ +139° (*c* 0·69 in EtOH). Re-treatment of the mother-liquors with methyl iodide and methanol in a sealed tube at 100° for 3 hr. afforded an additional quantity of the salt (0·8 g.) (Found : C, 49·8, 49·6; H, 5·1, 5·0; N, 3·1. $C_{18}H_{21}O_4N,MeI$ requires C, 49·9; H, 5·3; N, 3·1%).

Deoxytazettine (25 mg.) was refluxed for 3 hr. with methyl iodide (2 g.) in methanol (5 ml.)

to furnish a methiodide (quantitative yield), m. p. 221—223° (decomp.), identical with the sample prepared as above.

Deoxytazettine Methine.—The above methiodide (0·56 g.) in water (15 ml.) was stirred for 1 hr. with excess of freshly prepared silver oxide. The filtrate was evaporated to dryness and the residue heated at 100° for 25 min. at 2—3 mm. The product was taken up in ether, which was washed with water, then concentrated to dryness. Chromatography of the oily residue (0·36 g.) over activated alumina gave the crude *methine* (0·32 g.) from the benzene eluate; this had $[\alpha]_D^{17}$ −64·2° (*c* 1·25 in EtOH), $\lambda_{max.}$ 245 and 290 mμ (log ε 3·74 and 3·60) (Found: C, 67·7; H, 6·9. $C_{19}H_{23}O_4N$ requires C, 69·3; H, 7·0%).

The methine was converted into its *methiodide* by dissolving it (60 mg.) in methanol containing methyl iodide (3 g.) in the presence of potassium carbonate (50 mg.).

This derivative, crystallized from acetone, had m. p. 203—205° (decomp.), $[\alpha]_D^{18}$ −72·1° (*c* 0·6 in EtOH), $\lambda_{max.}$ 245 (shoulder) and 290 mμ (log ε 3·84 and 3·67) (Found: C, 51·0; H, 5·5; N, 3·0; OMe, 6·0. $C_{19}H_{23}O_4N,CH_3I$ requires C, 51·0; H, 5·6; N, 3·0; OMe, 6·6%).

Deoxytazettine neo*Methine.*—(*a*) The above methine (70 mg.) was dissolved in 5% hydrochloric acid (10 ml.); after a few minutes the clear solution became turbid and deposited crystals which were removed after 1 hr. by extraction with ether. Evaporation of the ether afforded 6-phenylpiperonyl alcohol (17 mg.), m. p. and mixed m. p. 102—104°. The aqueous acidic solution was made alkaline, then extracted with ether, to give the neo*methine* as an oil (52 mg.) which was characterized as its *methiodide*, m. p. 251° (decomp.) (from acetone), $[\alpha]_D^{18}$ ±0° (*c* 0·51 in EtOH) (Found: C, 52·1, 52·1; H, 4·8, 4·9; N, 3·7; OMe, 0·0. $C_{18}H_{19}O_3N,CH_3I$ requires C, 51·9; H, 5·1; N, 3·2%).

(*b*) Deoxytazettine methiodide (1·37 g.) in water was shaken with excess of freshly prepared silver oxide for 1 hr. After removal of the inorganic material, the filtrate and washings were evaporated to dryness *in vacuo* and heated at 100° for 30 min., then extracted with ether. Removal of the bases with 5% hydrochloric acid left 6-phenylpiperonyl alcohol as a neutral fraction (0·3 g.) which crystallized readily on concentration of the ether solution and had m. p. and mixed m. p. 101—102°. Regeneration of the basic fraction from the acidic solution gave the crude oily methine (0·55 g.) which was characterized as its methiodide (0·51 g.), m. p. 249—251° (decomp.) from acetone, identical with the *neo*methine methiodide, m. p. 251° (decomp.), described above.

2-*Methylene*-3 : 4-*benzo*-5 : 6-(3 : 4-*methylenedioxybenzo*)-*oxa*cyclo*hepta*-3 : 5-*diene* (5 : 7-*Dihydro*-7-*methylene*-2 : 3-*methylenedioxydibenz*[c,e]*oxepine*).—The above methine methiodide (0·45 g.) was converted into the hydroxide with silver oxide, then heated *in vacuo* at 100° for 15 min., after which it solidified. The ether extract, when washed with 5% hydrochloric acid, furnished the neutral optically inactive *product* (0·21 g.), m. p. 147—151° as leaflets [Found: C, 76·2, 76·0; H, 4·9, 4·6%; *M* (Rast), 250, 262. $C_{16}H_{12}O_3$ requires C, 76·2; H, 4·8%; *M*, 252] [2 : 4-*dinitrophenylhydrazone*, m. p. 227—229°, from ethanol (Found: C, 58·6; H, 4·3; N, 12·0. $C_{22}H_{18}O_7N_4$ requires C, 58·7; H, 4·0; N, 12·4%)].

