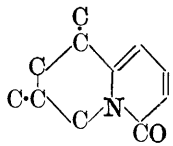
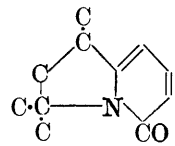
420. *Cytisine. Part II.*

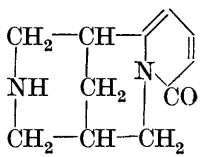
By H. RAYMOND ING.

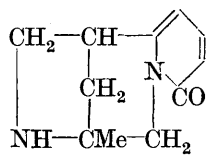
IN Part I (J., 1931, 2195) the structure of cytisine was discussed in the light of all the available evidence. Späth's quinolone formula (*Monatsh.*, 1919, **40**, 15, 95) was rejected and the new alternative skeleton formulæ (I) and (II) were suggested. Striking confirmation of the correctness of the arguments then put forward has recently been supplied by the work of Späth and Galinovsky (*Ber.*, 1932, **65**, 1526).

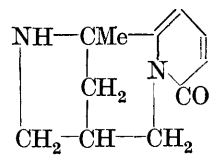
In Part I the discovery that the Hofmann degradation of the alkaloid led to a polymerised product was interpreted as necessitating a formula of type (II). Späth and Galinovsky have shown

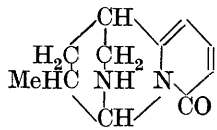
(I.)   (II.)

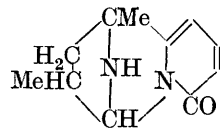
that this polymerisation can be avoided by use of a special technique. Polymerisation thus takes place after and not during the degradation and the reason previously urged in favour of (II) is no longer valid. Späth and Galinovsky also provided experimental evidence which shows that cytisine certainly possesses the alternative skeleton (I).


(III.)


(IV.)


(V.)

(VI.) 

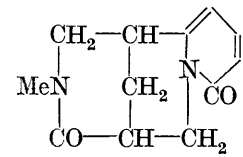
 (VII.)

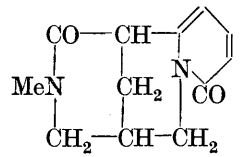
Five formulæ (III—VII) are then possible for cytisine (*locc. cit.*). There was no evidence upon which Späth and Galinovsky could

decide between these formulæ. It has now been found that the oxidation products of *N*-methylcytisine enable this decision to be made.

When methylcytisine, $C_{12}H_{16}ON_2$, is oxidised with barium permanganate, two isomeric compounds, $C_{12}H_{14}O_2N_2$, are formed. These compounds do not form methiodides, oximes, or acyl derivatives, but are hydrolysed by alkali to amino-acids, which were isolated as their *benzenesulphonyl* derivatives. They must consequently be lactams in which a CH_2·NMe group in methylcytisine has been oxidised to CO·NMe. It is proposed to designate these compounds α- and β-N-*methylcytisamides*, and the corresponding acids N-*methylcytisamic acids*. Formulæ (IV), (V), and (VII) are rendered impossible by these results, since substances (IV) and (V) could give only one lactam, and a substance (VII) no lactam without ring fission, which is excluded by the analytical results. Formula (VI) could lead to two lactams which would be geometrical isomerides, and (III) could give two lactams (VIII) and (IX) which would be structural isomerides. There is no reason to think that cytisine

(VIII.)





(IX.)

or methylcytisine is not homogeneous, and consequently it is improbable that the α- and β-methylcytisamides are geometrical isomerides. Moreover, as Späth and Galinovsky point out, oxidation of a substance of formula (VI) should give rise to methylsuccinic acid, which could not be isolated. Finally, *N*-benzenesulphonyl-*N*-methyl-β-cytisamic acid loses carbon dioxide at its melting point (130—131°) to yield a *benzenesulphonyl-base*, whereas the α-acid melts at 152—153° without decomposition. This difference between the α- and the β-derivative would be difficult to explain if they were derived from (VI), but is readily accounted for on the basis of (VIII) and (IX). By analogy with Collie's observation (J., 1897, **71**, 299) that 6-hydroxy-4-methylpyridyl-2-acetic acid loses carbon dioxide at its melting point to yield 6-hydroxy-2 : 4-dimethylpyridine, similar behaviour may be expected of the benzenesulphonyl derivative of the acid derived from (IX), but not of the derivative from (VIII). Consequently formulæ (VIII) and (IX) appear probable for α- and β-methylcytisamides, respectively.

