STUDIES IN THE STRUCTURE OF MARCKINE

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The alkaloid marckine, $C_{28}H_{35}N_3O_3$, isolated from *Alangium lamarckii* Thwaites, has been found to yield harman, $C_{12}H_{10}N_2$, on selenium dehydrogenation. On dehydrogenation with palladised asbestos, a base, $C_{18}H_{17}N_3O$, m.p. 122°, was obtained which has been named as marckyrine. Oxidative degradation with permanganate yields a mixture of compounds from which meta-hemipinic acid, oxamic acid and oxalic acid have been isolated. The N. M. R. spectrum of mono-N-acetyl marckine has been studied. On the basis of the information obtained from the degradative experiments as well as the physical evidence, two alternative structures have been proposed for marckine. The identity of marckine with tubulosine, $C_{29}H_{37}N_3O_3$, and the possibility of a C_{29} formulation for marckine have been discussed.

Although the isolation of several alkaloids from *Alangium lamarckii* Thwaites has been reported from time to time, very few of them have been subjected to structural investigation. At present, the only Alangium bases of known structure are emetine, cephaeline and psychotrine which have recently been isolated from the seeds [1] as well as the root bark [2] of the plant. The alkaloid alamarckine isolated by Siddiqui and Subbaratnam[3] from the seeds of this plant, after methylation of the total bases, has also been identified as N-methyl cephaeline.[1] The present paper deals with studies in the structure of marckine, one of the two alkaloids isolated by the authors[4-5] from the root bark of this plant.

From the ultra-violet spectrum, colour reactions and positive pine chip test, marckine appeared to be an indole alkaloid. On selenium dehydrogenation at 300°, it afforded a small quantity of a crystalline base, $C_{12}H_{10}N_2$, m.p. 232°, through chromatography over alumina, which could be identified as harman by mixed melting point determination, and comparison of its ultra-violet and infra-red spectra and X-ray powder photograph with those of an authentic sample of harman. The acid-insoluble fraction gave positive test (pink colour) with p-dimethylaminobenzaldehyde reagent and appeared to be a mixture of β-substituted indoles.

Dehydrogenation of marckine with palladised asbestos at 300°C. gave a crystalline degradation base, $C_{18}H_{17}N_3O$, m.p. 122°, which has provisionally been named as marckyrine (Infra-red spectrum shown in Fig. 1). In this process, ammonia and a mixture of organic volatile amines and β-substituted indoles were also obtained. From the ultra-violet spectrum (Fig. 2) which shows absorption maxima at 233 mμ (log ε, 4.66), and 297 mμ (log ε, 4.39), marckyrine appeared to be a β-carboline derivative. The spectrum very closely resembled that of 7-methoxy harman [6] indicating that, in marckine, there is a substitution at the benzene ring in the para-position with respect to the indole nitrogen. Marckyrine was characterised through a picrate, yellow needles, $C_{18}H_{17}N_3O$, $C_6H_3N_3O_7$, $2H_2O$, m.p. 274° (decomp.).

On oxidation with alkaline potassium permanganate at 50°, marckine yielded a mixture of acids from which oxalic acid, oxamic acid and meta-hemipinic acid were isolated in pure state. Oxalic acid was identified through mixed melting point with an authentic sample as well as by the preparation of its *p*-toluidide, m.p. 268°, and oxamic acid through comparison of its infra-red spectrum with that of an authentic specimen,[7] and its hydrolysis to oxalic acid and ammonia. On treatment of the acetone-soluble portion of the oxidation product with diazomethane and subsequent purification by chromatography on alumina, the dimethyl ester of meta-hemipinic acid was obtained in the crystalline form which melted at 88°, and could be hydrolysed to the parent acid, m.p. 188°. Potentiometric titration of the acid showed it to be dibasic. It formed the characteristic water-insoluble calcium salt and condensed with ethylamine giving the N-ethylimide derivative, m.p., 228°, (lit. m.p., 227°).[8]

The absence of an isolated ethylenic double bond in marckine is indicated from the observation that it is not hydrogenated catalytically at ordinary pressure. Also a chloroform solution of mono-N-acetyl marckine does not absorb bromine. Marckine is not reduced by lithium aluminium hydride or sodium borohydride.

