Tetrahedron, 1963, Vol. 19, pp. 1397 to 1407. Pergamon Press Ltd. Printed in Northern Ireland

DEGRADATIVE STUDY IN THE BERBERINE SERIES—I

ISTVÁN SALLAY and R. H. AYERS
Wyeth Laboratories, Radnor, Pennsylvania

(*Received* 5 *February* 1963)

Abstract—The von Braun degradation of tetrahydroberberine (I), base-B (IIIa) and dihydrobase-B (IIIb) are described. Compound I shows an N_7–C_6 and an N_7–C_{14} ring opening, producing two cyanamides IV and VII. Contrary to the von Braun rule, C_8 is not attacked by the bromide anion. Cyanogen bromide cleaves IIIa and IIIb unexpectedly between N_2–C_3, furnishing XXa and XXb, respectively. The structures of the above products and their derivatives have been established.

THE naturally occurring l-canadine and DL-tetrahydroberberine (I), members of the protoberberine alkaloids, have been thoroughly investigated and synthesized.[1] The Hofmann degradation of the quaternary base of both alkaloids led to two products: anhydromethyltetrahydroberberine-A, or simply base-A (II) and anhydromethyltetrahydroberberine-B, base-B (IIIa).[2]

In this communication we report the study of the von Braun degradation of DL-tetrahydroberberine (I) and DL-base-B (IIIa).

Tetrahydroberberine reacts with cyanogen bromide in a complex and unexpected manner. During the degradation two bromocyanamides (IV, V) were formed in 1:2·3 ratio. This proportion is due to the easier cleavage of N_7–C_{14} bond compared to that of N_7–C_6.* The secondary bromo derivative (V) lost hydrogen bromide during the course of the von Braun degradation and led to the unsaturated cyanamide (VII). Both isolated cyanamides (IV, VII) had a strong absorption at 4·55 μ (—CN). Because the nucleophilic strength of the cyanamide (VII) was sufficiently low, subsequent transannular rearrangement was excluded.†

Theoretically, the bromide anion could attack C_6, C_8, or C_{14} of I, giving three isomer possibilities. Because of the principles formulated by von Braun *et al.*,‡ it was expected that during the cyanogen bromide treatment of I the bromide anion would

---

* The chemistry of this group of alkaloids and related ten-membered ring derivatives is dominated by the ease of transannular reactions between N_7–C_{14}. An example is the formation of dihydroanhydroberberine-methochloride from base-A (II)[3] and from allocryptopine.[4]

† Pyman[2] proved that the Hofmann degradation of l-canadine (I) follows two different paths producing base-A (II) and optically active base-B (IIIa), but during the prolonged heating, II suffers a transannular rearrangement and provides DL-base-B (IIIa).

‡ Von Braun[5] systematically proved that those groups, such as allyl and benzyl with halides known to be highly reactive in displacement reactions are cleaved more easily than less reactive groups. For instance, hydrohydrastine: (2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline) readily reacted with cyanogen bromide and underwent ring opening with no detectable demethylation.[6]

[1] See Review: R. H. F. Manske and H. L. Holmes, *The Alkaloids* Vol. IV; pp. 77–118. Academic Press, New York (1954).

[2] A. Voss and J. Gadamer, *Arch. Pharm.* **248,** 43 (1910); F. L. Pyman and H. A. D. Jowett, *J. Chem. Soc.* **103,** 290 (1913); and F. L. Pyman, *ibid.* **103,** 817 (1913).

[3] R. D. Haworth, W. H. Perkin, Jr., *J. Chem. Soc.* **103,** 445 (1913).

[4] J. Gadamer, *Arch. Pharm.* **258,** 148 (1918).

[5] J. von Braun and O. Engel, *Liebigs Ann.* **436,** 299 (1924).

[6] J. von Braun, *Ber., Dtsch. Chem. Ges.* **49,** 2624 (1916).

attack at the C_8 atom. However, attack at C_8 could not result in an unsaturated cyanamide (VI or VII). Therefore, only isomers IV and V are possible. Although hydrogen bromide could not be eliminated directly from the bromocyanamide (IV) without affecting the cyanide group, another Hofmann degradation (IV → VIII → IX → VI) established the correlation between the bromocyanamide (IV) and its dehydrohalogenated derivative (VI). This unsaturated cyanamide (VI) (m.p. 165–167°; λ_{max} 210, 267, 298 mμ) is an isomer of the originally isolated unsaturated cyanamide (VII) (m.p. 216–217°; λ_{max} 210, 286 mμ). Thus, it is clear that the unsaturated cyanamide (VII) does not arise from the accompanying bromocyanamide (IV). Contrary to the von Braun rule, the cyanogen bromide attacks both C_6 and C_{14} of tetrahydroberberine (I).

It has been observed that primary bromo compounds readily produce substitution with diethylamine, whereas the secondary bromo derivatives suffer dehydrobromination.[7–10] Because diethylamine displaced the bromine in IV, giving rise to 2-cyano-3-(2β-diethylaminoethyl-4,5-methylenedioxyphenyl)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIII), a primary bromocyanamide structure was assigned to it. Hydrolysis of VIII resulted principally in the diamine, 3-(2β-diethylaminoethyl-4,5-methylenedioxyphenyl)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XI) and in a small amount of the amino urea, 2-carbamoyl-3-(2β-diethylaminoethyl-4,5-methylenedioxyphenyl)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (X).