The trimethylamine evolved during the degradation was collected in hydrochloric acid and precipitated as its aurichloride, m. p. and mixed m. p. 238° (decomp.) (Found: C, 9·2; H, 2·2; Au, 49·3. Calc. for $C_3H_9N,HAuCl_4$: C, 9·0; H, 2·5; Au, 49·4%).

2-*Hydroxymethyl*-4 : 5-*methylenedioxydiphenyl*-2′-*carboxylic Lactone.*—Potassium permanganate (0·4 g.) in acetone (30 ml.) was added dropwise at 50° during 6 hr. to the above methyleneoxa*cyclo*heptadiene (0·13 g.) in acetone (30 ml.). The mixture was set aside overnight and, after excess of sulphur dioxide had been bubbled in, water and 5% sulphuric acid (5 ml.) were added and the whole extracted exhaustively with ether. The extract, washed successively with 4% sodium carbonate solution and water, furnished a crystalline residue (80 mg.) which yielded the pure *lactone*, m. p. 151—152°, from acetone–methanol (Found: C, 71·3, 71·0; H, 3·9, 3·9. $C_{15}H_{10}O_4$ requires C, 70·9; H, 4·0%).

4 : 5-*Methylenedioxydiphenyl*-2 : 2′-*dicarboxylic Acid.*—(*a*) The above lactone (40 mg.) was refluxed for 1 hr. with 8% ethanolic potassium hydroxide (20 ml.), then neutralized with carbon dioxide and evaporated to dryness. To a solution of this salt mixture, potassium permanganate (0·1 g.) in water (30 ml.) was added during 5 hr. at 50°. After acidification with 20% sulphuric acid and decolorization with sulphur dioxide, the solution was extracted with ether, to give after extraction with 5% aqueous sodium carbonate the crude *diacid* (12 mg.), m. p. 251—252° after one crystallization from methanol (Found: C, 63·0; H, 3·5. $C_{15}H_{10}O_6$ requires C, 62·9; H, 3·5%).

(*b*) Methyl 6-bromopiperonylate (5 g.), methyl *o*-iodobenzoate (6 g.), and copper bronze (7 g.) were heated in a sealed tube at 225—230° for 5 hr., then cooled and taken up in chloroform.

The filtrate was washed with aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated, and the residue (8·7 g.) distilled to yield fractions : (i) not investigated (2·8 g.), b. p. 87—120°/0·3 mm.; (ii) (1·7 g.) b. p. 132—138°/0·2 mm., yielding dimethyl diphenyl-2 : 2′-dicarboxylate, m. p. 74° after three crystallizations from methanol; (iii) (2·9 g.) b. p. 170—186°/0·07 mm., which by a combination of crystallization, chromatography, and hydrolysis furnished dimethyl 4 : 5-4′ : 5′-bismethylenedioxydiphenyl-2 : 2′-dicarboxylate (0·78 g.), m. p. 155—157° (from methanol) (Found : C, 60·1; H, 3·9. Calc. for $C_{18}H_{14}O_8$: C, 60·3; H, 4·0%), and 4 : 5-methylenedioxydiphenyl-2 : 2′-dicarboxylic acid (0·55 g.), m. p. and mixed m. p. 251—252°, identical with the degradation product of tazettine above (Found : C, 62·6, 62·8; H, 3·4, 3·4%); and (iv) (0·6 g.), b. p. 190—204°/0·07 mm., which gave dimethyl 4 : 5-4′ : 5′-bismethylenedioxydiphenyl-2 : 2′-dicarboxylate (0·3 g.), m. p. 155—157° (from methanol).