Although marckine is insoluble in dilute alkali and gives no colour with alcoholic ferric chloride, a solution of the base in dilute hydrochloric acid does give a brownish red colour with an aqueous solution of the reagent. A phenolic group thus appears to be present in marckine, and this could be confirmed by the preparation of its diacetyl derivative, $C_{32}H_{39}O_5N_3$, H_2O or $C_{33}H_{41}O_5N_3$, H_2O, m. p. 175-78° (decomp.). Diacetyl marckine which was obtained as a microcrystalline powder, is basic in nature and shows a sharp peak at 1750 cm.$^{-1}$ in the infra-red spectrum (KBr) due to the O-acetyl group; this cannot be attributed to a secondary or tertiary amide carbonyl group as they absorb in ther ange 1680-1630 cm.$^{-1}$ and 1670-1630 cm.$^{-1}$ respectively.[9] Unlike marckine and mono-N-acetyl marckine, it gives no colour with aqueous ferric chloride in the acid medium. On chromatography over alumina, the diacetyl marckine is converted into mono-N-acetyl marckine.[5] The phenolic group seems to be present in the same position as in sarpagine, i.e., in the para-position with respect to the indole nitrogen, as is indicated by the ultra-violet spectrum of marckyrine. Interestingly, marckine is sensitive to alcoholic alkali like sarpagine, and the hydrolysis of the phenolic acetyl group, on chromatography over alumina, is also known to occur in sarpagine.[10]

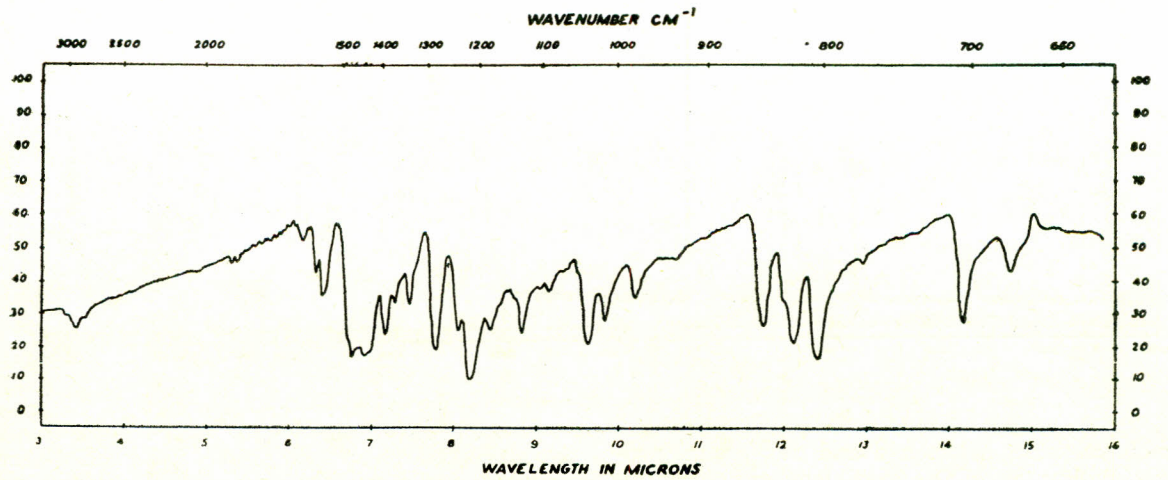


Fig. 1.— Infra-red spectrum of marckyrine in KBr.

