

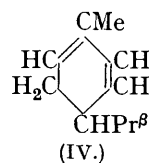
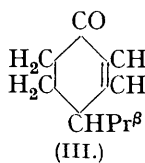
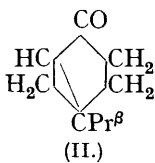
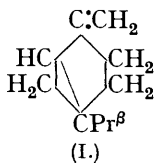
**301.** *Researches in the Thujone Series. Part III. A Contribution to the Chemistry of Sabina Ketone.*

By ANDREW G. SHORT and JOHN READ.

Additional data are given for crude sabina ketone (II), prepared by the permanganate oxidation of *d*-sabinene (I). The derived ketols and ketylamines have been investigated. Stereochemically pure *d*- $\alpha$ -sabina ketol has been isolated and

converted by oxidation into pure *l*-sabina ketone, which has been characterised. Some of the structural and stereochemical relationships of sabina ketone are discussed.

*d*-SABINOL, the subject of a recent communication (this vol., p. 1040), is accompanied in oil of savin by *d*-sabinene (I). This terpene, upon oxidation with either potassium permanganate (Wallach, *Annalen*, 1908, **359**, 266) or ozone (Schmidt, *Angew. Chem.*, 1929, **42**, 127), yields lævorotatory sabina ketone (II), a substance closely related to the thujones and containing only nine carbon atoms in its molecule.



Although it has not been found in Nature, sabina ketone may be regarded as a link between two important natural groups of substances, of which the thujones and the phellandrenes, severally, are representatives. A transition between the two groups has indeed been realised experimentally by the conversion of sabinene into  $\alpha$ -phellandrene through the intermediary of sabina ketone, in the following way.

Sabina ketone isomerises into 4-isopropyl- $\Delta^2$ -cyclohexen-1-one (III) when it is heated with aqueous or alcoholic sulphuric acid, and further treatment with methylmagnesium iodide, followed by dehydration of the ensuing  $\Delta^2$ -menthen-1-ol, yields  $\alpha$ -phellandrene (IV). The chemistry of these processes was elucidated by Wallach (*Annalen*, 1908, **359**, 267), but the stereochemical relationships remained uncertain, apart from the fact that the lævorotatory sabina ketone was evidently stereochemically analogous to the *d*-sabinene from which it was prepared.

Later, the ketone (III) was isolated in its *l*-form from the essential oil of *Eucalyptus cneorifolia* by Cahn, Penfold, and Simonsen (J., 1931, 1366), and this *l*-form was shown by Galloway, Dewar, and Read (J., 1936, 1595) to yield *l*- $\alpha$ -phellandrene (IV) when submitted to Wallach's procedure. The *l*-forms of (III) and (IV) are thus in stereochemical correspondence. The stereochemical connection between (II) and (III) is difficult to define, since it appears that (II) isomerises into (III) through the intermediate production of the symmetric 4-isopropyl- $\Delta^3$ -cyclohexen-1-one (Wallach, *loc. cit.*).

When reduced with sodium and alcohol, crude sabina ketone yielded a mixture of the two possible sabina ketols, having  $\alpha_D^{18} + 65.00^\circ$  (*l* 1). Fractional crystallisation of the derived *p*-nitrobenzoates led to the isolation of pure *d*- $\alpha$ -sabina ketol, having  $\alpha_D^{15} + 88.84^\circ$  (*l* 1). Catalytic hydrogenation of the ketone afforded a product containing more of the  $\beta$ -ketol, but this isomeride was not isolated in a pure condition. Oxidation of the pure  $\alpha$ -ketol with chromic acid yielded pure *l*-sabina ketone.

Amination of crude sabina ketone with ammonium formate furnished a ketylamine having  $\alpha_D^{18} + 43.8^\circ$  (*l* 1), which probably consisted of a mixture of the  $\alpha$ - and  $\beta$ -isomerides corresponding to the above ketols. The pure *p*-nitrobenzoate of one of these was isolated.

#### EXPERIMENTAL.

*Preparation and Properties of Sabina Ketone.*—Two successive fractional distillations under diminished pressure of oil of savin (150 g.) (this vol., p. 1041) yielded *d*-sabinene (45 g.) having b. p. 59–60°/10 mm.,  $n_D^{15}$  1.4718,  $\alpha_D^{18} + 68.48^\circ$  (*l* 1). When oxidised with alkaline potassium permanganate according to the method of Wallach (*Annalen*, 1908, **359**, 266), *d*-sabinene (25 g.) furnished sodium sabinenate (40 g.). The recovered *d*-sabinene,  $\alpha_D^{19} + 63.3^\circ$  (*l* 1), required less permanganate for oxidation than the original hydrocarbon, and gave a better yield of sodium sabinenate. In preparing this salt the filtrate and washings from the manganese sludge should be concentrated to about one-eighth of the original bulk; further concentration produces an impure product. The salt should not be washed with water, owing to its appreciable solubility; it is obtained in long, colourless needles,  $[\alpha]_D^{20} + 49.5^\circ$  (*c* 1.0, water).

