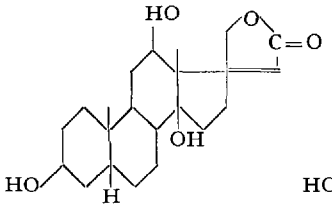
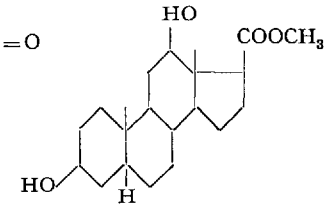
Wegen die Herren Dr. H. M. E. CARDWELL (Oxford), Dr. SYDNEY SMITH (Dartford) und Dr. D. A. H. TAYLOR, National Institute for Medical Research in London[1].

Die ausführliche Arbeit wird demnächst in der « Helvetica chimica Acta » publiziert.



I Digoxigenin



II 3β,12β-Dioxy-ätiansäuremethylester

Ausser Urezigenin[2] enthalten daher sämtliche bis heute konfigurativ aufgeklärten digitaloiden Aglykone eine 3β-Oxygruppe. Dasselbe gilt übrigens auch für die Sapogenine.

Herrn Prof. A. STOLL danken wir bestens für die Überlassung einer grösseren Menge Cedilanid.

S. PATAKI, K. MEYER
und T. REICHSTEIN

Pharmazeutische und Organisch-Chemische Anstalt der Universität Basel, den 21. Mai 1953.

Summary

The missing members of the four stereoisomeric 3,12-dihydroxyetianic acid methyl esters and their diacetates were synthetized. The ester obtained by degradation of digoxigenin was identical with the 3β,12β-derivative.

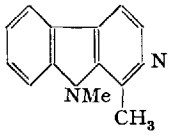
[1] Herr Dr. D. A. H. TAYLOR hat Digoxigenin ebenfalls erneut abgebaut und uns eine Probe des daraus gewonnenen 3,12-Diazetoxy-Ätiansäuremethylesters zum Vergleich gesandt. Es erwies sich nach Mischproben ebenfalls identisch mit dem synthetischen 3β,12β-Derivat.

[2] R. TSCHESCHE und K. H. BRATHGE, Ber. dtsch. Chem. Ges. *85*, 1042 (1952), haben kürzlich auf Grund ihrer *vorläufigen* Abbauversuche am Urezigenin angenommen, dass dieses sich von Uzarigenin nur durch die sterischen Verhältnisse an C-3 unterscheidet; damit käme Urezigenin die 3α-Konfiguration zu.

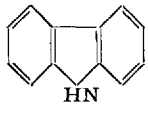
DISPUTANDUM

The Constitution of Ajmaline

Ajmaline, $C_{20}H_{26}O_2N_2$, m.p. 159–160°, the major alkaloid of *Rauwolfia serpentina* Benth, was first isolated from its roots by S. SIDDIQUI and R. H. SIDDIQUI[1] and almost simultaneously by VAN ITALLIE and STEENHAUER[2] from the same raw materials. These investigators[3] suggested the formula $\overline{\text{NMeR(NH)COO}}$ for the base. The chemistry of ajmaline has recently been studied by MUKHERJI, ROBINSON, and SCHLITTLER[3]. They have confirmed the above composition for the alkaloid and have shown that ajmaline is a monoacidic di-tertiary base, contains an isolated double bond and shows strychnidine-like reactions. A semi-acetal group has been found to be present in the alkaloid although the infrared spectrum of the base as reported by them shows the absence of carbonyl frequencies. On distillation over soda lime and zinc dust ajmaline has been found to yield Ind-N-methyl harman (I) $C_{13}H_{12}N_2$, m.p. 102°, and carbazole (II) $C_{12}H_9N$, m.p. 236°, as the major scission products.

