equivalents of hydrogen was absorbed under these conditions, and the reduction product, which was obtained as a colorless, amorphous glass by removal of the solvent, was oxidized without further purification. To a solution of 644 mg. of hydrogenated fungichromin in 25 ml. of methanol was added a solution of 3.0 g. of sodium periodate in 50 ml. of water and the mixture was allowed to stand at room temperature for 19 hr. After dilution with 200 ml. of water the mixture was extracted four times with chloroform. The extracts were dried over magnesium sulfate and then evaporated, leaving 719 mg. of a nearly-colorless viscous oil. Two grams of silver oxide and 30 ml. of 3 *N* sodium hydroxide solution were added to the oil and the mixture was heated at 90° on a steam-bath for 45 minutes. The solids were then removed by filtration and the filtrate, after acidification with dilute hydrochloric acid, was extracted four times with chloroform. Upon evaporation of the dried (magnesium sulfate) extracts 262 mg. of a light-yellow oil was obtained that slowly solidified. Digestion of the oil with boiling hexane left 101 mg. of insoluble material and cooling of the hexane gave 68 mg. of crystals. Several additional crystallizations from hexane gave colorless blunt needles, m.p. 73–74.4°. A Kuhn–Roth C-methyl determination on the dicarboxylic acid V showed 0.87 C-methyl (calcd. 1.0). A mixed melting point with a synthetic sample of 2-methyldodecanedioic acid[10] showed no depression and the infrared spectra of the two samples were identical in every respect. Subsequent studies of the reaction of hydrogenated fungichromin with sodium periodate for shorter periods of time[11] have indicated that the results described here can be explained only by hydrolysis of an ester or lactone group masking one of the hydroxyl groups in hydrogenated fungichromin prior to the cleavage with periodate.

2-Methyl-2,4,6,8,10-dodecapentaenedioic Acid from 2-Methyl-2,4,6,8,10-dodecapentaenedial (I).[11]—A solution of 1.05 g. of sodium hydroxide in 25 ml. of water was added slowly with swirling to 705 mg. of the dialdehyde I and 2.96 g. of silver nitrate in 50 ml. of ethanol and 25 ml. of water. After the addition was complete 25 ml. of water was added and the reaction mixture was allowed to stand overnight. The mixture then was filtered and the precipitate was washed with water several times. Ethanol was removed from the filtrate under reduced pressure, 25 ml. of water was added, and the filtrate was extracted with three 75-ml. portions of ether. The yellow aqueous phase was brought to *p*H 3.5 by the addition of hydrochloric acid. The precipitated yellow dicarboxylic acid was removed by filtration and dried under vacuum, giving 606 mg., m.p. 247–249° dec. An additional 16 mg. was obtained from the mother liquors. Recrystallization of the dicarboxylic acid from ethanol–water and from methanol–water yielded pure 2-methyl-2,4,6,8,10-dodecapentaenedioic acid, m.p. 252.5–253° dec.; λ_{max}^{EtOH} mμ (ε), 211 (8,000), 270 (4,400), 350 (56,000), 364.5 (86,000), 382.5 (81,000).

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.71; H, 6.03.

2-Methyldodecanedioic Acid from 2-Methyl-2,4,6,8,10-dodecapentaenedioic Acid.[11]—Hydrogenation of a 72-mg. sample of 2-methyl-2,4,6,8,10-dodecapentaenedioic acid in 15 ml. of glacial acetic acid over 103 mg. of prereduced platinum oxide resulted in the absorption of 5 molar equivalents of hydrogen. The catalyst was removed by filtration and washed with acetic acid. Evaporation of the acetic acid left a colorless oil that crystallized on cooling, yielding 73 mg. of colorless 2-methyldodecanedioic acid, m.p. 72–74°. Crystallization from hexane gave the pure dicarboxylic acid, m.p. 74–75°. A mixed melting point determination with authentic 2-methyldodecanedioic acid (m.p. 73–74.5°) was undepressed; m.p. 73.8–75°.