Upon further oxidation with acid potassium permanganate (Wallach, *loc. cit.*), sodium sabinenate furnished crude sabina ketone as a mobile liquid with a characteristic odour, b. p.

89°/10.5 mm.,  $n_D^{26}$  1.4676,  $d_4^{21.6}$  0.9568,  $d_4^{25}$  0.9510,  $\alpha_D^{21.6}$  — 24.54° (*l* 1, homogeneous),  $[\alpha]_D^{21.6}$  — 25.64° (homogeneous),  $[\alpha]_D^{18}$  — 35.8° (*c* 2.2, alcohol) (cf. Semmler, *Ber.*, 1900, **33**, 1465; Wallach, *loc. cit.*). The ketone dissolves appreciably in water, but is less soluble in a saturated solution of potassium chloride. The yield was 65% of the calculated amount (Wallach, *loc. cit.*, obtained 45%).

Pure *l*-sabina ketone was prepared by oxidising *d*- $\alpha$ -sabina ketol (see below) with Beckmann's chromic acid mixture, the product being washed in ethereal solution several times with saturated potassium chloride solution containing a little sodium hydroxide, and finally with neutral potassium chloride solution. The ketone had b. p. 97.5°/17 mm.,  $n_D^{25}$  1.4672,  $d_4^{25}$  0.9495,  $\alpha_D^{15.6}$  — 19.80° (*l* 1, homogeneous),  $[\alpha]_D^{15}$  — 34.2° (*c* 2.0, alcohol),  $[R_L]_D$  40.38 (calc., 39.51; exaltation, + 0.87). The semicarbazone separated from dilute aqueous methyl alcohol as a white, amorphous solid, m. p. 135—137°,  $[\alpha]_D^{15}$  + 137.5° (*c* 1.0, methyl alcohol). The 2 : 4-dinitrophenylhydrazone formed small, orange needles from methyl alcohol-chloroform, m. p. 124.5°,  $[\alpha]_D^{15}$  + 135.2° (*c* 1.0, chloroform) (Found : C, 55.5; H, 5.9.  $C_{15}H_{18}O_4N_4$  requires C, 56.6; H, 5.7%). The above-mentioned crude sabina ketone gave a semicarbazone almost identical with the above (cf. Semmler, *loc. cit.*), but the 2 : 4-dinitrophenylhydrazone had a markedly lower m. p. and rotatory power than the derivative made from the pure ketone; the oxime from the crude ketone was a viscous syrup, b. p. 125—126°/9 mm.,  $n_D^{19.5}$  1.5069,  $[\alpha]_D^{18}$  + 118.5° (*c* 2.7, chloroform).

Treatment of the ketone with alcoholic sodium ethoxide did not affect its rotatory power appreciably. Treatment with hot aqueous alcoholic sulphuric acid (Wallach, *loc. cit.*) yielded 4-isopropyl- $\Delta^2$ -cyclohexen-1-one, b. p. 87—89°/10.5 mm.,  $n_D^{22}$  1.4789,  $\alpha_D^{20}$  + 0.70° (*l* 1, homogeneous). The derived semicarbazone, after seven recrystallisations from absolute alcohol, formed lustrous needles, m. p. 190°, and was then optically inactive.

*Reduction of Sabina Ketone.*—(1) When the ketone was treated with aluminium isopropoxide in dry isopropyl alcohol, according to the method of Ponndorf (*Z. angew. Chem.*, 1926, **39**, 138; cf. J., 1934, 312), little reduction occurred, although the substance was affected, as the recovered material had  $\alpha_D^{19}$  + 3.06° (*l* 1). This was ketonic, since it yielded a mixture of semicarbazones, and was probably formed through fission of the cyclopropane ring (cf. *Ber.*, 1929, **62**, 105).

(2) A solution of crude sabina ketone (48 g.) in well-dried absolute alcohol (360 c.c.) was boiled under reflux on a sand-bath and treated gradually with sodium (40.5 g.), added in coarse pieces. More dry alcohol (40 c.c.) was added towards the end of the reaction, and finally the cooled and diluted product was neutralised with hydrochloric acid. Extraction with ether yielded an oil which gave two main fractions when distilled : (1) b. p. 96—101°/15 mm.,  $n_D^{16.5}$  1.4673,  $\alpha_D^{15}$  + 65.00° (*l* 1) (23.7 g.); (2) b. p. 126—132°/0.5 mm.,  $n_D^{17}$  1.4990,  $\alpha_D^{15}$  + 50.50° (*l* 1) (7.0 g.). The second fraction decolorised bromine in chloroform, but did not react with *p*-nitrobenzoyl chloride or 2 : 4-dinitrophenylhydrazine.

