377. Sophora *Alkaloids. Part I. The Alkaloids of the Seeds of* S. microphylla, *Ait.*

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The seeds of *Sophora microphylla* are shown to contain methylcytisine, matrine, cytisine, a *base*, m.p. 293—296° (possibly $C_{15}H_{23}O_4N_3$), and a *base*, m.p. 168—171°.

The presence of alkaloids is a characteristic of many of the natural order *Leguminosæ*, including the *Sophora* genus (cf. Wood, *Pharm. J.*, 1878, **3**, 1047; Greshoff, *Ber.*, 1890, **23**, 3537; Plugge, *Arch. Pharm.*, 1895, **233**, 430; Plugge and Rauwerda, *ibid.*, 1896, **234**, 685; Nagai, *J. Pharm. Soc. Japan*, 1899, 84; Kondo and co-workers, see Tsuda, *Ber.*, 1936, **69**, 429 for earlier references; Orékhov and co-workers, *ibid.*, 1935, **68**, 820 and earlier references).

In New Zealand the genus *Sophora* is represented by three species and the seeds of one of them, *S. microphylla*, Ait., syn. *Edwardsia microphylla* (Maori name " Kowhai "), have now been investigated. From the crude alkaloid fraction (1—2·5% yield) five different alkaloids have been isolated, *viz.*, methylcytisine and matrine in approximately equal amounts, cytisine and two other bases, the last three in less than 1% of the total alkaloid fraction. Although cytisine commonly occurs in *Sophora* species, methylcytisine has not hitherto been isolated from plants of this genus but only from the closely allied plants *Leontice thalictrum*, L., syn. *Caulophyllum thalictroides*, Mich. (Power and Salway, J., 1913, **103**, 191), *Thermopsis lanceolata*, R. Br., syn. *Sophora lupinoides* (Orékhov, Norkina, and Gurevitsch, *Ber.*, 1934, **67**, 1394), and *Anagyris foetida* (Ing, J., 1935, 1053). Matrine itself occurs in isomeric forms and further evidence indicates that some of the derivatives also occur in isomeric forms. Two of the bases are possibly new, but sufficient material was not available for complete investigation. They do not give the Van de Moer reaction and thus probably do not contain the cytisine nucleus.

Investigations on this and other species endemic to New Zealand are being continued.

Experimental.

S. microphylla is a tree 9—12 m. in height endemic to New Zealand and bears extremely hard, yellow seeds, 2—3 mm. in diameter.

Three lots of seeds were examined, the best procedure being as follows. The crushed seeds

(500 g.), obtained from the same tree at Henderson, were extracted exhaustively with alcohol containing 2% of acetic acid. After removal of a fatty layer the clear yellow extract was concentrated considerably, diluted with water (2 vols.), and steam-distilled to remove the alcohol. Further insoluble material was separated, and the acid aqueous portion extracted repeatedly with light petroleum and ether. The aqueous solution was made strongly alkaline with ammonia, which caused no precipitation of solids, and extracted with chloroform until the aqueous portion no longer gave a precipitate with Mayer's reagent. The chloroform extract yielded 12 g. (2·5%) of alkaloids as a brown oil (in two other extractions yields of 1 and 1·3% were obtained). The oil was purified by distillation in a vacuum, nearly all distilling as a clear oil, b. p. 225—230°/15 mm., solidifying on cooling to a yellowish-white greasy solid. The material was excessively soluble in water and nearly all organic solvents except light petroleum and the separation of alkaloids entailed a series of fractional recrystallisations from light petroleums of different b. p.'s with systematic working up of the mother-liquors.

The distilled alkaloids were digested exhaustively with petroleum (b. p. 80—100°), giving a solution and a small insoluble residue (M). On cooling, the solutions deposited colourless crystals of mixed bases, which were recrystallised six times from petroleum (b. p. 80—100°), extracted with light petroleum (b. p. below 40°), in which base A was very sparingly soluble and base B freely soluble, and again recrystallised from petroleum (b. p. 80—100°) to give colourless needles (base A), 2—2·5 cm. long, m. p. 136°, unchanged by further recrystallisation from the same solvent (yield, 2·45 g.). In one case a sample crystallised from a large excess of light petroleum (b. p. 40—50°) in prisms, m. p. 138°.

