suppression of this, as in the corresponding acid, or the reduced product, bisdihydrodioscorine ($C_{13}H_{20}O_2N)_2$, the picrotoxin-like action disappears.

Dioscorine has also been found in *D. hispida* tubers by Zeyva and Gutierrez.[46]

(1) *J. Chem. Soc.*, 1912, **101**, 946; *cf.* Barger *et al.*, *ibid.*, 1937, 1820. (2) *Proc. Linn. Soc. N.S.W.*, 1907, **32**, 1789; 1917, **41**, 815. (3) *Arch. Pharm.*, 1893, **231**, 117. (4) *J. pr. Chem.*, 1901, [iii], **64**, 274. (5) *Ber.*, 1889, **22**, 2159. (6) *Asclepiad*, June, 1888. (7) *Ber.*, 1901, **34**, 1023. (8) *J. pr. Chem.*, 1901, [iii], **64**, 274. (9) *J. Chem. Soc.*, 1908, **93**, 2077. (10) *Ibid.*, 1919, **115**, 487. (11) *Annalen*, 1871, **157**, 98. (12) *Ibid.*, 1880, **206**, 209. (13) Schmidt, *Arch. Pharm.*, 1892, **230**, 207; 1894, **232**, 409; Hesse, *Annalen*, 1892, **271**, 120; 1893, **276**, 84. (14) *Arch. Pharm.*, 1890, **228**, 139, 435; *cf.* Dunstan and Charton, *Pharm. J.*, 1889, [iii], **20**, 461. (15) *J. pr. Chem.*, 1928, [ii], **120**, 221; Shchukina *et al.*, *J. Gen. Chem. U.S.S.R.*, 1940, **10**, 803. (15*a*) *Farm. Revy.*, 1947, **46**, 221. (16) *Arch. exp. Path. Pharm.*, 1941, **197**, 275. (17) King, *J. Chem. Soc.*, 1919, **115**, 504; *cf.* Carr and Reynolds, *ibid.*, 1910, **97**, 1330. (18) *Ber.*, 1896, **29**, 1776. (19) *Arch. Pharm.*, 1898, **236**, 9, 47. (20) *Ibid.*, 1898, **236**, 382; *cf.* Hesse, *Annalen*, 1899, **309**, 75; *J. pr. Chem.*, 1901, [ii], **64**, 358; 1902, [ii], **66**, 194; and Kunz-Krause, *ibid.*, 1901, [ii], **64**, 569. (21) *J. Chem. Soc.*, 1919, **115**, 476. (22) *Cf.* Hesse, *Ber.*, 1896, **29**, 1776; Gadamer, *Arch. Pharm.*, 1898, **236**, 382. (23) *Cf.* Carr and Reynolds, *J. Chem. Soc.*, 1912, **101**, 949; Schmidt, *Arch. Pharm.*, 1894, **232**, 409; Finnemore and Braithwaite, *Pharm. J.*, 1912, **89**, 136. (24) *Cf.* Schmidt, *Arch Pharm.*, 1910, **248**, 641; Hesse, *J. pr. Chem.*, 1901, [ii], **64**, 274; Thoms and Wentzel,[7] Finnemore and Braithwaite.[23] (25) *Cf.* Jowett, *J. Chem. Soc.*, 1897, **71**, 680. (26) *Ibid.*, 1919, **115**, 974; *cf.* Willstätter and Hug, *Zeit. physiol. Chem.*, 1912, **79**, 146. (27) *J. Chem. Soc.*, 1910, **97**, 1793. (28) *Annalen*, 1892, **271**, 114; 1893, **276**, 84. (29) *Arch. Pharm.*, 1898, **236**, 11. (30) *Apoth. Zeit.*, 1902, **17**, 592 (*Chem. Soc. Abstr.*, 1903, [i], 51); *Arch. Pharm.*, 1905, **243**, 559. (31) *Arch. Pharm.*, 1909, **247**, 79. (32) *Ibid.*, 1916, **253**, 497; *cf.* Hess and Wissing, *Ber.*, 1915, **48**, 1907. (33) *Ibid.*, 1902, **35**, 2065. (34) *Ibid.*, 1915, **48**, 1907, 2057. (35) *Ibid.*, 1918, **51**, 1013; *cf.* Willstätter and Iglauer, *ibid.*, 1900, **33**, 1175. (35*a*) *Proc. Iowa. Acad. Sci.*, 1942, **49**, 288. (36) *Ber.*, 1919, **52**, 1947; *cf.* Gadamer and Hammer, *Arch. Pharm.*, 1921, **259**, 110. (37) *Ber.*, 1922, **55**, 1972; *cf.* Gadamer, *ibid.*, 1923, **56**, 130. (38) *Ibid.*, 1923, **56**, 1079. (39) *Compt. rend.*, 1925, **180**, 1755; 1928, **186**, 147; *Bull. Soc. Chim.*, 1928, [iv], **43**, 79, 590. (40) Gmelin, *Arch. Pharm.*, 1941, **279**, 112. (41) Nolle, *Khim. Farm Prom.*, 1934, No. 5, 39; Awrutowa, *Chem. Zentr.*, 1938, [i], 496. (42) *Meded. uit's Lands Plant*, 1894, 13. (43) *Chem. Zentr.*, 1897, [ii], 130. (44) *Ann. Jard. Bot. Buit.*, 1909, [ii], *Suppl.*, 3, 385. (45) *Rec. trav. Chim.*, 1911, **30**, 161. (46) *J. Phil. Isl. Med. Assoc.*, 1937, **17**, 349.