CAMBRIDGE, MASSACHUSETTS

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Alkaloids of *Ormosia panamensis* Benth. and Related Species

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Seeds of the Venezuelan tree *Ormosia dasycarpa* Jacks. were reported in 1919 to contain two alkaloids of unknown structure, one of which was described as possessing analgesic action. In an investigation of this problem, it was found that seeds of *Ormosia panamensis* Benth. and related species contained a number of alkaloids; three of these, panamine, ormosinine and ormosanine were oxygen-free bases, and at least two additional oxygen-containing (amide) bases also were present. The major alkaloid, panamine, was found to undergo air oxidation to yield a substance with potent hypotensive properties in dogs. This material may be a *t*-amine oxide. A substance corresponding to the analgesic alkaloid ormosine was not found, although there were some similarities between the properties of panamine and those described for ormosine.

In 1919, Hess and Merck[1] reported that seeds of a Venezuelan tree of the Leguminosae, *Ormosia dasycarpa* Jacks., contained two alkaloids of unknown structure. The major alkaloid, ormosine, was obtained as a hydrate $C_{20}H_{33}N_3 \cdot 3\text{–}4\ H_2O$, m.p. 85–87°; the other base, ormosinine, m.p. 203–205°, had the same molecular formula $C_{20}H_{33}N_3$, but it did not correspond to water-free ormosine. It was also reported that ormosine had a strong narcotic action resembling that of morphine.

In an investigation of this problem, ormosinine and several new alkaloids were isolated from seeds of *O. panamensis* Benth. (from Cuba and Panama) and *O. jamaicensis* Urb. (from Jamaica). These were also present, as indicated by paper chromatography, in several other *Ormosia* species from Central and South America.

The alkaloids were isolated by conventional extraction and fractionation procedures. It was found desirable to remove the wax–lipid components from the seeds by hexane extraction before proceeding with the alkaloid extraction with methanol. The total alkaloid content of the seeds, amounting usually to 2.5–2.8%, was extracted selectively from aqueous (basic) solution with ether to yield a fraction containing ormosinine, two new compounds which have been named ormosanine and panamine, and small quantities of several additional alkaloids. The remaining organic base fraction was extracted with chloroform and this provided a mixture whose major component was panamine. The composition of these fractions and the composition of column effluent fractions resulting from column chromatography separations were followed by paper chromatography.

Ormosinine was described previously as a colorless base, m.p. 203–205°, with only a slight solubility in alcohol and ether. The corresponding material obtained in this work had a higher melt-

(1) K. Hess and E. Merck, *Ber.*, **52**, 1976 (1919).

ing point, 219–220°, but it was unquestionably identical with the material isolated earlier by Hess and Merck. Although the free base crystallized in excellent form from a variety of solvents, attempts to obtain satisfactory derivatives met with little success. The hydrochloride, picrate, perchlorate, chloroplatinate, picrolonate and methiodide all had poor crystalline properties and their insolubility in most solvents prevented purification by recrystallization. This behavior may be due in part to the fact that the alkaloid has three basic nitrogen atoms. A satisfactory dipicrate was obtained after many trials, and the empirical formula $C_{20}H_{33}N_3$ was assigned to ormosinine (in agreement with Hess and Merck) on the basis of analyses for the base and the dipicrate. The infrared spectrum showed the presence of an NH group, and the base gave a weak Simon test for secondary amines. An N-methyl determination gave a low value, but this has been interpreted as indicating that one N-methyl group is present in ormosinine.[2] An active hydrogen determination indicated that one replaceable (at room temperature) hydrogen atom was present; this is presumably present in the secondary amine group. No C-methyl group was found by analysis. Hydrogenation experiments indicated that one double bond was present, but two unidentified reduction products were formed, and the site of the double bond is unknown.[3] While it seems reasonable to assign a tertiary amino structure to the third nitrogen atom, it is not possible to suggest additional structural features.

Ormosanine (m.p. 167–168°) was obtained best by direct crystallization. The usual agents did not yield satisfactory derivatives, although a dihydroiodide was prepared in crystalline form. The infrared spectrum showed an NH group, and an active hydrogen determination showed two replaceable atoms. No N-methyl group was found on analysis. These data may indicate two secondary amino groups and one tertiary amino group; however, the secondary amine test was negative and no reactions characteristic of a secondary amine were observed. The alkaloid showed no evidence of unsaturation. The empirical formula $C_{20}H_{33}N_3$ was the same as that found for ormosinine.