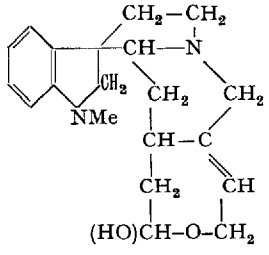


(I)

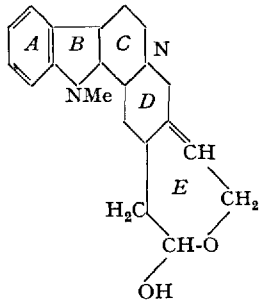


(II)

On the basis of these results the following two hypothetical structures (III) and (IV) have been postulated by ROBINSON and his collaborators[1].



(III)



(IV)

They are, however, of opinion that it would be reasonable to accept the structure (III) and not (IV) as the latter represents a dihydroindole derivative which as such has not yet been found to occur in nature.

The infrared spectrum of ajmaline studied by the present authors shows an absorption band at 5·82 μ indicating about 15–20% carbonyl absorption which definitely shows that ajmaline contains a carbonyl group. The presence of a cyclic acetal group (–CHOH–O–) group in ajmaline suggested by ROBINSON and his collaborators[1] has been confirmed from the spectrographic data. From the spectral data several other important informations have also been obtained. The spectrum shows an absorption band for $\rangle$CMe group at 7·24 μ, for ether bridge at 9 μ and that for dihydroindole at 6·2–6·8 μ and for hydroxyl at 3·02 μ in ajmaline.

It has also been observed in the present investigation that on fusion with potassium hydroxide ajmaline produces a crystalline base and two different acids, one of which has been proved to be identical with indole-2-carboxylic-acid (V) $C_9H_7NO_2$, m.p. 199°. (Found: C, 67·06; H, 4·34; N, 8·72. Calcd. for C, 67·09; H, 4·35; N, 8·70%). The second acid has been found to be free from nitrogen; the characterisation of this non-nitrogenous acid and the base is in progress. Formation of indole-2-carboxylic-acid (V) from ajmaline shows that α-position of the dihydroindole nucleus (B) in the base is substituted by a methyl or a methylene group. These observations do not seem to support the blocked hydroindole structure (III) for ajmaline postulated by ROBINSON *et al.*[1]. The structure (IV), however, can explain

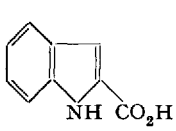
[1] S. SIDDIQUI and R. H. SIDDIQUI, J. Ind. Chem. Soc. *8*, 667 (1931); *9*, 539 (1932); *12*, 37 (1935).

[2] L. VAN ITALLIE and A. J. STEENHAUER, Arch. Pharm. *270*, 311 (1932).

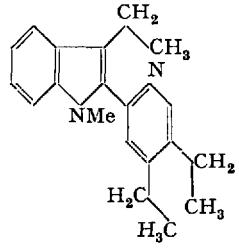
[3] S. SIDDIQUI and R. H. SIDDIQUI, J. Ind. Chem. Soc. *8*, 667 (1931); *9*, 539 (1932); *12*, 37 (1935). – L. VAN ITALLIE and A. J. STEENHAUER, Arch. Pharm. *270*, 311 (1932).

[1] D. MUKHERJI (Miss), R. ROBINSON, and E. SCHLITTLER, Exper. *5*, 215 (1949).

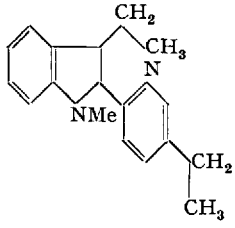
the formation of indole-2-acid from ajmaline by its degradation with alkali. But according to structure (IV), the base should produce on selenium dehydrogenation Ind-N-methyl derivatives of alstyrine, viz., N-methyl alstyrine (VI), desethyl-N-methyl alstyrine (VII) or desmethyl-N-methyl alstyrine (VIII).



