*On the Constitution of Myoporone** *(Natural Furan Derivatives. II.****)*

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The essential oil of the genus *Myoporum*, endemic to Australia and New Zealand, was examined by several investigators. McDowall(1) first isolated ngaione from the volatile oil of *Myoporum laetum* Forst. in 1925. Subsequently Birch, Massy-Westropp and Wright(2) isolated the same substance and 3-furoic acid from a specimen of *M. acuminatum*. They also examined the volatile oil of two other specimens of *M. acuminatum* and found that these oil contained at most traces of

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* T. Kubota and T. Matsuura, *Chemistry and Industry*, **1957**, 491.

** Part I. T. Matsuura, This Bulletin, **30**, 430 (1957).

1) F. H. McDowall, *J. Chem. Soc.*, **1925**, 2200.

2) A. J. Birch, R. A. Massy-Westropp and S. E. Wright, *Australian J. Chem. Soc.*, **6**, 385 (1953).

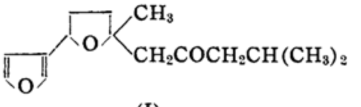
ngaione and an α,β-unsaturated furanoketone, $C_{15}H_{20}O_2$.

Ngaione was extensively investigated by several workers³⁾, but no complete formula has yet been put forward. Recently, we have succeeded in demonstrating that ngaione has the structure I⁴⁾, namely the enantiomorph of (+)-ipomeamarone, the toxic bitter principle of black rotten sweet potato. In connection with these works we have recently examined the essential oil from the Japanese *M. Bontioides* A. Gray (the only *Myoporum* found in Japan), and have found that ngaion is contained only in a small amount and the major constitutent is a new terpene ketone (the yield from undried leaves, ca. 0.2%). This ketone has been designated myoporone and the elucidation of its structure will be reported herewith. The essential oil contained also an unsaturated hydrocarbon, C_nH_{2n} of m. p. 63~64°C.

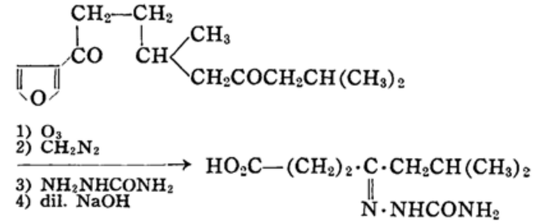
Myoporone (b. p. 117~119°C/10^{-2} mm.; n_D^{21} 1.4770) is a pale yellow oil with a slightly bitter taste, and shows no optical rotation, at D line, but its 2,4-dinitrophenylhydrazone (α-form, see below) has $[\alpha]_D^{23}$ −28.2°***.

It gives a purple coloration with Ehrlich's reagent, a pale brown coloration with concentrated hydrochloric acid, decolorized potassium permanganate, and yield a dark red Liebermann reaction. The molecular formula is $C_{15}H_{22}O_3$, and two bis-2,4-dinitrophenylhydrazones, $C_{27}H_{30}O_9N_8$ are obtained. The α-form has red color and melts at 193°C, while β-form is orange-yellow and turns into red at 143~145°C and melts at 193°C. These substances seem to be dimorphous⁵⁾. Infrared absorptions of myoporone in Nujol are shown at 3.19 (furan), 5.88 (ketone), 5.95 (conjugated ketone), 6.41 (furan), 6.63 (furan) and 11.45 μ (furan).

Oxidative degradation of myoporone ozonide followed by esterification of the acidic fraction yielded a methyl ester, b. p. 88~90°/10^{-2} mm., n_D^{18} 1.4378, λ_{max}^{nujol} 5.77 and 5.84 μ. Conversion of this ester into semicarbazone and subsequent hydrolysis gave a semicarbazone of ketonic acid, m. p. 139~140°C ($[\alpha]_D^{18}$ −9.18), which was found to be identical with the previously synthesized semicarbazone of dihydroanhydroipomic acid (III)⁶⁾ by the infrared absorption spectra in Nujol. These facts lead to structure II for myoporone and this has been confirmed by sythesis.