A further evidence for the structure of IV is that its dehydrobrominated derivatives: the unsaturated urea (XIV), the unsaturated secondary amine (XV), and the unsaturated cyanamide (VI) have a *styrene*-type absorption spectra (Fig. 1). Base-B (IIIa), which has a proven structure, possesses the same absorption spectrum. The final proof of the structure of IV laid in one more chemical step. Compound XV, 3-(2-vinyl-4,5-methylenedioxyphenyl)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline, was methylated and the free base was identified as the previously known base-B (IIIa).[2] The remethylated XV and IIIa were identical in every respect.

Because the original unsaturated cyanamide showed a *stilbenoid* U.V. absorption spectrum, the structure of 7-cyano-9,10-dimethoxy-2,3-methylenedioxy-13,14-didehydro-7,14-des-dihydroberbine (VII) can be assigned to it. In cyclohexane or in hydrochloric acid base-A (II) has a very similar spectrum.* Alkaline hydrolysis of the unsaturated cyanamide (VII) produced an unsaturated urea (XII) (λ_{max} 213, 293 mμ). Compound XII was isomeric with the unsaturated urea (XIV) (λ_{max} 211, 264, 297 mμ). The latter, accompanied by the unsaturated secondary amine (XV) was obtained by the alkaline hydrolysis of the bromocyanamide (IV). Reduction of VII produced the saturated cyanamide, 7-cyano-9,10-dimethoxy-2,3-methylenedioxy-13,14-dihydro-7,14-des-dihydroberbine (XIII).

---

* P. B. Russell (*J. Amer. Chem. Soc.* **78**, 3115 (1956)) found that the U.V. spectrum of Base-A (II) varies with the solvent employed. In alcohol the spectrum resembles that of tetrahydroberberine-methochloride. This would be expected because of the ready reversal of the Hofman degradation in this solvent. In solvents which prevent the above transannular interaction (e.g., hydrochloric acid, cyclohexane) the spectrum is related to that of a stilbene.

[7] J. B. Conant and R. E. Hussey, *J. Amer. Chem. Soc.* **47**, 476 (1925).

[8] A. B. Hass and H. C. Huffman, *J. Amer. Chem. Soc.* **63**, 1233 (1941).

[9] S. A. Morell, U. S. P., 2,424.184 (1947).

[10] R. C. Elderfield and H. A. Hageman, *J. Org. Chem.* **14**, 605 (1949).

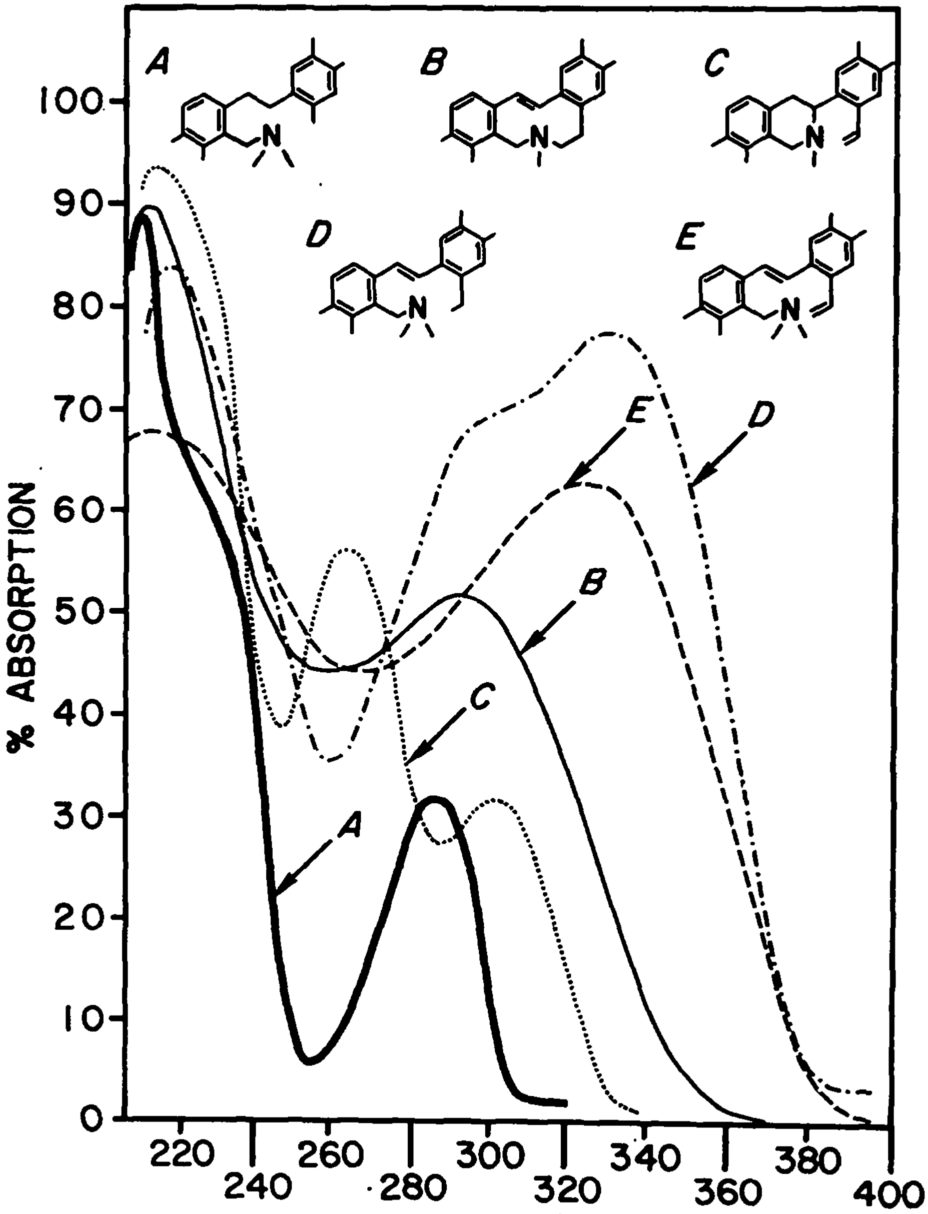
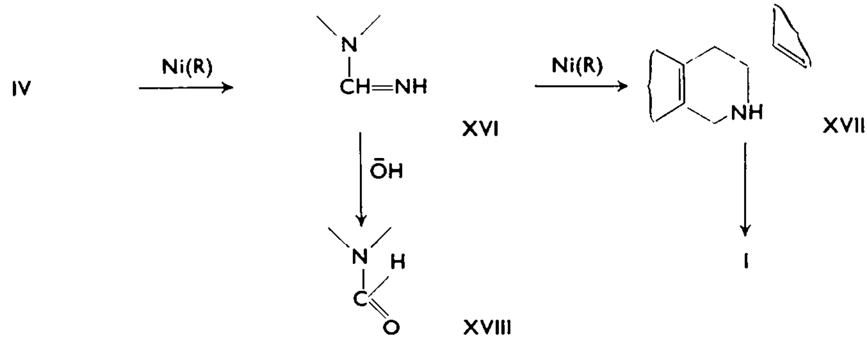