The first fraction (23.7 g.) was mixed carefully in dry pyridine (118.5 c.c.) with *p*-nitrobenzoyl chloride (34.6 g.; 1.1 mols.) and kept overnight. The resulting ester, after three recrystallisations from methyl alcohol, yielded long, soft needles of *d*- $\alpha$ -sabinaketyl *p*-nitrobenzoate, m. p. 89.5°,  $[\alpha]_D^{18}$  + 94.5° (*c* 1.0, chloroform) (Found : C, 66.8; H, 6.7.  $C_{16}H_{18}O_4N$  requires C, 66.4; H, 6.6%). *d*- $\alpha$ -Sabina ketol, obtained by hydrolysing this ester with hot methyl-alcoholic potassium hydroxide, was a very viscous liquid with a pleasant, sharp odour, b. p. 100°/16 mm.,  $d_4^{28}$  0.9397,  $n_D^{25}$  1.4670,  $\alpha_D^{15}$  + 88.84° (*l* 1, homogeneous),  $[\alpha]_D^{15}$  + 90.6° (*c* 1.2, alcohol),  $[R_L]_D$  41.36 (calc., 40.85; exaltation, + 0.51). The 3 : 5-dinitrobenzoate separated from aqueous methyl alcohol in small needles, m. p. 70.5°,  $[\alpha]_D^{20}$  + 81.5° (*c* 0.6, chloroform).

(3) Catalytic hydrogenation of sabina ketone (20 g.) in cyclohexane solution under conditions favourable to the absorption of 1 mol. of hydrogen yielded a viscous liquid (16.5 g.), b. p. 90—94°/10 mm.,  $n_D^{21}$  1.4675,  $\alpha_D^{18}$  + 30.76° (*l* 1, homogeneous),  $[\alpha]_D^{18}$  + 34.0° (*c* 1.0, alcohol). The derived *p*-nitrobenzoate, after repeated fractional recrystallisation from methyl alcohol, yielded *d*- $\alpha$ -sabinaketyl *p*-nitrobenzoate, m. p. 89.5°, identical with the substance obtained with considerably less difficulty by reducing sabina ketone with sodium and alcohol (see above). The alcohol (6.3 g.) recovered by hydrolysing the residual *p*-nitrobenzoate had b. p. 81—83°/8 mm.,  $n_D^{20}$  1.4671,  $\alpha_D^{18}$  + 25.16° (*l* 1). It was not found practicable to isolate a second homogeneous substance from this mixture of alcohols.

*Amination of Sabina Ketone.*—The crude ketone (17 g.) was heated with ammonium formate (25 g.) over wire gauze in a small Claisen flask set for distillation. After about 30 minutes the temperature reached 160° and the mixture became homogeneous. When the temperature reached 190° the non-aqueous part of the distillate was returned to the flask, and the temperature was kept at 200° for 3 hours. The cold mixture was treated with water and extracted with chloro-

form. The washed and dried extract yielded a viscid syrup, which after distillation under diminished pressure had  $n_D^{19.5^\circ}$  1.4935,  $[\alpha]_D^{17^\circ}$  + 52.7° (*c* 1.9, chloroform).

The syrup (12 g.) was heated under reflux for 12 hours with a 10% alcoholic solution of hydrogen chloride (120 c.c.). Basification, followed by steam-distillation, yielded sabinaketylamine as a mobile liquid with a strong basic odour, b. p. 63—64°/19.5 mm.,  $n_D^{20^\circ}$  1.4705,  $\alpha_D^{18^\circ}$  + 43.8° (*l* 1, homogeneous). The amine rapidly absorbed atmospheric carbon dioxide to form a solid derivative crystallising in needles. A *p*-nitrobenzoylsabinaketylamine was obtained as a homogeneous substance after three recrystallisations of the crude *p*-nitrobenzoyl derivative from methyl alcohol; it formed soft, feathery needles, m. p. 141°,  $[\alpha]_D^{18^\circ}$  + 84.0° (*c* 1.0, chloroform) (Found: C, 66.6; H, 6.7.  $C_{16}H_{20}O_3N_2$  requires C, 68.0; H, 6.7%). A hydrochloride was also obtained which crystallised from alcohol-acetone in glistening plates, m. p. 225° (decomp.),  $[\alpha]_D^{18^\circ}$  + 36.1° (*c* 0.8, water).

The non-volatile residue in the above steam-distillation, when extracted with ether and distilled under diminished pressure, furnished a yellowish-green, somewhat viscid oil, b. p. 166—167°/9.5 mm.,  $n_D^{21.5^\circ}$  1.4987,  $[\alpha]_D^{19^\circ}$  + 60.6° (*c* 1.2, chloroform). It had a basic odour, and formed an ill-defined solid compound with hydrochloric acid. The analysis corresponded to *disabinaketylamine* (Found: C, 82.3; H, 11.5; N, 6.1.  $C_{18}H_{31}N$  requires C, 82.8; H, 11.9; N, 5.4%) (cf. J., 1938, 2021).

We thank the Carnegie Trust for the Universities of Scotland for the award of a Research Scholarship to one of us (A. G. S.) and Imperial Chemical Industries, Ltd., for a grant.

THE UNIVERSITY, ST. ANDREWS.

[Received, July 21st, 1939.]