Chemistry of the Solanidane Ring System [1]

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The reaction of acetyldemissidine and acetylsolanidine with cyanogen bromide is described and the results of the lithium aluminium hydride reduction of the bromo-cyanamides so produced are discussed. The hydrolysis of acetyldemissidine bromo-cyanamide under very mild conditions caused a retro-von Braun reaction to afford the initial alkaloid.

ALKALOIDS having the solanidane hexacyclic structure are found in the extracts (usually combined as glycosides) obtained from a number of plants of the *Solanum* and *Veratrum* species.[2] Among the earliest known representatives, solanidine (Ia) and demissidine (IIa) have resisted degradation by the von Braun [3] and the Hofmann [3,4] reactions. Similarly the *N*-oxide of demissidine was unsuccessful as a degradation intermediate.[5] Although ring F of demissidine has been opened with consecutive oxidation reactions,[6] the opening of ring E, which could lead to synthetically useful quantities of 20-piperid-2-yl steroids and pregnane derivatives, was not achieved prior to this study.

von Braun Degradation.—Contrary to the earlier report[3] we have found that the acetyl derivatives of both solanidine and demissidine smoothly react with cyanogen bromide in refluxing chloroform to give good yields of the corresponding bromo-cyanamides (III) and (IV). In each case the formation of only one compound was supported by t.l.c. examination. The i.r. and n.m.r. spectra, as well as combustion analyses, were consistent with the inclusion of cyanogen bromide into (Ib) and (IIb).

In keeping with the postulated mechanism [7] of the von Braun degradation, frontside addition of the elements of cyanide to the nitrogen lone-pair of electrons in the *S*-configuration [8] is to be expected followed by a rearside approach of bromide ion to C-26, C-22, or C-16. That displacement of the quaternized nitrogen occurs on C-16 to give a 16α-bromo-steroid with concomitant opening of the E-ring follows from the identification of

[1] Preliminary communication, J. A. Beisler and Y. Sato, *Chem. Comm.*, 1968, 963.

[2] For a general introduction and leading references see K. Schreiber, in 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1968, vol. X, p. 1, and also S. M. Kupchan and A. W. By, *ibid.*, p. 193.

[3] C. Schöpf and R. Hermann, *Ber.*, 1933, **66**, 298.

[4] (*a*) K. Schaffnit, Ph.D. Thesis, University of Frankfurt a. M., 1932; (*b*) A. Soltys, *Ber.*, 1933, **66**, 762; (*c*) H. Dieterle and H. Rochelmeyer, *Arch. Pharm.*, 1935, **273**, 532.

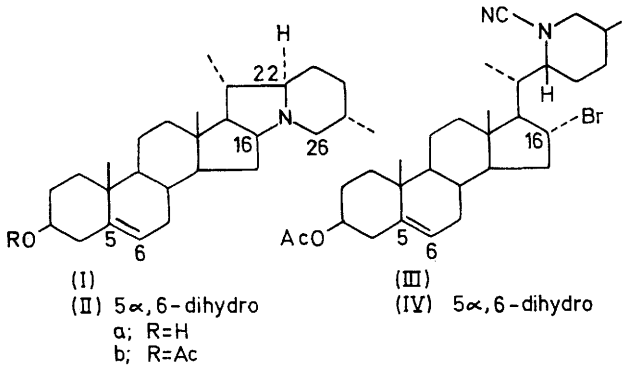
[5] L. H. Briggs, W. E. Harvey, R. H. Locker, W. A. McGillivray, and R. N. Seelye, *J. Chem. Soc.*, 1950, 3013.

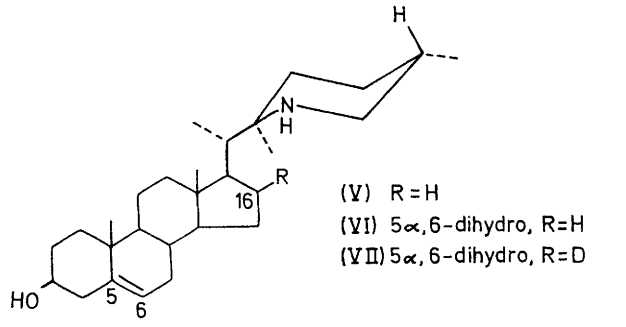
[6] K. Schreiber and C. Horstmann, *Chem. Ber.*, 1966, **99**, 3183.