Fig. 1

Two unexpected ring closures were also observed. In the first, a hydrogen transfer of desmethyl-base-B (XV) in strong acidic media regenerated tetrahydroberberine (I). This reaction can be regarded as a reversed Hofmann degradation. In the other closure a large excess of Raney nickel reduced IV and also reconstructed tetrahydroberberine. Also detected was a formamide (XVIII) with a band at 5·78 μ. During the reduction one might conceive of a formylimino-type of intermediate XVI. A hydrolytic cleavage of XVI would lead to XVIII.* Reduction of XVI in two consecutive steps would presumably produce a secondary amine XVII, which by ring closure would yield tetrahydroberberine (I).



On the basis of the von Braun rule (loc. cit.), it was expected that during the cyanogen bromide treatment of base-B (IIIa) and dihydrobase-B (IIIb) the bromide anion would attack at the C_1 atom. However, both compounds (IIIa,b) suffered a ring opening between the N_2–C_3 atoms and resulted in XXa and XXb, respectively.

An interesting difference was observed between the behavior of IIIa and IIIb during the degradation. Dihydrobase-B (IIIb) treated with cyanogen bromide at low temperature produced the unsaturated cyanamide (XXb) in 50% yield. The other half of the material was identified as the hydrogen bromide salt of the starting material. Intermediate XIXb could not be detected. The infrared spectrum of XXb showed a band at 4·55 μ (—CN).

Base-B (IIIa), nevertheless, behaved differently during similar treatment. One third of the starting material separated out as the hydrogen bromide salt. The remainder was a 1:1 mixture of the bromocyanamide (XIXa) and the dienecyanamide (XXa), but elevated temperature and/or higher speed of the addition of the cyanogen bromide increased the ratio of XXa. It is conceivable that the relative stability of the bromocyanamide (XIXa), compared with XIXb is caused by the conjugated styrene system.

We turned finally to the problem of proving the structures of the two unsaturated cyanamides (XXa, XXb). Perkin, Jr., in his illuminating work on cryptopine[11] converted methyl-isotetrahydroberberine-A (II) to the crystalline methosulphate (XXI), which, when digested with methanolic potassium hydroxide, was readily decomposed to produce N-dimethyl-isotetrahydroberberine (XXIIa). The same substance (XXIIa) was obtained when the methosulphate of base-B (XXIIIa) was similarly decomposed. The structure of XXIIa was supported by further degradations.[11]

We wished to correlate the unsaturated cyanamides (XXa and XXb) and Perkin's diene-amine (XXIIa). The alkaline hydrolysis of the diene–cyanamide (XXa) resulted only in the diene-urea derivative (XXIVa). Because of this obstacle, we turned

---

* F. Walls, O. Collera and A. Sandoval L., (*Tetrahedron* **2**, 179 (1958)) reported a similar type of aldehyde, obtained from the cyanogen bromide degradation of voacangine. Raney nickel treatment of the bromocyanamide, by the reduction of the nitrile moiety, furnished a substance having a band at 5·80 μ.

[11] W. H. Perkin, Jr., *J. Chem. Soc.* 815 (1916).

