Die Gleichgewichte sämtlicher Reaktionen scheinen ganz rechts zu liegen, wofür ersichtlicherweise weniger deren kleine Endothermie oder Exothermie verantwortlich ist, als vielmehr die Vermehrung der Molekelzahl (abgesehen von der Dismutation (6)).

Zürich, Physikal.-chem. Laboratorium der Eidg. Techn. Hochschule, Dezember 1932.

Constitution of Carpaine, Part II

by **G. Barger, A. Girardet** and **R. Robinson.**

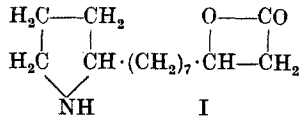
(15. XII. 32.)

Some insight into the constitution of carpaine, the alkaloid in the leaves of *Carica papaya* L. was obtained by one of us[1]) long ago. We have recently been able to confirm and extend these earlier observations, chiefly by demonstrating the presence of a pyrrolidine ring, and by definitely identifying suberic and azelaic acids as oxidation products. The former was previously surmised, but not proved, to be α,δ-dimethyladipic acid. We have further found that carpamic acid $C_{14}H_{27}O_3N$ is formed from carpaine $C_{14}H_{25}O_2N$ not only by the action of acids, as previously described, but also readily by that of alkali in alcoholic solution, thus supplying further evidence of a lactone structure. Since it appears to be impossible to regenerate the lactone from the hydroxy acid, carpaine is probably not a γ- or a δ-lactone. The pyrrolidine nucleus is shown by dehydration with selenium, when four hydrogen atoms are lost and a pyrrole derivative is formed, for which the name *carpyrine* is suggested; on subsequent catalytic hydrogenation these four hydrogen atoms are again taken up and a base results, closely resembling the original alkaloid, and doubtless differing from it only in the stereochemical arrangement of one carbon atom.

The place of attachment of the long carbon chain to the pyrrolidine ring has not been proved conclusively but the α-position appears to be very probable. *A priori* it is tempting to assume some relationship to a naturally occurring fatty acid and to place all the carbon atoms of the molecule in an unbranched chain, which would make carpaine an α-pyrrolidine derivative, like nicotine, hygrine and cocaine (compare *Willstätter*'s phytosynthetical speculations[2]). The constitution might then be that of formula I, which we put forward merely as a basis of discussion.

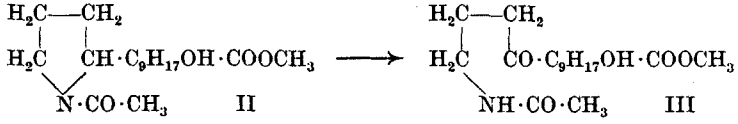
[1]) Soc., **97**, 466 (1910), where the older literature is mentioned.

[2]) B. **33**, 1161 (1900).



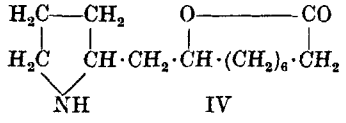
I

Apart from speculation, there is also experimental evidence for the α-position. Methyl N-acetylcarpamate (II) on oxidation with permanganate in cold acetone yields a substance $C_{17}H_{31}O_5N$ (III), containing one additional oxygen atom; this substance probably arises from the opening of the ring, which is most readily explained if the side chain is in the α-position: e. g. on the basis of formula I:



II III

The failure of carpamic acid to yield carpaine by dehydration might be accounted for in another way: the lactone ring might not be four-membered, but many-membered. *Perkin*, in the case of cryptopine, and *Ruzicka* have shown that many-membered rings exist in nature and possess considerable stability, and carpaine might have some such structure as IV.



IV

It is at present impossible to decide between formulae like I and IV, but perhaps formula I explains better the formation of a pyrrole derivative $C_{11}H_{17}N$ ($C_{10}H_{15}N$ or $C_{12}H_{19}N$?), for which we suggest the name *apocarpyrine*. It results when carpaine is distilled with selenium under atmospheric pressure (carpyrine is formed under reduced pressure). The formation of apocarpyrine is readily understood on the basis of formula I and would merely consist in the removal of the hydroxylated and some other carbon atoms; according to formula IV we would have to assume the reduction of the hydroxylated carbon atom to a methylene group, but this might be brought about by the shifting of a double bond or equivalent group, as in the formation of α-n-butyl and α-n-hexylpyrrolidine[1]) by heating octamethylene and decamethylene diamine hydrochloride respectively, and as in the formation of palmitic[2]) and hypogaeic[3]) acid by potash fusion of oleic and stearolic acid respectively.