The solvent was removed from the mother-liquors from the above recrystallisations, and the product extracted with successive portions of boiling light petroleum (b. p. below 40°), yielding a solution and a residue (N). The crystals obtained on cooling the solutions were recrystallised four times from the same solvent, giving stout needles (base B), 1—1·5 cm. in length, m. p. 77°, unchanged by further recrystallisation (yield, 3·45 g.). In one case, prisms of the same m. p. were obtained by recrystallisation with the same solvent.

The residue (N) was extracted with petroleum (b. p. 80—100°), giving a solution and a further residue (O). From the solution a further quantity of base A was worked up. The residue (O) was extracted with light petroleum (b. p. 40—50°), and the product separating recrystallised from petroleum (b. p. 100—120°) to give colourless hygroscopic plates, m. p. 148—150°, raised to 152—152·5° after four further recrystallisations from excess of petroleum (b. p. 80—100°). The yield of this base, base C, was 6 mg.

The original residue (M) was insoluble in petroleums of different b. p.'s. From boiling acetone solutions it separated as a brownish powder, base D, m. p. 293—296° (yield, 150 mg.). The base was purified through the picrate; this crystallised from water in long needles (*ca.* 1 cm. long), which charred at higher temperatures but did not melt below 350°.

In a similar experiment utilising approximately the same amount of crude alkaloid material derived from another lot of seeds, the residues from which base C was extracted gave on crystallisation from methyl alcohol–acetone 3 mg. of hair-like needles, base E, which after recrystallisation from the same solvent had m. p. 168—171°, with previous softening at 162°.

Base A.—This base, m. p. 136°, has been identified as methylcytisine (Found, in dried material: C, 70·8, 70·4; H, 7·4, 7·5; N, 13·75, 13·9. Calc. for $C_{12}H_{16}ON_2$: C, 70·6; H, 7·8; N, 13·7%). $[\alpha]_D^{20°}$ − 217° (*l* = 0·5, *c* = 2·258 in water). Power and Salway (*loc. cit.*) give m. p. 137°, $[\alpha]_D$ − 221·6°; Orékhov, Norkina, and Gurevitsch (*loc. cit.*) m. p. 132—133°, $[\alpha]_D$ − 190·0°; and Ing (*loc. cit.*) m. p. 136—137°. Methylcytisine obtained by methylation of cytisine (Partheil, *Arch. Pharm.*, 1892, **230**, 448; Rauwerda, *ibid.*, 1900, **238**, 484; Ing, J., 1931, 2200) has m. p. 134°. The alkaloid is freely soluble in water and most organic solvents, but difficultly soluble in ether and petroleum, more soluble in higher-boiling than in the lower-boiling petroleum. It gives the Van de Moer colour reaction (red coloration with ferric chloride, going blue on addition of hydrogen peroxide) typical of cytisine and its derivatives.

The aurichloride crystallised from acetone in yellow plates, m. p. 206° (decomp.). Power and Salway (*loc. cit.*) record needles, m. p. 205° (decomp.). The salt decomposed on boiling with water, depositing gold.

The picrate crystallised from hot water in long yellow needles which sintered at 220° and melted at 229°. Power and Salway obtained yellow needles sintering at 200° and melting at 229°. Ing (*loc. cit.*) records m. p. 228°.

Methiodide. After the base had been refluxed in acetone solution with methyl iodide, a methiodide separated on cooling, m. p. 247°, raised to 248° with sintering at 240° after crystallisation from methyl alcohol–water. The same methiodide, m. p. 245°, also separated on cooling

after the base had been refluxed in dry benzene solution with methyl iodide. The mother-liquors from the latter preparation deposited needles, m. p. 267°, after some months. Ing (*loc. cit.*) records m. p. 276° (decomp.).