[7] H. A. Hageman, in *Org. Reactions*, 1953, **7**, 202.

[8] E. Höhne, K. Schreiber, H. Ripperger, and H. H. Worch, *Tetrahedron*, 1966, **22**, 673.

the lithium aluminium hydride reduction products obtained from (III) and (IV) as well as from the results of the hydrolysis of (IV) (see below). A similar mechanism in cleaving the C-16, N-bond of a solanidane was



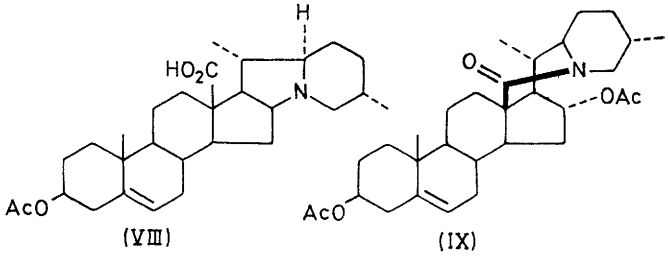


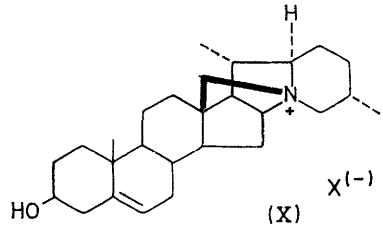
observed by Sheehan *et al.*[9] in the rearrangement of 3β-acetoxy-5-solanidene-18-oic acid (VIII) to the amide (IX). Thus, heating (VIII) under reflux in acetic anhydride caused breakage of the C-16, N-bond *via* a concerted attack by the carboxy-group (of necessity from the frontside) on the nitrogen lone-pair and by a rearside nucleophilic displacement by acetate on C-16. The amide (IX) readily reverts to the solanidane skeleton on acid hydrolysis.

Reduction and Hydrolysis of the Bromo-cyanamides.—The structures of the von Braun products were verified indirectly through isolation of the piperidyl steroids, (V) and (VI), from the lithium aluminium hydride reduction mixtures of (III) and (IV), respectively. Thus, reduction of (IV), derived from acetyl-demissidine, with lithium aluminium hydride in refluxing tetrahydrofuran gave a mixture which by g.l.c. showed the presence of (VI) (49%), an unidentified substance (27%), and surprisingly, solanidanol (IIa) (24%) resulting from recyclization. The mixture was readily separated by column chromatography and crystallization. The major product was assigned structure (VI) which was confirmed by comparison of the m.p., $[\alpha]_D$, and i.r. with values recorded in the literature.[10] The *NO*-diacetyl derivative compared satisfactorily in m.p., i.r. spectrum, and rotation with the published values.[10] A mixed m.p. with an authentic sample * showed no depression. Moreover, structure (VI) was further indicated by an intense peak at *m/e* 98 in the mass spectrum due to the ready loss of a 4-methyltetrahydropyridine [11] fragment.

Similarly, the lithium aluminium hydride reduction product of the bromo-cyanamide (III) when analysed by g.l.c. showed the presence of a 20-piperid-2-yl steroid (V) (47%), solanidine (Ia) (35%), and an unidentified product (18%). Separation as before with column chromatography and crystallisation provided a sample of (Ia) for identification in addition to the ring-opened product whose i.r. and mass spectrum were consistent with the assigned structure (V). Since solanidine (Ia) and demissidine (IIa) were also isolated from among the reduction products of (III) and (IV), respectively, the 16α-location of the bromine substituent in the bromo-cyanomides seems justified by virtue of its sterically favourable orientation for displacement by the nearby piperidyl nitrogen.