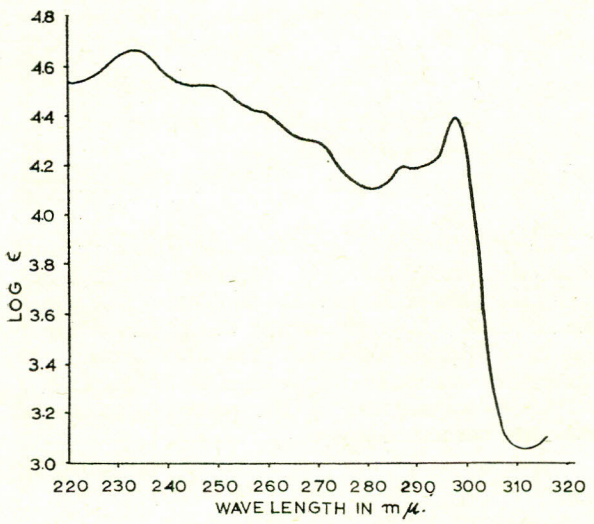


Fig. 2.— Ultra-violet spectrum of marckyrine in absolute ethanol.

The N.M.R. spectrum of mono-N-acetyl marckine* in $CDCl_3$ (Fig. 3) shows a singlet at 8.25 p.p.m. (indole NH), a multiplet between 6.5 and 7.0 p.p.m. representing 5 aromatic protons, a singlet at 5.9 p.p.m. most probably due to a tertiary proton in the α-position to the nitrogen bearing the acetyl group and a sharp doublet at 3.75 and 3.87 p.p.m. corresponding to six protons of the two aromatic methoxyl groups. There is a broad

*The mono-N-acetyl derivative of marckine was used for N.M.R. studies as the parent alkaloid is insoluble in chloroform. The spectrum was obtained using an HA-100 spectrometer. The lock signal was derived from the protons of tetramethylsilane.

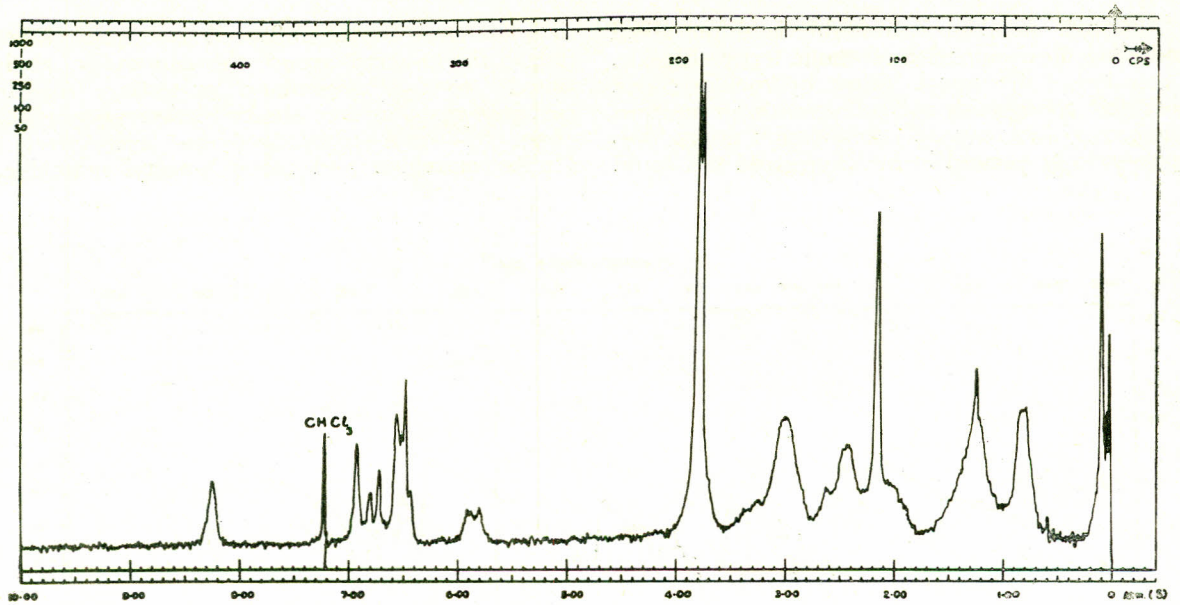
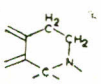