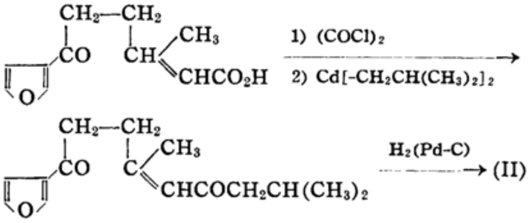


(I)



(II)

The synthesis of (±)-myoporone was started from the previously synthesized 2-methyl-4-(3′-furoyl)-1-butene-1-carboxylic acid (IV)⁷⁾ and effected according to the following sequence.



The melting point of the 2,4-dinitrophenylhydrazone (red, α-form) of the synthetic (±)-myoporone was 208~210°C, but its infrared absorption spectrum in Nujol was completely in agreement with that of α-form of 2,4-dinitrophenylhydrazone of the natural product.

Myoporone may probably be produced in vivo through intramolecular oxido-reductive cleavage of the tetrahydrofuran ring of ngaione (I). The isolation of ngaione ((−)-ipomeamarone), myoporone and 3-furoic acid²⁾ from the essential oil of *Myoporum*, and the isolation of (+)-ipomeamarone (I), batatic acid⁸⁾ (VI) ipomeanine⁹⁾ (VII) and 3-furoic acid

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3) F. H. McDowall, *J. Chem. Soc.*, **1927**, 731; **1928**, 1324; C. W. Brandt and D. J. Ross, ibid., **1949**, 2778; A. J. Birch, R. A. Massy-Westropp, S. E. Wright, T. Kubota and T. Matsuura, *Chemistry & Industry*, **1954**, 175.

4) T. Kubota and T. Matsuura, ibid., **1956**, 521.

*** In the preliminary paper (T. Kubota and T. Matsuura, ibid., **1957**, 491), we reported that natural myoporone is in racemic form, because of its lack of optical activity at D line. This measurement was performed by the courtesy of Professor Y. Hirata, Nagoya University.

5) W. Dirscherl and H. Nahm, *Ber.*, **73**, 448 (1940).

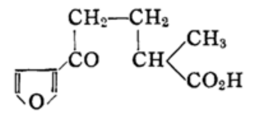
6) T. Kubota and T. Matsuura, *J. Chem. Soc. Japan, Pure Chem. Sec.*, (*Nippon Kagaku Zassi*), **74**, 105 (1953).

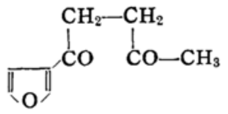
7) T. Kubota and T. Matsuura, *Chemistry & Industry*, **1956**, 521; T. Matsuura, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zassi*), **77**, 248 (1956).

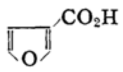
8) T. Kubota and K. Naya, ibid., **77**, 86, 252 (1956).

9) T. Kubota and N. Ichikawa, ibid., **75**, 450 (1954).

(VIII)[10] from black rotten sweet potatoes is quite interesting in relation to the metabolism of terpenes and β-substituted furan derivatives in plant.


(VI)


(VII)


(VIII)

Experimental

Isolation of Myoporone.—Leaves (10.06 kg.) of *Myoporum bontioides* A. Gray, which were collected at fructifying time in Tanegasima Island, Kagoshima Prefecture, Japan, were roughly cut and digested in methanol (15 l.) for about three months. After distilling off the solvent, water was added, and the liquor was extracted with ether (500 cc.×4). The ethereal solution was concentrated to a small volume and was shaken with sodium bicarbonate solution. From the bicarbonate solution, a small amount of the acidic matter was obtained. Evaporation of the ethereal solution left a brownish green liquid (45.5 g.). Vacuum-distillation of the liquid gave a yellow liquid (A; 27.1 g.), b. p. 90～150°C/10^{-2} mm. and n_D^{23} 1.4750, which was fractionally distilled as shown in Table I.

TABLE I

	Fraction	b. p./10^{-2} mm.	Yield	n_D^{23}	Color
A	-I	<121°	1.8 g.	1.4812	yellow
	-II	121 ～125°	23.4 g.	1.4752	yellow
	-III	125°<	1.1 g.	1.4718	yellow
	Fraction	b. p./10^{-2} mm.	Yield	$n_D^{23.5}$	Color
II	-I′	<113°	1.7 g.	1.4780	yellow
	-II′	113 ～116°	20.5 g.	1.4733	yellow
	-III′	116°<	0.8 g.	1.4685	yellow
	Fraction	b. p./10^{-2} mm.	Yield	n_D^{21}	Color
II′	-I″	<117°	1.4 g.	1.4776	pale yellow
	-II″	117 ～119°	13.8 g.	1.4770	pale yellow
	-III″	119°<	3.2 g.	1.4760	pale yellow

The fraction (II″) consists of almost pure myoporone.

