

The Chemistry of Terpenes. Part 25.¹ A Synthesis of Car-2-, Car-3-, and Car-3(10)-ene (β -Carene)

By Wesley Cocker,* Niall W. A. Geraghty, and David H. Grayson, Trinity College, Dublin 2, Ireland

Reaction of dibromocarbene with 4,4-dimethoxycyclohexene (7) affords 3,3-dimethoxy-7,7-dibromobicyclo[4.1.0]heptane (8), which with lithium dimethylcuprate(II) and methyl iodide, and treatment of the product with acid, yields 7,7-dimethylbicyclo[4.1.0]heptan-3-one, \pm (2). In the absence of methyl iodide, 7-*exo*-methylbicyclo[4.1.0]heptan-3-one, \pm (12), is the major product. Treatment of the ketone (2) with methylenetriphenylphosphorane gives car-3(10)-ene (β -carene) (11) and reaction of the ketone \pm (2) with methylmagnesium iodide affords the epimeric caran-3-ols (13) and (14). On dehydration these yield a mixture of carenes.

In Part 8² we described some products of oxidation of (+)-car-3-ene (1). One product formed in very small yield was considered to be (+)-7,7-dimethylbicyclo[4.1.0]heptan-3-one (norcaran-3-one) (2). A recent comparison of its n.m.r. spectrum with that³ of (+)-nopinone (3) revealed a close similarity. The oxidation product was shown to be (+)-nopinone by comparison of its spectra with those of an authentic specimen prepared from (–)- β -pinene (4). The glycol (5), obtained by permanganate oxidation of β -pinene, was smoothly oxidised with sodium bismuthate⁴ to (+)-nopinone (3). It thus seems probable that in our earlier work² this (3) was derived from a trace of (–)- β -pinene present in the (+)-car-3-ene.

We have now synthesised norcaran-3-one \pm (2) and from it β -carene (11) and car-2- and car-3-ene [(6) and \pm (1), respectively].

Birch reduction⁵ of anisole and acetalisation of the product gave 4,4-dimethoxycyclohexene (7), which reacted⁶ with dibromocarbene to give 3,3-dimethoxy-7,7-dibromobicyclo[4.1.0]heptane (8) as a low melting solid. Thermal instability precluded satisfactory elemental analysis, but its structure can be unambiguously inferred from spectral data. I.r. spectroscopy showed four bands between 1 137 and 1 065 cm^{-1} , characteristic of acetals, n.m.r. showed signals at τ 9.0–7.3 (8 H) and 6.84 and 6.81 (2MeO), and its mass spectrum had fragments at m/e 285/283/281 ($M^+ - \text{MeO}$), and 235/233 ($M^+ - \text{Br}$). This acetal (8) was treated with lithium dimethylcuprate(II) using a modification of Corey's method.⁷ In this modification the mixture of dibromocompound and cuprate is stirred for 4 days and then methyl iodide is added.⁸ The dimethylated acetal (9) is thus formed in enhanced yield and with virtual exclusion of the monomethylated compound (10). The

former was converted with toluene-*p*-sulphonic acid into norcaran-3-one \pm (2) whose u.v. and i.r. spectra showed maxima at 290 nm ($\log \epsilon$ 1.63) and 1 707 cm^{-1} , respectively. Its n.m.r. spectrum showed $\tau(\text{CCl}_4)$ 9.07 and 8.94 (Me_2C), 9.1 and 8.9 (cyclopropyl H), and 8.0–7.5 (CH_2), and its mass spectrum a strong signal at m/e 138 (M^+). Fragments at m/e 81 and 67 are characteristic of a number of terpene ketones including *cis*- and *trans*-caran-4-one.⁹ Norcaran-3-one \pm (2) gave a good yield of β -carene (11) by the Wittig reaction.¹⁰ β -Carene showed i.r. maxima at 1 645 and 893 cm^{-1} ($>\text{C}=\text{CH}_2$) and n.m.r. signals at τ 9.5–9.2 (cyclopropyl H), 9.08 and 9.03 (Me_2C), 9.0–7.5 (CH_2), and 5.38 ($\text{C}=\text{CH}_2$).

Reaction of the dibromo compound (8) with cuprate in the absence of methyl iodide followed by removal of the protecting group gave 7-*exo*-methylbicyclo[4.1.0]heptan-3-one \pm (12) as the major product (68%; g.l.c.) and norcaranone \pm (2) (32%). Assignment of configuration of the 7-methyl group of \pm (12) is based on precedent⁷ and on its n.m.r. signal at τ 8.91 which is similar to that of the 7-*exo*-methyl group of \pm (2). In both cases this group is deshielded by the 3-oxo-group.