Methyl 2-Formyl-4 : 5-methylenedioxydiphenyl-2′-carboxylate.—6-Bromopiperonaldehyde (2·1 g.), methyl *o*-iodobenzoate (3·5 g.), and copper bronze (4 g.) were heated in a sealed tube for 5 hr. at 230°. The resultant mixture was extracted with chloroform, the extract was filtered and evaporated; the residue, crystallized from ether, gave 2 : 2′-*diformyl*-4 : 5 : 4′ : 5′-*bismethylenedioxydiphenyl* (0·12 g.), m. p. 238—240° after many crystallizations from acetone–benzene (Found : C, 64·1; H, 3·6. $C_{16}H_{10}O_6$ requires C, 64·4; H, 3·4%). The ethereal mother-liquor was distilled and thus afforded dimethyl diphenyl-2 : 2′-dicarboxylate (0·91 g.) (m. p. 72—74°, from methanol). The distillation residue was chromatographed in benzene over activated alumina (20 g.), and the first eluate (100 ml.) was separated by fractional crystallization in methanol into the less soluble 5-*methoxycarbonyl*-2 : 3-*methylenedioxyfluorenone* (15 mg.), m. p. 180° (Found : C, 68·0; H, 3·5. $C_{16}H_{10}O_5$ requires C, 68·1; H, 3·6%), and the more soluble *aldehydo-ester* (0·37 g.), m. p. 103—104° (Found : C, 67·3; H, 4·2; OMe, 10·8, 11·3. $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·3; OMe, 10·9%). Oxidation of the latter compound with potassium permanganate gave 4 : 5-methylenedioxydiphenyl-2 : 2′-dicarboxylic acid. The second benzene eluate (100 ml.) gave, from benzene–methanol, orange-red leaflets of 1 : 2-6 : 7-*bismethylenedioxyfluorenone* (25 mg.), m. p. 278—280° (Found : C, 66·4; H, 3·0. $C_{15}H_8O_5$ requires C, 67·2; H. 3·0), and 2 : 3-methylenedioxy-5-methoxycarbonylfluorenone.

The Synthetic Lactone.—Sodium borohydride (50 mg.) in methanol (5 ml.) was added to the aldehydo-ester (142 mg.) in methanol (10 ml.). After 1 hr., potassium hydroxide was added and the whole refluxed for a further hour. The solvent was then removed *in vacuo* and the ether extract of the residue in water furnished 2 : 2′-*bishydroxymethyl*-4 : 5-*methylenedioxydiphenyl* (15 mg.), m. p. 134—135° (from ether) (Found : C, 69·5; H, 5·3. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·5%). The aqueous solution was acidified with 20% sulphuric acid and extracted with ether which was then washed with water, dried, and evaporated to dryness. The residual oil after 0·5 hr. at 100° gave the solid lactone (103 mg.), obtained pure (65 mg.) after crystallization from acetone and then ether (m. p. and mixed m. p. 151—152° with the degradation product of tazettine described above) (Found : C, 70·5; H, 4·0. Calc. for $C_{15}H_{10}O_4$: C, 70·9; H, 4·0%). When reduction of the aldehydo-ester was carried out with excess of sodium borohydride, the main product was the diol described above.

3 : 4-*Benzo*-5 : 6-(3 : 4-*methylenedioxybenzo*)-*oxa*cyclo*heptadiene* (5 : 7-*Dihydro*-2 : 3-*methylenedioxydibenz*[c,e]*oxepine*).—The above diol (70 mg.) was refluxed in ethanol (20 ml.) containing concentrated sulphuric acid (0·6 g.) for 3 hr., then after concentration to one-third of the volume water was added and the precipitate was filtered off to furnish from acetone the pure *ether*, m. p. 138—139° (Found : C, 74·7; H, 4·9. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0%).

10-*Methyl*-6 : 7-*methylenedioxyphenanthridone.*—Tazettine (0·5 g.), aluminium phenoxide (5 g.), *cyclo*hexanone (50 ml.), and xylene (50 ml.) were heated under reflux for 6 hr. After addition of ice-water, the mixture was extracted repeatedly with 10% hydrochloric acid, and the combined aqueous extracts were basified with sodium hydroxide solution, extracted with chloroform, and dried (K_2CO_3). Evaporation afforded an oil (0·17 g.), which with 5% hydrochloric acid furnished a crystalline chloride (75 mg.). On recrystallization from pyridine–ethanol this gave pure 10-*methyl*-6 : 7-*methylenedioxyphenanthridinium chloride* (30 mg.), m. p. 274 (decomp.) (Found : C, 61·3; H, 4·9; N, 4·4; NMe, 3·9. $C_{15}H_{12}O_2NCl,H_2O$ requires C, 61·7; H, 4·8; N, 4·8; NMe, 5·1%), $\lambda_{max.}$ 265 and 340 mμ (log ε 4·51 and 4·07 respectively).

The iodide was obtained by addition of sodium iodide to an aqueous solution of the chloride and had m. p. >310° (Found : C, 46·8; H, 3·6; N, 3·6. Calc. for $C_{15}H_{12}O_2NI,H_2O$: C, 47·0; H, 3·7; N, 3·7%).

The phenanthridinium chloride (30 mg.) in ethanol (25 ml.) was heated on a water-bath for 1 hr. with sodium hydroxide (0·1 g.). Removal of the ethanol *in vacuo* followed by addition of dilute hydrochloric acid gave a water-insoluble substance which was taken up in chloroform.