The major alkaloid of the seeds, panamine, was obtained by column chromatography as a clear resin which could not be induced to give crystalline material when anhydrous solvents were employed. With wet ether or aqueous alcohol, the alkaloid gave a crystalline hydrate, m.p. 38–40°. This material lost its crystal form after drying *in vacuo*, but the anhydrous form gave satisfactory analytical values. The dipicrate, diperchlorate and methiodide were prepared, and the analytical data were in accord with the formula $C_{20}H_{33-35}N_3$ (data in the Experimental section are based on $C_{20}H_{33}N_3$). A positive Simon test was observed. Although a well defined product could not be obtained, there was evidence of nitrosamine formation with nitrous acid. An N-methyl determination showed one such group.[2] The structure of the methiodide was found to be that of N-methylpanamine methiodide hydroiodide, by comparison of the N-methylpanamine methiodide prepared both from panamine and from N-methylpanamine. N-Methylpanamine was prepared by the reductive (catalytic) methylation of panamine with formaldehyde. No evidence of unsaturation was found for panamine. Since this alkaloid resembles the ormosine of Hess and Merck in the formation of a low-melting hydrate, it may seem possible that the material described earlier and panamine are identical. However, in view of the fact that no analgesic action was found for the base, that the derivatives of Hess and Merck were not observed, and that the melting point of the hydrate (38–40°) was quite different from that given by Hess and Merck, it seems best to distinguish the present compound by a new name, and to retain the name ormosine for material fitting the description of Hess and Merck. These data are summarized in Table I.

TABLE I

	Ormosine[1]	Panamine
Formula	$C_{20}H_{33}N_3$	$C_{20}H_{33-35}N_3$
Functional groups	*sec.*-Amino	*sec.*-Amino
Hydrate, m.p., °C.	85–87	38–40
Methiodide, m.p.,[a] °C.	245–250	206–208
Dipicrate, m.p., °C.	178	237 (dec.)
Physiol. action	Analgesic	.....

[a] The formula $C_{24}H_{45}N_3I_2$ was assigned to this compound.[1]

Perhaps the most striking property of panamine was its ability to undergo air oxidation to an ether-insoluble product which was found to have a profound hypotensive action in dogs.[4] This effect was detected when old samples of panamine were found to have a hypotensive action, while freshly isolated material showed no effect of this kind. It was found that air oxidation and peroxide oxidation gave materials with almost identical physical properties and infrared spectra, but the air oxidation product alone had a hypotensive action. This substance may have an amide or a *t*-amine oxide structure, and it is also possible that both groups are present. A *t*-amine oxide structure is currently under consideration. However, attempts to demonstrate a reduction (zinc–acid) of oxypanamine to panamine were not successful; the unidentified products did not include panamine, and the oxidation reaction may therefore not be a simple one. Oxidation at the secondary amine functional group may be eliminated from consideration, since N-methylpanamine gave on air oxidation a similar product with identical physiological activity.

Two other alkaloids were obtained in small quantity by column chromatographic separations. These materials were not obtained in sufficient purity to warrant detailed description. Both showed carbonyl (amide) absorption in the infrared. Paper chromatography was particularly helpful in guiding the separation of these components, and in establishing their existence.

(2) Less than the calculated values were also found for panamine and N-methylpanamine.

(3) Ormosinine in ethanol solution showed only end absorption near 220 mμ; acidified solutions showed a shift of the absorption to a longer wave length, and this effect may aid in determining the double bond site.

(4) Summaries of the physiological experiments may be found in N. C. Moran, G. P. Quinn and W. R. Butler, *Federation Proc.*, **15**, 462 (1956); **16**, 324 (1957); G. P. Quinn, W. R. Butler and N. C. Moran, *ibid.*, **15**, 470 (1956).

TABLE II

Species	Source	Alkaloid content[a,b] I	II	III	IV	V	VI	VII
O. avilensis Pittier	Venezuela		Tr.	+++	+			
O. coccinea Jacks	Panama	Tr.	+	+++	+	+	Tr.	
O. jamaicensis Urb.	Jamaica	+	++	++	++	Tr.		+
O. macrophylla Harms	Venezuela	+	+	+++	+	+		
O. monosperma (Sw.) Urb.	Cuba	Tr.	++	++	Tr.	++	Tr.	
O. panamensis Benth.	Panama	Tr.	+	++	+	+	Tr.	
O. panamensis	Panama	+	+	+++	+	+		
O. panamensis	Cuba	+	+	+++	+	+	Tr.	
O. tovarensis Pittier	Venezuela	++	+	+++	+	+		

[a] The tests are indicated as strong, medium, weak and trace. [b] The named alkaloids are listed in Table IV.

