

587. *The Constitution of Ngaione.*

By C. W. BRANDT and D. J. ROSS.

Ngaione, $C_{15}H_{22}O_3$, obtained from the essential oil of *Myoporum laetum* Forst, has been shown by oxidation with potassium permanganate and potassium ferricyanide to possess the partial structure (I), incorporating 3-furyl, acetyl, and *isobutyl* groups, and a residue, C_3H_7O . Experiments designed to open one or both of the oxide rings are described, and the absorption spectrum of ngaione is recorded.

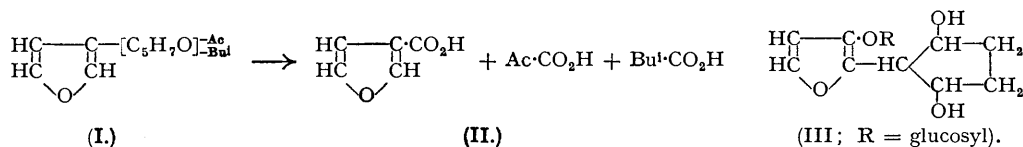
NGAIONE occurs to the extent of about 80% as a liquid ketone in the essential oil obtained by steam-distillation of the leaves of the New Zealand tree *Myoporum laetum* Forst. It was first studied by McDowall (*J.*, 1925, 2200; 1927, 731; 1928, 1324) who established the formula $C_{15}H_{22}O_3$ and the presence of a carbonyl group and of two ethylenic linkings, and concluded that the remaining two oxygen atoms were probably present in two oxide rings, possibly furan or reduced furan rings (Thesis, Univ. London, 1927). Simonsen ("The Terpenes," Vol. II, Cambridge Univ. Press, 1932) also states that ngaione is probably a furan derivative, like the ketone elsholtzione. McDowall carried out many transformations of ngaione, *e.g.*, he prepared ngaiol and dehydrongaione dioxide and their hydrogenated derivatives. Catalytic hydrogenation of ngaiol in acetic acid opened one oxide ring, and an oxido-glycol was obtained. By the action of halogen acids on ngaione derivatives and subsequent dehalogenation he obtained straight-chain alcohols and hydrocarbons, but owing to the poor yield and complexity of the products no detailed examination of these compounds was carried out.

In an attempt to determine the position of the carbonyl group, McDowall (Thesis) oxidised tetrahydrongaione with sodium hypobromite and obtained a dibromo-derivative, $C_{15}H_{24}O_3Br_2$, with a trace of acids similar in odour to *isobutyric* acid; a trial oxidation with potassium permanganate gave a small yield of acids, but no definite conclusions were drawn. With chromic acid ngaione gave only a little oxalic acid, whilst oxidation with silver oxide gave no identifiable products.

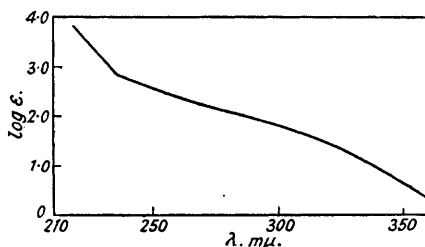
The following is a summary of the results obtained by the present authors from oxidation experiments on ngaione and tetrahydrongaione: (a) A trial ozonisation of ngaione in carbon tetrachloride gave a mixture of complex liquid acids but no simple carbonyl compounds;

(b) In neutral acetone, some permanganate was absorbed and ngaione was recovered as a colourless oil (when purified by distillation ngaione always retains a pale yellow colour which is apparently removed by potassium permanganate); in pyridine, ngaione gave mixed acids (mainly oxalic acid), and in suspension in sodium carbonate solution yielded pyruvic acid in small amount and mainly a mixture of liquid acids of high molecular weight; tetrahydra ngaione in aqueous suspension yielded oxalic and isovaleric acid. (c) Ngaione when oxidised with alkaline potassium ferricyanide gave 3-furoic (II), pyruvic, isobutyric, and isovaleric acid.

These results establish the presence of a 3-furyl group in ngaione and thus the position of the ethylenic linkings. The formation of isovaleric and pyruvic acid demonstrates the presence of isobutyl and acetyl side-chains. Confirmatory evidence for the presence of the latter group is provided by the positive iodoform test given by ngaione. It is thus possible to write the partial structure of ngaione with its potassium ferricyanide oxidation products as follows:



The only reported occurrence, among essential oils, of a solely 3-substituted furan ring is that of perillene (3-4'-methylpent-3'-enylfuran) from *Perilla citriodora* (Kondo and Suzuki, *Ber.*, 1936, 69, B, 2459), but various 2-substituted furan derivatives are known, *viz.*: elsholtzine (2-isovaleryl-3-methylfuran), from the oil of *Elsholtzia cristata* (Asahina, Murayama, Shibata, Kariyone, Kuwada, and Asano, *Acta Phytochim.*, 1924, 2, 1); aucubin (III), a glycoside present in many seed plants (Karrer and Schmid, *Helv. Chim. Acta*, 1946, 29, 525); carlina oxide (benzyl-2-furylacetylene) (Gilman, Van Ess, and Burtner, *J. Amer. Chem. Soc.*, 1933, 55, 3461); and anisoxide (which contains a reduced 2-furyl group) (Jackson and Short, *J.*, 1937, 513). It is of interest to note that three of the compounds possessing a 3-substituted furan ring, *viz.*, ngaione, perillene, and elsholtzine, are grouped botanically in the Lamiales.