Evaporation of the chloroform followed by recrystallization of the residue from ethanol–benzene gave 10-methyl-6 : 7-methylenedioxyphenanthridone (18 mg.), m. p. and mixed m. p. 236—238° (Found : C, 70·92; H, 4·3; N, 5·3. Calc. for $C_{15}H_{11}O_3N$: C, 71·1; H, 4·4; N, 5·5%), $\lambda_{max.}$ 250, 270, 285, 299, 310, 325, and 340 mμ (log ε 4·50, 4·23, 4·01, 4·05, 4·05, 3·93, and 3·84 respectively).

O-*Methyltazettine*.—(*a*) Tazettine (0·3 g.) in methanol (20 ml.) was kept for 10 days at room temperature in excess of ethereal diazomethane (fresh portions being added every 3 days). The mixture was evaporated to dryness, the residue extracted with 5% hydrochloric acid was then basified, and the bases were taken up in ether. Concentration of the ethereal solution afforded crystals of unchanged tazettine (84 mg.), m. p. and mixed m. p. 208°. The mother-liquor was concentrated to dryness and chromatographed in benzene over activated alumina. The first benzene eluate afforded oily *O*-methyltazettine (0·158 g.), and the second eluate a further quantity of tazettine (36 mg.). *O*-Methyltazettine was readily soluble in organic solvents and did not crystallize even after long storage at 0°; it was, however, characterized through its crystalline *styphnate*, m. p. 198° (decomp.) from methanol (Found : C, 50·6; H, 4·3; N, 9·5; OMe, 10·5. $C_{19}H_{23}O_5N,C_6H_3O_8N_3$ requires C, 50·8; H, 4·4; N, 9·5; 2OMe, 10·5%), and gave with tazettine styphnate (m. p. 204°) a depressed mixed m. p. *ca.* 184°. A sample of *O*-methyltazettine regenerated from the styphnate had $[\alpha]_D^{26}$ +88·1° (*c* 0·8 in EtOH).

(*b*) Tazettine (0·2 g.) and thionyl chloride (7 ml.) were heated on a water-bath for 40 min., then the excess of chloride was removed *in vacuo*, and the residue refluxed for 3 hr. in sodium methoxide solution prepared from sodium (0·5 g.) in methanol (50 ml.). Water was added and the whole extracted with ether which in turn was extracted with 3% hydrochloric acid. The bases were liberated with sodium carbonate and extracted with benzene. The dried extract was chromatographed over activated alumina, and the first fraction (40 mg.) furnished on addition of ethereal styphnic acid crude *O*-methyltazettine styphnate, m. p. 188—190°. The second fraction (40 mg.) gave the pure derivative, m. p. and mixed m. p. 198° with the sample prepared as above. Succeeding fractions afforded amorphous material (100 mg.) which was not further investigated.

O-Methyltazettine with methyl iodide in methanol yielded the methiodide, m. p. 138° (decomp.) (from methanol) raised to 150—152° by drying at 110° *in vacuo* (Found : C, 47·7; H, 5·5. Calc. for $C_{19}H_{23}O_5N,CH_3I,H_2O$: C, 47·5; H, 5·6%). No m. p. depression was observed when the sample was mixed with the methiodide prepared by Kondo and Ikeda by use of dimethyl sulphate and sodium hydroxide, and then potassium iodide. The *methopicrate*, formed readily on addition of saturated aqueous picric acid to *O*-methyltazettine methiodide in hot water, had m. p. 189—190° (from methanol) (Found : C, 53·0; H, 4·7; N, 9·5; OMe, 10·9. $C_{20}H_{26}O_5N,C_6H_2O_7N_3$ requires C, 53·1; H, 4·8; N, 9·5; 2OMe, 10·5%).

O-Methyltazettine (40 mg.) and lithium aluminium hydride (70 mg.) were refluxed in tetrahydrofuran (15 ml.) for 2 hr. It was isolated unchanged, being characterized as its styphnate, m. p. and mixed m. p. 198° (decomp.).