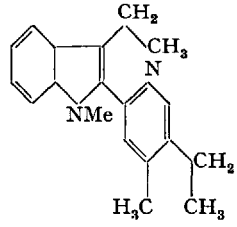
(V)



(VI)

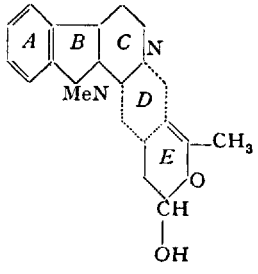


(VII)



(VIII)

Ajmaline on dehydrogenation with selenium at 300° has been found to produce none of these products but only Ind-N-methyl harman (I), $C_{13}H_{12}N_2$, m.p. 102° (Found: C, 79·8; H, 5·99; N, 14·31. Calcd. for C, 79·6; H, 6·12; N, 14·28%) and a few uncharacterized indole derivatives as nonbasic fragments. During alkali fusion and dehydrogenation of the base with selenium the formation of carbazole could not be established. Ind-N-methyl harman, however, seems to be the common degradation product of the alkaloid obtained during its

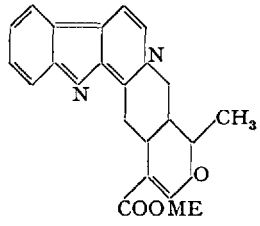


(IX)

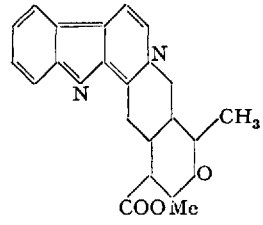
distillation over soda lime, zinc dust[1] as also during its dehydrogenation with selenium. It is therefore suggested that ajmaline contains the fused ring system *A*, *B*, and *C* as shown in structure (IX). The ring *D* appears to be involved in a weak linkage as a result of which Ind-N-methyl harman is readily produced from the base during its degradations and not the Ind-N-methyl alstyrine derivatives. (IX) represents a dihydroindole derivative. Such derivatives have been found to occur in Nature, viz., the erythrina alkaloids[2] (*Fam. Leguminosae*). ROBINSON *et al.*[3] and SCHÖPF[4] and his collaborators have also suggested that the biogenesis of such dihydroindole alkaloids is possible in Nature.

The probable location of the >CMe group, the characteristic band of which appears in its I.R. spectrum at 7·24 μ and the presence of which has been established by KUHN-ROTH method (found >CMe, 4·47. Calculated for one >CMe, 4·60 %) seems to be in ring *E* as shown in (IX).

In such a case *E* would be a six-membered heterocyclic ring-like that of alstonine[1] (X) or serpentine[2] (XI) and not seven-membered (IV) as advocated by ROBINSON and his collaborators.

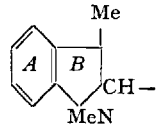


(X)

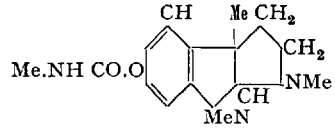


(XI)

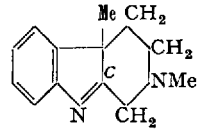
There might be, however, another possibility that the >CMe group in the alkaloid might be in ring *B* as shown in (XII) like that of physostigmine[3] (XIII) or calycanthidine[4] (XIV)*a* or (XIV)*b*.



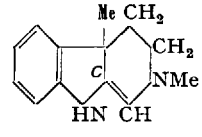
(XII)



(XIII)



(XIV)*a*



(XIV)*b*

But from the simultaneous occurrence of ajmaline with alstonine in *Rauwolfia vomitoria* and *R. obscura*[5] (*Fam. Apocynaceae*) and with serpentine in *R. serpentina*[6] it seems probable that the >CMe group in ajmaline would be in ring *E* (IX).

A. CHATTERJEE and S. BOSE

Department of Pure Chemistry, University College of Science and Technology, Calcutta, India, February 3, 1953.

Zusammenfassung

Das IR.-Absorptionsspektrum des Alkaloids Ajmalin zeigt die typische >CMe-Bande (7,24 μ) in der Seitenkette (festgestellt mit KUHN-ROTH); bei 5,92 μ er-

[1] D. MUKHERJI (Miss), R. ROBINSON, and E. SCHLITTLER, Experientia *5*, 215 (1949).