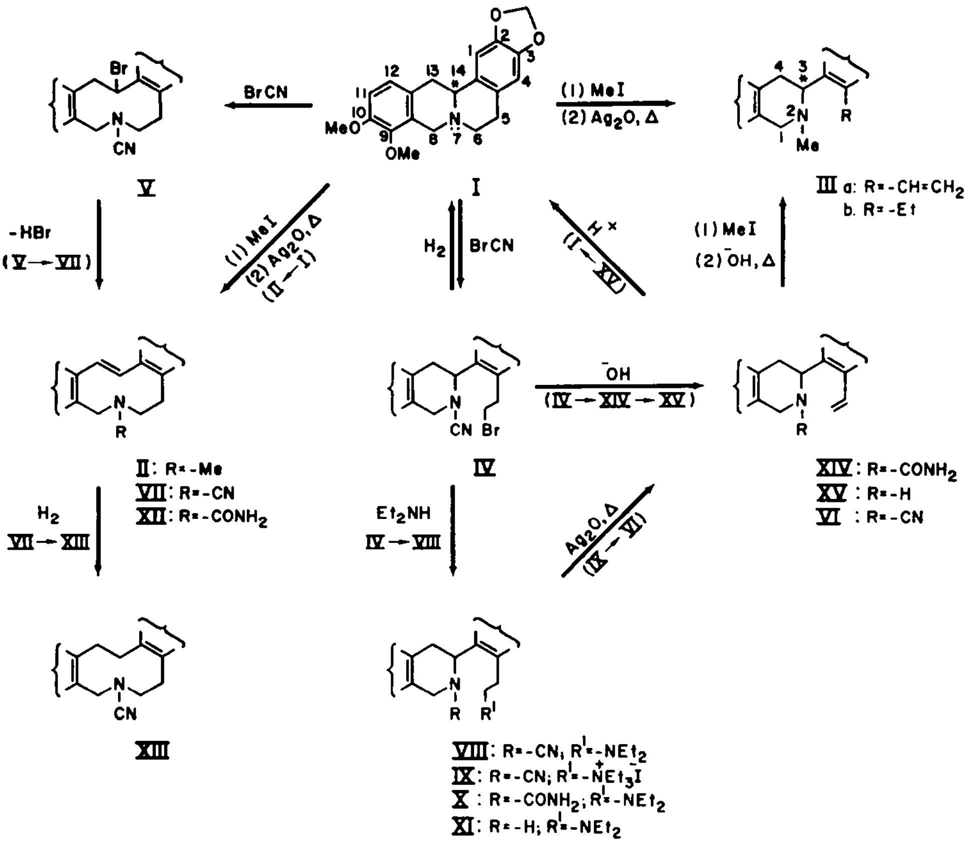


TABLE 1

to the analogous cyanamide (XXb) which, interestingly enough, readily furnished the saturated amine (XXVb), and only a small quantity of N-carbamoyl derivative (XXIVb). The secondary amine (XXVb) was then methylated to XXVIb and the free amine was reduced to the tertiary base (XXVII). Catalytic reduction of Perkin's diene-amine (XXIIa) produced a compound which proved to be identical with the above XXVII in every respect.

The U.V. absorption spectra aided greatly both in establishing the structural correlation of the degradation products of tetrahydroberberine (I), Base-B (IIIa) and dihydrobase-B (IIIb) and in providing some information about the stereochemistry of compounds VII, XII, XXa, XXb, XXIIa, XXIIb, XXIVa and XXVb. The characteristic spectroscopic data are collected in Table 3. Among the degradation products five types of absorption curves (A–E) were observed (Fig. 1).

Compounds I, IIIb, IV, VIII, X, XI, XIII, XXVII showed spectra, type-A, with two maxima at 209 mμ (ϵ, 31,000) and 284 mμ (ϵ, 5,200) and a shoulder at 230 mμ (ϵ, 12,000). These bands are tentatively interpreted as "benzene" bands.[12] Products in this series must have a structure in which there is no conjugation of pi-electrones with either of the two aromatic rings. A second group of derivatives (VII, XII) had substituted *stilbene*-type spectra, type-B, with two maxima at 210 mμ (ϵ, 29,500) and

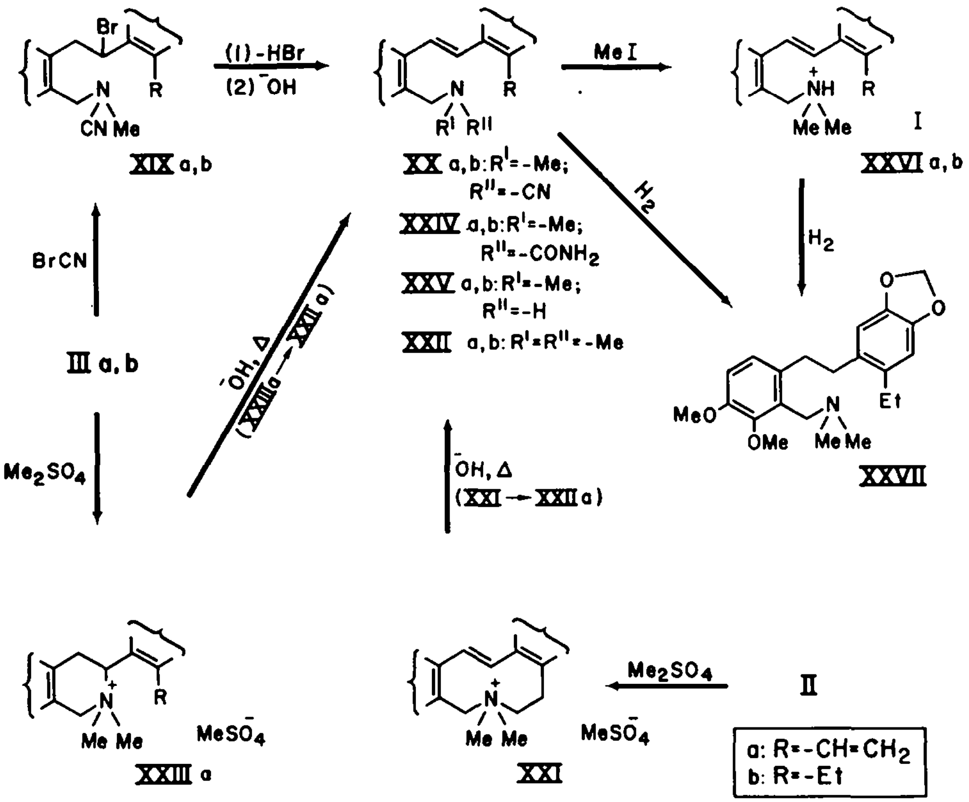


TABLE 2

286 mμ (ε, 9,400) and a minimum at 253 mμ (ε, 6,900). A third group of the degradation products (IIIa, VI, XIV, XV) had substituted *styrene*-type spectra, type-C, with three maxima at 212 mμ (ε, 35,700), 263 mμ (ε, 10,000) and 300 mμ (ε, 4,300).