Absorption spectrum of ngaione in hexane.

In an attempt to obtain further information about the oxide ring systems in ngaione experiments were conducted to open one or both rings. One of the oxide rings in ngaione was opened by hydrogenation in glacial acetic acid with Adams's platinum oxide catalyst. Three molecules of hydrogen were slowly absorbed at atmospheric or at 4 atmospheres pressure. The product consisted chiefly of a mixture of an oxido-alcohol, $\text{C}_{15}\text{H}_{28}\text{O}_3$, and its acetate, $\text{C}_{17}\text{H}_{30}\text{O}_4$, the former being obtained pure by hydrolysis and distillation, and the latter by repeated acetylation of the crude hydrogenation product. Vanillin and concentrated hydrochloric acid gave a red colour with the oxido-alcohol similar to that obtained by McDowall with the oxido-glycol formed by hydrogenation of ngaiol with Skita's catalyst. The oxido-alcohol gave no solid semicarbazone, and its acetate gave no solid oxime or 2:4-dinitrophenylhydrazone, but survival of the carbonyl group was proved by its determination with hydroxylamine hydrochloride (Bennett, *Analyst*, 1909, 34, 14) and by a positive colour test with sodium nitroprusside. The failure of ngaione and its transformation products to form well-defined solid derivatives was frequently observed by McDowall.

McDowall observed a reaction on heating ngaione under reflux with acetic anhydride and concluded from determination of the ester value that an enolic acetate of ngaione was produced in small yield. This experiment was repeated by us but with longer reaction periods. Fractional distillation of the heterogenous product gave an acetate in which the presence of the carbonyl group was indicated by a positive nitroprusside reaction and determination with hydroxylamine hydrochloride. Hydrolysis apparently gave ngaione. It appears therefore that acetolysis opens one of the oxide rings, but that hydrolysis of the acetate leads, not to an oxido-alcohol, but to the more stable dioxide ngaione.

The absorption spectrum of ngaione (see figure) was determined in hexane solution. No absorption maxima were observed within the wave-length range 217—360 mμ.

EXPERIMENTAL.

Essential Oil.—Leaves and terminal branches (1 ton) of *Myoporum laetum* Forst were steam-distilled and the distillate was collected in a receiver containing light petroleum. The aqueous distillate was extracted twice with light petroleum. The combined solutions yielded a pale reddish-brown essential oil (700 g.), which on fractional vacuum-distillation yielded approx. 80% of ngaione, b. p. 124°/0.4 mm., d_4^{15} 1.028, n_D^{15} 1.4800, $[R_L]_D$ 69.14 (Calc. for 2= : 69.43) (Found : C, 71.9; H, 8.9. Calc. for $C_{15}H_{22}O_3$: C, 71.9; H, 8.9%).

Oxidation with Potassium Permanganate.—(a) Ngaione (5.0 g.) in pyridine (90 g.) absorbed potassium permanganate in acetone (2%; 300 c.c.) in 24 hours when stirred at room temperature. The manganese dioxide was filtered off and the acetone evaporated from the filtrate. The residual solution and hot-water washings of the sludge were made slightly acid with sulphuric acid and extracted with ether. The ethereal solution, after extraction with sodium carbonate and sodium hydroxide solutions, yielded ngaione (4.7 g.). The sodium carbonate solution on acidification and extraction with ether yielded liquid acids (0.35 g.) smelling of lower fatty acids; on storage, white crystals separated which on recrystallisation from water had m. p. 90—95°, not depressed on admixture with oxalic acid. Acidification of the dilute sodium hydroxide solution yielded partly crystalline, odoriferous acids (0.1 g.) which were not further examined.