Reaction of norcaran-3-one \pm (2) with methylmagnesium iodide gave (\pm)-*cis*- and (\pm)-*trans*-caran-3-ol* [(13) and (14), respectively] in the ratio 1:3. This is to be expected since the side opposite the cyclopropane group is the more exposed to attack by Grignard reagent. The alcohols were identified by comparison (g.l.c. and n.m.r.) with specimens of the known^{11,12} (+)-*cis* and (+)-*trans*-caran-3-ol. These alcohols have been dehydrated giving a mixture of carenes.¹¹ In a similar dehydration we obtained (g.l.c.) car-2-ene (24%), car-3-ene (61%), and β -carene (16%).

Removal of the acetal group from (8) gave 7,7-dibromonorcaran-3-one \pm (15).

In another approach to a synthesis of β -carene (11), cyclohex-3-enone (16)¹³ was treated with 2-mercapto-

* These alcohols are related to *cis*- and *trans*-carane respectively.

¹ Part 24, W. Cocker, K. J. Crowley, and K. Srinivasan, *J.C.S. Perkin II*, 1978, 159.

² W. D. P. Burns, M. S. Carson, W. Cocker, and P. V. R. Shannon, *J. Chem. Soc. (C)*, 1968, 3073.

³ G. W. Shaffer, A. B. Doerr, and K. L. Purzycki, *J. Org. Chem.*, 1972, **37**, 25.

⁴ W. Rigby, *J. Chem. Soc.*, 1950, 1907.

⁵ R. D. Stipanovic and R. B. Turner, *J. Org. Chem.*, 1968, **33**, 3261.

⁶ L. Skattebøl, *Acta Chem. Scand.*, 1963, **17**, 1683.

⁷ E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, 1967, **89**, 3911; cf. K. Kitatani, H. Yamamoto, T. Hiyama, and N. Nozaki, *Bull. Chem. Soc. Japan*, 1977, **50**, 2158.

⁸ G. H. Posner, personal communication.

⁹ E. Stenhagen, S. Abrahamsson, and F. W. McLafferty, 'Registry of Mass Spectral Data,' Wiley, New York, 1974, vol. 1, pp. 402–403.

¹⁰ R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, 1963, **28**, 1128.

¹¹ P. J. Kropp, *J. Amer. Chem. Soc.*, 1966, **88**, 4926.

¹² H. Kuczynski and K. Piatkowski, *Roczniki Chem.*, 1957, **31**, 59 (*Chem. Abs.*, 1957, **51**, 15,460h); H. Kuczynski and Z. Chabudzinski, *ibid.*, 1960, **34**, 177 (*Chem. Abs.*, 1960, **54**, 19,748g).

¹³ D. S. Noyce and M. Evett, *J. Org. Chem.*, 1972, **37**, 394.

ethanol¹⁴ in the expectation that the resultant $\beta\gamma$ -unsaturated monothioacetal (17) would undergo the reactions of the acetal (7), and that the protecting group could be removed with Raney nickel.¹⁵ Two products were obtained, the desired monothioacetal (17) and the

addition of 2-mercaptoethanol to cyclohex-2-enone formed from cyclohex-3-enone. Since the yields of the desired monothioacetal (17) were low this approach to β -carene was not pursued further.

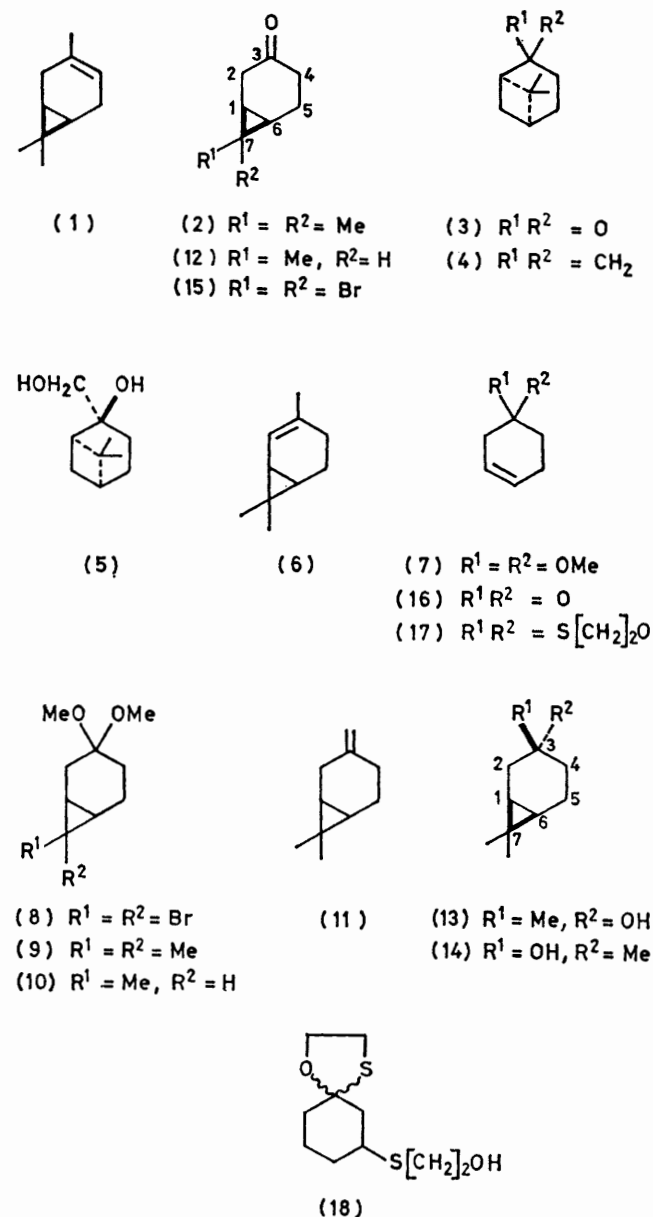
With the exception of peaks of diagnostic value, i.r. and mass spectra are given in Supplementary Publication No. 22311 (12 pp.),* which also includes some n.m.r. data.