Dihydrotazettine Methine.—Dihydrotazettine (0·5 g.) was refluxed with methyl iodide (1·5 ml.) and methanol (15 ml.) to furnish the methiodide (0·4 g.), m. p. 183° (decomp.) (from ethanol) (Found : C, 47·7; H, 5·6; N, 2·9. Calc. for $C_{18}H_{23}O_5N,CH_3I$: C, 48·0; H, 5·5; N, 3·0%). This (0·3 g.) was converted into the hydroxide with silver oxide, then heated *in vacuo* for 45 min. at 100°. The product taken up in ether was converted into the *methine picrate* (0·19 g.) which was purified by crystallization from ethanol to m. p. 129—131°, raised to 137—139° on drying *in vacuo* (Found : C, 52·4; H, 5·0; N, 9·7. $C_{19}H_{25}O_5N,C_6H_3O_7N_3$ requires C, 52·1; H, 4·9; N, 9·7%). The methine generated from its picrate is an oil, $[\alpha]_D^{25}$ +15·8° (*c* 1·2 in EtOH), $\lambda_{max.}$ 245 and 290 mμ (log ε 3·74 and 3·60 respectively).

Reduction of Dihydrotazettine Methine with Lithium Aluminium Hydride.—The methine (0·22 g.) and lithium aluminium hydride (0·2 g.) in ether (10 ml.) were refluxed for 2 hr. After addition of water and filtration, the ethereal solution was concentrated and treated with a saturated solution of picric acid. The precipitated picrate (25 mg.), m. p. 92—94° was identical with dimethylaminoethanol picrate. The neutral portion (0·15 g.) of the reduction product did not crystallize and had $\lambda_{max.}$ 240 and 290 mμ (log ε 3·64, 3·55).

Tazettamide.—Tazettine (1·3 g.) in chloroform (130 ml.) was stirred with manganese dioxide (13 g.) for 48 hr. at room temperature. Chromatography of the crude product over activated alumina gave, from the benzene fraction, tazettamide (0·45 g.), m. p. 174° (lit., 176—178°), $[\alpha]_D^5$ +113° (*c* 0·6 in EtOH) (lit., $[\alpha]_D^{25}$ +106° in $CHCl_3$), $\lambda_{max.}$ 240 and 293 mμ (log ε 3·57 and 3·6 respectively), ν(C=O) 1666 and 1724 cm.$^{-1}$ in Nujol mull (Found : C, 62·3; H, 5·3; N, 4·0. Calc. for $C_{18}H_{19}O_6N$: C, 62·6; H, 5·6; N, 4·1%).

Dihydrotazettamide.—Hydrogenation of tazettamide in ethanol over palladium–charcoal furnished the dihydro-compound, m. p. 157—158°, $[\alpha]_D^5$ +63° (*c* 0·6 in EtOH) (lit., m. p. 161—162°, $[\alpha]_D^{25}$ +73·3 in $CHCl_3$) (Found : C, 62·9; H, 6·1. Calc. for $C_{18}H_{21}O_6N$: C, 62·2; H, 6·1%).

Reduction of Dihydrotazettamide.—Dihydrotazettamide (0·5 g.) in tetrahydrofuran was reduced with lithium aluminium hydride (0·3 g.) at room temperature. The crude oily basic fraction was heated in 3% sulphuric acid (20 ml.) at 100° for 2 hr. Basification and extraction with ether afforded the amino-ether (315 mg.), whose *picrate* crystallized in yellow needles (from ethanol), m. p. 226—228° (decomp.) (Found : C, 52·8; H, 5·2; N, 10·1. $C_{18}H_{25}O_4N,C_6H_3O_7N_3$ requires C, 52·6; H, 5·2; N, 10·2%).

Emde Degradation of the Amino-ether.—The above amino-ether (297 mg.) with methyl iodide in boiling methanol gave the methiodide (360 mg.), $[\alpha]_D^5$ −31·2° (*c* 0·7 in EtOH), which did not crystallize. The methiodide (150 mg.) was converted into its methochloride by shaking with silver chloride, then filtered and concentrated to 4 ml. 5% Sodium amalgam (20 g.) was added and the mixture heated at 100° for 6 hr., during which an oil separated and trimethylamine was liberated. The oil was taken up into ether, washed with dilute hydrochloric acid, then water, and dried (K_2CO_3). Removal of the ether gave an oil which on chromatography over activated alumina furnished, from the benzene eluate, 4-*methoxy*cyclo*hexane*spiro-4-(6 : 7-*methylenedioxy*-iso*chroman*) (XVIII) (46 mg.), m. p. 56—58° (from ethanol), $[\alpha]_D^5$ ±0° (*c* 0·6 in EtOH) (Found : C, 70·2; H, 7·2. $C_{16}H_{20}O_4$ requires C, 69·6; H, 7·3%). Repetition of this experiment gave the same product also with zero rotation.