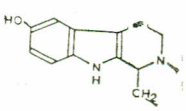
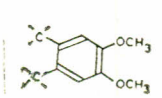
Fig. 3.— N. M. R. spectrum of mono-N-acetyl marckine in $CDCl_3$.

jumble of peaks between 2 and 2.5 p.p.m. probably arising out of the methylene protons in an environment such as:

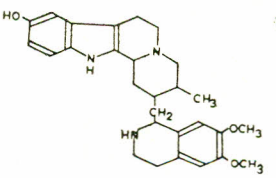


The sharp peak at 2.15 p.p.m. can be attributed to the protons of the acetyl group. The remaining resonances are suitable for aliphatic protons β or further from deshielding groups. The broad pattern between 1 and 1.5 p.p.m. is probably from various methylene protons while the resonance above 1 p.p.m. may be assigned to that of a C-methyl or methyls, either as a secondary methyl or as a primary methyl, where the ethyl methylene protons have been shielded because of the molecular configuration.

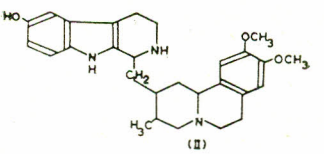
On the basis of degradative studies it might be concluded that marckine contains the following moities in its structure:

 and 

Considering the N.M.R. data as well as the probable genetic relationship of marckine with the other Alangium alkaloids, namely emetine, cephaeline and psychotrine, the following alternative structures (I and II) were considered by the present authors as fairly plausible for marckine, providing a working hypothesis for the elucidation of its constitution.

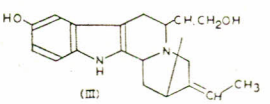


(I)

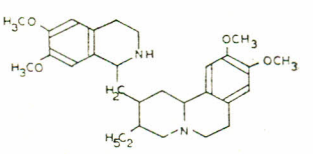


(II)

The structure (I) contains the basic carbon skeleton of sarpagine (III) together with the *iso*-quinoline part of the emetine molecule (IV) while the structure (II) contains the benzoquinolizidine system of Ipecac alkaloids. The above structures agree with the molecular formula, $C_{28}H_{35}O_3N_3$, provisionally assigned by the present authors in previous communications (*loc. cit.*). Considering



(III)

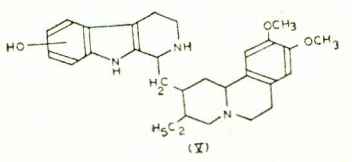


(IV)

the fact, however, that the postulated structures (I) and (II) both provide a secondary and a tertiary

basic nitrogen and the analytical data of methiodides of marckine and monoacetyl marckine can be fitted only with the $C_{29}H_{37}O_3N_3$ formulation for marckine, the C_{28} formulation suggested in the earlier communications has to be revised. In support of the C_{29} formulation it may be stated that the microanalytical data recorded earlier fit with it equally well and that the platinum value of the chloroplatinate is comparatively more in favour of it (Found: Pt., 21.49%. Calculated for $C_{28}H_{35}O_3N_3,H_2PtCl_6$: Pt., 22.39% while $C_{29}H_{37}O_3N_3$, H_2PtCl_6 requires: Pt., 22.05%). The formulae of the methiodides of marckine and monoacetyl marckine could then be represented as $C_{29}H_{36}N_3O_3$ (CH_3) $(CH_3I)_2$, H_2O and $C_{31}H_{39}N_3O_4$ (CH_3I), H_2O. On the basis of 29 carbon atoms in marckine, the presence of an ethyl group in place of methyl in structures (I) and (II) seems to be more probable and this provides further proximity to the structure of emetine and sarpagine.