ALKALOIDS OF *ERYTHROXYLON COCA*

The habitat of *Erythroxylon* spp. is principally the western side of South America, and although indigenous species occur in India, Africa and Australia, they have no economic value. Two kinds of coca leaves are available in commerce, Bolivian or Huanuco leaves derived from *E. coca* Lam. and Peruvian or Truxillo leaves obtained from *E. truxillense* Rusby; both are cultivated in Java. In South America coca leaves are chewed with lime by the Indians as a stimulant, and are exported to Europe for use in medicine and for the preparation of cocaine, but the principal source of coca leaves is Java. Crude cocaine is manufactured in South America and exported for refining and some aspects of this industry have been discussed recently.[1]

The alkaloids of coca leaves belong to six groups :—

1. *Cocaines* (methylacylecgonines): Cocaine (methylbenzoylecgonine); cinnamylcocaine (methylcinnamoylecgonine); α-truxilline (methyl-α-truxilloylecgonine), β-truxilline (methyl-β-truxilloylecgonine).

2. *Tropeines* or *ψ-tropeines*: Benzoyltropine; tropacocaine (benzoyl-*ψ*-tropeine).

3. *Acylecgonines*: Benzoylecgonine.

4. *Alkylecgonines*: Methylecgonine, methylecgonidine.

5. *Dihydroxytropane.*

6. *Hygrines*: Hygrine, β-hygrine, cuscohygrine (cuskhygrine), hygroline.

The alkaloidal content of coca leaves varies from 0·5 to 1·5 per cent., but higher percentages have been recorded by de Jong [2] for Java leaves (season 1908, 1·0–2·5). Truxillo and Java cocas are richer in alkaloid than Bolivian coca, but the proportion of cocaine present is said to be about 50 per cent., whereas it may be 70–80 per cent. of the total alkaloid in Bolivian leaves. Coca leaves grown experimentally in India and examined by Howard contained 0·4–0·8 per cent. of alkaloid, largely cocaine. Small quantities of alkaloids have also been found in the leaves of *E. pulchrum* (South America), *E. monogynum* (India), *E. montanum*, *E. laurifolium*, *E. retusum*, *E. areolatum* and *E. ovatum*.[2a] de Jong has pointed out that the youngest leaves are richest in cinnamylcocaine; in the older leaves this is replaced by cocaine or truxilline.[3]

A process of estimation for the total alkaloids was given in the 8th Revision of the U.S. Pharmacopœia and a survey of methods available was published by Bierling, Pape and Viehover in 1910.[4] More recently processes have been described by Peyer and Gstirner [5] and Goris and Chalmeta,[5] who provide a critical review of methods. The proportion of cocaine in the total alkaloids is important and various methods are available by which this may be estimated.[6] Most of the cocaine of commerce is not obtained directly from the leaves, but from ecgonine got by the hydrolysis of the secondary alkaloids and for that reason methods for estimation of the total ecgonine obtainable from coca leaves are of importance and have been devised by Greshoff and by de Jong.[7]

Cocaine, $C_{17}H_{21}O_4N$. Cocaine is made either from the crude alkaloid as exported from *South America* [8] or from ecgonine obtained by hydrolysis of the total alkaloids extracted from Java coca leaves,[9] the ecgonine being then methylated and benzoylated to cocaine by recognised methods.[10] According to Merck the conversion of ecgonine into cocaine may be accomplished in one operation by heating the former with methyl iodide and benzoic anhydride under pressure.[11] Einhorn and Willstätter [12] found that the truxillines and cinnamylcocaine can be converted into ecgonine methyl ester by boiling their solutions in methyl alcohol (6 parts) containing sulphuric acid (2 parts) for several hours, or by passing hydrogen chloride into a solution of the alkaloids in methyl alcohol. The methyl ester can then be benzoylated to cocaine.

Cocaine crystallises from alcohol in monoclinic, four- to six-sided prisms, m.p. 98°, and is slowly volatile above 90°, b.p. 187–8°/0·1 mm. It

is lævorotatory, $[\alpha]_D$ — 15·8°, slightly soluble in cold water, readily soluble in alcohol, ether, benzene or light petroleum. The aqueous solution is alkaline to litmus, has a slightly bitter taste and when applied to the tongue produces a characteristic numbness. The hydrochloride, B . HCl, the salt chiefly used in medicine, crystallises from alcohol in short prisms, m.p. 200–2° (*dry*), $[\alpha]_D$ — 71·95° ($c = 2$; H_2O), — 67·5° (aqueous alcohol). It is readily soluble in water (1 in 0·4 at 25°) or alcohol (1 in 2·6 at 25°), but insoluble in ether or light petroleum. To ensure absence of cinnamylcocaine and α-truxilline (*iso*atropylcocaine) a permanganate test, and some form of Maclagan's test are used respectively : the latter depends on the fact that on adding ammonia to a solution of cocaine hydrochloride, a wholly crystalline precipitate is formed if the salt is not contaminated with appreciable quantities of truxilline. The chromate, $B . H_2CrO_4 . H_2O$, is precipitated as orange-yellow leaflets, m.p. 127°, when potassium chromate is added to an acid solution of the hydrochloride. The platinichloride, $B_2 . H_2PtCl_6$, is microcrystalline and sparingly soluble in water. Aqueous mercuric chloride gives with a solution of cocaine hydrochloride a bulky precipitate of the mercurichloride $B . HCl . HgCl_2$, which may be crystallised from alcohol. The nitrate, $B . HNO_3 . 2H_2O$, m.p. 58–63°, periodide, B . HI . I_2, m.p. 161°, formate, m.p. 42°, salicylate, which is triboluminescent and other salts, have also been used in medicine.

When heated with mineral acids *l*-cocaine is hydrolysed into *l*-ecgonine (p. 96), benzoic acid and methyl alcohol and a like change takes place with baryta water. If the alkaloid is boiled with water, methyl alcohol is split off and a new base, benzoyl-*l*-ecgonine is formed, which in turn can be hydrolysed by acids or alkalis into *l*-ecgonine and benzoic acid. Cocaine is, therefore, methylbenzoyl-*l*-ecgonine.