Extraction of leaves, which were collected at flowering time, gave the same results as described above.

Isolation of C_nH_{2n}-hydrocarbon.—Dried leaves (430 g.) of *Myoporum bontioides* A. Gray were digested with ether (4 l.). Evaporation of the ethereal solution gave a brownish green semi-solid (14 g.). When the semi-solid was well mixed with ethanol (60 cc.) and filtered, there were obtained crystals (3.7 g.) which crystallized from ethanol in wax-like colorless plates, m. p. 63～65°C.

Anal. Found: C, 85.85; H, 14.71%. Calcd. for C_nH_{2n}: C, 85.63; H, 14.37%.

Distillation of the liquid part of the extract gave a liquid (1.0 g.), b. p. 105～120°C/10^{-2} mm. and n_D^{17} 1.4890. It showed a positive reaction with the Ehrlich's reagent and its infrared spectrum showed the presence of furan ring (3.18, 6.41, 6.65 and 11.42 μ), hydroxyl group (2.85 μ), and two carbonyl groups (5.88 and 5.98 μ) in the molecule, but its semicarbazone could not be obtained in crystalline state.

Detection of Ngaione.—The fraction II′ (0.5 g.), semicarbazide hydrochloride (0.5 g.), and potassium acetate (0.5 g.) were dissolved in dilute ethanol and the whole was kept overnight. Water was added and the resulting sticky mass (0.7 g.) was collected and dried. It was dissolved in benzene (20 cc.) and was purified by chromatography with alumina. From the benzene eluate, a small amount of crystal was obtained. It was recrystallized from benzene and light petroleum as colorless plates, m. p. 130～132°C, which showed no depression on admixture with the semicarbazone of ngaione, kindly supplied by Professor A. J. Birch, m. p. 132～133°C. The further elution with benzene-ethanol gave a semicarbazone as a syrup, which did not crystallize.

Bis-2, 4-dinitrophenylhydrazones of Myoporone.—When the fraction II″ (0.4 g.) was mixed with a solution of 2,4-dinitrophenylhydrazine (1.0 g.) in concentrated sulfuric acid (1 cc.) and ethanol (100 cc.), orange red precipitates made their appearance in a few minutes. After standing for 2 hr., the precipitates were filtered. Yield 0.5 g. Repeated treating of the precipitates with ethyl acetate gave red crystals, which was slightly soluble in ethyl acetate. They were recrystallized from benzene to afford red prisms, m. p. 193°C, which were designated as α-bis-2,4-dinitrophenylhydrazone $[\alpha]_D^{23}$ −28.2 (Chloroform, C=0.18).

Anal. Found: C, 53.20; H, 4.92; N, 18.89%. Calcd. for $C_{27}H_{30}O_9N_8$: C, 53.2; H, 4.92; N, 18.33%.

From the mother liquor of the above recrystallization, a mixture of the red α-bis-2,4-dinitrophenylhydrazone and yellow needles separated, and the latter were collected mechanically, which was designated as β-bis-2,4-dinitrophenylhydrazone. It melted at 193°C after changing to red color at 143～145°C. Recrystallization of β-compound from benzene gave α-compound and its mother liquor deposited a mixture of α- and β-compounds.

Anal. Found: N, 18.64%. Calcd. for $C_{27}H_{30}O_9N_8$: N, 18.33%.

Ozonization of Myoporone.—Myoporone (2.0 g.) in chloroform (30 cc.) was saturated with ozone and the solvent was evaporated under reduced pressure. The resulting ozonide was decomposed under ice-cooling with a bichromate

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[10] T. Kubota, H. Yamaguchi, K. Naya and T. Matsuura, ibid., **73**, 897 (1952).

mixture, the latter being composed of the admixture of potassium bichromate (3.2 g.), concentrated sulfuric acid (2 cc.), and water (20 cc.). After two days' standing the mixture was extracted with ether. The ethereal solution was extracted with a bicarbonate solution. The acidic substance, obtained from the bicarbonate extract, was methylated with diazomethane in ether. Distillation of the methyl ester gave a colorless liquid, b. p. 88~90°C/10^{-2} mm. and n_D^{18}1.4378. Its refractive index coincides with that of synthetic methyl dihydroanhydroipomate, $n_D^{17.5}$ 1.4390[6]. IR-spectrum: 5.77 μ (ester) and 5.84 μ (ketone).