The alternative structures arrived at for marckine by the present authors gained added support from the fact that tubulosine, subsequently isolated by Brauchi *et al.* [11] from *Pogonopus tubulosus* Schumann and assigned the structure (V) mainly on the basis of mass spectral studies, seemed to have close relationship with the structures suggested for marckine.



(V)

In view of the striking resemblance of the physical data of marckine and tubulosine, and the structures proposed for them, a comparison of the physical data of the two alkaloids was carried out in parallel observations. The infra-red spectra of tubulosine and of marckine were found to be completely superimposable (Fig. 4). Moreover, the comparison of optical rotatory power, ultraviolet spectra, X-ray powder photograph of marckine and of tubulosine,[12] as well as the mixed melting point determination of marckine with an authentic sample of tubulosine,* show that the two alkaloids are identical.

Further studies in the structure of marckine through physical and chemical means are in progress.

Experimental

Melting points were determined in sulphuric acid bath and are uncorrected; ultra-violet and infra-red absorption spectra were determined with an Unicam SP 500 and a Beckmann IR-5 spectrophotometer, respectively. Brockmann alumina, activity I, was used im chromatography. Analyses were performed by Dr. Alfred Bernhardt, Mikroanalytisches Laboratorium im Max Planck Institut, 433, Mulheim, Ruhr, West Germany and by Dr. Franz Pascher, Mikroanalytisches Laboratorium, Buschstrasse 54, Bonn, West Germany.

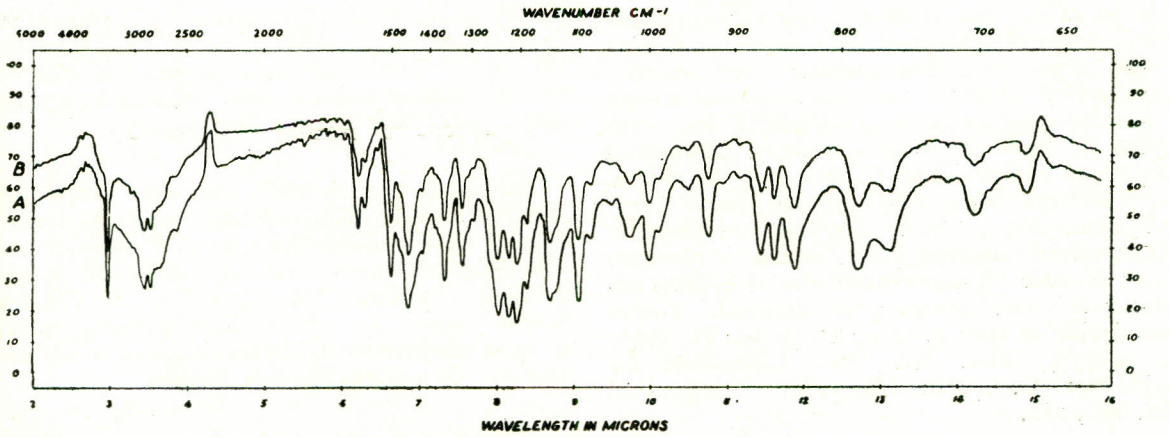


Fig. 4.— Infra-red spectra of marckine (A) and tubulosine (B).

*An authentic sample of tubulosine was supplied through the courtesy of Dr. Venancio Deulofeu, Universidad de Buenos Aires, Argentina. The melting point of this alkaloid was found by the authors to be 275° (decomp.) in sulphuric acid bath whereas Deulofeu *et al.* reported the melting point as 259-60° (decomp.) on a Kofler block.

