Action of *N*-Bromosuccinimide on Some Indolizidine and Quinolizidine Systems

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Oxidation of the alkaloids (-)tylocrebrine, (-)septicine and (±)canadine by *N*-bromosuccinimide gave the corresponding tetradehydroiminium salts in which the six-membered heterocyclic rings were aromatized. Evidence was provided for the preferred path of the two available alternatives. Reduction of these salts with sodium borohydride regenerated the starting bases but without the optical activity. In contrast to the simpler 1,2,3,4-tetrahydroisoquinolines, hydrastine gave a brominated isoquinolinium salt with the loss of dimethoxy phthalide anion. A discussion of the stoichiometry and a probable mechanism is presented.

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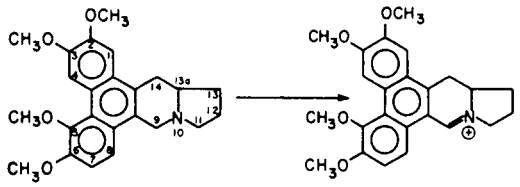
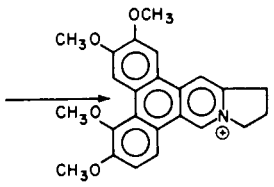
Dunstan and Henbest (2) showed that oxidation of tertiary amines by *N*-bromosuccinimide (NBS) resulted in the cleavage of a C-N bond and formation of a mixture of a secondary amine and an aldehyde, with enamines postulated as intermediates. They recognized a 'colored intermediate' which was later pictured by Horner *et al.*, (3) as an iminium salt generated from an α-bromo tertiary amine through an internal nucleophilic displacement. Such an iminium salt can either undergo deprotonation to an enamine or hydrolysis to the above products. Conversion of a number of *N*-alkyl tetrahydroisoquinolines to 3,4-dihydroisoquinolinium salts with NBS was reported by Eckhart although no mechanism was proposed (4). In the present study which involved some alkaloids with cyclic tertiary amine function, we observed that oxidation with NBS could proceed further to give fully aromatized heterocyclic systems and other novel products.

Treatment of (-)tylocrebrine (**1**) (5) in chloroform with NBS gave a yellow crystalline solid whose chemical and spectral properties showed agreement with the structure **2**: a tetradehydroimminium salt. The oxidation most likely proceeded *via* the didehydroiminium salt **3** because, incomplete reaction due either to insufficient reagent or time gave varying amounts of **3**. The nmr spectrum of **2** gave convincing evidence for the aromatized ring D such as: (numbers in parentheses represent positions) τ 0·13, s, 1H (9); τ 0·62, s, 1H (14); τ 4·83, t, 2H (11); τ 6·20, t, 2H (13) and τ 7·22, quintet, 2H (12). The rest of the aromatic proton signals were similar to those of **1**.