EXPERIMENTAL

4,4-Dimethoxycyclohexene (7).—Anisole (100 g) in dry ether (100 ml), liquid ammonia (550 ml), and ethanol (200 ml) was reduced with lithium according to the published procedure.⁵ The crude product was set aside overnight with methanol (1 250 ml) containing toluene-*p*-sulphonic acid (60 mg) and the mixture was then refluxed for 1.5 h. Sodium carbonate (0.5 g) was added with stirring, methanol was removed under reduced pressure, and the residue was distilled giving the acetal (7) (77 g), b.p. 60° at 15 mmHg, ν_{\max} (liquid film) 1 656 (C=C), 1 113, and 1 050 cm^{-1} (ether), $\tau(\text{CCl}_4)$ 8.7—7.7 (6 H, m, 3 CH_2), 6.76 (6 H, s, 2 MeO), and 4.50 (2 H, m, olefinic H).

3,3-Dimethoxy-7,7-dibromobicyclo[4.1.0]heptane (8) (see ref. 6).—Bromoform (50.2 g) was added over 4 h to a stirred mixture of the acetal (7) (22 g), potassium *t*-butoxide [from potassium (7 g)], and pentane (88 ml) kept below -30 °C under nitrogen. The mixture was stirred at this temperature for 3 h and then overnight at room temperature. Water was added and the product was extracted with ether. Evaporation gave a red oil which was eluted from silica (800 g) with hexane-ether (7 : 3) to afford a pale yellow oil (30.2 g, 48%) which solidified at -15 °C. The acetal (8) crystallised from ice-cold pentane as rhombs, m.p. 37—39°, ν_{\max} (Nujol) 1 137, 1 118, 1 092, 1 065 (acetal), 827, 761, and 721 cm^{-1} , $\tau(\text{CCl}_4)$ 9.0—7.3 (8 H, m, 3 CH_2 and cyclopropyl H), 6.84 (3 H, s, MeO), and 6.81 (3 H, s, MeO), *m/e* 285/283/281 ($M^+ - \text{MeO}$) and 235/233 ($M^+ - \text{Br}$).

7,7-Dimethylbicyclo[4.1.0]heptan-3-one (Norcaran-3-one) $\pm(2)$.—Methyl-lithium in ether (1M; 100 ml) was added dropwise over 5 min to a stirred mixture of copper(I) iodide (9.53 g) in ether (67 ml) kept at -10 °C under nitrogen. Stirring was continued for 10 min to give a clear, pale yellow solution. The bromo-compound (8) (1.57 g) in ether (5 ml) was added from a syringe through a septum and the mixture was kept at -15 °C for 4 days. Methyl iodide (1 ml) was then added and the mixture was kept at 15 °C for 12 h and at room temperature for a further 6h. Four such experiments were performed simultaneously and the combined products were poured into a saturated solution of ammonium chloride. Insoluble copper salts were collected and washed with ether, and the mother liquor was extracted several times with ether. The combined extracts gave a deep yellow oil which was added to acetone (300 ml) and toluene-*p*-sulphonic acid (1.1 g). After 12 h, 5% sodium hydrogen carbonate solution was added and the product was extracted with ether; the extract was dried, and the solvent removed. The residue was eluted from silica (80 g) with hexane-ether (9 : 1) giving the ketone $\pm(2)$ as an oil (1.07 g) (Found: C, 78.05; H, 10.2. $\text{C}_9\text{H}_{14}\text{O}$ requires C, 78.2; H, 10.2%); *semi-carbazone*, m.p. 186—187° (EtOH- H_2O) (Found: C, 61.9; H, 8.7; N, 21.5. $\text{C}_{10}\text{H}_{17}\text{N}_3\text{O}$ requires C, 61.5; H, 8.8; N, 21.5%).