In an attempt to elucidate some aspects of the mechanism of the reduction, the bromo-cyanamide (IV) was treated with lithium aluminium deuteride and the products were isolated as before. Mass spectral analysis





of the ring-opened product showed the incorporation of one deuterium atom as evidenced by the upward isotopic shift of the molecular ion by one unit. The base peak [*m/e* 98 in (VI)], however, was not shifted. Therefore, the label could not be on the piperidyl moiety but rather must be on the steroid nucleus, most probably at the 16β-position (VII). Consequently, an azomethine as a reduction intermediate formed by elimination of HCN from (IV) is not compatible with the labelling results because subsequent reduction of the azomethine would place a deuterium adjacent to the heteroatom in the piperidine ring. Thus, a plausible mechanism for the reduction can be better envisioned as concurrent nucleophilic attacks by hydride energetically partitioned between attack on C-16 and attack on the cyano-carbon

* We are grateful to Professor K. Schreiber, Berlin, D.D.R., for this sample and its i.r. spectrum.

[9] J. C. Sheehan, R. L. Young, and P. A. Cruickshank, *J. Amer. Chem. Soc.*, 1960, **82**, 6147.

[10] K. Schreiber and G. Adam, *Chem. Ber.*, 1964, **97**, 2358.

[11] E. Bianchi, C. Djerassi, H. Budzikiewicz, and Y. Sato, *J. Org. Chem.*, 1965, **30**, 754.

atom. If the cyano-group of the bromo-cyanamide is first reductively removed, rapid cyclisation with ejection of bromide would result in a solanidanol. Accordingly, no deuterium was found in the demissidine (IIa) isolated from the lithium aluminium deuteride reduction of (IV). On the other hand, if the bromine atom is first lost by reduction, a piperidyl steroid is subsequently produced.

The remarkable ease of formation of the solanidane skeleton is strikingly demonstrated by the hydrolysis of acetyldemissidine bromo-cyanamide (IV). Normally, von Braun intermediates hydrolyse with difficulty, prolonged heating with concentrated acid is the usual method.[12] However, (IV) hydrolyses under the neutral conditions of refluxing aqueous ethanol. After 4 hr. acetyldemissidine (IIb) can be isolated from the hydrolysate, and after 44 hr. under reflux all the starting material is consumed giving a mixture of (IIa) and (IIb).* Hydrolysis of (IV) in an ethanol–water–methylamine medium is retarded in rate, but nevertheless, after 44 hr. under reflux considerable quantities of (IIa) and (IIb) were isolated along with starting material.

As a further example of the inert character of solanidanols toward degradation, we have found that solanidine (Ia) methiodide gives no evidence of ring fission when treated with sodium in liquid ammonia, but rather returns (Ia) in quantitative yield by simple demethylation. In contrast, the internal salt (X) derived from isorubijervine when treated with alkali metal[14] gave mostly a product resulting from C-16, N-cleavage as well as (Ia).

CONCLUSIONS

The chemistry of the solanidanols is characterized by the exceptional stability of the indolizidine ring system. Thus, several standard degradation procedures were ineffective in opening the indolizidine portions of (Ia) and (IIa). Although the von Braun reaction provides an adduct attended by opening of the E-ring, lithium aluminium hydride reduction occurs with considerable reclosure of the ring system while hydrolysis gives exclusively ring closed products.

In retrospect, it would seem that the early success of a solanidanol synthesis from sarsasapogenoic acid dioxime[15] was, at least in part, due to the favourable energy requirements that promote the formation of the E- and F-rings.

EXPERIMENTAL

Equipment.—M.p. (uncorr.), Kofler hot-stage apparatus; optical rotation, Perkin-Elmer 141 in $CHCl_3$ solution with a 1-dm. microcell; i.r., Perkin-Elmer 421; n.m.r., Varian A-60 ($CDCl_3$, TMS as internal standard); mass spectra, Hitachi–Perkin-Elmer RMU-6 and A.E.I. MS9 (direct insertion for deuterium studies).

Chromatography.—Silica gel, Fisher 28—200 mesh, grade 12 for columns, and Merck silica-G (250 microns) for plates; alumina, Woelm, neutral, activity II or III; gas chromatography, nickel column (0·25 in. × 10 ft.), containing 1% SE-20 on Chromosorb, operated at 230°.

Solvents.—Chloroform was purified by passing it through basic Woelm alumina, activity I. Extracts were dried over anhydrous sodium sulphate.