[2] K. FOLKERS, F. KONIUSZY, and J. SHAVEL, Jr., J. Amer. Chem. Soc. *64*, 2146 (1942).

[3] R. ROBINSON and S. SUGASAWA, J. chem. Soc. *789* (1932); R. ROBINSON, ibid., 1079 (1936).

[4] C. SCHÖPF and K. THIERFELDER, Lieb. Ann. Chem. *497*, 22 (1932).

[1] R. C. ELDERFIELD and A. P. GRAY, J. Org. Chem. *16*, 506 (1951). – E. SCHLITTLER, H. SCHWARZ, and F. BADER, Helv. chim. Acta *35*, 271 (1952).

[2] F. BADER und H. SCHWARZ, Helv. chim. Acta *35*, 1594 (1952).

[3] R. ROBINSON and H. SUGINOME, J. chem. Soc. *1932*, 298, 304.

[4] P. R. LEVY and R. ROBINSON, Festschrift Karrer (April, 1949), p. 40.

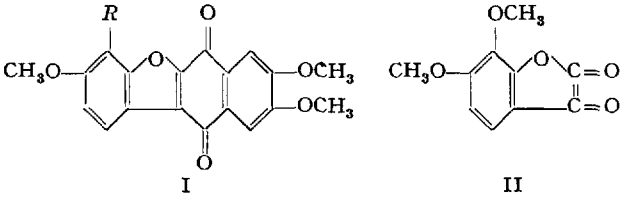
[5] E. SCHLITTLER, H. SCHWARZ, and F. BADER, Helv. chim. Acta *35*, 271 (1952).

[6] E. SCHLITTLER und H. SCHWARZ, Helv. chim. Acta, *33*, 1463 (1950).

scheint die Bande der Karbonylgruppe. Ajmalin wurde durch Abbau mit Selen in Ind-N-methyl-harman übergeführt. Durch Kalischmelze lässt sich Ajmalin in eine kristalline Base (in kleiner Menge), eine stickstoffreie Säure und Indol-2-Karbonsäure aufspalten. Auf Grund dieser Spaltstücke wurde eine mögliche Strukturformel für Ajmalin diskutiert.

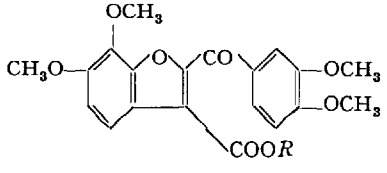
Synthesis of 3:8:9-Trimethoxy- and 3:4:8:9-Tetramethoxy-β-Brazanquinone

KOSTANECKI and his coworkers prepared 3:8:9-trimethoxy-β-brazanquinone (I, R = H, m.p. 260°C)[1] and 3:4:8:9-tetramethoxy-β-brazanquinone (I, R = OCH_3, m.p. 264°C)[2] by the oxidation of 3:8:9-trimethoxy-6-hydroxy- and 3:4:8:9-tetramethoxy-6-hydroxy-β-brazan respectively with chromic acid. In an earlier communication, a synthesis of (I, R = H) was described[3]. An independent method of synthesis of the two abovementioned quinones is now reported.



I

II



III

6:7-dimethoxycoumaranone[4] was converted into 6:7-dimethoxy-2-oximinocoumaranone (m.p. 194°) and then hydrolized to 2-hydroxy-3:4:dimethoxyphenylglyoxalic acid (m.p. 178°C; methyl ester, m.p. 99–100°C). The latter on treatment with acetic anhydride gave 6:7-dimethoxycoumarandione (II, m.p. 153°C). On interaction with ω-bromoacetoveratrone in presence of sodium ethoxide this afforded ethyl 6:7-dimethoxy-2-veratroylcoumarone-3-carboxylate (III, R=C_2H_5, m.p. 99–101°C). The corresponding acid (III, R = H, m.p. 205°C) on cyclisation through the acid chloride furnished (I, R = OCH_3, m.p. 265°C) purified by sublimation in vacuum. The identity was confirmed by colour reaction and by reductive acetylation to 3:4:8:9-tetramethoxy-6:11-diacetoxy-β-brazan (m.p. 235°C)[2].