Detection. Owing to the illegitimate use of cocaine much ingenuity has been expended in devising easy means of detecting and identifying it alone, or in admixture with synthetic local anæsthetics and other organic materials. A useful and critical summary of tests has been given by Evers.[13] Cocaine may be detected by the numbness it produces when a drop of a solution is applied to the tongue. In a half-saturated solution of alum it gives a characteristic crystalline precipitate with a drop of saturated solution of potassium permanganate.[14] The alkaloid forms a colourless solution with sulphuric acid, which on warming at 100° followed by addition of a little water, develops an odour of methyl benzoate and deposits crystals of benzoic acid on cooling.

Reference may also be made to descriptions of tests, classified as indicated in brackets, published by various authors,[15] ((*a*) microchemical); ((*b*) distinction from ψ-cocaine); ((*c*) distinction from other local anæsthetics, especially procaine). The series of papers by Offerhaus and Baert (*c*) may be specially mentioned as dealing exhaustively with means of identification of drugs of this type, and especially with the detection of small quantities of cocaine in mixtures likely to be met with in illicit traffic in drugs. Strait, Aird and Weiss have described a method for the isolation and spectrographic measurement of cocaine from brain tissue.[16]

d-ψ-**Cocaine** (*iso*Cocaine, *d*-Cocaine). This substance was isolated from coca leaves by Liebermann and Giesel,[17] but is believed to have been produced by the action of alkali on *l*-cocaine in the process of extraction. It was synthesised from ψ-ecgonine (*d*-ψ-ecgonine) by Einhorn and Marquardt [18] and was obtained by Willstätter and collaborators [19] by the resolution of *dl*-ψ-ecgonine methyl ester, followed by benzoylation. It differs considerably from *l*-cocaine in character ; m.p. 45°, the salts crystallise well and are less soluble than those of *l*-cocaine ; B . HCl, m.p. 205°, $[\alpha]_D^{20°}$ + 43·0 (H_2O); hydrogen *d*-tartrate, m.p. 139°, $[M]_D^{20°}$ + 191° ; aurichloride, $B . HAuCl_4$, m.p. 148°. The nitrate is sparingly soluble in water.

dl-ψ-**Cocaine.** This was prepared by Willstätter and collaborators [19] from synthetic *dl*-ψ-ecgonine. It crystallises in hexagonal plates, m.p. 81·5°, gives a hydrochloride, m.p. 208°, and differs from natural *l*-cocaine in giving a sparingly soluble nitrate, m.p. 172°. The hydrogen *d*-tartrate has m.p. 164°, $[M]_D^{20°}$ + 39° and the *d*-α-bromocamphor-β-sulphonate, m.p. 182–3°, $[M]_D^{20°}$ + 312°. The aurichloride, $B . HAuCl_4 . 2H_2O$ is crystalline, m.p. 65–70° or 164–5° (*dry*).

Cinnamylcocaine, $C_{19}H_{23}O_4N$. This alkaloid was isolated by Giesel [20] from Java coca leaves after it had been prepared by Liebermann [21] by heating ecgonine at 100° with cinnamic anhydride and methylating the resulting cinnamoylecgonine (colourless needles, m.p. 216°). It is almost insoluble in water, but easily soluble in organic solvents and crystallises from benzene or light petroleum in rosettes of needles, m.p. 121°. $[\alpha]_D$ — 4·7° ($CHCl_3$). The hydrochloride, B . HCl . $2H_2O$, forms flattened needles, m.p. 176° (*dry*) from water. The platinichloride, m.p. 217°, as precipitated, is amorphous, but crystallises on standing. The aurichloride forms yellow needles, m.p. 156°. When warmed with hydrochloric acid the base is hydrolysed, furnishing *l*-ecgonine, cinnamic acid and methyl alcohol.

The isomeric *d*-CINNAMYLCOCAINE (methylcinnamoyl-*d*-ψ-ecgonine) prepared by Einhorn and Deckers [22] by the action of cinnamoyl chloride at 150–60° on *d*-ψ-ecgonine methyl ester, crystallises in prisms, m.p. 68°, $[\alpha]_D$ + 2° (EtOH). The hydrochloride, B . HCl, forms needles, m.p. 186° ; the platinichloride, needles, m.p. 208°, and the aurichloride orange needles, m.p. 164°.

Truxillines, $C_{38}H_{46}O_8N_2$. In 1887 Hesse isolated from Peruvian coca leaves an amorphous alkaloid which he named cocamine [23] ; a year later Liebermann [24] examined this material, and by fractionation of its solutions by addition of petroleum proved it to be a mixture of at least two isomeric bases, which he named α- and β-truxillines. The pure alkaloids have not been obtained from coca leaves owing to the difficulty of separating them, but each has been prepared synthetically.[25]

α-TRUXILLINE (*Cocamine, γ-isatropylcocaine*). An amorphous white powder, m.p. 80°, easily soluble except in light petroleum and water. Solutions of the base are lævorotatory and possess a bitter taste. When warmed with hydrochloric acid the base undergoes hydrolysis with the production of *l*-ecgonine, methyl alcohol and α-truxillic acid $(C_9H_8O_2)_2$

(γ-isatropic acid), m.p. 228°. The synthesis of the alkaloid was accomplished by the action of α-truxillic anhydride on *l*-ecgonine and methylation of the resulting α-truxilloylecgonine.