Details of the mass spectra for (V) and (VI) (MSDC 2605 and 2604, respectively) are available from the United Kingdom Atomic Energy Authority, A.W.R.E., Mass Spectrometry Data Centre, Aldermaston, Berks.

Reaction of Acetyldemissidine (IIb) *with Cyanogen Bromide.*—A solution of (IIb) (454 mg.) and cyanogen bromide (660 mg.) in chloroform (7 ml.) was heated under reflux ($CaCl_2$ tube) and stirred for 24 hr. Volatile material was removed under reduced pressure and the remaining gum, in benzene solution, was applied to a 17 × 2 cm. column of silica gel. After elution with benzene (150 ml.), a crystalline product (495 mg.) was obtained with benzene–ethyl acetate (9 : 1) as eluant. Recrystallisation from aqueous methanol gave colourless needles of the *bromo-cyanamide* (IV) which exhibited an unclear, double m.p. that depended on heating rate, m.p. 155° then 250—280° (decomp.); t.l.c. (benzene–ethyl acetate, 10 : 1) showed only one spot. The product gave a positive Beilstein test for halogen but did not give an immediate precipitate with silver nitrate in aqueous ethanol (Found: C, 65·65; H, 8·6; Br, 14·55. $C_{30}H_{47}BrN_2O_2$ requires C, 65·8; H, 8·65; Br, 14·6%), $\nu_{max.}$ ($CHCl_3$) 2945, 2860, 2205 (C≡N), 1728 (C=O), 1461, 1374, and 1030 $cm.^{-1}$; δ 4·63 (1H, m, H·C·O), 4·02 (1H, m, H·C·Br), 2·01 (3H, s, OAc), 1·04, 0·94, 0·83, and 0·74 p.p.m. (each 3H, s, Me).

Reaction of Acetylsolanidine (Ib) *with Cyanogen Bromide.*—A solution of (Ib) (206 mg.) in chloroform (5 ml.) containing cyanogen bromide (320 mg.) was heated under reflux ($CaCl_2$ tube) for 24 hr. The residue, after removal of volatile material *in vacuo*, was taken up in benzene and chromatographed on a 2 × 9 cm. silica gel column. Elution with benzene (80 ml.) and benzene–ethyl acetate (200 ml.; 9 : 1) gave the pure (t.l.c.) crystalline *bromo-cyanamide* (III) (228 g.). Recrystallisation from aqueous methanol gave prisms (196 mg.), m.p. 185° then 245—260°. An ethanol solution of the product slowly gave a precipitate with aqueous silver nitrate (Found: C, 66·25; H, 8·3; Br, 14·6. $C_{30}H_{45}BrN_2O_2$ requires C, 66·05; H, 8·3; Br, 14·65%), $\nu_{max.}$ ($CHCl_3$) 2955, 2901, 2868, 2850, 2202 (C≡N), 1733 (C=O), 1464, 1370, and 1036 $cm.^{-1}$; δ 5·38 (1H, m, C=CH), 4·60 (1H, m, H·C·O), 4·10 (1H, m, H·C·Br), 2·03 (3H, s, OAc), 1·02, 0·93, 0·83, and 0·77 (p.p.m. (each 3H, s, Me).

Reduction of Acetyldemissidine Bromo-cyanamide (IV).—A solution of (IV) (192 mg.) in dry tetrahydrofuran (10 ml.) was treated with an excess of lithium aluminium hydride and then heated under reflux ($CaCl_2$ tube) for 15 hr. After hydrolysis with water the product was extracted with ether from a sodium hydroxide solution. The dried extract was evaporated to give a syrup (138 mg.) that slowly crystallised.

* Another alkaloid, aspidospermine, which also contains an indolizidine nucleus, reacts with cyanogen bromide to afford a von Braun product that similarly undergoes smooth hydrolytic ring closure in refluxing aqueous ethanol to regenerate the alkaloid.[13]

[12] For some typical transformations of von Braun bromocyanamides see R. C. Elderfield and H. A. Hageman, *J. Org. Chem.*, 1949, **14**, 605.