Products having curve types B,D (XXb, XXVb, XXIIb, XXIVb, XXVIb) or E (XXa, XXIIa) have a correlation with substituted stilbene spectra. Laarhoven, Nivard and Havinga[12] demonstrated that by introduction of alkyl groups in the *ortho*-position of the stilbene molecule, the stilbene absorption band shows a hypsochromic shift which parallels the increase in steric hindrance and the resulting decrease in coplanarity. Our observation is in full agreement with this concept. In comparison with products having curve types E and D, compounds having curve type-B show a strong hypsochromic shift (32–44 mμ). Possibly, compounds having spectra of types D and E approach coplanar structure, while in compounds having spectra type-B the two aromatic rings are confined to a non-planar configuration.

EXPERIMENTAL

U.V. spectra were determined in 95% ethanol on a Beckmann-DU Spectrophotometer equipped with a Process and Instrument Recorder. The data are summarized on Table 3. I.R. spectra were taken in KBr on a Perkin-Elmer Infrared Spectrophotometer (Model-21). M.p.'s were taken on a hot stage and are uncorrected.

---

[12] W. H. Laarhoven, R. J. F. Nivard and E. Havinga, *Rec. Trav. Chim.* 79, 1153 (1960).

TABLE 3

Compound	Type of spectrum	λ_{max} in mμ (ε)	λ_{min} in mμ (ε)
I	A	209 (28,300); 230*(12,000); 284 (5,200)	252 (600)
IIIb	A	209 (31,000); 230*(12,000); 284 (5,400)	254 (700)
IV	A	209 (46,000); 230*(11,200); 284 (5,400)	262 (2,100)
VIII	A	209 (42,900); 230*(12,300); 284 (5,600)	260 (1,800)
X	A	210 (35,000); 230*(12,400); 284 (4,700)	257 (1,200)
XI	A	210(31,100); 230*(12,300); 284 (5,400)	254 (800)
XIII	A	209 (36,300); 230*(12,100); 288 (6,900)	256 (1,800)
XXVII	A	206 (37,000); 233*(10,000); 287 (5,600)	256 (1,000)
VII	B	210 (29,500); 286 (9,400)	253 (6,900)
XII	B	213 (32,500); 293 (10,400)	258 (8,500)
IIIa	C	212 (35,700); 263 (10,100); 300 (4,300)	245 (6,500) 288 (3,600)
VI	C	209 (34,900); 267 (9,600); 298 (3,900)	247 (5,400) 293 (3,800)
XV	C	211 (34,800); 264 (10,300); 297 (4,400)	246 (5,200) 288 (3,900)
XXb	D	215 (26,500); 300*(16,500); 330 (21,200)	260 (6,200)
XXVb	D	215 (25,800); 300*(15,700); 330 (20,200)	260 (5,900)
XXIIb	D	215 (26,300); 300*(17,800); 333 (22,300)	261 (6,400)
XXIVb	D	215 (26,000); 300*(20,100); 330 (16,600)	260 (5,500)
XXVIb	D	215 (26,000); 300*(14,500); 335 (21,200)	262 (6,100)
XXa	E	209 (20,300); 324 (17,800)	268 (10,500)
XXIIa	E	232 (19,800); 325 (23,100)	283 (12,400)

* These maxima are shoulders.

Reduction of berberine-chloride to tetrahydroberberine (I)[13]

A solution of 179 g berberine-chloride* in a mixture of 2700 ml methanol and 270 ml water was treated with 18 g $NaBH_4$ dissolved in 50 ml methanol, then was refluxed for ½ hr. From the chilled solution 132,7 g I was filtered (89·5%) and recrystallized from ethanol, m.p. 173–174°.[14] (Found: C, 70·65; H, 6·13; N, 4·08. Calc. for $C_{20}H_{21}O_4N$: 70·78; H, 6·24; N, 4·13%).

Preparation of N-*methyl-tetrahydroberberine-iodide*

A solution of 50 g tetrahydroberberine (I) in 1500 ml acetone was treated with 137 g methyliodide. After the addition, the slurry was heated at 50° for 45 min. From the cooled reaction mixture 60·6 g white crystals were filtered off; m.p. 248° Lit. m.p. 248°.[5]

Base-A (II) *and base-B* (IIIa) were prepared by the method of Pyman[2] from tetrahydroberberine-methoiodide.

Hydrogenation of base-B (IIIa) *to dihydrobase-B* (IIIb)

A solution of 31 g base-B (IIIa) in 150 ml acetic acid was hydrogenated over 1 g Adams-catalyst at 40 lb/sq. in. at room temp (1 hr.). The catalyst was filtered off, the solvent evaporated and the gummy

---

* S. B. Penick and Company, New York 8, N.Y.

[13] R. Mirza, *J. Chem. Soc.* 4400 (1957).

[14] P. B. Russell, *J. Amer. Chem. Soc.* **78**, 3115 (1956).

residue covered with ethanol resulting in 30 g crystalline IIIb. It was recrystallized from ethanol, m.p. 99·5–100°. (Found: C, 70·84; H, 7·00; N, 3·90. $C_{21}H_{25}O_4N$ requires: C, 70·96; H, 7·09; N, 3·94%).