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[1]) *Phookan* and *Krafft*, B. **25**, 2254 (1892); *Krafft*, B. **39**, 2193 (1906); *Blaise* and *Houillon*, C. r. **142**, 1541 and **143**, 361 (1906).

[2]) *Varrentrap*, A. **35**, 195 (1840); *Edmed*, Soc. **73**, 632 (1898).

[3]) *Marasse*, B. **2**, 359 (1869); *Bodenstein*, B. **27**, 3397 (1894).

Against formula I there may be mentioned the observation that the methylation of carpamic acid by formaldehyde does not result in a ketone (see experimental part) and hence may imply the presence of a tertiary hydroxyl group, and branched chain.

Experimental.

Carpaine for the present investigation was obtained from 260 kilograms of dried leaves of seedlings specially grown for us in 1929—30 by Mr. *A. Howard* at the Institute for Plant Industry, Indore, India, and from 110 kilograms of young leaves of older trees. The alkaloid was extracted under the supervision of Dr. *H. E. Watt* in the works of Messrs. *T.* and *H. Smith* at Edinburgh. We are greatly indebted to all these gentlemen for the help they have given us. The yield from seedling leaves was 56 g. or 0,022%, from the others 40 g. or 0,036%. There appears to be an optimum age of the leaves, for in 1910 one of us obtained 0.07% from the older leaves of adult trees, as did *Greshoff*, the discoverer of carpaine[1]). *Greshoff* states that "young" leaves contain 3 to 4 times this amount, but contrary to our expectation, the leaves of seedlings are unsuitable. The alkaloid is readily soluble in ether and in chloroform, and crystallises well from 60% alcohol, and even better from methylethylketone. A determination of N-methyl groups according to *Herzig* and *Meyer* yielded a negative result (9 mg. heated for 2 hours). A solution of carpaine in dilute sulphuric acid did not decolorize potassium permanganate at room temperature in 5 minutes, and after shaking 0.5 g. dissolved in acetic acid, with 0.25 g. of platinum oxide according to *Adams* in a hydrogen atmosphere, the whole of the alkaloid was recovered unchanged. There is one active hydrogen atom, demonstrable by the method of *Zerewitinoff*, but only on heating.

13.47 mg. gave 0.81 c.c. CH_4 at 17° and 1.25 c.c. at 95°
16.30 mg. gave 1.00 c.c. CH_4 at 17° and 1.60 c.c. at 95°
(All volumes reduced to 0° and 760 mm.)

$C_{14}H_{24}O_2NH$ calc. active hydrogen 0.42%
Found at 17° = 0.27, 0.28; at 95° 0.42, 0.44%. At 95° the solution becomes turbid.

The yield of N-methylcarpaine[2]) could not be increased beyond 50—60% by working in the cold in acetone or ether.

N-butylcarpaine was prepared by heating 1 g. carpaine for 15 hours to 125° with 10 c.c. butyl bromide in a sealed tube. On dissolving the residue in dilute acid, adding sodium nitrite, removing the precipitated nitroso carpaine with ether, and making alkaline, the butyl derivative, then extracted with ether, crystallised from acetone in long silky needles, m. p. 97—98°; yield 25—30%.

4.298 mg. gave 11.53 mg. CO_2 and 4.325 mg. H_2O.
$C_{14}H_{24}O_2N \cdot C_4H_9$ Calc. C 73.16 H 11.27%
Found „ 73.16 „ 11.26%

[1]) Mededeelingen uit 's Lands Plantentuin, No. 7, Batavia, 1890, p. 5.
[2]) *Van Rijn*, Arch. Pharm., **231**, 184 (1893).