(b) (i) Ngaione (3.0 g.) was stirred in suspension in aqueous sodium carbonate solution (15%; 100 c.c.), and aqueous potassium permanganate solution (2%; 506 c.c., equiv. to 8 atoms of oxygen) added at room temperature during 2.5 hours. The manganese dioxide was filtered off and the acidified filtrate, after continuous ether extraction, yielded partly crystalline material (2.9 g.) which on recrystallisation from water proved to be oxalic acid. (ii) Oxidation of ngaione (5.0 g.) in sodium carbonate solution (10%; 100 c.c.) with aqueous potassium permanganate (2%; 422 c.c., equiv. to 4 atoms of oxygen) for 5.5 hours at 0° yielded liquid acids (2.0 g.) which distilled without decomposition as follows: up to 160°/760 mm., 0.2 g.; 145—150°/0.2 mm., 0.6 g.; 150—155°/0.2 mm., 1.3 g. The *p*-bromophenacyl esters (Judefind and Reid, *J. Amer. Chem. Soc.*, 1920, **42**, 1043) of the first fraction were prepared and when recrystallised from ethanol gave white platelets, m. p. 130°, not depressed on admixture with *p*-bromophenacyl pyruvate, m. p. 134°.

(c) Tetrahydrongaione (3.6 g.) in aqueous suspension (100 c.c.) was oxidised at 100° with aqueous potassium permanganate (2%; 1058 c.c., equiv. to 14 atoms of oxygen) for 4 hours. The filtrate and washings from the residual manganese dioxide gave insoluble calcium salts (2.7 g.) from which oxalic acid was isolated. The filtrate from the precipitated calcium salts was acidified and extracted with ether. The resulting liquid acids (0.3 g.) were treated with *p*-bromophenacyl bromide, forming an ester which on recrystallisation from aqueous ethanol gave white needles, m. p. 67—68°, not depressed on admixture with the ester, m. p. 68.5°, of isovaleric acid.

Oxidation with Potassium Ferricyanide.—Ngaione (26.6 g.) was oxidised with powdered potassium ferricyanide (1 kg.) in aqueous potassium hydroxide (10%; 1 l.) by heating the mixture under reflux with stirring for 4.5 hours. The reaction mixture was steam-distilled and the distillate (450 c.c.) extracted with ether which on evaporation yielded an oil (15.3 g.), apparently ngaione. The ethereal distillate gave a negative nitroprusside ketone reaction. The steam-distillation residue was extracted with ether to remove the remaining neutral material, diluted with water until excess of salts were in solution, acidified, and extracted with ether. The resultant acids (3.7 g.) partly crystallised when cooled in an ice-salt mixture. The crystals were filtered off, pressed free of liquid acids, and decolorised in aqueous solution with charcoal. Recrystallisation from water and sublimation gave white needles, m. p. 120—121°, not depressed on admixture with authentic 3-furoic acid (Found : C, 53.3; H, 3.3%; equiv., by titration with 0.1N-sodium hydroxide, 113. Calc. for $C_5H_4O_3$: C, 53.6; H, 3.6%; equiv., 112). 3-Furoic acid gave no colour with tetranitromethane in carbon tetrachloride. The Levine-Shaughnessy test (*Biochem. J.*, 1933, **27**, 2047) for furan and its derivatives gave an indefinite result. When 3-furoic acid was warmed on the steam-bath with isatin and concentrated sulphuric acid a brownish-red colour resulted, in contrast to the violet-blue colour developed with 2-furoic acid.

The liquid acids (1.81 g.) were distilled at atmospheric pressure as follows: (i) 100—108°, 0.04 g., sharp-smelling liquid; (ii) 110—158°, 0.27 g., liquid; (iii) 158—159°, 0.28 g., liquid; (iv) 159—182°, 0.41 g., liquid containing a few crystals; (v) 195—206°, 0.39 g., yellow, partly crystalline. Fraction (i) gave with *p*-phenylphenacyl bromide a crystalline product, m. p. 115—125°, which was not identified. In further oxidation experiments colour tests were employed to detect formic acid but none was found. Fraction (ii) gave a partly crystalline *p*-bromophenacyl ester in poor yield; recrystallisation from methanol gave white needles, m. p. 121—125°, which were not identified. Fraction (iii) gave a *p*-bromophenacyl ester which on recrystallisation from ethanol gave white needles, m. p. 74.5°, not depressed on admixture with the same ester, m. p. 75.5°, of isobutyric acid. The liquid acids were decanted from the solid material present in fraction (iv) and with *p*-bromophenacyl bromide gave oily crystals which on recrystallisation from ethanol yielded an ester, m. p. 59°, not depressed on admixture with the same ester of isovaleric acid; further crystallisation of the ethanolic mother-liquors gave white platelets, m. p. 136°, not depressed on admixture with the same ester of pyruvic acid. No identifiable *p*-bromophenacyl ester was obtained from the yellow oily acids of fraction (v); the crystalline acid present in this fraction was 3-furoic acid.