The occurrence of amides along with oxygen-free polycyclic bases in *Ormosia* seeds suggests relationships of the type found among the lupine alkaloids. The absence of C-methyl groups and the carbon–hydrogen ratio is in accord with a polycyclic structure for the *Ormosia* alkaloids. The relatively high degree of reactivity of the functional groups of panamine, compared with that for ormosinine and ormosanine, suggests that the panamine amino groups are far less sterically hindered than those of ormosinine and ormosanine.

A survey of the alkaloids of a number of *Ormosia* species was carried out by examination of the paper chromatographic patterns in three solvent systems. A small sample of the crushed seeds was defatted, and a methanol extract was used for the alkaloid examination. While the identifications were based solely on chromatographic identity, there is little reason to believe that the composition was other than that indicated by the patterns. Table II contains these data. The major alkaloid, panamine, was found in all of the species, and the chief differences in a qualitative sense were largely confined to the trace alkaloids.

Current studies are directed to the isolation of alkaloids IV and V, and to the study of oxidation and dehydrogenation products of the three principal alkaloids.

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Experimental[5]

Isolation of Alkaloid Fractions.—A 450-g. quantity of ground *Ormosia panamensis* seeds was defatted by hexane extraction; the extract was alkaloid-free and yielded 29 g. of viscous yellow oil. The extraction was continued in a Soxhlet apparatus with methanol until the alkaloids of the seeds were removed completely. The methanol was removed from the extract by distillation under reduced pressure; water was added near the end of the distillation to ensure the removal of all of the methanol. The aqueous solution was acidified with hydrochloric acid and washed with methylene chloride. The organic extract gave negative alkaloid tests and it was discarded. The aqueous solution was neutralized with solid potassium carbonate (to *p*H 10; a little concentrated ammonium hydroxide was also added), and extracted continuously with ether for 48 hours. The colorless ether extract was dried (magnesium sulfate) and reduced in volume to 100 ml. At this point a crystalline material separated. This fraction (E-1, m.p. 213–215°, 1.21 g.) was substantially pure ormosinine. After removal of the crystalline product, the ether solution was concentrated to a viscous fluid. Small colorless crystals formed slowly on standing; these were removed after several weeks by filtration and washing with acetone. This fraction (E-2, m.p. 165–168°, 0.25 g.) contained ormosanine. A residual alkaloid fraction was obtained by removing the organic solvents *in vacuo* from the combined filtrate and washings. This fraction (E-3) amounted to 9.53 g.; it was a viscous amber sirup.

The continuous ether extraction was followed by chloroform extraction; this was continued until the aqueous solution gave negative alkaloid tests. The chloroform solution was dried (magnesium sulfate) and the solvent was removed under reduced pressure to yield fraction C; this amounted to 2.95 g. The total yield of organic bases was 2.75%.

The choice of organic solvents described here has the advantage of giving relatively pure samples of ormosinine and ormosanine, and of giving a fraction (E-3) which consists predominantly of panamine. The composition of these fractions was studied by paper chromatography. The system was 1-butanol, concd. hydrochloric acid and water (system A) and the ascending method was used with Whatman 1 paper. The visualizing agent was a spray of Dragendorff's reagent. The results are given in Table III.

TABLE III

Fraction	R_f	Intensity[a]
E-1	0.35	
E-2	.64	
E-3	.34	++
	.51	+++
	.65	++
	.70	Trace
	.80	+
	.98	Trace
C	.50	+++
	.80	++

[a] Indicated as a strong, medium or weak test.

The R_f values for pure samples of ormosinine, ormosanine and panamine were 0.35, 0.64 and 0.51, respectively. The alkaloid with R_f 0.80 found in fractions E-3 and C has not been named. It occurs normally in *O. panamensis* seeds and it is a usual constituent of fraction C.