N-Acetylcarpaine. 3 g. carpaine in 30 c.c. acetic anhydride at 100° for 20 minutes. After decomposing the excess of anhydride, the product was extracted with ether and washed with hydrochloric acid and with sodium carbonate. On evaporation a syrup resulted which crystallised slowly; recrystallisation from acetone + petrol: m. p. 114°; yield quantitative.

4.863 mg. gave 12.2 mg. CO_2 and 4.14 mg. H_2O
$C_{14}H_{24}O_2N \cdot COCH_3$ Calc. C 68.28 H 9.68%
Found „ 68.42 „ 9.53%

At 20° the yield is 30% after 4 days, 80% after 15 days.

N-Carbo-ethoxycarpaine. 1 g. carpaine in 25 c.c. chloroform was treated repeatedly at 0° with equivalent quantities of ethyl chloroformate and sodium hydroxide (in all 12 molecules). After extraction of a small amount of unchanged base, a neutral oil resulted which crystallised badly. On warming with excess of methyl iodide and keeping for some weeks, the crystalline methiodide was obtained, m. p. 167°.

5.210 mg. gave 9.12 mg. CO_2 and 3.44 mg. H_2O
$C_{14}H_{24}O_2N \cdot COOC_2H_5 \cdot CH_3I$ Calc. C 47.66 H 7.12%
Found „ 47.74 „ 7.39%

Carpamic acid, prepared by boiling carpaine with 20% hydrochloric acid for 1 hour *(Barger,* 1910) was found to yield a crystalline *methyl ester,* m. p. 70°.

3.711 mg. gave 0.166 c.c. N_2 (17°, 761.5 mm.)
$C_{15}H_{29}O_3N$ Calc. N 5.17 Found N 5.28%

The ethyl ester hydrochloride, m. p. 173—174° shows only two active hydrogen atoms, when treated according to *Zerewitinoff:*

156.7 mg. gave 20.36 c.c. CH_4 at 17° and 21.48 c.c. at 95°
131.7 mg. gave 18.86 c.c. CH_4 at 17° and 19.8 c.c. at 95°
10.145 mg. gave 0.95 c.c. CH_4 at 17° and 1.24 c.c. at 95°
11.27 mg. gave 0.98 c.c. CH_4 at 17° and 1.33 c.c. at 95°
All volumes reduced to 0° and 760 mm.
$C_{16}H_{29}O_2NH(OH) \cdot HCl$ Calc. 2 H 0.62%; 3 H 0.93%.
Found: at 17° 0.58, 0.64, 0.42, 0.39%.
at 95° 0.62, 0.68, 0.55, 0.53%.

Whilst the iminohydrogen atom of carpaine only reacted fully at 95° (see above), warming produced no such effect on its hydrochloride; nor does increased temperature affect the present determination, and the imino group hardly reacts. Likewise with nitrous acid ethyl carpamate yields a nitrite, not a nitroso compound.

0.1236 g. gave 0.2618 g. CO_2 and 0.1059 g. H_2O
$C_{16}H_{29}O_3NH \cdot HNO_2$ Calc. C 57.96 H 9.43%
Found „ 57.77 „ 9.59%

The imino group in this ester was however demonstrated by acetylation, by heating 1 g. for 2 hours with 10 c.c. acetic anhydride, 2 g. sodium acetate and 5 drops of pyridine; the product was distilled at 15 mm. from a bath at 280°.

3.86 mg. gave 9.16 mg. CO_2 and 3.20 mg. H_2O
3.896, 6.685 mg. neutralised 1.43, 2.47 c.c. 0.01 N-sodium hydroxide.

$C_{16}H_{29}O_3N(COCH_3)_2$ Calc. C 64.99 H 9.55 2 $COCH_3$ 23.3%
Found „ 64.72 „ 9.28 15.79, 15.90%

By hydrolysing for 20 minutes the N-acetyl group is hardly attacked[1]).

Ethyl N-methylcarpamate. 2 g. carpamic acid hydrochloride was heated for 4 hours in a sealed tube at 120—130° with 4 c.c. water and 2 c.c. of 40% formaldehyde. After evaporation the residue was esterified with hydrogen chloride in ethyl alcohol, and the base distilled at 225°/15 mm.