Platinichloride. When the base in alcoholic solution was treated with choroplatinic acid, orange needles separated, m. p. 238° (decomp.). In another experiment, the base in absolute alcoholic solution containing 2—3 drops of concentrated hydrochloric acid was treated with a solution of platinic chloride in absolute alcohol. The yellow amorphous material decomposed at 267° after shrinking at 249°. It was insoluble in alcohol and acetone, but crystallised from alcohol–water in yellow plates which did not melt or decompose below 300°.

The picrolonate, from the base and picrolonic acid in absolute alcohol, crystallised from absolute alcohol in small yellow needles, m. p. 224°.

The perchlorate, from the base in ethyl acetate solution and 20% aqueous solution of perchloric acid, crystallised from absolute alcohol in long colourless needles, decomp. 250—252° (Found : N, 9·1. Calc. for $C_{12}H_{16}ON_2,HClO_4$: N, 9·2%).

The methosulphate is hygroscopic and was not obtained crystalline.

Base B.—This base, m. p. 77°, has been identified as α-matrine (Found, in dried material: C, 72·7; H, 9·5; N, 11·2; NMe, 0. Calc. for $C_{15}H_{24}ON_2$: C, 72·6; H, 9·7; N, 11·3%). $[\alpha]_D^{15°}$ + 40·93° (l = 1, c = 2·272 in water). The m. p. was not depressed by authentic specimens of α-matrine kindly provided by Professors Kondo and Orékhov (cf. Orékhov and Proskurnina, *Ber.*, 1935, **68**, 429). Matrine has so far been identified only from the root bark of *Sophora angustifolia*, syn. *S. flavescens*, by Nagai (*loc. cit.*) (cf. Tsuda, *loc. cit.*, and Kondo, *Arch. Pharm.*, 1928, **266**, 1, for references to constitutional work), from the seeds and leaves of *S. pachycarpa* (Orékhov and Proskurnina, *Ber.*, 1934, **67**, 77; Orékhov, Rabinovitsch, and Konovalova, *ibid.*, 1934, **67**, 1850), and from the seeds and leaves of *S. alopecuroides* (Orékhov, Proskurnina, and Konovalova, *ibid.*, 1935, **68**, 431). The rotations recorded for matrine are $[\alpha]_D^{10°}$ + 39·11 (Kondo, *loc. cit.*) and $[\alpha]_D^{15°}$ + 38·38° (Orékhov and Proskurnina, *loc. cit.*).

The base is freely soluble in most organic solvents, less readily in ether and difficultly soluble in petroleum but more soluble in the higher-boiling than in the lower-boiling petroleums. It is more soluble than methylcytisine in light petroleum (b. p. below 40°). It does not give the Van de Moer reaction.

The aurichloride crystallised from hot water in yellow needles and prisms, m. p. 199—200° (Kondo, *loc. cit.*, records m. p. 199°), which gradually decomposed on standing (cf. Orékhov and Proskurnina, *loc. cit.*).

Methiodide. The base in absolute methyl alcohol was refluxed with excess of methyl iodide for 6 hours. After removal of the solvent, the residue crystallised from methyl alcohol–acetone (2 : 1) in small plates, which sintered at 245°, melted at 250°, and decomposed at 254°. The mother-liquors on standing deposited long colourless needles, m. p. 304°. The methiodides recorded by Kondo and Orékhov have m. p.'s 211° and 208—209° respectively with no mention of higher-melting isomerides.

Platinichloride. The base in alcoholic hydrogen chloride was mixed with an absolute alcoholic solution of platinic chloride. On standing overnight, long orange needles separated, m. p. 229—230° (decomp.). Matrine platinichloride occurs as orange prisms, m. p. 249° (Kondo, *loc. cit.*), and orange plates, m. p. 228—230° (Orékhov and Proskurnina, *loc. cit.*), again indicating isomerism of the salts of matrine as with the free base.

Picrate. This salt separated as an oil after the base and picric acid were mixed in hot benzene solution. It crystallised from hot water in long needles, m. p. 50—130°, the indefinite m. p. being probably due to water of crystallisation.

Hydrolysis of matrine. The base was refluxed with alcoholic potash for 3 hours and gave a crystalline residue of the potassium salt when the alcohol was removed. The residue was freely soluble in water (cf. Kondo, *loc. cit.*, and Orekhov, *loc. cit.*), but was recrystallised from alcohol containing a trace of water and ether, forming hair-like needles, m. p. 204° with darkening at 190°.