Action of Hydrochloric Acid on Tazettine.—Tazettine (0·5 g.) in 10% hydrochloric acid (50 ml.) was heated on a water-bath for 4 hr., then cooled, washed once with benzene, basified (K_2CO_3), and extracted thoroughly with chloroform. The dried chloroform extracts on concentration afforded a syrup (0·45 g.) which was chromatographed in benzene over activated alumina. The benzene–chloroform (1 : 1) eluate gave iso*tazettinol* (0·3 g.), m. p. 204—206°, $[\alpha]_D^{20}$ +261·7° (*c* 0·5 in EtOH), after crystallization from ethanol (Found : C, 64·6, 64·3; H, 6·1, 6·2; N, 4·5; OMe, 0·0. $C_{17}H_{19}O_5N$ requires C, 64·3; H, 6·0; N, 4·4%). This compound depressed the m. p. of tazettine (207°) to 172—180°, but gave no depression on admixture with a sample of the " iso-tazettine " obtained by Kondo and Ikeda.[5b] *iso*Tazettinol gave a *picrate*, m. p. 223—226° (decomp.), needles from ethanol (Found : C, 51·3; H, 4·1; N, 10·4. $C_{17}H_{19}O_5N,C_6H_3O_7N_3$ requires C, 50·6; H, 4·1; N, 10·3%).

The mother-liquor from the crystallization of *iso*tazettinol was concentrated, and the residue in ethereal solution was converted into a picrate. Fractional crystallization gave a *picrate* (20 mg.), m. p. 173—175° (decomp.) with ν(C=O) at 1750 $cm.^{-1}$ (Found : C, 52·8, 52·6; H, 3·8, 3·7; N, 10·5. $C_{17}H_{17}O_4N,C_6H_3O_7N_3$ requires C, 52·7; H, 3·8; N, 10·6%). Acetylation of *iso*tazettinol with sodium acetate and acetic anhydride gave the *diacetyl derivative*, m. p. 149—151°, $[\alpha]_D^{26}$ +198° (*c* 0·6 in EtOH) (from ethanol), ν(C=O) 1740 and 1750 $cm.^{-1}$ in Nujol mull (Found : C, 62·1; H, 5·6; N, 3·3; Ac, 21·7. $C_{21}H_{23}O_7N$ requires C, 62·8; H, 5·8; N, 3·5; 2Ac, 21·5%). Hydrolysis with 3% ethanolic potassium hydroxide regenerated *iso*tazettinol.

Further elution of the column with acetone afforded *tazettinol* (0·1 g.), m. p. 187—188°, $[\alpha]_D^{26}$ +119° (*c* 0·5 in EtOH) (from water) (Found, in a sample dried at 100° over P_2O_5 for 3 days : C, 64·3; H, 5·7%). Its picrate had m. p. 206—208° (from water) (Found : C, 49·2; H, 4·3; N, 10·2. $C_{17}H_{19}O_5N,C_6H_7O_7N_3,0{\cdot}5H_2O$ requires C, 49·7; H, 4·2; N, 10·1%), and its *diacetyl derivative* m. p. 199—200°, $[\alpha]_D^{26}$ +55° (*c* 0·4 in EtOH) (from ethanol), ν(C=O) 1760 and 1730 $cm.^{-1}$ (Nujol mull) (Found : C, 62·7; H, 5·4; N, 3·4; Ac, 20·4%). Hydrolysis with 3% ethanolic potassium hydroxide regenerated tazettinol.

*Deoxy*iso*tazettinol.*—(*a*) *iso*Tazettinol (70 mg.) and lithium aluminium hydride (50 mg.) were refluxed in tetrahydrofuran (10 ml.) for 3 hr., then treated with water and filtered, and the precipitate washed with chloroform. The combined organic filtrates were concentrated to dryness, to yield an oily triol (70 mg.). This was heated on a water-bath for 1 hr. with 2·5% sulphuric acid (5 ml.), then basified and extracted with ether to furnish *deoxy*iso*tazettinol* (40 mg.), m. p. 122—123° (from ether), $[\alpha]_D^{10}$ +328° (*c* 0·39 in EtOH) (Found : C, 67·1, 67·2; H, 6·3, 6·2. $C_{17}H_{19}O_4N$ requires C, 67·8; H, 6·4%). The picrate had m. p. 203—206° (from ethanol), and the p-*nitrobenzoate* (from methanol) had m. p. 185—186° (Found : C, 63·6; H, 4·9; N, 6·3. $C_{24}H_{22}O_7N_2$ requires C, 63·9; H, 4·9; N, 6·2%).