β-TRUXILLINE (iso*Cocamine*, δ-*isatropylcocaine*). This base sinters at 45° and decomposes above 120°, $[\alpha]_D$ — 29·3°. It undergoes hydrolysis, furnishing β-truxillic acid (δ-isatropic acid), m.p. 206°, with ecgonine and methyl alcohol. It also has been synthesised by Liebermann and Drory.[25]

Methylcocaine (*Ethylbenzoylecgonine*). This base was isolated by Günther [26] from commercial cocaine, by dissolving the latter in an alcoholic solution of hydrogen chloride and fractional precipitation with ether, the new alkaloidal hydrochloride being precipitated last. The base melts at 110°, possesses the same physiological properties as cocaine and yields an aurichloride and a platinichloride closely resembling the corresponding salts of that base. It probably results from the use of ethyl alcohol as a solvent in the commercial preparation of cocaine from ecgonine, but it is stated by Günther to be isomeric, not identical, with cocaethyline (ethylbenzoylecgonine) prepared synthetically by esterifying benzoylecgonine with ethyl alcohol.[27]

Benzoylecgonine, $C_9H_{14}(CO \cdot C_6H_5)O_3N$. This acyl ester of ecgonine was isolated about the same time by Skraup and by Merck from Peruvian coca leaves. According to de Jong [28] it does not occur in Java coca. It was subsequently prepared by Paul [28(a)] by the action of water on cocaine and later synthesised by Liebermann and Giesel [29] by the action of benzoic anhydride on ecgonine. It crystallises from water with $4H_2O$ in needles, m.p. 86° or 195° (*dry*, *dec.*), $[\alpha]_D$ — 63·3°, and dissolves readily in alkaline liquids forming salts. When boiled with dilute hydrochloric acid, it is hydrolysed into ecgonine and benzoic acid, and on esterification with methyl alcohol furnishes cocaine, and with other aliphatic alcohols yields homologues of cocaine : of these the ethyl ester (cocaethyline), m.p. 108–9°, the propyl ester (cocapropyline), m.p. 78–79·5°, and the *iso*butyl ester, m.p. 61–2°, among others, have been prepared.

l-ECGONINE, $C_9H_{15}O_3N \cdot H_2O$. This substance was first obtained by Lossen [30] as the final basic hydrolytic product of the action of acids on cocaine, and is obtainable in like manner from several of the alkaloids occurring with cocaine (*see above*). It crystallises from dry alcohol in monoclinic prisms, m.p. 198° (*dec.*), 205° (*dry*), $[\alpha]_D$ — 45·4°, is soluble in water, sparingly so in alcohol, insoluble in most organic liquids. Ecgonine forms salts with bases and acids ; the hydrochloride crystallises in rhombs, m.p. 246°, $[\alpha]_D$ — 57·1° ; the aurichloride, $B \cdot HAuCl_4$, forms yellow prisms, m.p. 202° (*dry*) and the platinichloride, red needles, m.p. 226° (*dry*). Barium-ecgonine $[Ba(C_9H_{14}O_3N)_2]$ crystallises in prismatic needles, readily soluble in water or alcohol.

Ecgonine is readily esterified in presence of hydrogen chloride, and in this way various alkylecgonines have been prepared. The most important of these is the methyl ester, b.p. 177°/15 mm., which according to de Jong [28] occurs in Java coca. It was prepared by Einhorn and Klein [10] in 1888 as the hydrochloride crystallising, with 1 H_2O, in colourless prisms, m.p. 212°

(*dec.*). When benzoylated it furnishes cocaine. Ecgonine also reacts with acid chlorides and anhydrides to form acyl derivatives and in addition to benzoylecgonine, cinnamoyl-, *iso*valeroyl-, anisoyl- and truxilloyl-ecgonines have been prepared ; these, in turn, by esterification with methyl alcohol furnish the corresponding cocaines.

d-ψ-ECGONINE (*d*-ECGONINE). This isomeride of ecgonine was prepared by Einhorn and Marquardt [31] by the action of potassium hydroxide solution on ecgonine and is formed when the cocaines are hydrolysed by alkalis. It crystallises from dry alcohol in tablets, for which m.p. 254°, 257° and 264° have been recorded, $[\alpha]_D$ + 21·1° (c = 4·3 : H_2O) : the hydrochloride forms monoclinic prisms, m.p. 236°, α_D + 1·6° (c = 4·4 : l = 2 dcm.) ; the aurichloride, $B \cdot HAuCl_4$, has m.p. 220° (*dec.*). It forms esters like those yielded by *l*-ecgonine, and from it *d*-ψ-cocaine (*methylbenzoyl*-d-ψ-*ecgonine*) has been prepared (p. 95).

dl-ψ-ECGONINE. This was prepared by Willstätter and Bode by the reduction of tropinonecarboxylic acid.[32] It forms rhombic crystals, m.p. 251° (*dec.*) and yields a hydrochloride, $B \cdot HCl \cdot \frac{1}{2}H_2O$ crystallising in slender needles, m.p. 149° (*dry*, *dec.*) and an aurichloride, glistening needles, m.p. 213°. On benzoylation and methylation it yields *dl*-ψ-cocaine (p. 95). According to Willstätter and Bommer,[33] the *d*-ecgonine of the earlier workers has the same relation to natural *l*-ecgonine as ψ-tropine has to tropine and they renamed the *d*- and *dl*-ecgonines, *d*-ψ-ecgonine and *dl*-ψ-ecgonine respectively, and these names have been used throughout the foregoing descriptions, with the derivatives benzoyl-*d*-ψ-ecgonine and *d*-ψ-cocaine, etc., in their appropriate places.

Constitution of Ecgonine, $C_9H_{15}O_3N$. The facts recorded above furnish evidence of the existence of a hydroxyl and a carboxyl group in ecgonine. Einhorn observed [34] that dehydrating agents remove the elements of a molecule of water from ecgonine, forming ANHYDROECGONINE, $C_9H_{13}O_2N$ (ecgonidine), which crystallises in needles, m.p. 235°, $[\alpha]_D$ — 84·6°, is unsaturated, combining with two atoms of bromine, and still contains the —COOH group of the parent base, since it esterifies alcohols. The methyl ester, $D_{20°}^{20°}$ 1·0921 ; $n_D^{20°}$ 1·5040 ; $[\alpha]_D^{20°}$ — 54·96° ; $B \cdot HBr$, m.p. 147°, has been prepared by Ugriumov.[34] Ethyl anhydroecgonine has been found in residues obtained in working up the secondary alkaloids of coca leaves [35] and may be formed in this process, but Matchett and Levine [35] have isolated the methyl ester (methylecgonidine) from both Java and Peruvian coca seeds. When heated with hydrochloric acid at 280°, anhydroecgonine loses a molecule of carbon dioxide with the formation of tropidine (p. 74), whence it appears that anhydroecgonine is a carboxylic acid of tropidine.[36]

The close relationship of ecgonine to tropine is brought out by its oxidation products, which when chromic anhydride in acetic acid is the agent used are [37] : tropinone, $C_8H_{13}ON$ (p. 74), tropinic acid, $C_8H_{13}O_4N$ (p. 75) and ecgoninic acid, $C_7H_{11}O_3N$. The latter crystallises from benzene in colourless needles, m.p. 93°, and has been shown by Willstätter and Bode to be *N*-methylpyrrolidone-2-acetic acid, [38] and this was confirmed by Willstätter and Hollander's [39] synthesis of the acid.