4.511 mg. gave 11.22 mg. CO_2 and 4.48 mg. H_2O
2.74 mg. gave 2.17 mg. AgI (*Zeisel*) and 2.18 mg. AgI (*Herzig* and *Meyer*)

$C_{16}H_{30}O_3N \cdot CH_3$ Calc. C 68.17 H 11.12 OC_2H_5 15.05 NCH_3 9.70%
Found „ 67.83 „ 11.11 „ 15.19 „ 9.83%

By this treatment the hydroxyl group was not oxidized, as it was during the similar methylation of pyrrolidylpropanols by *Hess*[2]), who so obtained N-methylpyrrolidylketones. That the hydroxyl group is still intact was next proved directly by acetylation, yielding an oil, b. p. 230°/15 mm.

7.268, 5.252 mg. neutralised 2.08, 1.51 c.c. 0.01-N sodium hydroxyde

$C_{16}H_{29}O_2NCH_3 \cdot OCOCH_3$ Calc. $COCH_3$ 12.61%
Found „ 12.31; 12.37%

These experiments establish the presence in carpamic acid of both an imino and a hydroxyl group.

N-acetylcarpamic acid. 1 g. N-acetylcarpaine was kept for 12 hours at room temperature in 25 c.c. 2% methyl alcoholic potassium hydroxide. After dilution with 25 c.c. water and making slightly acid, the alcohol was evaporated on the water bath. After extraction with chloroform or warm ether an oil was obtained which was esterified with diazomethane and distilled at 15 mm. from a bath at 290°. After some months it sets to a solid mass of crystals of *N-acetylmethylcarpamate;* washed with cold acetone on porous earthenware, they melted at 64°.

4.630 mg. gave 11.090 mg. CO_2 and 4.055 mg. H_2O

$C_{17}H_{31}O_4N$ Calc. C 65.18 H 9.90%
Found „ 65.33 „ 9.80%

That the hydroxyl group is still intact was demonstrated by the method of *Zerewitinoff:*

9.667 mg. gave 0.62 c.c. CH_4 at 23° and 0.82 c.c. at 95°
12.355 mg. gave 0.81 c.c. CH_4 at 23° and 1.09 c.c. at 95°
All volumes reduced to 0° and 760 mm.

$C_{13}H_{24}NCOCH_3 \cdot COOCH_3 \cdot OH$ Calc. active hydrogen 0.32%
Found at 23° 0.29, 0.29; at 95° 0.38, 0.40%.
At 95° the solution becomes turbid.

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[1]) Mikrochemie **7**, 8 (1929). [2]) B. **46**, 4107 (1913).

This experiment illustrates the ease with which the lactone ring of acetylcarpaine is opened by *alcoholic* potash; to aqueous alkali carpaine itself is very resistant.

Attempts were made to dehydrate this methyl ester of N-acetylcarpamic acid. 1 g. was heated with 5 g. phosphorus pentoxide for 1½ hours at 100°. After adding water 0.2 g. of the unchanged ester, m. p. 106—107°, was extracted with ether. Found C 64.68, H 10.08%. By further extraction with chloroform an oil was obtained. In an experiment with 1.6 g. of the ester in 6.5 c.c. 95.5% sulphuric acid, kept 40 hours at 20° no crystalline material could be isolated after mixing with ice and successive extraction with ether, chloroform and ethyl acetate. Hence the oily residues from both experiments were united, yielding 2.11 g. of which 1.59 was soluble in acetone. This was oxidized at + 5° during 40 hours with 2.0 g. $KMnO_4$ = 4 O. On filtration the acetone yielded no residue: the manganese dioxide was extracted with dilute sodium carbonate, the solution was concentrated, acidified and extracted with ether; the residual acid esterified with diazomethane. The ester crystallised from ether in needles, m. p. 91—92°.