Preparation of the bromocyanamide (IV) *and the unsaturated cyanamide* (VII) *from tetrahydroberberine* (I)

To a solution of 20·4 g tetrahydroberberine (I) in 1500 ml benzene, 6·66 g cyanogen bromide was added. The reaction mixture was refluxed 24 hr and after cooling 6·65 g I. HBr was filtered off and recrystallized from ethanol, m.p. 206–208°. (Found: C, 56·81; H, 5·33. $C_{20}H_{22}NO_4Br$ requires: C, 57·15; H, 5·28%).

The benzene mother liquor was extracted with dil. hydrochloric acid, then with water. The benzene layer produced a gummy residue which was dissolved in a small amount dichloromethane and chromatographed on 200 g Florisil. The first 600 ml eluate produced 3·87 g IV, which was twice recrystallized from ethanol and had a m.p. 174–175°. (Found: C, 56·83; H, 4·79; N, 6·04; Br, 17·80. $C_{21}H_{21}O_4N_2Br$ requires: C, 56·64, H, 4·75; N, 6·29; Br, 17·95%). The I.R. spectrum had a band at 4·55 μ (—CN). The second 650 ml of the eluate gave 1·25 g of crystalline mixture of IV and VII. The third fraction (2 1.) produced 5·8 g crystalline VII, m.p. 214–216°. After recrystallization from acetone melted at 216.5–7.5°. (Found: C, 69·11; H, 5·41; N, 7·30. $C_{21}H_{20}N_2O_4$ requires: C, 69·21; H, 5·53; N, 7·69%). The I.R. spectrum showed the expected band at 4·53 μ (—CN).

Hydrogenation of the bromocyanamide (IV)

A suspension of 1 g bromocyanamide (IV) and 200 mg 10% Pd–C catalyst in 100 ml acetic acid was hydrogenated in a Parr-apparatus for 18 hr. After the catalyst was filtered off and the solution was evaporated to dryness, the residue was dissolved in ether and extracted with dil. hydrochloric acid. The acidic layer was basified and extracted with ether which afforded a crystalline I, m.p. 168–171°. The I.R. spectra of this compound and I were superimposible.

Preparation of the diethylamino-cyanamide (VIII) *from bromocyanamide* (IV)

A solution of 1·5 g bromocyanamide (IV) in a mixture of 20 ml diethylamine and 80 ml chloroform was heated to reflux for 3 hr, then evaporated to dryness. The gummy residue was triturated with ether to remove the reaction product from 0·53 g crude, crystalline starting material. The ethereal extracts containing the diethylamino-cyanamide (VIII) were washed with water, then with dil. hydrochloric acid. The crude VIII.HCl (0·67 g) which precipitated was recrystallized from acetone, to yield a purified product, m.p. 202–204°. (Found: C, 63·21; H, 7·30; N, 8·54; Cl, 7·29. $C_{25}H_{32}O_4N_3Cl$ requires: C, 63·34; H, 6·81; N, 8·87; Cl, 7·48%). The free base melted at 127–128°. (Found: C, 68·63; H, 7·05; N, 9·72 $C_{25}H_{31}O_4N_3$ requires: C, 68·63; H, 7·14; N, 9·60%). I.R. spectrum possessed the expected band at 4·55 μ (—CN).

Preparation of the quaternary ammonium-salt (IX) *and its Hofmann degradation to the unsaturated cyanamide* (VI)

Diethylamino-cyanamide (VIII; 9·3 g) was dissolved in 125 ml acetone and was treated with 4·2 g ethyliodide to yield 6·46 g crystalline IX, m.p. 246–248°. (Found: C, 54·86; H, 6·21; I, 21·00. $C_{27}H_{36}N_3I$ requires: C, 54·66; H, 6·12; I, 21·38%).

A suspension of 3 g of the quaternary-salt (IX) in 200 ml hot water was stirred with 0·63 g Ag_2O. The iodide-free filtrate was evaporated and the residue was extracted with hot ethanol to yield stout prisms of VI, m.p. 165–167°. (Found; C, 69·03; H, 5·34; N, 7·78. $C_{21}H_{20}O_4N_2$ requires: C, 69·21; H, 5·53; N, 7·69%). The I.R. spectrum possessed a band at 4·55 μ (—CN).

Hydrolysis of the diethylamino-cyanamide (VIII) *to the* N-*carbamoyl-amine* (X) *and to the diamine* (XI)

A solution of 3·71 g VIII in 250 ml 10% NaOH (ethanol:water = 1:1) was refluxed for 24 hr. The reaction mixture was evaporated to ½ volume and was extracted with ether to result in 3·1 g of a colorless oil. It was refluxed in 50 ml n-hexane to remove 2·11 g free base (XI), which after recrystallization from n-hexane resulted in silky needles, m.p. 85–86°. (Found: C, 70·01; H, 7·85; N, 6·60. $C_{24}H_{32}O_4N_2$ requires: C, 69·87; H, 7·82; N, 6·79%).

The dipicrate of the diamine (XI) from methanol melted at 226–227° (dec). (Found: C, 49·82; H, 4·69; N, 12·60. $C_{36}H_{38}O_{18}N_8$ requires: C, 49·65; H, 4·39; N, 12·87%). The dihydrochloride of XI, m.p, 240–242° (dec) was recrystallized from ethanol–ether. (Found: C, 59·19; H, 7·07; N, 5·89; Cl, 14·50. $C_{24}H_{34}O_4N_2Cl_2$ requires: C, 59·38; H, 7·06; N, 5·77; Cl, 14·61%).