Ormosinine.—The crystalline material designated as fraction E-1 was recrystallized several times from ethyl acetate to yield colorless needles, m.p. 219–220°, $[\alpha]^{25}_{436}$ +16.0°, $[\alpha]^{25}_{559}$ +8.9° (*c* 1.29, chlf.). Since this substance is almost certainly the same as the high-melting base (m.p. 203–205°) of Hess and Merck, the name ormosinine has been retained. The ultraviolet spectrum (alc.) showed only end absorption. The infrared spectrum showed an NH band. A weak Simon test was observed.

Anal. Calcd. for $C_{20}H_{33}N_3$: C, 76.14; H, 10.54; N, 13.32; NCH_3, 4.78 (one); active H, 0.32 (one); neut. equiv., 105.1. Found: C, 75.96; H, 10.53; N, 13.31;

(5) All melting points were taken on a Kofler stage. Optical rotations were taken with a Rudolph photoelectric-matching polarimeter.

NCH_3, 1.52; CCH_3 none; active H (24°), 0.35; neut. equiv., 105.

The dipicrate was prepared in aqueous solution. It was not soluble in most solvents, and decomposed when recrystallization was attempted. The m.p. was 146–148°.

Anal. Calcd. for $C_{20}H_{33}N_3 \cdot 2C_6H_3N_3O_7 \cdot H_2O$: C, 48.41; H, 5.23. Found: C, 48.30; H, 5.07.

Ormosanine.—The material in fraction E-2 was recrystallized several times from ethyl acetate. Small colorless prisms of m.p. 167–168°, $[\alpha]^{25}_{436}$ +2.4°, $[\alpha]^{25}_{589}$ +3.3° (*c* 1.04, chlf.), were obtained. The ultraviolet spectrum (alc.) showed only end absorption. The infrared spectrum contained an NH band. The Simon test was negative.

Anal. Calcd. for $C_{20}H_{33}N_3$: C, 76.14; H, 10.54; N, 13.32; active H, 0.32 (one); neut. equiv., 105.1. Found: C, 76.08; H, 10.63; N, 13.40; NCH_3, none; OCH_3 none; active H (24°), 0.64; neut. equiv., 106.

The dihydriodide was prepared by adding solid potassium iodide to a solution of the alkaloid in dilute acetic acid. It was recrystallized from water to give small colorless prisms, m.p. 249° dec. The analytical data indicated that this was a dihydriodide.

Anal. Calcd. for $C_{20}H_{35}N_3I_2$: C, 42.04; H, 6.17; N, 7.35. Found: C, 42.26; H, 5.92; N, 7.02.

Panamine.—Fraction E-3 was dissolved in benzene and subjected to chromatography on 220 g. of alumina (Merck, acid-washed). The column was eluted with benzene, benzene–ethyl acetate (3:1) and ethyl acetate–methanol (9:1). Each fraction (200 ml.) was examined separately by paper chromatography, with the following result. Fractions 1–10, with benzene, yielded a total of 2.26 g. of colorless material giving R_f values of 0.34, 0.53 and 0.63; the areas were of approximately equal intensity. Fractions 11–50, with benzene–ethyl acetate, yielded 4.25 g. of amber material showing only one area with R_f 0.51. Fractions 51–60, with ethyl acetate–methanol, yielded 1.08 g. of dark material giving R_f values of 0.51 and 0.81, with traces of alkaloids with R_f 0.72 and 0.96.

The combined material from fractions 11–50 was recrystallized from wet ether and from aqueous alcohol to give fine colorless needles, m.p. 38–40°, $[\alpha]^{25}_{436}$ −21.3°, $[\alpha]^{25}_{589}$ −11.0 (*c* 0.928, ethanol). After drying *in vacuo* at room temperature the compound lost its crystalline form and gave a glassy resin; the weight loss was about 19%. The analytical sample was obtained from crystalline material by drying for 24 hours *in vacuo* over phosphorus pentoxide. The ultraviolet spectrum (in alcohol) showed only end absorption. The infrared spectrum showed an NH band. A positive test for a secondary amino group was observed.