(*b*) Tazettadiol (0·1 g.), when heated with 10% hydrochloric acid (10 ml.) for 4 hr., basified, and extracted with ether, gave a residue (80 mg.) which on chromatography in ether over activated alumina afforded, from the first eluate, deoxy*iso*tazettinol (20 mg.), m. p. and mixed m. p. 120—121°. Further elution of the column with chloroform furnished oils which were combined and converted into a mixture of *p*-nitrobenzoates. Chromatography of these esters

gave in small yield pure deoxytazettinol *p*-nitrobenzoate (5 mg.), m. p. and mixed m. p. 171—172° which depressed greatly the m. p. of the same derivative of deoxy*iso*tazettinol.

Methylation of Tazettinol.—10% Aqueous potassium hydroxide (14 ml.) was added at a rate of 30 drops an hour to a stirred mixture of tazettinol (30 mg.) and dimethyl sulphate (2·6 g.). The mixture was then neutralized with dilute sulphuric acid and extracted with chloroform. Evaporation of the chloroform solution to dryness and re-extraction of the residue with chloroform gave *O*-methyltazettine methiodide (30 mg.), m. p. and mixed m. p. 152—154° (decomp.), $[\alpha]_D^{24}$ +66° (*c* 0·95 in EtOH) (from acetone–methanol).

Methylation of iso*Tazettinol.*—*iso*Tazettinol (0·1 g.) was methylated in a way similar to that described for tazettinol, to yield O-*methyliso*tazettine *methiodide* (0·1 g.), $[\alpha]_D^{24}$ +143° (*c* 0·95 in EtOH) (Found: C, 49·5; H, 5·4; N, 2·9; OMe, 13·1, 12·9. $C_{20}H_{26}O_5NI$ requires C, 49·3; H, 5·4; N, 2·9; 2OMe, 12·7%). The *methopicrate* had m. p. 204—205° (from methanol) (Found: C, 53·1; H, 4·7; N, 9·9. $C_{20}H_{26}O_5N,C_6H_2O_7N_3$ requires C, 53·1; H, 4·8; N, 9·5%).

Deoxytazettinone.—(*a*) Deoxy*iso*tazettinol (0·27 g.) in dry ether (30 ml.) was stirred over manganese dioxide (3 g.) for 6 days during daylight hours. The mixture was filtered and the manganese dioxide washed well with ether. Fractional crystallization, from ethanol, of the product from the ethereal filtrate gave starting material (148 mg.) and *deoxytazettinone* (30 mg.), m. p. 174—175°, $[\alpha]_D^{10}$ +398° (*c* 0·2 in EtOH), $\lambda_{max.}$ 235 and 290 mμ (log ε 4·07 and 3·79 respectively), ν(C=O) 1680 cm.$^{-1}$ (Found: C, 68·1; H, 5·7. $C_{17}H_{17}O_4N$ requires C, 68·2; H, 5·7%).

(*b*) Deoxy*iso*tazettinol (0·1 g.) in pyridine (1 ml.) was added to a suspension of chromic oxide (0·1 g.) in pyridine (1 ml.). After 12 hr. the mixture was poured into water, then the solvent was removed *in vacuo*. The residue was extracted with 3% hydrochloric acid which, after being washed with ether, was basified with ammonia, and the bases were extracted with ether to furnish the crude ketone (55 mg.) which was obtained pure (32 mg.), m. p. and mixed m. p. 172—174°, after one crystallization from methanol.

*Reduction of Deoxyiso*tazettinone.—The above ketone (26 mg.) in methanol (2 ml.) containing sodium borohydride (20 mg.) was set aside for 2 days. After removal of the methanol *in vacuo*, water was added and the mixture was extracted with ether, then concentrated to dryness and chromatographed over activated alumina. The light petroleum–benzene (1 : 1) eluate gave an oil (3 mg.); elution with benzene then gave deoxy*iso*tazettinol (20 mg.), m. p. and mixed m. p. 121—122°. The infrared spectrum and optical rotation of this were also identical with an authentic sample.