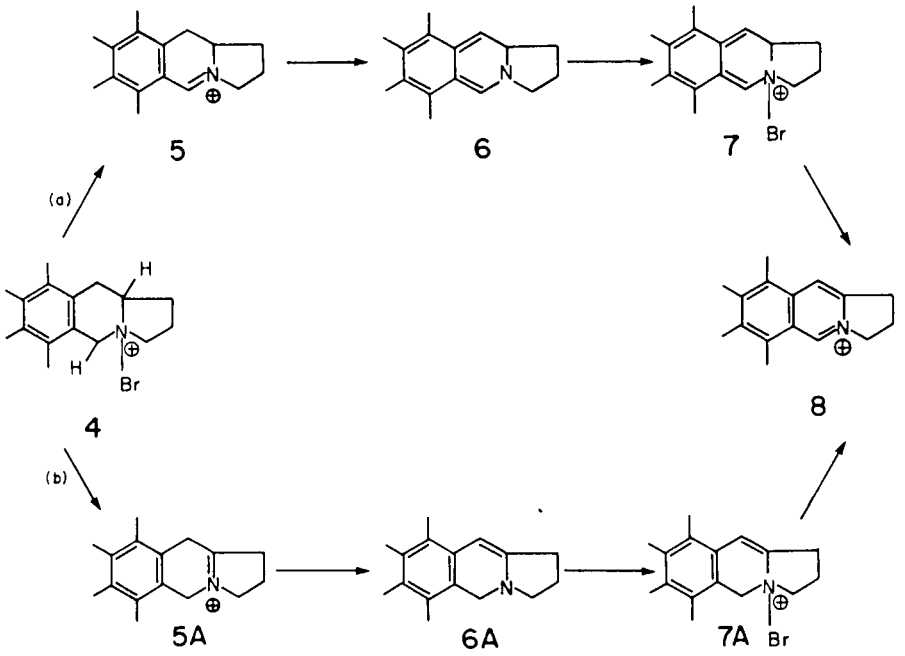


1 **3**



2

Reduction of **2** with sodium borohydride gave a base identical with **1** except that it was optically inactive. This and the fact that **2** was also optically inactive gave further support for the aromatized D-ring. Another significant point was the simultaneous reduction of both double bonds introduced during the oxidation. Samples of **2** which contained varying amounts of **3** also showed negligible optical rotation but, on reduction, generated varying degrees of specific rotation (20-40% of that of **1**). Complete

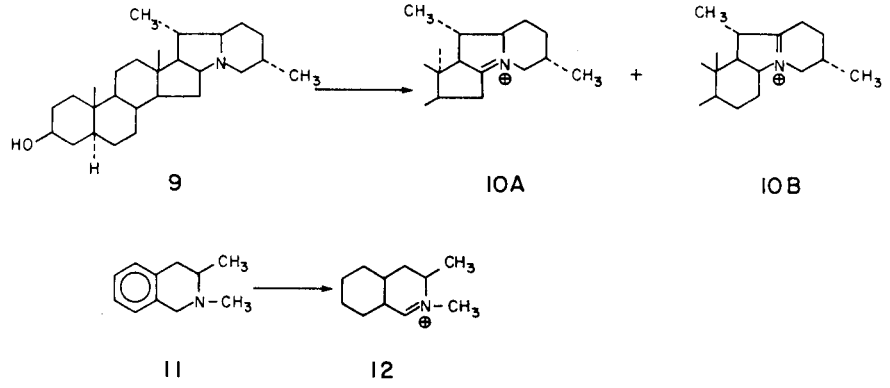


conversion of **1** to **2** was possible by the use of three moles of reagent while two moles gave mixtures of **2** and **3**. Purification of **3** (free from **2**) was not possible. Although separation was possible by a quick tlc on alumina, a preparative plate gave only **2**. This was because of the facile conversion of **3** to **2** which could be readily shown by stirring an ethanolic solution of **3** with alumina.

A mechanism for the oxidation may be proposed similar to that of Leonard *et al.*, (6) for the oxidation of tertiary amines by mercuric acetate. Attack of the basic nitrogen by the 'positive' bromine to form the *N*-bromo-quarternary complex **4** is postulated as the first step. The extremely rapid reaction between the base and NBS suggests that **4** is more probable than a benzylic bromination product visualized by Horner *et al.*, (3). An elimination step involving either the benzylic proton (path a) or the tertiary proton (path b) of **4** to form the iminium salt **5** or **5a** follows. Next deprotonation of **5** (or **5a**) to the enamine **6** (or **6a**) which can again be oxidized by NBS *via* the *N*-bromo-quarternary complex **7** (or **7a**) to the final product **8** completes the sequence.

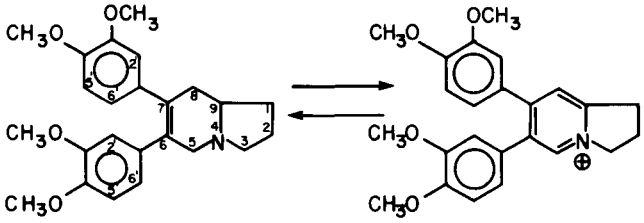
A choice between the two alternative routes (a) and (b) is difficult to make at this point. Results of Eckhart (4) favor (a) while those of Schreiber and Horstmann (6) on the oxidation of demissidine **9** by NBS (or mercuric acetate) which gave the same product mixture **10a** and **10b** indicate that (b) is also probable.