Hydrogenation of Ngaione.—Ngaione (12.0 g.) in glacial acetic acid (75 c.c.) was shaken with Adams's catalyst (0.6 g.) and hydrogen at a pressure of 4 atmospheres, 3 mols. (3540 c.c. at N.T.P.) being absorbed in 27 hours. Two additions of fresh catalyst were required during the reaction. The product was recovered in the usual way, and a portion (7.6 g.) distilled at 0.3 mm. to give the following fractions of colourless oil: (i) 86—90°, 0.6 g., sweet odour; (ii) 93—120°, 2.3 g., sweet odour; (iii) 118—122°, 2.5 g.; (iv) 122—125°, 0.4 g.; (v) 125—135°, 0.9 g. {Found, for fraction (iv) : ester val., 40; $[R_L]_D$ 83.1. Calc. for the oxido-acetate, $C_{17}H_{30}O_4$: ester val., 188; $[R_L]_D$ 81.8}. The crude reduction product (1.43 g.) was hydrolysed in a pressure-bottle with 2N-alcoholic potash at 100° for 4 hours. Three fractional distillations of the recovered neutral oil yielded the colourless *oxido-alcohol* (0.54 g.), b. p. 108—111°/0.2 mm., d_4^{20} 0.9757, n_D^{20} 1.4662, $[R_L]_D$ 71.7 (Calc. : 72.3) (Found : C, 70.6; H, 11.0. $C_{15}H_{28}O_3$ requires C, 70.3; H, 11.0%). Heating the crude reduction product (3.3 g.) with acetic anhydride (17 c.c.) and fused

sodium acetate (1.7 g.) under reflux for 2.5 hours gave a somewhat viscous oil (3.3 g.); repeated distillation then gave the *acetate* (0.67 g.) as a colourless oil, b. p. 134—136°/0.4 mm., d_4^{18} 0.9874, n_D^{19} 1.4575, $[R_L]_D$ 82.4 (Calc. : 81.8) (Found : C, 68.7; H, 10.2; CO, determined by hydroxylamine hydrochloride, 9.1. $C_{17}H_{24}O_4$ requires : C, 68.4; H, 10.1; CO, 9.4%).

Action of Acetic Anhydride on Ngaione.—(i) *With sodium acetate.* Ngaione (2.5 g.) was heated under reflux for 16 hours with acetic anhydride (15 c.c.) and fused sodium acetate (1.9 g.). Water (100 c.c.) was added and the mixture heated on the steam-bath for 30 minutes. The product was extracted with ether, and the ethereal solution washed with sodium carbonate solution (5%) and then with water until neutral. Evaporation of the dried ethereal solution yielded a brown, mobile, sweet-smelling oil (2.6 g.). Two distillations gave, as main fraction, the odourless, light-yellow *acetate*, b. p. 144—146°/0.6 mm., d_4^{20} 1.027, n_D^{20} 1.4874, $[R_L]_D$ 81.9 (Calc. for $3\bar{I}^-$: 80.5) (Found : CO, determined as above, 9.7%, ester val., 178. $C_{17}H_{24}O_4$ requires CO, 9.6%; ester val., 192). Hydrolysis of the acetate (3.5 g.) with 1.5N-ethanolic potash for 1.5 hours gave a brown, mobile oil (3.0 g.); distillation yielded ngaione (?) as an odourless, pale yellow oil (2.5 g.), b. p. 125—126°/0.8 mm., d_4^{20} 1.028, n_D^{20} 1.4797, $[R_L]_D$ 69.07 (Calc. for $2\bar{I}^-$: 69.43. Calc. for $3\bar{I}^-$: 71.0) (Found : C, 72.0; H, 8.9. Calc. for $C_{15}H_{22}O_3$: C, 71.9; H, 8.9%).

(ii) *With zinc chloride.* Ngaione (1.35 g.) was heated under reflux with acetic anhydride (3.7 c.c.) and fused zinc chloride (0.01 g.) for 2.5 hours, yielding a dark brown, soft resin (1.4 g.) (Found : ester val., 123. Calc. for $C_{17}H_{24}O_4$: ester val., 192). The resin decomposed on distillation at 0.3 mm.

(iii) *With acetic-sulphuric acid.* Ngaione (2.2 g.) was added to acetic anhydride (21 c.c.), glacial acetic acid (9 c.c.), and concentrated sulphuric acid (0.6 c.c.) at 0°, and kept at room temperature for 24 hours. Extraction of the product with chloroform yielded a dark brown, soft resin (Found : ester val., 256. Calc. for the diacetate, $C_{19}H_{28}O_6$: ester val. 318). The resin decomposed on distillation at 0.3 mm.

We are indebted to Professor Henry Gilman, Iowa State College of Agriculture, for determining the mixed m. p. of 3-furoic acid, to Dr. F. H. McDowall for samples of ngaione and its derivatives, and to the Department of Scientific and Industrial Research, New Zealand, for a grant towards collection of leaves and for laboratory facilities.

DOMINION LABORATORY, WELLINGTON, NEW ZEALAND.

[Received, July 18th, 1949.]