Anal. Calcd. for $C_{20}H_{33}N_3$: C, 76.14; H, 10.54; N, 13.32; NCH_3, 4.78 (one). Found: C, 75.82; H, 10.73; N, 13.19; NCH_3, 3.60; CCH_3, none.

The diperchlorate was prepared by adding perchloric acid to a methanol solution of panamine. It was recrystallized from methanol–ether to yield small colorless prisms, m.p. 283–285°.

Anal. Calcd. for $C_{20}H_{33}N_3 \cdot 2HClO_4$: C, 46.51; H, 6.83; N, 8.14. Found: C, 46.62; H, 6.93; N, 8.01.

The dipicrate was prepared in ethanol and recrystallized from acetone–ethanol to yield fine yellow needles, m.p. 237° dec.

Anal. Calcd. for $C_{20}H_{33}N_3 \cdot 2C_6H_3N_3O_7$: C, 49.67; H, 5.09; N, 16.29. Found: C, 49.54; H, 5.33; N, 16.25.

The methiodide was found to correspond to **N-methylpanamine methiodide hydriodide.** It was prepared directly from panamine by adding an excess of methyl iodide to a solution of panamine in ethanol, and allowing the product to crystallize at room temperature. The product was recrystallized from ethanol to yield colorless needles, m.p. 206–208°.

Anal. Calcd. for $C_{22}H_{39}N_3I_2$: C, 44.08; H, 6.56; N, 7.01; NCH_3, 7.52 (for three). Found: C, 43.93; H, 6.83; N, 7.23; NCH_3, 5.70.

Hydrogenation Experiments.—Ormosinine, ormosanine and panamine were subjected to hydrogenation conditions. No evidence of unsaturation was found for ormosanine and panamine. Ormosinine required one mole equivalent of hydrogen when the reduction was carried out in dilute hydrochloric acid with Adams catalyst. The product, a viscous oil which did not crystallize on long standing, was found to contain two substances (R_f 0.35 and 0.64 in system A); these materials are presumably stereoisomers corresponding to a dihydroörmosinine structure. No further work was attempted with this mixture.

Additional Alkaloids.—Column chromatography separations were continued with fractions E-3 and C. Two new components, corresponding to R_f values of 0.81 and 0.70 (system A), were separated. Compound IV (R_f 0.81) was present in both fractions, and it was isolated best from *O. jamaicensis* by way of fraction C. Compound V (R_f 0.70) was present only in very small amount in both *O. jamaicensis* and *O. panamensis*. The isolation of adequate samples for analysis and further study is in progress. The infrared spectra of IV and V contained bands at 6.16 μ (IV) and 6.13 μ (V), indicating that these substances are amides.

In the course of these separations, very small quantities of alkaloids VI and VII were found; these were present in still smaller amounts. In order to provide a qualitative analytical procedure for *Ormosia* seeds, three paper chromatographic systems were used to obtain R_f values for compounds I–VII. These data are in Table IV. For the examination of seed samples of different species or of different origin, a single seed was crushed (hammer) and the tissue was defatted with hexane. A boiling methanol extraction removed the alkaloids; the methanol extract was evaporated to dryness, and the residue was taken up in dilute hydrochloric acid. Solutions obtained in this way were chromatographed on Whatman #1 paper in three systems; the visualizing spray was Dragendorff reagent, and the solvent systems are noted in Table IV. The results of these examinations are in Table II.

TABLE IV
R_f DATA

Compound	A[a]	B[b]	C[c]
Ormosinine (I)	0.35	0.09	0.35
Ormosanine (II)	.64	.47	.68
Panamine (III)	.51	.31	.56
Compound (IV)	.81	.73	.87
Compound (V)	.70	.61	.75
Compound (VI)	.96	.84	..
Compound (VII)	.40	.16	0.43

[a] System: 1-butanol, hydrochloric acid, water (100:20:36). [b] System: *t*-butyl alcohol, hydrochloric acid, water (100:10:20). [c] System: *sec*-butyl alcohol, hydrochloric acid, water (100:20:36).