4.432 (− 0.025 ash = 4.407 mg.) gave 10.045 mg. CO_2 and 3.770 mg. H_2O
6.846 (− 0.039 ash = 6.807 mg.) gave 0.275 c.c. N_2 at 762 mm. and 24°
5.925 mg. gave 0.221 N_2 at 761 mm. and 24°
8.818 mg. gave 0.335 N_2 at 762 mm. and and 24°

$C_{17}H_{31}O_5N$	Calc.	C 61.96	H 9.49	N 4.25%
$C_{17}H_{29}O_5N$	Calc.	„ 62.34	„ 8.93	„ 4.28%
	Found	„ 62.16	„ 9.57	„ 4.65; 4.30; 4.38%

The analyses fit the first formula best, with simple addition of one oxygen atom; the second formula implies the further loss of two hydrogen atoms; in either case the additional oxygen atom is probably introduced in accordance with constitution III (theoretical part). Compare also the formation of a benzoyl-amino decoic acid $C_{17}H_{25}O_2N$ from benzoyl α-n-hexylpyrrolidine $C_{17}H_{25}ON$[1]).

Action of chlorine on carpaine. Chlorine passed into a solution of 1 g. carpaine in 12 c.c. N hydrochloric acid at 0° gave a voluminous precipitate which after drying on porous earthenware was dissolved in much cold acetone and furnished on slow evaporation of the solvent leaflets m. p. 265° (darkening at 240°).

4.528 mg. gave 10.145 mg. CO_2 and 3.59 mg. H_2O

$C_{14}H_{24}O_2NCl$	Calc.	C 61.39	H 8.84%
	Found	„ 61.11	„ 8.87%

This substance, resulting from carpaine by the replacement of one hydrogen atom by chlorine, is neutral and appears to be a chloramine. In solution at 20° it changes to the hydrochloride of an unsaturated feeble base. By evaporation of the solvent a few crystals

[1]) *Krafft*, B. **39**, 2193 (1906); *Blaise* and *Houillon*, C. r. **143**, 361, (1906).

of this hydrochloride were obtained, but the product was mainly an oil, also formed by the action of alkaline carbonate in the presence of ether. This oil (a pyrroline derivative?) is colourless when first prepared at 0°, but becomes pink on exposure to air, rapidly at 80°. It does not distil without decomposition and yields an amorphous picrate and methiodide, but no nitroso compound.

The pyrrolidine nucleus. We were first led to suspect the presence of this nucleus in attempts to recover carpaine from residues by distillation. The distillate reddened a match soaked in hydrochloric acid. A pyrrole derivative was also formed by distilling carpaine with lime, with zinc dust, and best with selenium. The pyrrolidine nucleus may have been the cause of a rather indefinite reaction observed by *van Rijn* between N-methylcarpaine and benzoyl chloride, which reaction led him wrongly to postulate a free hydroxyl group in carpaine. The reaction is probably more complex and may involve the opening of a ring. We observed something similar with ethyl chloroformate; 0.5 g. N-methylcarpaine dissolved in 15 c.c. chloroform was heated with 6 equivalents of ethyl chloroformate for one hour on the water bath; after taking to dryness, the residue was again repeatedly evaporated with alcohol to remove volatile chlorine compounds. The residue, still containing chlorine, was soluble in ether and lost hydrochloric acid to 20% alkali, leaving an unsaturated oil, which was not examined further. An attempt to dehydrogenate carpamic acid hydrochloride by boiling with zinc dust failed; by this method *Orechoff* and *Menschikoff*[1]) dehydrogenated anabasine to dipyridyl, but we recovered carpamic acid unchanged.

The pyrrolidine nucleus can however be dehydrogenated by distillation with selenium; under reduced pressure merely four hydrogens are lost, but under atmospheric pressure a portion of the molecule containing the two oxygen atoms is split off as well.

I. An intimate mixture of 1 g. carpaine and 5 g. selenium was gradually heated to 280° at 15 mm. when a greenish oil distilled, followed at 320° by a pale solid; both gave the pyrrole reaction with p-dimethyl-aminobenzaldehyde. The oil dissolved in ether and chloroform and left behind crystals m. p. 163° which were not homogeneous (C 68.16, H 10.62%). The oil was redistilled and the most volatile fraction, b. p. 210°/5 mm., obtained in a yield of 10%, was analysed.

4.262 mg. gave 11.140 mg. CO_2 and 3.50 mg. H_2O

$C_{14}H_{21}O_2N$ Calc. C 71.44 H 9.00%

Found „ 71.29 „ 9.19%

This substance, *carpyrine*, was reduced with platinum oxide *(Adams)*, when 0.30 g. absorbed in 30 minutes 52.5 c.c. H_2; calc. for 2 double bonds 57.2 c.c.