[13] H. Conroy, P. R. Brook, M. K. Rout, and N. Silverman, *J. Amer. Chem. Soc.*, 1958, **80**, 5178.

[14] S. W. Pelletier and W. A. Jacobs, *J. Amer. Chem. Soc.*, 1953, **75**, 4442.

[15] F. C. Uhle and W. A. Jacobs, *J. Biol. Chem.*, 1945, **14**, 605.

The t.l.c. plate (ether–methanol, 25 : 1) indicated a three-fold mixture. Gas chromatography also separated three substances: T_R 12·75 (49%), 8·15 (27%), and 6·8 min. (24%). *Demissidine* (IIa) had a retention time of 6·7 min. under the identical conditions.

The crude amine mixture in benzene solution was applied to a column of alumina (25 g.) (activity II). Elution with benzene (100 ml.) gave small amounts of oils, but *demissidine* (IIa) (26 mg.) was obtained with benzene-ether (300 ml.; 17 : 3). Recrystallisation of the (IIa) from methanol produced fine needles, m.p. 216—218°, $[\alpha]_D^{20}$ +25° (*c* 0·475); its i.r. spectrum was identical to that of an authentic sample.

Continued elution of the column with ether–methanol (200 ml.; 19 : 1) gave a crystalline solid (97 mg.). Recrystallization from aqueous methanol gave 55 mg. of pure (t.l.c. and g.l.c.) (22*R* : 25*S*)-22,26-*epimino*-5α-*cholestan*-3β-*ol* (VI) as prisms, m.p. 214—216°, $[\alpha]_D^{20}$ +11 (*c* 0·5) (lit.,[10] m.p. 218—220°, $[\alpha]_D^{18}$ +22·2°). The i.r. spectrum (Nujol) was identical to the spectrum reported [10] for (VI), *m/e* 401 (M^+), 98 ($CH_2C_5H_9N^+$, 100%). The product having a retention time of 8·15 min. and remaining in the methanolic mother liquor, could not be induced to crystallize, and was not further investigated.

(22R : 25S)-3β-*Acetoxy*-22,26-*acetylepimino*-5α-*cholestane*.—The *NO*-diacetyl derivative of (VI) was formed in pyridine solution with acetic anhydride in the usual way. Recrystallization from aqueous methanol provided fine needles, m.p. 210—212°, $[\alpha]_D^{20}$ +29° (*c* 0·5) (lit.,[10] m.p. 219—220°, $[\alpha]_D^{18}$ +31·5°). The i.r. spectrum of an authentic sample was superimposable with the spectrum (Nujol) of the present material. Mixture m.p. with the authentic sample was undepressed.

Reduction of Acetylsolanidine Bromo-cyanamide (III).—To a solution of (III) (138 mg.) in dry tetrahydrofuran (10 ml.) was added an excess of lithium aluminium hydride; the mixture was heated under reflux ($CaCl_2$ tube) for 15 hr. The usual work-up produced a syrup (97 mg.) which slowly crystallized. The t.l.c. plate (ether–methanol, 25 : 1) separated three components, R_F 0·12, 0·20, and 0·79. The latter value corresponded to solanidine. Analysis with g.l.c. similarly indicated three components: T_R 16·2 (47%), 9·8 (18%), and 8·25 min. (35%). Under the same conditions *solanidine* had a retention time of 8·2 min.

The product was chromatographed on alumina (14 g.) (activity II). After elution with benzene (50 ml.) a crystalline fraction (23 mg.) was obtained with benzene–ether (200 ml.; 4 : 1) which was recrystallized from methanol, m.p. 207—209°, $[\alpha]_D^{19}$ −28·5° (*c* 0·365). Its i.r. spectrum was identical to an authentic sample of *solanidine*.