Oxypanamine.—On long standing it was observed that fractions containing panamine gradually changed in composition, and yielded an ether-insoluble material. This change was effected also in direct experiments by blowing air on warm (60–80°) samples of panamine. After 24 hours, the mixture was fractionated by ether trituration. The ether–insoluble product (yield 10–15%) was a flocculent, amorphous material possessing no definite melting or decomposition point. It was very soluble in ethanol and chloroform, and slightly soluble in water. No suitable solvent for paper chromatography was found. The analytical data indicated that oxygen was present (*Anal.*: C, 62.92; H, 8.63; N, 9.89) but the values do not correspond to a recognizable functional group change. The infrared spectrum contained a medium intensity band near 6.1 μ, and successive preparations gave identical spectra. This product was found to have a profound hypotensive action in dogs.

Since the physical properties of this material suggested that a *t*-amine oxide structure was present, an oxidation of panamine was carried out with hydrogen peroxide under the usual conditions for amine oxide formation. The product had the same solubility properties as oxypanamine, and the infrared spectrum was almost identical with that of the material obtained by air oxidation. A broad medium intensity peak at 6.07 μ was present.[6] This material had no hypotensive properties.

(6) It is not possible to identify the structure feature responsible for the bands near 6.1 μ. An amide structure may be present. Since there are three nitrogen atoms in the molecule it is also possible that two amino groups were involved in or responsible for the oxidative reaction. There are no specific bands that can be associated with an amine oxide structure, but trimethylamine oxide hydrate shows a

When N-methylpanamine was subjected to identical air-oxidation conditions, an ether-insoluble product was obtained. This substance had the same physiological properties as oxypanamine, and it seems reasonable to conclude that analogous structural changes occurred in this case.

Reduction of oxypanamine in zinc–acetic acid gave a mixture of ether-soluble bases. It was anticipated that panamine would be among the products, but an examination of the mixture indicated four products (R_f 0.59 (major product), 0.30, 0.20 and 0.09 (trace) in system A), none of which was panamine.

Two functional groups that might be formed during air oxidation include a hydrated *t*-amine oxide group,[7] and an amide group; we are currently of the belief that the oxide group probably is present.

N-Methylpanamine.—A solution of 1.00 g. of panamine hydrate in 75 ml. of 20% acetic acid containing 5 ml. of 37% formaldehyde was subjected to hydrogenation with 0.5 g. of 10% Pd–C Catalyst; the reduction was carried out in a Parr hydrogenator at room temperature for 15 hours. After removal of the catalyst by filtration, the solution was concentrated under reduced pressure and the organic base was isolated by extraction of the alkaline solution (solid potassium carbonate was added) with chloroform. The yield was 0.75 g.; this material gave a single alkaloid spot on paper chromatography in the usual system (R_f 0.70). An analytical sample was obtained by sublimation *in vacuo;* the product formed colorless prisms, m.p. 101–102°, $[\alpha]^{25}_{436}$ +19.1°, $[\alpha]^{25}_{589}$ +5.3° (*c* 0.715, ethanol).

Anal. Calcd. for $C_{21}H_{35}N_3$: C, 76.54; H, 10.71; N, 12.75; NCH_3, 9.12 (two). Found: C, 76.47; H, 10.70; N, 12.66; NCH_3, 3.80; CCH_3, none; active H, none.

The dipicrate of N-methylpanamine was recrystallized from ethyl acetate; m.p. 130–134° dec.

Anal. Calcd. for $C_{21}H_{35}N_3 \cdot 2C_6H_3N_3O_7$: C, 50.31; H, 5.25; N, 16.00. Found: C, 50.25; H, 5.29; N, 15.75.

The diperchlorate was prepared in ethanol and recrystallized from methanol; m.p. 178–179°.

Anal. Calcd. for $C_{21}H_{35}N_3 \cdot 2HClO_4$: C, 47.55; H, 7.03; N, 7.92. Found: C, 47.44; H, 7.08; N, 7.88.

The methiodide was prepared by adding an excess of methyl iodide to a solution of N-methylpanamine in methanol. It was recrystallized from methanol–ether to yield an analytical sample with m.p. 201–202°. The same methiodide was obtained when an aqueous solution of panamine methiodide (N-methylpanamine methiodide hydriodide) was treated with 40% sodium hydroxide solution. The gummy precipitate was extracted with chloroform, and after removal of the solvent the residue was recrystallized from methanol–acetone to yield N-methylpanamine methiodide. The m.p. of 201–202° was not depressed in mixture with a sample prepared from N-methylpanamine, and the infrared spectra were identical.