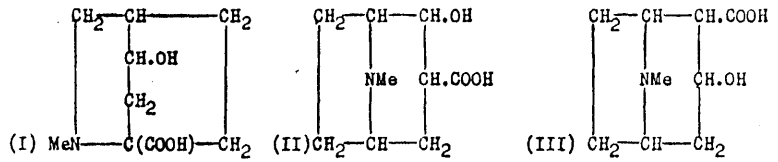
When ecgonine is treated with permanganate in acid solution a new base, *nor*ecgonine, $C_8H_{13}O_3N$, is the principal product. It stands in the same relation to ecgonine as the similarly produced tropigenine (*nor*tropine) does to tropine (p. 75) and, like its analogue, is a secondary base produced by the oxidation of a methyl group attached to nitrogen. It crystallises in long needles, m.p. 233°, is very soluble in water and gives a characteristic aurichloride, m.p. 211°, crystallising in yellow needles.[40] Similarly on degradation by Hofmann's reaction [41] anhydroecgonine gives rise to δ-*cyclo*heptatrienecarboxylic acid, $C_8H_8O_2$, whilst tropidine yields the corresponding *cyclo*heptatriene (p. 77).

The close relationship existing between ecgonine and tropine is evident from the following diagrammatic summary of the results of reactions :—

DEHYDRATION :
Tropine $C_8H_{15}ON$ → *Tropidine* $C_8H_{13}N$ ←
DEHYDRATION AND DECARBOXYLATION :
Ecgonine $C_9H_{15}O_3N$ → *Anhydroecgonine* $C_9H_{13}O_2N$
OXIDATION : (a) Chromic acid
Tropine $C_8H_{15}ON$ → *Tropinone* $C_8H_{13}ON$ → *Tropinic acid* $C_8H_{13}O_4N$ → *Ecgoninic acid* $C_7H_{11}O_3N$
Ecgonine $C_9H_{15}O_3N$ →
(b) Permanganate
Tropine $C_8H_{15}ON$ → *Tropigenine* $C_7H_{13}ON$
Ecgonine $C_9H_{15}O_3N$ → nor*Ecgonine* $C_8H_{13}O_3N$
EXHAUSTIVE METHYLATION :
Tropidine $C_8H_{13}N$ → *Tropilidene* C_7H_8 (*δ-cyclo* Heptatriene)
Anhydroecgonine $C_9H_{13}O_2N$ → δ-cyclo*Heptatrienecarboxylic acid* $C_8H_8O_2$

It will be seen that ecgonine and its derivatives differ from tropine and its derivatives throughout by CO_2, so that the former probably stands to the latter in the relation of a carboxylic acid, and hence the formulæ assigned at various times to tropine by Ladenburg, Merling and Willstätter have been suitably modified to represent ecgonine : thus Einhorn [42] at first represented ecgonine as *N*-methyltetrahydropyridyl-β-hydroxypropionic acid, $C_5H_7NMe.CHOH.CH_2.COOH$, which was modified to (I) (after Merling) by Einhorn and Tahara.[43]

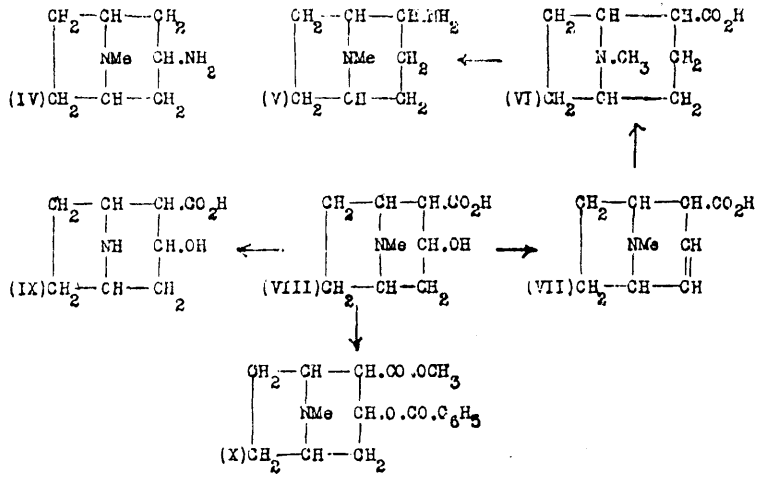
There are two probable formulæ (II) and (III) for ecgonine derivable [44] from Willstätter's representation of tropine (p. 76).



The position assigned to the hydroxyl group in formula (III) explains (1) the formation of anhydroecgonine by loss of water between the —CHOH group and the neighbouring —CH_2 group ; and (2) Willstätter and Müller's observation [45] that an unstable β-ketonic acid precedes the formation of tropinone, when ecgonine is oxidised by chromic acid. Further, when anhydroecgonine ethyl ester is reduced by sodium in alcohol, it yields

dihydroecgonidine (VI), a —CHOH—group in ecgonine having been converted into —CH_2— and the amide corresponding to this on oxidation with sodium hypobromite yields *iso*tropylamine, isomeric with tropylamine (or ψ-tropylamine (IV)) obtained by the reduction of tropinoneoxime, but not identical with either ; it follows that the amino group in the latter amines must occupy a position different from that in *iso*tropylamine (V) and, therefore, from the carboxyl group in dihydroecgonidine (VI) and in ecgonine.