Elution of the column with ether containing 5% methanol (200 ml.) released a second crystalline fraction (58 mg.). Purification by recrystallization (MeOH–H_2O) gave crystalline plates of (22R : 25S)-22,26-*epiminocholest*-5-*en*-3β-*ol* (V), m.p. 218—219°, $[\alpha]_D^{19}$ −45° (*c* 0·5). Although t.l.c. indicated a pure material, combustion analysis gave a persistently low value for carbon; $\nu_{max.}$ (Nujol) 3450 (NH, broad), 3180 (OH, broad), 1312, 1245, 1194, 1120, 1069, 1050, 1022, 957, 930, 891, 839, 798, 760, 720, 615, and 588 $cm.^{-1}$; *m/e* 399·3507 (M^+) ($C_{27}H_{45}NO$ requires 399·3501), 98 ($CH_3C_5H_4N^+$, 100%). The substance corresponding to T_R 8·15 min. in the gas chromatogram remained in the recrystallization solvent (noncrystallisable) and was not further investigated.

Lithium Aluminium Deuteride Reduction of Acetyldemissidine Bromo-cyanamide (IV).—A solution of (IV) (77 mg.) in dry tetrahydrofuran (10 ml.) was reduced with an excess of lithium aluminium deuteride during 18 hr. under reflux. The product (61 mg.) was chromatographed over alumina (14 g.) as before to give *demissidine* (IIa), m.p. 218—220° (from MeOH), which was deuterium-free by mass spectral analysis. Continued elution with 200 ml. of ether containing 5% methanol gave the *piperidyl steroid* (VII) as needles, m.p. 209—212° (from methanol). The molecular ion peak in the mass spectrum was shifted one unit higher to *m/e* 402. The base peak remained at *m/e* 98.

Methylamine Hydrolysis of Acetyldemissidine Bromo-cyanamide (IV).—The bromo-cyanamide (263 mg.) in warm ethanol (50 ml.) was combined with 40% aqueous methylamine (10 ml.), and the solution was heated under reflux for 44 hr. After removal of volatile materials at reduced pressure the residue was taken up in methylene chloride, washed with dilute potassium carbonate solution, and dried. Evaporation of the solvent provided a colourless oil (220 mg.) which was chromatographed on alumina (75 g.; activity III). Elution with benzene gave needles (50 mg.), m.p. 196—197° (MeOH), $[\alpha]_D^{25}$ +16° (*c* 0·50), which was identified as *acetyldemissidine* (IIb) by t.l.c., i.r., and mixed m.p. Continued elution with benzene gave crystals (44 mg.), which were (t.l.c., i.r.) starting material, and further elution with benzene–chloroform (7 : 3) produced *demissidine* (45 mg.) (mixed m.p., i.r., t.l.c.). Subsequent elution with solvent mixtures of increasing polarity gave only small amounts of unresolvable material.

Neutral Hydrolysis of Acetyldemissidine Bromo-cyanamide (IV).—A solution of (IV) (23 mg.) in 80% aqueous ethanol (3 ml.) was heated under reflux for 4 hr., poured into water, made basic with dilute sodium hydroxide solution, and extracted with methylene chloride. The solution was dried and solvent was removed to give a glass (20 mg.) which was chromatographed on alumina (8 g.) (activity III). Benzene as eluant gave *acetyldemissidine* (IIb) (3 mg.) (t.l.c., m.p.) and then starting material (17 mg.).

The bromo-cyanide (IV) (50 mg.) in 80% aqueous ethanol (6 ml.) was heated under reflux for 44 hr. to give a crude product (44 mg.), devoid of starting material (t.l.c.), from which *acetyldemissidine* (IIb) and *demissidine* (IIa) could be separated by column chromatography.

Sodium–Ammonia Reduction of Solanidine Methiodide.—Solanidine (Ia) was quaternized with a large excess of methyl iodide in a sealed tube heated at 100° for 4·5 hr. A quantitative yield of methiodide was obtained as prisms, m.p. 278—279° (decomp.) (lit.,[4b] m.p. 280°).

Solanidine methiodide (120 mg.) was dissolved in freshly distilled liquid ammonia (35 ml.) and treated with small pieces of sodium until the blue colour of the solution persisted for 10 min.; the reduction was then terminated by addition of ammonium chloride. Water was added after evaporation of solvent, and the product was collected by ether extraction. Evaporation of the dried extracts gave *solanidine* (87 mg., quantitative) (Ia), m.p. 205—208°. The product was identified by mixed m.p. and comparison of its i.r. spectrum with one obtained from an authentic sample.

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