However, preference for path (a) was observed in the case of oxidation of 2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline **11** by NBS which gave the 3,4-dihydroisoquinolinium salt **12**. In addition, the fact that reduction of mixtures of **2** and **3** gave **1** with partial retention of optical activity while that of **2** gave optically inactive **1**, strongly indicate that the dihydro iminium salt must have the structure **3**



which would be formed by path (a).

In order to ascertain whether aromatization of ring D might have been favored by the presence of a phenanthrene skeleton in **1**, the reaction was studied with the closely related *seco* alkaloid, (-)septicine (**13**) (8). The product **14** was readily formed. Although noncrystalline, **14** showed nmr spectral data which clearly indicated that the

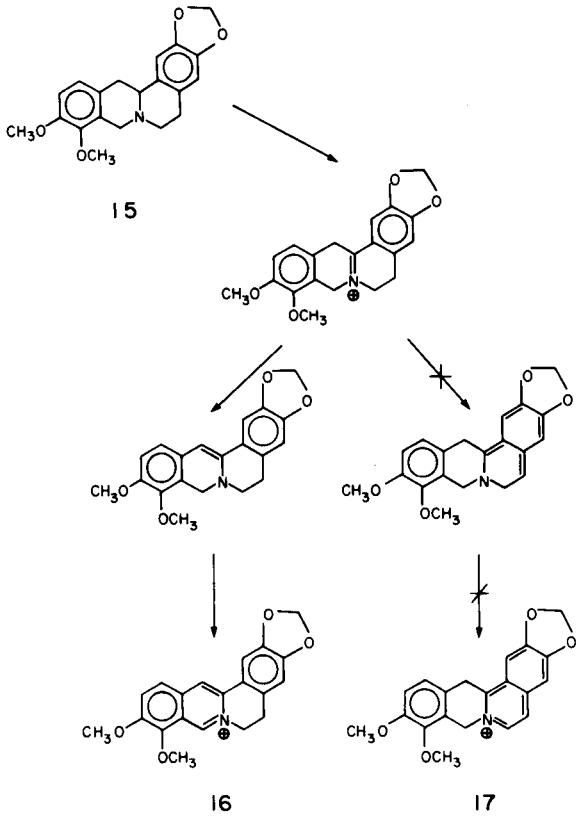


13 14

six-membered heterocyclic ring was aromatic: τ 0·67, s, 1H (5); τ 2·13, s, 1H (8); τ 3·00-3·33, m, 6H (2′,5′,6′); τ 4·75, t, 2H (3); τ 6·38, t, 2H (1) and τ 7·33, quintet, 2H (2). Reduction of **14** gave **13** but with no optical activity.

A similar behavior was observed in the oxidation of (±)canadine (**15**) by NBS. The crystalline product **16**, obtained in high yield, showed chromatographic and spectral behavior identical with that of authentic berberine. There was no trace of the other alternative product, isoberberine **17**.