Accepting this view of the constitution of ecgonine, the formulæ of its derivatives and of cocaine may be written as follows : anhydroecgonine (VII), ecgonine (VIII), *nor*ecgonine (IX) and cocaine (X).



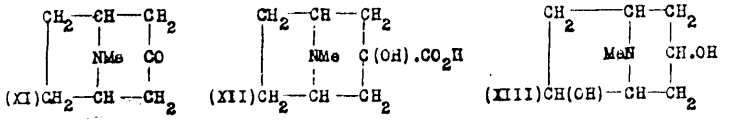
Cocaine (methylbenzoylecgonine)

Willstätter and Bommer [46] made it clear that the synthesis of ecgonine and consequently of cocaine had not been effected, a point on which there had been some confusion owing to the fact that the alkali labile natural ecgonine had been regarded as the optical antipode of the alkali-stable so-called *d*-ecgonine, whilst the optically inactive isomeride synthesised by Willstätter and Bode [47] has been regarded as the *dl*-form of natural ecgonine. The view taken by the former authors is that the alkali-stable form (*d*-ecgonine) is a ψ-ecgonine having the same relation to natural *l*-ecgonine as ψ-tropine (p. 101) has to tropine, whilst the inactive form is one of four possible racemates.[48]

Willstätter and Bode [49] converted tropinone into ψ-ecgonine by treating sodium tropinone with carbon dioxide and sodium, when it yielded sodium tropinonecarboxylate. This on reduction with sodium in alcohol gave some *dl*-ψ-ecgonine (p. 97), which on esterification with methyl alcohol and benzoylation yielded a *dl*-cocaine. A simpler synthesis of ψ-ecgonine was achieved by Willstätter and Bommer,[46] and reference is made on p. 80 to this and other processes, some of which have been protected by patents. These improvements having enabled the prepara-

tion of methyl tropinonecarboxylate to be undertaken, Willstätter, Wolfes and Mäder [50] reinvestigated the reduction of this ester and found that both *dl*-ψ-ecgonine and *dl*-ecgonine methyl esters are formed, and from these the corresponding *dl*-ψ-cocaine and *dl*-cocaine were obtained by benzoylation. *dl*-Cocaine was resolved into its optically active components by crystallisation of the hydrogen-*d*-tartrate to give the *l*-base (natural cocaine) and of the hydrogen *l*-tartrate to give the *d*-base. *dl*-ψ-Cocaine could not be resolved directly, but its components were obtained by resolving *dl*-ψ-ecgonine methyl ester and benzoylating the two forms.

α-ECGONINE (XII) is the name given to a base, isomeric with ecgonine, and prepared by Willstätter [51] by the addition of hydrocyanic acid to tropinone (XI) and hydrolysis of the cyanohydrin so formed :



It occurs in brilliant snow-white crystals, m.p. 305° (*dec.*) and is readily soluble in water or aqueous alcohol. The benzoyl derivative, m.p. 209°, is crystalline and on methylation gives α-cocaine, a base crystallising in prisms, m.p. 87°, and yielding an aurichloride, m.p. 222° (*dec.*), crystallising in leaflets. It is bitter to the taste but has no local anæsthetic action.

Dihydroxytropane, $C_8H_{15}O_2N$. This base was isolated from the mixture of hydrolysed bases obtained in working up the alkaloids of Java coca ; it occurs in the fraction less soluble in ether than tropine and ψ-tropine, has m.p. 209–209·5°, $[\alpha]_D^{27°}$ — 22° (EtOH), yields a hydrochloride, $[\alpha]_D^{27°}$ + 1·75° (H_2O), a picrate, m.p. 253° (*dec.*) and furnishes a dibenzoate, whose sulphate has $[\alpha]_D^{26°}$ + 52·1° (EtOH) and hydrochloride, B . HCl . $2H_2O$, m.p. 115° or 205° (*dry*), $[\alpha]_D^{22°}$ + 41·8° (dilute alcohol) and nitrate, B . HNO_3, m.p. 197°. On reduction with hydriodic acid and red phosphorus the dihydroxytropane is converted into tropane and on treatment with phosphorus oxychloride it yields a base, $C_8H_{13}ON$, b.p. 188°/752 mm., picrate, m.p. 177° (*dec.*). This dihydroxytropane is probably represented by formula (XIII).[52] The dibenzoyl-derivative has local anæsthetic properties. The *iso*valeryl ester is the alkaloid valeroidine found in *Duboisia myoporoides* (p. 90).

Tropacocaine (*Benzoyl-ψ-tropëine*), $C_{15}H_{19}O_2N$, was discovered by Giesel [53] in Java coca leaves and has since been found in Peruvian coca.[54] Its preparation from the former source has been described by Hara and Sakamoto.[55] It crystallises in needles, m.p. 49°, is insoluble in water, but soluble in alcohol, ether or dilute ammonia and is generally prepared by benzoylating ψ-tropine, and purified as the hydrochloride. Its alcoholic solution is alkaline and optically inactive. The hydrochloride forms needles, m.p. 271° (*dec.*), and the hydrobromide leaflets. The aurichloride separates in minute yellow needles, m.p. 208°, from hot aqueous solutions ; the picrate has m.p. 238–9°. When heated with hydrochloric acid or baryta water the alkaloid is hydrolysed to benzoic acid and ψ-tropine.[56]

ψ-TROPINE, $C_8H_{15}ON$. This base is a stereoisomeride of tropine

(p. 73). It crystallises in colourless tablets or prisms, m.p. 108°, b.p. 240°, is miscible with water, ether or alcohol, alkaline in reaction and optically inactive. The hydrochloride forms hygroscopic needles ; the aurichloride crystallises in brilliant yellow plates, m.p. 225° (*dec.*), and the picrate in long needles, m.p. 258–9° (*dec.*). ψ-Tropine esterifies with organic acids, furnishing a series of derivatives, which from their analogy with the tropeines have been called ψ-tropëines, but unlike the former exert little or no mydriatic action.