This methyl ester (0.25 g.), semicarbazide hydrochloride (0.2 g.), and potassium acetate (0.2 g.) were dissolved in dilute ethanol and, after standing overnight, water was added. The precipitates, which had separated in the meanwhile, were collected through decantation and then hydrolyzed with 1 N sodium hydroxide (2 cc.). Acidification of the hydrolysate gave white precipitates, which were recrystallized from ethanol. Colorless plates, m. p. 139~141°C. This substance was identical with the synthetic dihydroanhydroipomic acid semicarbazone, i. e. 3,7-dimethyl-5-keto-octane-1-carboxylic acid semicarbazone, m. p. 140~141°C in infrared spectrum. No remarkable depression of melting point was recognized on admixture of both samples.

Synthesis of Myoporone

1-Isovaleryl-2-methyl-4-(3′-furoyl)-1-butene (V). — 2-Mtheyl-4-(3′-furoyl)-1-butene-1-carboxylic acid (IV), m. p. 103~104°C[11], was converted into the acid chloride with oxalyl chloride, according to the method of Barkley et al.[12] The acid (4.2 g.) was dissolved in absolute methanol (20 cc.) and neutralized with 1 N sodium methoxide solution in methanol. After the solvent was evaporated in vacuo, dry benzene was added and evaporated again to dryness in vacuo. The resulting sodium salt was suspended in dry benzene (25 cc.) and oxalyl chloride (4 g.) in benzene (10 cc.) was added in portions under ice-cooling. After the mixture was kept at 40°C for 20 min., benzene and excess of oxalyl chloride were distilled off under reduced pressure. The acid chloride, which was obtained as brown liquid, was dissolved in benzene (20 cc.).

To a Grignard solution, which was prepared from isobutyl bromide (5.5 g.), magnesium (1.0 g.), and absolute ether (30 cc.), dried cadmium chloride (4.0 g.) was added under ice-cooling, and the mixture was refluxed until a Gilman-Schulz test was negative. After distillation of ether, benzene (30 cc.) was added.

To the stirred diisobutyl cadmium solution thus obtained, the acid chloride solution in benzene was rapidly added with constant refluxing. The mixture was refluxed for 30 min. or more and then was decomposed with dilute hydrochloric acid under ice-cooling. The organic layer was separated, washed with a bicarbonate solution, dried and evaporated. Twice distillations of the resulting dark brownish liquid (3.0 g.) gave a pale yellow liquid (1.2 g.), b. p. 119~122°C/10^{-2}mm. and n_D^{12} 1.4925, and its color changed to brownish yellow on standing. IR-spectrum: 3.18 (furan), 5.96 (furyl ketone and α,β-conjugated ketone), 6.08 (double bond), 6.41 (furan), 6.63 (furan), and 11.44 μ (furan).

1-Isovaleryl-2-methyl-4-(3′-furoyl)-butane. (Myoporone).—The above obtained liquid (0.28 g.) was dissolved in ethanol (10 cc.) and hydrogenated in the presence of 5% palladium-charcoal (0.1 g.). After 1.1 moles of hydrogen were absorbed (about one hr.), the catalyst was filtered off. To the filtrate 2,4-dinitrophenylhydrazine (0.4 g.) in ethanol was added in the presence of sulfuric acid. Twice recrystallizations of the resulting precipitates from ethyl acetate gave a red prism, m. p. 208~210°C, which showed no depression on admixture with α-bis-2,4-dinitrophenylhydrazone of myoporone, m. p. 193°C and was identical with α-compound in infrared spectrum.

The writers wish to express their thanks to Professor S. Miki, Department of Biology, Osaka City University, for collection and identification of *Myoporum Bontioides* A. Gray. Cordial thanks are also due to Mr. T. Kurokawa, Kagoshima Prefectural Industrial Research Institute and Mr. T. Uehara, Tanegashima Branch of the Kyushu Goverment Agriculture Experiment Station, for gathering the same plants.

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[11] T. Matsuura, ibid., **78**, 389 (1957).

[12] L. Barkley et al., *J. Am. Chem. Soc.*, **76**, 5017 (1954).