Anal. Calcd. for $C_{22}H_{38}N_3I \cdot CH_3OH$: C, 54.86; H, 8.41; N, 8.35. Found: C, 54.56; H, 8.13; N, 8.17.

This methiodide was converted to the hydriodide by the addition of solid potassium iodide to a solution of the methiodide in dilute acetic acid. The product was identical (m.p., infrared spectrum) with the methiodide hydriodide prepared from panamine.

Infrared spectra were obtained with a Perkin–Elmer model 21 instrument. The spectra for ormosinine, ormosanine, panamine hydrate and N-methylpanamine were taken for reference purposes.[8]

broad weak band at 6.02 μ. This band is not present in the spectrum of the anhydrous form (E. Y. Spencer, R. D. O'Brien and R. W. White, *J. Agric. Food Chem.*, **5**, 123 (1957)).

(7) Air oxidation is not a normal reaction route for the preparation of amine oxides, but in our experience the extended manipulation of *t*-amines in air may result in oxide formation.

(8) These spectra have been deposited as Document Number 5425 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting in advance $1.25 for photoprints or $1.25 for 35 mm. microfilm, payable to Chief, Photoduplication Service, Library of Congress.

Bethesda 14, Md.

[Contribution from the L. G. Ryan Research Laboratories of Monsanto Canada Ltd.]

Amino Acids. V. 1,3-Di-(ω-carboxyalkyl)-thioureas and Their Chemistry

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A series of 1,3-di-(carboxyalkyl)-thioureas have been prepared by condensing the alkali salts of amino acids with carbon disulfide. These thiourea derivatives have been oxidized to the corresponding urea derivatives with either sodium hypochlorite or hydrogen peroxide solutions. The urea and thiourea dibasic acid derivatives were esterified with various alcohols in the presence of acid catalysts. Dehydration of 1,3-di-(γ-carboxypropyl)-thiourea and 1,3-di-(γ-carboxypropyl)-urea gave, respectively, 1-(γ-carboxypropylthiocarbamyl)-2-pyrrolidone and 1-(γ-carboxypropylcarbamyl)-2-pyrrolidone. Unsymmetrical urea derivatives have been prepared by the reaction of amines with 1-nitroso-1,3-di-(ω-carboxylalkyl)-ureas. 1-Nitroso-1,3-di-(ω-carboxydecyl)-urea combines with excess hexamethylenediamine to give a new amino acid, 1-(ω-aminohexyl)-3-(ω-carboxydecyl)-urea.

Recently[1] the preparation of 1,3-di-(carboxyalkyl)-ureas by the reaction of phosgene with amino acids was reported. Prior to this work, 1,3-di-(θ-carboxyoctyl)-urea[2] (m.p. 158°) and 1,3-di-(ω-carboxyhenicosanyl)-urea[3] (m.p. 110°) were described as by-products in the preparation of θ-aminopelargonic acid and ω-aminobehenic acid, respectively. The present work describes a number of new urea and thiourea derivatives of amino acids and new procedures for their preparation.

The amino acids with the exception of 15-aminopentadecanoic acid, which were used in this investigation, were prepared by the hydrolysis of the corresponding lactams. 15-Aminopentadecanoic acid hydrochloride (VII) was synthesized from 1,14-dicarboxytetradecane (I) by the following series of reactions which were used by Triebs and Hauptmann[4] in the synthesis of ω-amino acids from dicarboxylic acids.

The 1,3-di-(ω-carboxyalkyl)-thioureas (XI) listed in Table I were prepared by condensing two equivalents of an ω-amino acid with one equivalent of carbon disulfide in the presence of two equivalents of sodium or potassium hydroxide. The hydrolysis of the lactams VIII to the amino acids IX and the condensation of the amino acids with carbon disulfide have been combined to give, in gen-

(1) Thüringsche Zellwolle German Patent Appl. T 4485.

(2) B. Flaschenträger and F. Halle, *Z. physiol. Chem.*, **192**, 253 (1930).

(3) B. Flaschenträger, B. Blechman and F. Halle, *ibid.*, **192**, 257 (1930).

(4) W. Triebs and S. Hauptmann, *Ber.*, **89**, 117 (1956).