Deoxytazettinol.—Tazettinol (163 mg.) and lithium aluminium hydride (100 mg.) were heated in tetrahydrofuran (6 ml.) for 5 hr. under reflux. After 12 hr. a little water was added and the precipitate removed by filtration, then washed with chloroform. The combined filtrates were concentrated to dryness, then dissolved in 3% sulphuric acid (20 ml.) and heated on a water-bath for 2 hr. Basification and extraction of the acidic solution afforded an oil (130 mg.) which after chromatography in benzene over activated alumina gave *deoxytazettinol* (32 mg.), m. p. 122—123°, $[\alpha]_D^{16}$ +210° (*c* 0·34 in EtOH) (from ether–light petroleum) (Found: C, 67·6; H, 6·3; N, 4·4. $C_{17}H_{19}O_4N$ requires C, 67·8; H, 6·4; N, 4·7%). The *picrate* (from ethanol) had m. p. 225° (decomp.) (Found: C, 51·8; H, 4·0; N, 10·8. $C_{17}H_{19}O_4N,C_6H_3O_7N_3$ requires C, 52·1; H, 4·2; N, 10·6%). The p-*nitrobenzoate* had m. p. 171—172° (from ethanol) (Found: C, 63·9; H, 4·9; N, 6·3. $C_{24}H_{22}O_7N_2$ requires C, 64·0; H, 4·9; N, 6·2%). The first eluate and the mother-liquors from the crystallization of deoxytazettinol were combined and converted into a mixture of picrates which was separated into a slightly soluble and a more soluble compound. The former picrate in acetone–chloroform gave, on filtration through activated alumina, deoxytazettinol (35 mg.), and the latter picrate by the same procedure furnished deoxy*iso*tazettinol (40 mg.).

Deoxytazettinone from Deoxytazettinol.—Deoxytazettinol (20 mg.) in ether (10 mg.) was stirred with manganese dioxide (0·2 g.) at room temperature for 1 hr. After removal of the manganese dioxide and concentration to dryness, the residue was chromatographed over activated alumina to yield from the benzene eluate deoxytazettinone (17 mg.), m. p. and mixed m. p. 174—175°, $[\alpha]_D^{10}$ +395° (*c* 0·5 in EtOH) [*oxime*, m. p. 204—206° after crystallization first from ethanol and then benzene, $\lambda_{max.}$ 235 and 290 mμ (log ε 4·21 and 3·68 respectively) (Found: N, 9·0. $C_{17}H_{18}O_4N_2$ requires N, 8·9%)].

6-p-*Methoxyphenylpiperonyl Alcohol from Tazettinol.*—Tazettinol (0·2 g.) and manganese dioxide (2 g.) in chloroform (20 ml.) were shaken at room temperature for 2 hr., then filtered. The filtrate was evaporated to dryness to afford a residue (54 mg.). The manganese dioxide was dissolved in aqueous sulphurous acid which was then basified with potassium carbonate and

extracted with chloroform. This solution yielded a further oxidation product (133 mg.) which was combined with the 54 mg. isolated as above and taken up again in chloroform and extracted with dilute acid which removed some unchanged starting material (20 mg.). Concentration of the chloroform solution afforded a 6-p-*hydroxyphenylpiperonyl alcohol* (32 mg.), m. p. 186—188°, $\lambda_{max.}$ 230, 257, and 292 mμ (log ε 4·16, 4·01, and 3·80 respectively) (Found: C, 69·1; H, 5·1. $C_{14}H_{12}O_4$ requires C, 68·8; H, 5·0%). Treatment of the phenol (12 mg.) with excess of diazomethane furnished 6-*p*-methoxyphenylpiperonyl alcohol, m. p. and mixed m. p. 147—149°.

Hofmann Degradation of O-*Methyl*iso*tazettine Methiodide*.—The methiodide (0·62 g.) in water (10 ml.) was shaken with excess of silver oxide, then filtered and evaporated to dryness. The residue was heated *in vacuo* at 100° for 30 min., then taken up in ether which was extracted with 3% sulphuric acid. From the ether layer 6-phenylpiperonyl alcohol (28 mg.), m. p. 102—104°, was obtained. The crude methine base (0·32 g.) isolated from the acidic solution was refluxed with methyl iodide (3 g.) in methanol (3 ml.). The crude gummy methiodide was converted into the hydroxide by means of silver oxide, and the resulting solution concentrated and heated at 100° *in vacuo* for 30 min. The product was taken up in ether, washed with 3% sulphuric acid and water, then dried and concentrated to dryness, and the residue (65 mg.) chromatographed over activated alumina. The benzene eluate afforded 6-*p*-methoxyphenylpiperonyl acetate (10 mg.), m. p. 86—88° after crystallization from light petroleum; and from the benzene methanol eluate 6-*p*-methoxyphenylpiperonyl alcohol (30 mg.), m. p. 145—147°, was obtained. Both compounds were identical with authentic samples.

Dissociation Constants.—pK_a's were found for the following compounds measured in 80% Methylcellosolve–water and in parentheses in 40% methanol–water: tazettine, 6·14 (6·86); dihydrotazettine, 6·10; tazettadiol, 6·23; *iso*tazettinol, (7·75); diacetyl*iso*tazettinol, (6·53); acetyltazettine, (5·92); deoxy*iso*tazettinol, (8·7); deoxytazettinol, (7·1).

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