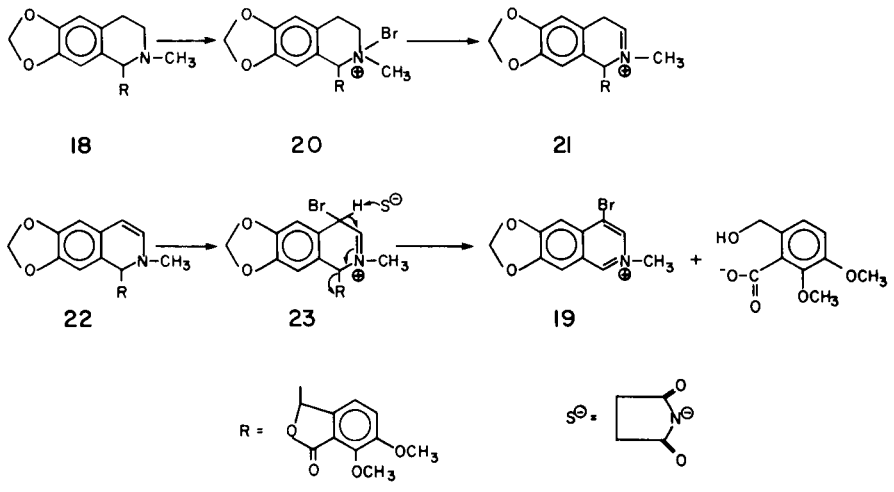
In contrast to the simpler 1,2,3,4-tetrahydroisoquinolines, oxidation of the alkaloid (-)hydrastine (**18**) with NBS in chloroform was found to give a mixture of products, the major one being a crystalline solid, $C_{11}H_9Br_2^+ NO_2^-$. One of the bromine atoms was ionic. Its nmr spectrum was relatively simple: τ 0·34, s, 1H; τ 1·57, s,



15 16 17

1H; τ 2·47, s, 1H; τ 2·37, s, 1H; τ 3·64, s, 2H and τ 5·53, s, 3H. The mass spectrum did not show a molecular ion but did show a fragment at M^+-CH_3Br which still contained a bromine. These results were consistent with the structure **19**. A probable path of the reaction is shown below:

Formation of the 1,3-dihydroisoquinolinium salt **21** (instead of the alternative 3,4-dihydroisoquinolinium salt) is proposed as the first step. Molecular models of **20** show



18 20 21

22 23 19

possible steric inhibition for the abstraction of the tertiary benzylic proton. Deprotonation of **21** to the enamine **22** and bromination (analogous to the known mode of protonation of **21** to the enamine **22** and bromination (analogous to the known mode of protonation of enamines) gives **23** which undergoes elimination to form the product **19** and the dimethoxyphthalide anion. The presence of other products in the reaction mixture suggests that alternative reactions were also occurring.

The stoichiometry of the NBS-oxidations was determined by iodometric titration (9) of the reaction mixtures. The results shown in Table I indicate that formation of didehydro products requires two moles of reagent and that of tetradehydro products, three moles of reagent. Tetrahydroisoquinolines which form 3,4-dihydroisoquinolinium salts represent the first type. This result, however, contradicts that of Eckhart (4) who reported a near quantitative yield of the 3,4-dihydroisoquinolinium salt with one mole of reagent. Our titration result (2 moles) was confirmed further by tlc and spectrophotometry; with one mole of the reagent, the reaction was incomplete (tlc) although the reagent was not detectable. With the second mole of NBS, the concentration of the iminium salt (λ 280) was double that seen after one mole. Only a trace of the reagent could be detected. With the third mole of NBS, the iminium salt did not increase and excess reagent remained.

Table I

Stoichiometry of NBS-Oxidations (a)

Compound oxidized	Moles of NBS per mole
1	3.2
1	2.8 (b)
1	3.0 (c)
1	3.2 (d)
13	3.2
15	3.2
18	3.1
1,2,3,4-Tetrahydroisoquinolines	
2-Methyl	2.1 (e)
2,3-Dimethyl	2.1
2-Methyl-6,7-methylenedioxy	1.9
Tylocrebrine methiodide	0.3 (f)
2,2-Dimethyl-1,2,3,4-tetrahydroisoquinolinium iodide	0.15 (f)

(a) All oxidations were performed in chloroform for 30 minutes. (b,c,d) Solvent used: dichloromethane, benzene and acetic acid respectively. (e) The same compound studied by Eckhart (4). (f) At the end of 30 minutes, a gradual consumption of the reagent took place on standing with starting material being still present at 24 hours.

Konigsburg *et al.*, (10) reported that oxidative decarboxylation of amino acids required two moles of NBS, although in this case the ammonia could account for the second mole of reagent.