Selenium Dehydrogenation of Marckine.—Marckine (2 g.) was intimately mixed with selenium powder (2 g.) and the mixture heated in ten sealed tubes at 300° for two hours. The tubes were then cooled, the hard black mass was mixed with an equal quantity of sand and ground to a fine powder which was extracted exhaustively with ether (500 ml.) in a soxhlet apparatus. The ethereal extract, after concentrating to about 50 ml., was shaken with dilute hydrochloric acid (5 percent, 30 ml.). The acid insoluble fraction which remained in ether appeared to contain β-substituted indoles as it gave a positive test (pink colour) with *p*-dimethylaminobenzaldehyde reagent. No crystalline compounds could, however, be isolated from this fraction.

The acid layer was basified with ammonia, saturated with sodium chloride and extracted with ether. The extract was washed with a small quantity of water, dried (Na_2SO_4) and freed of the solvent. The dark coloured residue was dissolved in a small quantity of benzene and chromatographed over a column of alumina (20 g.) using benzene for elution. The eluate of the lowest fluorescent blue band (in ultra-violet), on removal of solvent, yielded a crystalline residue which, when recrystallised from benzene, formed prisms, m.p. 232°. The melting point was not depressed on admixture with an authentic sample of harman. Ultra-violet spectrum of the compound in absolute ethanol showed absorption maxima at 234 mμ (log ε, 4.60), 250 mμ (log ε, 4.40), 288 mμ (log ε, 4.25), 335 mμ (log ε, 3.73) and 348 mμ (log ε, 3.72). The infra-red spectrum was completely superimposable on that of harman. X-ray powder photographs of this dehydrogenation product and harman were identical. Found after drying at 100° *in vacuo*: C, 79.38; H, 5.53; N, 14.54%, Mol. Wt., 200. Calculated for $C_{12}H_{10}N_2$: C, 79.01; H, 5.49; N, 15.29%; Mol. Wt., 182.

Dehydrogenation of Marckine with Palladised Asbestos.—Marckine (4 g.) was intimately mixed with an equal quantity of palladised asbestos (10 percent, E. Merck) and heated at 300° in a tube in a current of nitrogen. The evolved gases were led through an ice-cooled receiver to a trap containing 50 ml. of 5 percent hydrochloric acid. At the end of three hours the tube was cooled, the oily substance collected at the upper part of the tube and the receiver was washed out with a small quantity of ether and the solid content of the tube was exhaustively extracted with ether in a soxhlet apparatus. The combined ether extract and the washings were shaken once with 5 percent and twice with 20 percent hydrochloric acid. The ethereal layer, on removal of solvent, yielded a residue which seemed to contain β-substituted indole derivatives as it had a strong faecal smell, and gave positive test with *p*-dimethylaminobenzaldehyde reagent. No crystalline compounds could, however, be isolated from this fraction.

The acidic aqueous portion was basified with ammonia and extracted thrice with ether. The extract was washed with water, dried (Na_2SO_4), filtered and freed of the solvent. The residue (0.4 g.) was dissolved in benzene and chromatographed on a column of alumina (20 g.). The benzene eluate of the lowest fluorescent blue band (in ultra-violet) gave an oil on removal of the solvent. The upper green-coloured band (in ultra-violet) was eluted with benzene-chloroform (98:2) and the eluate, on complete evaporation, yielded a residue which, on crystallisation from ether-light petroleum (b.p. 60-80°), was obtained in the form of straw coloured prismatic rods, m.p. 122°. This base, which has provisionally been named as marckyrine, analyses for the molecular formula, $C_{18}H_{17}N_3O$. (Found after drying at room temperature *in vacuo:* C, 73.83; H, 6.09; N, 14.40%; Mol. Wt., 282. Calculated for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42%; Mol. Wt. 291). The ultra-violet spectrum of marckyrine in absolute ethanol shows maxima at 233 mμ (log ε, 4.66) and 297 mμ (log ε, 4.39).

The contents of the acid trap were evaporated and the residue extracted with absolute alcohol. The alcohol-insoluble part gave a positive test with Nessler's reagent and was identified as ammonium chloride. The alcohol-soluble fraction gave a positive test with ninhydrin and appeared to be a mixture of the hydrochlorides of volatile amines. It was not pursued further.