Analogously, 6-methoxycoumarandione[5] was converted into ethyl 6-methoxy-2-veratroylcoumarone-3-carboxylate (m.p. 127–128°C). The related acid (m.p. 208°C) on cyclisation gave (I, R = H, m.p. 262°C) identical with the specimen synthesized earlier.

J. N. CHATTERJEA

Chemical Laboratory, Science College, Patna, India, February 19, 1953.

[1] V. KOSTANECKI and L. LLOYD, Ber. dtsch. chem. Ges. *36*, 2200 (1903).

[2] V. KOSTANECKI and A. ROST, Ber. dtsch. chem. Ges. *36*, 2205 (1903).

[3] J. N. CHATTERJEA, Exper. *7*, 374 (1951).

[4] A. FELIX and P. FRIEDLANDER, Mh. Chem. *31*, 55 (1910).

[5] K. FRIES and K. SAFTIEN, Ann. Chem. *442*, 291 (1925).

Résumé

Cet article décrit une méthode sans ambiguïté pour la synthèse des 3:4:8:9-tétraméthoxy- et 3:8:9-triméthoxy-β-brazanquinone.

The Stereochemistry of the Reaction of Nitrous Acid with Cyclohexylamines

BARTON and ROSENFELDER[1] have observed that ionic elimination reactions involving substituents on adjacent carbon atoms in a cyclohexane derivative proceed most readily when the two substituents form polar bonds (that is the two carbon atoms and the two substituents involved are in one plane). They have also pointed out that the formation of olefines by the action of nitrous acid on primary amines shows the same geometric specificity and cited menthylamines as examples.

We have found that, on the basis of the concept of polar and equatorial bonds, the behaviour of cyclohexylamines with nitrous acid can be correlated as follows:

When the amino group forms an equatorial bond the main reaction product is the corresponding alcohol with the hydroxy group equatorial (that is no WALDEN inversion takes place).

When the amino group is linked by a polar bond, considerable amounts of cyclohexenes are formed along with a mixture of both epimeric forms of the alcohol (that is WALDEN inversion occurs).

We have tested these rules for a number of cyclohexylamines (Table I, II). The conformation of cyclohexylamines and cyclohexanols was determined in most cases on the basis of the observation that sodium and alcohol reduction of a ketone or an oxime leads predominantly to the thermodynamically more stable epimer of the corresponding alcohol or amine[2]. Cyclohexanols and cyclohexylamines produced by such reduction should therefore in general have their hydroxy and amino groups equatorially bonded, while catalytic reduction in presence of platinum in acid media should mainly afford epimers in which the hydroxy and the amino groups will be polar linked.

HÜCKEL and coworkers[3] have carried out epimerization experiments with decalols. On the basis of their work the equatorial position can be assigned to the hydroxy and the amino groups in the following compounds: trans-α-decalol, m.p. 63°, trans-α-decalylamine, m.p. – 1°, trans-β-decalol, m.p. 75°, trans-β-decalylamine, m.p. 15°.

The data presented in tables I and II testify to the validity of the rules postulated by us. As the result of their studies on the action of nitrous acid on decalylamines HÜCKEL and coworkers found that those trans-decalylamines that are obtained by the sodium and alcohol reduction of oximes react with nitrous acid to afford decalols that are predominantly produced by the sodium and alcohol reduction of decalones[3]. It should be noted that this rule is the same as the rule described above in terms of polar and equatorial bonds.

[1] D. H. R. BARTON and W. J. ROSENFELDER, J. Chem. Soc. *1951*, 1048.

[2] G. VAVON, Bull. Soc. chim. *49*, 937 (1931). – W. HÜCKEL, Ann. Chem. *533*, 1 (1938).

[3] W. HÜCKEL, Ann. Chem. *533*, 1 (1938).