Formula (III) thus becomes the most probable one for cytisine. The bridged ring of this formula has not been observed in natural

products before, but compounds containing it have been synthesised by Thole and Thorpe (J., 1911, **99**, 427). It may be noted that the Hofmann degradation of (III) must lead in the first instance to either a vinylpyridone or an allylamine derivative, and consequently subsequent polymerisation is not unlikely.

Experimental.

Oxidation of Methylcytisine.—Methylcytisine (20 g.), dissolved in H_2O (400 c.c.), was cooled to 5° and treated slowly with 10% $Ba(MnO_4)_2$ aq. until the solution remained pink for 3—5 min. after addition of 10 c.c. of permanganate solution. The temp. was kept below 7° and 320—340 c.c. of permanganate solution were required (*i.e.*, 2—3 O). The MnO_2 was washed, and the filtrate and washings were neutralised and concentrated to small bulk on the steam-bath in vac. After pptn. of the Ba by H_2SO_4, the solution was made alkaline with NH_3 aq. and repeatedly extracted with $CHCl_3$. The extract was dried with Na_2SO_4 and evaporated completely. The residual yellow gum was stirred with cold EtOAc and after some time the pptd. solid was collected and crystallised from C_6H_6. *N-Methyl-α-cytisamide* formed needles, m. p. 214—215° (Found : C, 66·0; H, 6·4; N, 12·9. $C_{12}H_{14}O_2N_2$ requires C, 66·0; H, 6·4; N, 12·8%).

The EtOAc mother-liquor was evaporated, and the residue taken up in acetone and kept at 0°. Crystals separated slowly and a second crop was obtained on concentrating the solution. After several crystns. from acetone *N-methyl-β-cytisamide* was obtained in rectangular prisms, m. p. 179—180° (Found : C, 65·9; H, 6·3; N, 12·9. $C_{12}H_{14}O_2N_2$ requires C, 66·0; H, 6·4; N, 12·8%).

After separation of the two lactams a red gum was left which could not be further purified. It was dissolved in H_2O and treated with more $Ba(MnO_4)_2$ aq. until the pink colour remained for at least 10 min. The product was worked up as before and further small amounts of the α- and β-lactams were obtained.

Hydrolysis of the Lactams.—The α-lactam was dissolved by boiling in 20% KOH aq. for a few min. and the cooled solution shaken with excess of benzenesulphonyl chloride. The clear solution was acidified to Congo paper with HCl, the oily ppt. dissolved in *N*-$NaHCO_3$, boiled with charcoal, filtered, and acidified at 0°. The amorphous *N-benzenesulphonyl-N-methyl-α-cytisamic acid* so obtained crystallised slowly when kept. M. p. 152—153° (Found : C, 57·5; H, 5·3. $C_{18}H_{20}O_5N_2S$ requires C, 57·4; H, 5·3%).

The β-lactam was treated similarly and *N-benzenesulphonyl-N-methyl-β-cytisamic acid* obtained; m. p. 130—131° (decomp.) (Found : C, 57·3; H, 5·2. $C_{18}H_{20}O_5N_2S$ requires C, 57·4; H, 5·3%). This acid lost CO_2 at its m. p. (Found : CO_2, 11·5. $C_{18}H_{20}O_5N_2S$ requires CO_2, 11·7%) and the residual *benzenesulphonyl-base* crystallised from hot H_2O in plates, m. p. 141—142° (Found : C, 61·6; H, 6·1. $C_{17}H_{20}O_3N_2S$ requires C, 61·4; H, 6·0%).

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University College, London. [*Received, October 25th*, 1932.]