[1]) B. **64**, 273 (1931).

After filtration, evaporation of the acetic acid, making alkaline and extraction with ether, crystals were obtained from dilute alcohol, m. p. 118—119°, very similar in appearance to the natural alkaloid, m. p. 121°, with which it is no doubt stereoisomeric: on account of the small yield it has not yet been fully examined.

After the carpyrine fraction had distilled, a second fraction b. p. 270°/5 mm. was obtained.

5.100 mg. gave 13.08 mg. CO_2 and 4.23 mg. H_2O

$C_{13}H_{21}O_2N$	Calc.	C 69.90	H 9.49%
	Found	„ 69.95	„ 9.28%

In spite of the good agreement this fraction may have been a mixture, for it is difficult to imagine how carpaine could lose methane or carpyrine could lose one carbon atom only.

II. Carpaine was heated with ten parts of powdered selenium rapidly to 360°; if this temperature is reached more slowly or if heating is continued under reflux, the yield becomes smaller and smaller. The distillate is extracted with ether and the ethereal solution is washed with lead acetate and sodium hydroxide and is finally dried with potassium carbonate; b. p. 145—150°/21 mm. Yield 40—70% of the theory.

4.533 mg. gave 13.485 mg. CO_2 and 4.19 mg. H_2O

$C_{11}H_{17}N$	Calc.	C 80.91	H 10.50%
$C_{10}H_{15}N$	Calc.	„ 80.47	„ 10.14%
$C_{12}H_{19}N$	Calc.	„ 81.29	„ 10.81%
	Found	„ 81.13	„ 10.34%

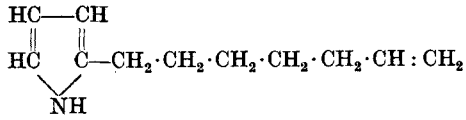
This substance *apocarpyrine* gave a coloration when boiled with p-dimethylaminobenzaldehyde and hydrochloric acid. On reduction with colloidal palladium one molecule of hydrogen is taken up.

0.100, 0.130 g. absorbed 14.1, 18.4 c.c. H_2

Calc. for one double bond 13.7, 17.8 c.c.

After filtration and addition of platinum oxide (*Adams*) the first sample absorbed a further 28.7 c.c. in 25 minutes; calc. for two double bonds (of the pyrrole nucleus) 27.4 c.c.

After making alkaline and extracting with ether a colourless oil was obtained, strongly alkaline to litmus and having an amine-like odour; no crystalline derivative could be obtained, perhaps because the substance was a mixture of homologues. Apocarpyrine is evidently a pyrrole with a side chain of 6—8 carbon atoms, containing one double bond, e. g.



Oxidation of carpamic acid by permanganate. 3 g. of carpamic acid hydrochloride was dissolved in 20 c.c. of water, made feebly

alkaline with sodium carbonate and treated with 2% potassium permanganate. The first four oxygen atoms were taken up within 20 minutes in the cold; the next three required each 20 minutes on the water bath; another three took respectively 30, 35 and 45 minutes. The solution was then concentrated to 100 c.c.; 6 c.c. of concentrated hydrochloric acid were added and produced a turbidity. In the ice chest crystals separated melting between 63 and 75°; extraction with ether hardly gave any more. After several crystallisations from water the melting point rose to 109°. Left in a steam oven on porous earthenware, the crystals melted at 120°, after recrystallisation from carbon tetrachloride at 133°. A mixture with suberic acid (m. p. 138.5°) kindly supplied by Mrs. *G. M. Robinson*, melted at 136.5—137°.

The aqueous mother liquor was concentrated to 10 c.c. and then deposited in addition to inorganic salts an oil which was extracted with acetone, and esterified with diazomethane. In this way crystals of methyl carpamate were obtained, m. p. 70°, not lowered by admixture of an authentic specimen. Hence the hydroxyl group and the pyrrolidine nucleus are both rather resistant to permanganate.