Mandelyl-ψ-tropëine (ψ-homatropine), $C_{16}H_{21}O_3N$, is a thick uncrystallisable oil. *Tropyl-ψ-tropëine*, $C_{17}H_{23}O_3N$, crystallises in colourless needles, m.p. 86°.

Tropine and ψ-tropine are mutually convertible as already described. Mixtures of tropine and ψ-tropine can be separated by means of the picrates, that of ψ-tropine being the more soluble in water [57] (1·48 per cent. in water at 16°). By the action of sodium amyloxide on tropine, Willstätter has shown that ψ-tropine is produced [58] and this has been confirmed by Barrowcliff and Tutin,[59] who also support Willstätter's view that both bases are internally compensated, the relation being that of *cis-trans*-isomerism.[60] The synthesis of ψ-tropine has been described already (p. 77).

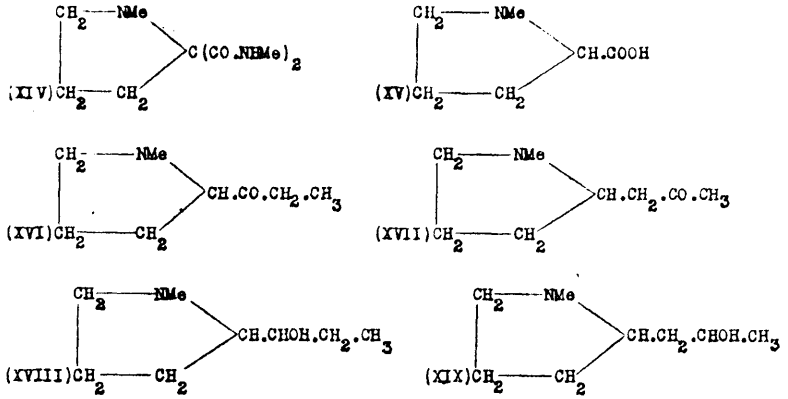
Tröger and Schwarzenberg [61] have isolated a base (m.p. 53°, b.p. 225–30° ; picrate, m.p. 237° (*dec.*)) isomeric with tropine and ψ-tropine, from coca leaves.

HYGRINES. This group of coca alkaloids was discovered by Lossen [62] in an ethereal extract of a slightly alkaline percolate of Peruvian coca leaves. Liebermann and his pupils [63] re-investigated Lossen's supposed homogeneous base, and observed that by distillation under reduced pressure it could be separated into two products, hygrine and β-hygrine. Hygrine has also been found in *Convolvulus hamadæ* (p. 67).

Hygrine, $C_8H_{15}ON$, b.p. 92–4°/20 mm., 111–3°/50 mm. or 193–5°/760 mm., $D_4^{17°}$ 0·940, $[\alpha]_D$ — 1·3°, is a colourless, strongly alkaline liquid which absorbs carbon dioxide from the air and decomposes on exposure to light. It forms an aurichloride and a characteristic picrate, yellow needles, m.p. 158°, *dl*-form, 149–50°. On oxidation by chromic acid hygrine yields hygric acid, $C_6H_{11}O_2N$, m.p. 164°, which heated alone or with strong sulphuric acid loses carbon dioxide, giving *N*-methylpyrrolidine, $C_5H_{11}N$. Both hygric acid and hygrine are tertiary amines and hygrine gives a crystalline oxime, m.p. 116–20° (*dl*-form, m.p. 125°).

Hygric acid was synthesised by Willstätter by the following method.[64] Ethyl bromopropylmalonate, $CH_2Br . CH_2 . CH_2 . CH(CO_2Et)_2$, obtained by condensation of trimethylene bromide with ethyl sodiomalonate, on bromination yielded ethyl αδ-dibromopropylmalonate, $CH_2Br . CH_2 . CH_2 . CBr(CO_2 . C_2H_5)_2$. This reacts with methylamine forming two products both derived from *N*-methylpyrrolidine-2 : 2-dicarboxylic acid, viz., the dimethylamide (XIV) and the diethyl ester. The former on heating with hydrochloric acid at 125°, and the diethyl ester with water at 160°, both undergo hydrolysis and partial decarboxylation

to *N*-methyl-pyrrolidine-2-carboxylic acid, which proved to be *dl*-hygric acid (XV) (m.p. 169–170° (*dry*)): aurichloride (m.p. 190–5° (*dec.*)). Subsequently Karrer and Widmer [64] obtained *l*-hygric acid by oxidising *N*-methylnicotone with chromic acid. This product as a monohydrate had m.p. 116°, $[\alpha]_D$ −80·12° (H_2O). Willstätter suggested that of the two formulæ (XVI and XVII) available for the representation of hygrine, (XVII) was the more probable and this was confirmed by K. Hess's synthesis [65] of *dl*-hygrine. The secondary alcohols corresponding to the ketones represented by the two formulæ (XVI and XVII) were prepared (1) by treating magnesium pyrryl bromide with propionyl chloride, reducing the 2-propionylpyrrole so formed and methylating the product to (XVIII); (2) by the addition of propylene oxide to magnesium pyrryl bromide, hydrogenation of the product in presence of spongy platinum and methylation of the resulting pyrrolidyl*iso*propyl alcohol, giving (XIX).