Marckyrine Picrate.—A solution of marckyrine (4 mg.) in ether was mixed with an ethereal solution of picric acid. The yellow precipitate of marckyrine picrate (7 mg.) was filtered, washed well with ether and crystallised from 95 percent ethanol——yellow needles, m.p. 274° (decomp.). (Found after drying at 100° *in vacuo*: C, 51.67; H, 4.05; N, 15.15%. Calculated for $C_{18}H_{17}N_3O$, $C_6H_3N_3O_7$, $2H_2O$: C, 51.80; H, 4.35; N, 15.10%).

Permanganate Oxidation of Marckine.—Sulphuric acid (50 percent, 10 ml.) was added to a suspension of marckine (3 g.) in water (100 ml.) and the mixture slightly warmed till all the base went into solution. The pH of the solution was then adjusted to 6 by

the addition of 10 percent sodium carbonate solution. A 5 percent solution of potassium permanganate was added dropwise to the above solution kept at 50° while the mixture was stirred vigorously. The consumption of permanganate was very rapid in the beginning and stopped after the addition of about 450 ml. (equivalent to 34 atoms of oxygen) when no further decolourisation took place. The stirring was continued for one hour after which the precipitated manganese dioxide was filtered and the precipitate extracted with hot water. The combined filtrate and washings were decolourised with sulphurous acid and filtered once again. The light yellow filtrate was neutralised with dilute hydrochloric acid and concentrated to about 30 ml. under reduced pressure. It was then made acidic (Congo paper) with hydrochloric acid and extracted with ether in a liquid-liquid extractor for ten hours. The yellow ethereal extract, on complete removal of solvent, yielded a crystalline residue which was extracted with dry ether. The ether extract, after concentration, was treated with light petroleum (b.p. 60-80°) and the supernatant liquid was decanted off from the yellow sticky precipitate which was again extracted with ether. The combined ether solution was purified several times in this way, charcoaled, and the colourless filtrate evaporated when a crystalline residue was obtained (0.25 g.). It was recrystallised from ether—colourless rods, m.p. 100° and identified as oxalic acid through a mixed melting point determination with an authentic sample. The substance gave a *p*-toluidide which melted at 268° (decomp.) (lit. m.p. of oxalic acid di-para-toluidide, 268°, decomp.).[13]

The total ether-insoluble fraction was treated with a small quantity of acetone and filtered. The acetone-insoluble residue, thus obtained, was crystallised from methanol in small colourless needles, m.p. 205-6° (decomp.) (yield 100 mg.). This substance was acidic in nature and readily dissolved in water. (Found after drying at 100°: C, 27.12; H, 3.70; N, 16.39%. Calculated for $C_2H_3NO_3$: C, 26.97; H, 3.40; N, 15.73%). The infra-red spectrum of the acid in KBr showed absorption peaks due to NH_2 (3330 and 3230 cm.$^{-1}$) and carbonyl group of the acid (1740 cm.$^{-1}$) and primary amide (1675 cm.$^{-1}$). In addition, a strong band at 1240 cm.$^{-1}$ and weak bands at 1470 (broad), 1359, 1090, 836 and 814 cm.$^{-1}$ were also present. The compound was identified as oxamic acid on comparison of its infra-red spectrum with a standard spectrum of the compound [7] and also by its hydrolysis (alkaline) to oxalic acid and ammonia.

The acetone-soluble fraction was completely freed of the solvent, and the methanolic solution of the residue obtained was treated with an excess of ethereal diazomethane and left overnight. The solvent was then completely removed, the residue dissolved in benzene and chromatographed on a column of alumina (30 g.). The first few fractions of the benzene eluate gave crystalline residues which were combined and recrystallised from ether-light petroleum (b.p. 60-80°) in the form of bunches of colourless prismatic rods, m.p. 88°. (Found after drying at room temperature *in vacuo:* C, 56.80; H, 5.55; O, 37.92; OCH_3, 48.13%; Mol. Wt., 264. Calculated for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55; O, 37.76; $4\times OCH_3$, 48.81%; Mol. Wt., 254).