Oxidation with nitric acid. Whether carpaine, carpamic acid or its esters be employed, whether the concentration of the nitric acid be varied within certain limits and whether the solution be heated in a sealed tube or on the water bath, the result is qualitatively the same, but the time required for the operation may vary from several hours to several days. The best yield was obtained as follows: 1 g. of carpaine is dissolved in 10 c.c. of cold concentrated nitric acid; after an hour it is heated on the water bath, and after the first reaction has subsided, the solution is boiled for 48 hours under a reflux condenser (ground joint); after the first 24 hours 10 c.c. of nitric acid are added. Finally the solution is evaporated to dryness on the water bath and the residue is crystallised from water; yield of crude product 0.65—0.7 g. If the oxidation has been pushed to a suitable limit, the first crystallisation already yields perfectly colourless crystals, m. p. 95—102°: C 55.7, H 8.2%. The product gives a fluoresceine reaction with resorcinol, which reaction is no longer obtained after distillation at 200°/10 mm. by a fraction of lower molecular weight, m. p. 119°; C 54.2, H 7.7. The latter product however was not rendered much purer by a second distillation, nor by leaving it at 100° on porous earthenware (m. p. raised to 128°), nor by distillation of its methyl ester (C 56.25, H 8.43, found for the acid).

5.3 g. of the mixed dry acids was extracted with 53 c.c. of ether; the residue of 1.3 g. was again extracted with 13 c.c. of ether; the

second extraction left 1.2 g., m. p. 138—138.5°, containing 97% of *suberic acid*[1]); mixed with an authentic specimen, m. p. 138.5°.

3.902, 3.762 mg. gave 7.87, 7.60 mg. CO_2 and 2.835, 2.79 mg. H_2O
16.25 mg. neutralized 1.80 c.c. of 0,1035 N·NaOH

$C_8H_{14}O_4$	Calc. C 55.14	H 8.11%;	equivalent	87
	Found „ 55.01; 55.1	„ 8.13; 8.30%;	„	87.2

Solubility in water at 20°.
10 c.c. of a saturated solution left 20.9 mg. (20.8).
After drying for 2 hours at 120° 19.8 mg. (19.75).

The figures in brackets refer to an authentic specimen treated in the same way (the corresponding figure according to *Beilstein* is 16).

The anilide was prepared by refluxing 0.1 g. with 3 c.c. of aniline for 6 hours, distilling off most of the solvent and cooling. The product was recrystallised from alcohol and then softened at 176° and melted at 179°; authentic specimen m. p. 183—184°: the mixture softened at 179° and melted at 182°.

The two ethereal extracts of the mixed crude acid were evaporated together and their residue was dissolved in the minimum amount of dilute ammonia. The addition of 10 c.c. of 10% calcium chloride produced a slight flocculent precipitate which was filtered off. Heating on the water bath caused the separation of a calcium salt, which yielded 0.83 g. acid, m. p. 104—107°. This first fraction contains the major part of the *azelaic acid.* It was dissolved in ammonia and fractionally precipitated with 3 × 3 c.c. of 10% calcium chloride. The fractions of acid obtained from the three precipitates melted at 102°, 102.5° and 112°. Azelaic acid from *British Drug Houses Ltd.* melted at 102.5° and this melting point was not lowered by admixture with the middle fraction.

3.919 mg. gave 8.22 mg. CO_2 and 2.95 mg. H_2O

$C_9H_{16}O_4$	Calc. C 57.41	H 8.57%	
	Found „ 57.20	„ 8.42%	

The anilide, made as described for suberic acid, but recrystallised from ethyl acetate, melted at 182°; authentic specimen 181.5°, mixture 182°.

Since the anilides of azelaic and suberic acid melt at the same temperature, the melting point of their mixtures was determined and found to be 167.5° in the case of the authentic specimens, and 166° in that of the two anilides from carpaine, which alkaloid therefore furnishes on oxidation two distinct acids.

We desire to express our great indebtedness to the Swiss Committee of the Ramsay Memorial Fund for the fellowship awarded to one of us, to Mr. *A. Howard* for having procured the Papaw leaves, to Dr. *H. E. Watt,* and Messrs. *T.* and *H. Smith* for having extracted them, and to the *Moray Fund* of Edinburgh University for defraying the greater part of the expenses of the investigation.

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[1]) *Gantter* and *Hell,* B. **14,** 1545 (1881).