Base C.—This base, m. p. 152—152·5°, has been identified as cytisine (Found, in dried material : C, 68·9; H, 7·6; N, 14·0. Calc. for $C_{11}H_{14}ON_2$: C, 69·5; H, 7·4; N, 14·7%). The m. p. was not depressed on admixture with authentic cytisine kindly provided by Dr. Ing. The base is hygroscopic, soluble in water and most organic solvents, and insoluble in cold petroleum. It is more soluble in petroleum (b. p. 100—120°) than in petroleum (b. p. 80—100°), but the latter solvent gives a better product. It gives the Van de Moer reaction. The literature records m. p.'s from 150° to 156° (cf. Moer and Plugge, *Arch. Pharm.*, 1891, **229**, 48; Buchka and Magalhaes, *Ber.*, 1891, **24**, 253; Partheil, *ibid.*, p. 634; Ing, J., 1931, 2200).

The aurichloride crystallised from hot dilute hydrochloric acid in reddish plates, m. p. 219° (decomp.), which did not depress the m. p. of authentic cytisine aurichloride. Partheil (*Ber.*, 1890, **23**, 3201) and Gorter (*Arch. Pharm.*, 1897, **235**, 301) record m. p. 212—213°.

The picrate crystallised from aqueous alcohol in long needles or prisms, which decomposed at 278° (Clemo and Raper, J., 1935, 10, obtained yellow prisms, decomp. 270°) (Found : N, 16·2. Calc. for $C_{11}H_{14}ON_2,C_6H_3O_7N_3$: N, 16·7%).

Base D.—The base itself, m. p. 293—296°, was not obtained crystalline. It is soluble in water, methyl and ethyl alcohols, slightly soluble in ethyl acetate, and insoluble in chloroform, acetone, benzene and petroleum. It does not give the Van de Moer reaction and hence probably does not belong to the cytisine group. The m. p. so far as we are aware is the highest recorded in this group of alkaloids and for this reason it may be a new base. The *picrate* prepared from the base with alcoholic picric acid darkened and charred above 270° without melting below 370°. The picrate prepared from the crude bases containing base D exploded at 265°. On purification from hot water a little amorphous material separated, accompanied by needles (*ca.* 1 cm. long). The crystalline material was carefully separated and recrystallised from hot water (final yield, 10 mg.). It then darkened at higher temperatures but did not melt below 350° [Found : C, 46·9, 47·2; H, 4·7, 4·85; N, 15·4. $C_{15}H_{23}O_4N_3,C_6H_3O_7N_3$ (?) requires C, 46·8; H, 4·8; N, 15·6%].

Picrolonate. 0·2 C.c. of a saturated alcoholic solution of picrolonic acid was added to the base (10 mg.) in alcohol. The amorphous picrolonate which separated darkened at 250°, sintered at 257—258°, and melted at 261°.

Base E.—This base, m. p. 168—171°, was obtained in insufficient amount for analysis or for full characterisation. It is very soluble in water and methyl alcohol, moderately soluble in ethyl alcohol, and insoluble in benzene, chloroform, acetone and petroleum. It does not give the Van de Moer reaction.

The aurichloride, decomp. 211°, was obtained as a yellow amorphous precipitate on adding a solution of auric chloride to the base (*ca.* 3 mg.) in very dilute hydrochloric acid (0·15 c.c.).

The properties of this base indicate that it may be a new base. [In this connection, compare sophoramine, m. p. 164—165° (aurichloride, m. p. 183—184°), isolated by Orékhov (*Ber.*, 1933, **66**, 948) from the foliage of *S. alopecuroides*; retamine, m. p. 162°, obtained from *Retama spaerocarpa* (Battandier and Malosse, *Compt. rend.*, 1897, **125**, 360, 450); and a base, $C_{15}H_{20}O_5N_2$, m. p. 170°, isolated from the young shoots of *Ulex europæus* by Clemo and Raper (J., 1935, 10).]

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