100 mg. of the above ester was refluxed with 10 percent sodium hydroxide solution in dilute methanol (70 percent) for two hours, during which the sodium salt of the acid separated out which was kept in solution by the addition of some more water. The solvent was then completely removed, the residue dissolved in a small quantity of water and extracted with ether. The aqueous solution was acidified with hydrochloric acid and the liberated acid extracted with ethyl acetate. The ethyl acetate extract was washed with a small quantity of water, dried (Na_2SO_4) and freed of the solvent. The residue crystallised from acetone-light petroleum (b.p. 60-80°) in the form of colourless needles, m.p. 188° (decomp.). (Found after drying at 100° *in vacuo*: C, 53.24; H, 4.57; O, 42.58%; Mol. Wt., 227. Calculated for $C_{10}H_{10}O_6$: C, 53.10; H, 4.46; O, 42.44%; Mol. Wt., 226). On potentiometric titration of this acid with N/100 sodium hydroxide solution, a curve was obtained which showed two turning points (pKa= 3.25 and 4.50, water). Infra-red spectrum of the compound in KBr showed peaks at 2625w (carboxylic OH), 2400m, 1710s (acid carbonyl), 1625s (aromatic), 1590s, 1525s, 1495s, 1450s, 1410s, 1390s, 1360s, 1300s, 1260s, 1220s, 1190s, 1150s, 1050s, 1030s, 972s, 915s and 760s cm.$^{-1}$. The ultra-violet spectrum in absolute ethanol showed maxima at 228 mμ (log ε, 4.40) and 274 mμ (log ε, 3.96) and a minimum at 250 mμ (log ε, 3.76). The compound was identified as meta-hemipinic acid through the preparation of its N-ethylimide, m.p., 228° (lit. m.p. 227°).[8]

Diacetyl Marckine.—Marckine (0.2 g.) was dissolved in acetic anhydride (1 ml.) with slight warming, a drop of pyridine added and the mixture left at room temperature for two hours. The solvent from the reaction mixture was then completely removed *in vacuo* and the fluffy colourless

residue dissolved in water. Addition of ammonia to the solution precipitated the base which was extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried over anhydrous sodium sulphate, filtered and freed of the solvent. The residue was dissolved in ether and purified by fractional precipitation with light petroleum (b.p. 60-80°). Diacetyl marckine was obtained from the final fractions as colourless microcrystalline powder, m.p., 175-8° (decomp.), which on thin layer chromatography on silica gel G (Merck) plates gave a single spot (R_f=0.76, benzene: methanol: diethylamine, 80: 10:10). Infra-red spectrum of diacetyl marckine shows a strong peak at 1750 cm.$^{-1}$ (O-acetyl). (Found after drying at 100° *in vacuo*: C, 68.51; H, 7.44; N, 7.20%. $C_{32}H_{39}O_5N_3$, H_2O requires: C, 68.18; H, 7.33; N, 7.46%. $C_{33}H_{41}O_5N_3$, H_2O requires: C, 68.60; H, 7.50; N, 7.27%).

Monoacetyl Marckine.—Diacetyl marckine (0.1 g.) was dissolved in benzene and passed through a column of alumina (20 g.) using benzene-methanol (98:2) as eluant. A number of intermediate fractions which crystallised from dilute alcohol were combined and rec ystallised from the same solvent yielding mono-N-acetyl marckine [5]— colourless needles, m.p. 225-8° (decomp.) with initial sintering at 200°, R_f=0.62 (silica gel G plates, benzene: methanol: diethylamine, 80: 10:10).

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