The hexane insoluble carbamoyl-amine was separated from the above diamine (XI) and twice recrystallized from chloroform–pet. ether, yielding 55 mg X, m.p. 149·5–151°. (Found: C, 66·17; 7·44; N, 9·08. $C_{25}H_{33}O_5N_3$ requires: C, 66·05; H, 7·04; N, 9·24%). The I.R. spectrum showed bands at 3·0 μ (amide NH), 5·98 μ but not at 4·55 μ.

Hydrolysis of the stilbene-type cyanamide (VII) *to the* N-*carbamoyl stilbene-derivative* (XII)

A suspension of 1·82 g VII in 100 ml 10% NaOH (ethanol:water = 1:1) was refluxed for 24 hr. After cooling 1·88 g crystalline XII (96·7%) was filtered off and had a m.p. 247–248°. (Found: C, 66·03; H, 5·96; N, 7·23. $C_{21}H_{22}O_5N_2$ requires: C, 65·95; H, 5·80; N, 7·32%). The I.R. spectrum had the expected maxima at 2·93 μ (amide NH), 5·95 μ (amide).

Hydrogenation of the unsaturated cyanamide (VII) *to* XIII

A solution of 1·1 g unsaturated cyanamide (VII) in 220 ml ethylacetate was hydrogenated over 0·1 g 10% Pd–C catalyst. After removal of the catalyst and evaporation of the solvent a solid remained, which was twice recrystallized from ethanol to yield 1·0 g XIII, m.p. 224–226°. (Found: C, 68·65; H, 5·94; N, 7·66. $C_{21}H_{22}O_4N_2$ requires: C, 68·83; H, 6·05; 7·65%). The infrared spectrum showed a band at 4·55 μ (—CN).

Alkaline hydrolysis of the bromocyanamide (IV) *to the desmethyl-base*-B (XV) *and the styrene-type urea derivative* (XIV)

Bromocyanamide (IV; 2·23 g) was refluxed in 100 ml 10% NaOH (ethanol:water = 1:1) for 24 hr. The reaction mixture was evaporated to ½ volume, then extracted with ether to yield 1·7 g solid foam. It was extracted with hot n-hexane, producing 1·06 g XV, m.p. 103–104°. (Found: C, 70·90; H, 6·02; N, 3·97. $C_{20}H_{21}O_4N$ requires: C, 70·78; H, 6·24; N, 4·13%). The I.R. spectrum had a weak band at 3·05 μ (secondary amine), but no absorption at the —CN region was observed. A sample of the free base was transformed into the hydrobromide salt, m.p. 233–234°. Found: C, 57·14; H, 5·14; N, 3·21. $C_{20}H_{22}O_4NBr$ requires: C, 57·15; H, 5·27; N, 3·33%).

The hexane insoluble portion was recrystallized from ethanol and yielded 80 mg rock–salt-like crystals (XIV), m.p. 192–194°. The I.R. spectrum showed the expected bands at 2·91 μ (amide NH), 6·0 μ (amide oxo).

Methylation of the desmethyl-base-B (XV)

A solution of 0·35 g desmethyl-base-B (XV) in 5 ml methanol was treated with 1·4 g methyliodide to yield 0·47 g IIIa.HI salt. The alkalized water solution of the above salt was extracted with chloroform to produce 0·24 g crude base-B (IIIa) which was chromatographed on a Florisil column, prepared and eluted with dichloromethane. The solid residue of the eluate was recrystallized from n-heptane containing a small amount of ethanol to yield 35 mg rosettes, m.p. 113–114°. Mixed m.p. with authentic IIIa was 113–114°. (Found: C, 71·25; H, 6·62; N, 4·02. Calc. for $C_{21}H_{23}O_4N$; C, 71·37; H, 6·65; N, 3·96%). The I.R. spectra of this compound and IIIa were superimpossible.

Isomerization of the desmethyl-base-B (XV) *to tetrahydroberberine* (I)

The secondary amine (XV; 0·5 g) was gently refluxed in a mixture of 4 ml acetic acid and 12 ml 30% hydrochloric acid for 2 hr. The cooled and alkalized solution was extracted with chloroform. The U.V. and I.R. spectra of the chromatographed and recrystallized material and I were superimpossible. The mixed m.p. did not show depression.

Cyanogen bromide degradation of the dihydro-base-B (IIIb) *to the cyanamide stilbene derivative* (XXb)

Dihydro-base-B (IIIb; 1·06 g) dissolved in 30 ml benzene was dropped between 10–15° into a solution of 0·32 g cyanogen bromide in 30 ml benzene. During the addition 0·65 g IIIb.HBr salt (50%) separated and was collected after 6 hr and recrystallized from ethanol, m.p. 239–240°. (Found: C, 57·75; H, 6·03; N, 3·34; Br, 17·92. $C_{21}H_{26}O_4NBr$ requires: C, 57·80; H, 6·00; N, 3·20; Br, 17·74%).

The benzene filtrate of the above salt was extracted with dil. hydrochloric acid and afforded 0·55 g crude XXb (50%). It was recrystallized from methanol, m.p. 97–98°. (Found: C, 69·47; H, 6·16; N, 7·39. $C_{22}H_{24}O_4N_2$ requires: C, 69·45; H, 6·34; N, 7·36%). The I.R. spectrum possessed a strong band at 4·55 μ (—CN).