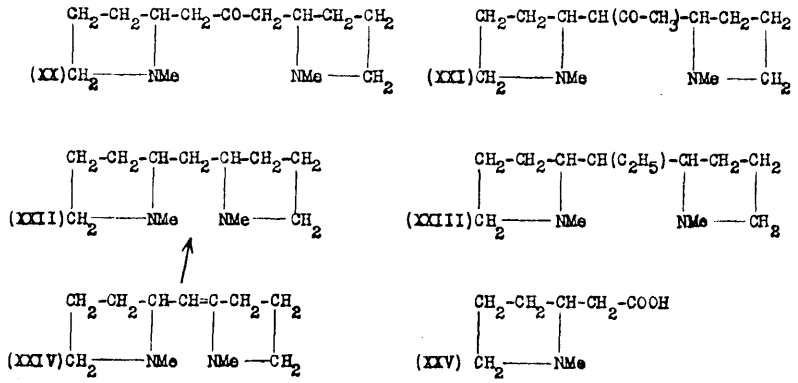
When the final methylation of either product is effected with formaldehyde, oxidation of the secondary alcohol group occurs simultaneously in each case, and of the two resulting ketones that from product (XIX) proved to be *dl*-hygrine, which must therefore have formula (XVII) given above. Another synthesis of *dl*-hygrine has been effected recently by Sorm.[65]

Hygroline, $C_8H_{17}ON$. This alkaloid was isolated by Späth and Kittel [65(a)] from a fraction, b.p. 78–82°/12 mm., of the residual liquid alkaloids of coca leaves. It has m.p. 33–4°, $[\alpha]_D^{23°}$ − 63·2°, (c = 11·4, H_2O) is soluble in water or organic solvents and yields an oily *O*-benzoyl derivative, b.p. 105–10°/0·003 mm., characterised by an aurichloride, m.p. 114–5°, a platinichloride, m.p. 150–2° and a 3 : 5-dinitrobenzoate, m.p. 65°. On oxidation by chromic acid it furnishes hygrine, which is optically inactive, possibly due to racemisation, identified by the picrate, m.p. 153–4° and oxime, m.p. 124–5°. Hygroline is therefore regarded as the alcohol, (XIX) corresponding to the ketone hygrine (XVII).

β-Hygrine, $C_{14}H_{24}ON_2$. This, the second fraction of Lossen's hygrine,[66] decomposes when distilled under atmospheric pressure, but boils at

215°/50 mm. and has specific gravity 0·982 at 18°. It gives an aurichloride, $C_{14}H_{24}ON_2 . 2HAuCl_4$, and forms a colourless crystalline dimethiodide. When oxidised by chromic acid, it yields a small quantity of hygric acid.

Cuscohygrine, $C_{13}H_{24}ON_2$ (*Cuskhygrine*). This third hygrine, first recognised in "cusco" leaves by Liebermann and Cybulski,[67] was characterised by these authors and by Hess and Bappert.[68] It has now been found in *Convolvulus hamadæ*. It boils at 169–70°/23 mm., has specific gravity 0·9767 at 17°, is optically inactive, absorbs carbon dioxide forming an unstable carbonate, is miscible with water and gives a crystalline hydrate, $B . 3\frac{1}{2}H_2O$, m.p. 40°. The alkaloid forms crystalline salts with acids; hydrobromide, m.p. 234°, nitrate, m.p. 209° (*dec.*), and yields a methiodide, m.p. 244°, and a crystalline oxime, m.p. 53–4°. It contains two tertiary nitrogen atoms and, on oxidation with chromic acid, furnishes hygric acid. Liebermann assigned to it formula (XX), which Hess and Fink [69] modified to (XXI) mainly on the following evidence. On long standing in ethereal solution over potassium hydroxide, the alkaloid is partly converted into *dl*-hygrine. It does not condense with benzaldehyde as it should if it contained the chain —$CH_2 . CO . CH_2$—. Cuscohygrine yields two hydrazones, regarded as stereoisomeric, which on reduction furnish di-*N*-methyl-2-pyrrolidylmethane (XXII) and αα-di-*N*-methylpyrrolidylpropane (XXIII). On treatment with nitric oxide in presence of sodium ethoxide,[70] the alkaloid yields homohygric acid (*N*-methyl-2-pyrrolidylacetic acid (XXV)) and a mixture of bases believed to be of the type (XXIV), since on reduction they furnish di-*N*-methyl-2-pyrrolidylmethane (XXII). Sohl and Shriner [71] have confirmed the formation of *N*-methyl-2-pyrrolidylacetic acid from cuscohygrine and have synthesised the acid. The latter has also been prepared by King, Clifton and Openshaw [72] but the acid has not yet been converted into substance (XXII). The identity of the di-*N*-methylpyrrolidylmethane (XXII) formed in these reactions remains in doubt, since the synthetic product, which exists in two stereoisomeric forms, subsequently prepared by Hess and Anselm [73] proved not to be identical with the substance derived from cuscohygrine. Hess and Bappert [68] found that, although cuscohygrine could not be exhaustively methylated, it yielded on reduction two stereoisomeric



alcohols, which proved amenable to this process and furnished *n*-undecane and *n*-undecan-ζ-ol as final products. This piece of evidence supports Liebermann and Cybulski's formula (XX) for cuscohygrine, for which Sohl and Shriner [71] have also provided further evidence on several points.

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Pharmacological Action in the Tropane Series. *Atropine.* When administered internally in toxic doses, atropine at first stimulates but eventually depresses the central nervous system, giving rise to hallucinations, inconsequent speech, delirium and convulsions, followed by stupor and coma. It paralyses muscles and secretory glands to the effects of stimulation by post-ganglionic, cholinergic, nerve fibres. It is to this action that the dryness of throat and mouth characteristic of belladonna poisoning is due. The kidney is but little affected; consequently there is little or no change in the secretion of urine. The initial, transitory, slowing of the heart, results from stimulation of the vagus nuclei in the medulla and the later quickening is due to paralysis of the pacemaker to inhibitory vagal stimuli. Respiration becomes quicker and deeper, but eventually slower and shallower, and death is due to respiratory failure. There is often a marked rise in temperature. Atropine affects all organs containing unstriped muscle, lessening their movements, and is antagonistic in this respect to muscarine and nicotine, and in general to the action of pilocarpine.

The alkaloid is principally used in medicine to cause dilatation of the pupil of the eye (mydriasis), due to paralysis of the circular muscle of the iris. The accommodation is also paralysed as a result of action on the ciliary muscle (cycloplegia). Atropine is also used in conditions where