Compounds **1**, **13**, **15** and **18** which gave tetradehydroiminium salts required three moles of NBS. Here again, spectrophotometry and tlc (using **1**) confirmed this stoichiometry. At present, no explanation for the requirement of 2 and 3 moles of reagent for the oxidation can be offered consistent with the proposed mechanism. Further studies in this area are in progress.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and were uncorrected. The following instruments were used for the spectra described here. Beckman DB (UV), Beckman Acculab 3 (ir), Varian A60 A with tetramethylsilane as internal standard (nmr) and Hitachi-Perkin-Elmer single focusing mass spectrometer (mass spectra).

Oxidation of (-)Tylocrebrine to the Iminium Salt **2**.

To a solution of (-)tylocrebrine (**8**, 0.39 g., 1 mmole) in chloroform (10 ml.) was added *N*-bromosuccinimide (0.78 g., 4 mmoles) in small portions with stirring. The solution turned orange red and began to deposit an orange crystalline solid. After 30 minutes following the addition, the solid was filtered and washed with methanol-ethyl acetate (1:3). It was recrystallized from methanol-ethyl acetate (1:1), m.p. 230-231°; yield, 0.35 g. (75%).

Anal. Calcd. for $C_{24}H_{24}BrNO_4$: C, 61.28; H, 5.14; Br, 16.99; N, 2.98. Found: C, 61.04; H, 5.20; Br, 16.72; N, 2.84.

Reduction of the Iminium Salt **2** to (±)Tylocrebrine.

The iminium salt **2** (0.1 g.) was suspended in methanol (2 ml.) and treated with sodium borohydride (0.02 g.). Immediate decolorization followed and a nearly colorless crystalline solid began to separate. The mixture was diluted with water and extracted twice with chloroform. Concentration of the solvent layer gave a crystalline solid which was recrystallized from chloroform-methanol (1:9); m.p. alone or in admixture with (-)tylocrebrine 219-221°; yield, 0.075 g. (90%).

Oxidation of (-)Septicine.

The oxidation of (-)septicine (**8**, 0.195 g., 0.5 mmole) with *N*-bromosuccinimide (0.39 g., 2 mmoles) in chloroform (5 ml.) was carried out as under **2**. The iminium salt was precipitated by the addition of 2 volumes of ether. The solid was filtered, redissolved in chloroform and reprecipitated with ether to give a yellow amorphous solid, m.p. 110°; yield, 0.3 g. (70%).

Anal. Calcd. for $C_{24}H_{26}BrNO_4$: C, 61.02; H, 5.54; Br, 16.92; N, 2.96. Found: C, 61.31; H, 5.48; Br, 16.68; N, 3.02.

(±)Canadine **15**.

A suspension of berberine sulfate (Nutritional Biochemicals, 1.45 g.) in methanol (20 ml.) was stirred with sodium borohydride (0.15 g.) for 10 minutes. It was diluted with chloroform (100 ml.), washed with water and the solvent layer concentrated to dryness. The solid was crystallized from methanol, m.p. 172-173° (reported (**11**), m.p. 172°), yield, 0.77 g. (75%).

Oxidation of (±)Canadine to Berberine (**16**).

The oxidation of (±)canadine (0.34 g., 1 mmole) with *N*-bromosuccinimide (0.78 g., 4 mmoles) in chloroform (10 ml.) was carried out as described under **2**. The precipitated solid was filtered and crystallized from methanol; m.p. 210-212°, yield 0.33 g. (80%). It was identical with berberine bromide, prepared by ion-exchange from berberine sulfate.

Oxidation of Hydrastine to the Iminium Salt (**19**).

A solution of hydrastine (Nutritional Biochemicals, 0.38 g., 1 mmole) in chloroform (10 ml.) was stirred with *N*-bromosuccinimide (0.8 g., 4.5 mmoles) for 2 hours in a stoppered flask. The solid which separated was filtered, triturated with acetone (5 ml.) and refiltered. The colorless solid was recrystallized from methanol, m.p. >300°, yield, 0.045 g. (42%).

Anal. Calcd. for $C_{11}H_9Br_2NO_2$: C, 38.07; H, 2.61; Br, 46.06; N, 4.04. Found: C, 38.18; H, 2.62; Br, 46.24; N, 3.96.

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