Preparation of the stilbene-type cyanamide (XXa) *and its hydrolysis to* XXIVa

Into a solution of 12·37 g base-B (IIIa) in 300 ml benzene, 3·71 g cyanogen bromide was added at room temp. The reaction mixture was stirred overnight and 5·85 g IIIa. HBr salt (38·5%) was filtered off. The water extracted and dried benzene solution furnished 9·3 g of a solid foam (XIXa and XXa), which was chromatographed on a Florisil column (30 g) eluted with benzene–methanol (4:1). The eluate was diluted with 150 ml benzene and washed with water, dil. hydrochloric acid, dil. sodium hydroxide and water. The material remaining after evaporation of the dried benzene solutions yielded white crystals from n-heptane (XXa), m.p. 69·5–71·5°. (Found: C, 69·41; H, 5·93. $C_{21}H_{21}N_2O_4$ requires; C, 69·06; H, 5·79. $C_{21}H_{22}N_2O_4Br$ requires: C, 56·51; H, 4·9%). The I.R. spectrum had a band at 4·55 μ (—CN).

The crude mixture of XIXa and XXa was refluxed in 10% sodium hydroxide (ethanol:water = 1:1) for 14 hr. The solution was evaporated to ½ volume and extracted with ether. The ether layer after extraction with dil. hydrochloric acid resulted in a foam (XXIVa) which failed to crystallize. The I.R. spectrum possessed bands at 3·0 μ (NH) and 6·10 μ (amide). The above acidic extract was basified and extracted with ether. No amine (XXVa) was detected.

Hydrolysis of the stilbene-cyanamide (XXb) *to the stilbene-type secondary amine* (XXVb) *and to the stilbene-urea* (XXIVb)

In a solution of 50 ml ethanol and 50 ml 20% NaOH, 3·8 g XXb was refluxed for 24 hr. The cooled reaction mixture was extracted with ether and the extract was washed with 3 × 25 ml of 1*N* hydrochloric acid whereupon crystalline amine salt (XXVb) separated, m.p. 180–181°. (Found: C, 64·17; H, 6·56; N, 3·50; Cl, 9·07. $C_{21}H_{26}O_4NCl$ requires: C, 64·36; H, 6·68;, N, 3·57; Cl, 9·04%). There was no band at 4·55 μ (—CN).

After the ethereal mother liquor of the above salt was dried and evaporated to dryness, 0·25 g crystalline XXIVb was isolated which after recrystallization from ethanol–water had a m.p. 155–156°. (Found: C, 66·64; H, 6·68; N, 6·73. $C_{22}H_{26}O_5N$ requires: C, 66·31; H, 6·58; N, 7·03%). The I.R. spectrum had bands at 2·93, 3·15 μ (NH), 6·05 μ (amide).

Methylation of the stilbene-type secondary amine (XXVb) *to* (XXVIb)

To an alcoholic solution of 6·0 g secondary amine (XXVb) 5 ml methyliodide was added. After standing for 1 hr, the reaction mixture was carefully treated with pet. ether and the precipitated XXVIb was filtered off. After 2 recrystallizations from ethanol–pet. ether, 2·6 g white crystalline hydroiodide (XXVIb) was obtained, m.p. 184–186°. (Found: C, 53·40; H, 5·89; I, 25·57. $C_{22}H_{28}NO_4I$ requires: C, 53·13; H, 5·68; I, 25·52%).

Preparation of the unsaturated tertiary amine (XXIIb) *from dihydro-base-B* (IIIb)

To a solution of 5 g dihydro-base-B (IIIb) in 20 ml benzene, 5 ml dimethylsuphate was added at once. After 1 min refluxing 4·9 g crystalline XXIIIb separated out. The methanolic solution of the crude XXIIIb was treated with 25 ml 25% potassium hydroxide solution in methanol. The reaction mixture was refluxed for 10 min, taken to dryness and extracted with ether, which yielded 3·2 g crystalline XXIIb. It was recrystallized from n-heptane, m.p. 89·5–90·5°. (Found: C, 71·52; H, 7·37; N, 3·79. $C_{22}H_{27}NO_4$ requires: C, 71·74; H, 7·20; N, 4·09%).

Preparation of the quaternary salt (XXIIIa) *and its Hofmann degradation to the diene-tertiary amine* (XXIIa)″

Reduction of the diene-tertiary amine (XXIIa) to (XXVII). A solution of 0·6 g diene (XXIIa) in 50 ml of 1*N* hydrochloric acid was hydrogenated over 0·1 g Adams catalyst for 24 hr. The filtrate was made alkaline and extracted with ether. The dried ether solution furnished crystalline XXVII upon being treated with dry ethereal hydrogen bromide. The crude XXVII was recrystallized from ethyl-acetate, then from butyl acetate. It then had m.p. 123–124° (dec). (Found: C, 58·62; H, 6·71; N, 3.15; Br, 17·80. $C_{22}H_{30}NO_4Br$ requires: C, 58·42; H, 6·69; N, 3·09; Br, 17·65%).

Reduction and methylation of the stilbene-type secondary amine (XXVb)

A solution of 3 g hydrochloride of XXVb in 160 ml 0·5*N* hydrochloric acid was hydrogenated for ½ hr over 0·25 g Adams-catalyst at 50°. The filtrate was basified to give a gummy precipitate that was extracted into ether. The colourless oily residue of the ether extract was dissolved in 15 ml methyl-iodide and after 1 hr., pet. ether was added. The crude hydroiodide salt of XXVII was transformed into the hydrobromide salt by the usual method and twice recrystallized from butyl acetate to afford XXVII, mp. 123–124° (dec). (Found: C, 58·38; H, 6·75; N, 3·16; Br, 17·85. $C_{22}H_{30}NO_4Br$ requires: C, 58·42; H, 6·69; N, 3·09; Br, 17·65%).

Acknowledgment—The authors are grateful to Dr. Peter B. Russell for his constant interest and encouragement in this work. Microanalyses, U.V. and I.R. spectra were carried out by our Analytical Department.