monothioacetal of 3-(2-hydroxyethylthio)cyclohexanone (18). The latter shows strong broad i.r. bands at 3 400 (OH) and 1 060 cm^{-1} (C-O), but lacks a band in the 2 560 cm^{-1} (SH) region of its Raman spectrum. Its n.m.r. spectrum (see Experimental section) is consistent with an equimolar mixture of stereoisomers. It is presumably formed by an acid-catalysed Michael-type

* See Notice to Authors No. 7 in *J.C.S. Perkin I*, 1977, Index issue.

¹⁴ G. E. Wilson, M. G. Huang, and W. Schloman, *J. Org. Chem.*, 1968, **33**, 2133.

¹⁵ J. Romo, G. Rosenkranz, and C. Djerassi, *J. Amer. Chem. Soc.*, 1951, **73**, 4961.

Car-3(10)-ene (β -*Carene*) (11).—Anhydrous pentane was added through a septum to a suspension of sodium hydride (55%) (0.31 g) in paraffin oil in a closed flask containing nitrogen and the solvent was withdrawn by a syringe. After four such operations, dimethyl sulphoxide (3.5 ml) was added by syringe and liberated hydrogen was similarly removed. The flask was kept at 75 °C for 0.75 h, cooled to 15 °C, and methyltriphenylphosphonium bromide (2.24 g) in dimethyl sulphoxide (6.2 ml) was slowly added. The red product was stirred for 10 min, norcaran-3-one (0.56 g) in dimethyl sulphoxide (2.5 ml) was added, and the mixture was stirred at 51–54 °C for 24 h. Water was added and the product extracted with pentane. After removal of solvent, the residue was eluted from silica (40 g) with pentane giving β -carene (11) (0.3 g), b.p. 60° at 15 mmHg, λ_{max} (hexane) 222 nm ($\log \epsilon$ 2.0), ν_{max} (liquid film) 1 645 and 893 cm^{-1} (>C=CH_2), $\tau(\text{CCl}_4)$ 9.5–9.2 (2 H, m, cyclopropyl H), 9.08 and 9.03 (6 H, 2s, Me_2C), 9.0–7.5 (6 H, m, CH_2), and 5.38 (2 H, m, C=CH_2), m/e 136 (M^+ ; 10%) and 67 (100) (Found: C, 87.9; H, 12.1. Calc. for $\text{C}_{10}\text{H}_{16}$: C, 88.2; H, 11.8%).

7-exo-Methylbicyclo[4.1.0]heptan-3-one \pm (12).—When the bromo-compound (8) was methylated without addition of methyl iodide, two products were formed (*cf.* ref. 7) in the ratio (g.l.c.) 68 : 32. Preparative g.l.c. (Carbowax) gave (g.l.c., i.r., and n.m.r.) norcaran-3-one \pm (2) as the minor product. The major product was the ketone \pm (12), ν_{max} (liquid film) 1 703 cm^{-1} , $\tau(\text{CCl}_4)$ 9.5–9.0 (3 H, m, cyclopropyl H), 8.91 (3 H, d, MeCH), 8.0–7.75 (4 H, m, CH_2), and 7.55–7.35 (2 H, m, CH_2) (Found: C, 77.2; H, 9.8. $\text{C}_8\text{H}_{12}\text{O}$ requires C, 77.4; H, 9.7%).

(\pm)-cis-Caran-3-ol (13) and (\pm)-trans-Caran-3-ol (14).—Norcaran-3-one \pm (2) (0.14 g) in ether (2 ml) was slowly added to a stirred solution of methylmagnesium iodide [from magnesium (0.17 g) and methyl iodide (0.9 g) in ether (4 ml)], and the mixture was refluxed for 5 h. Usual work-up gave an oil (0.15 g) containing (g.l.c.) cis-caran-3-ol (13) (25%) and trans-caran-3-ol (14) (75%), ν_{max} (liquid film) 3 340 cm^{-1} , $\tau(\text{CCl}_4)$ 9.7–9.2 (2 H, m, cyclopropyl H), 9.08 [s, 7-Me(13)], 9.02 [s, Me_2C (14)], 8.98 [s, 7-Me(13)], 8.84 [s, 3-Me(13)], 8.77 [s, 3-Me(14)], 8.7–8.59 [2 H, 5- CH_2 (13, 14)], 8.47 [s, OH(14)], and 8.3–7.7 [hidden singlet, OH(13), CH_2 (13, 14)] identical (g.l.c.) with specimens prepared by published methods.

7,7-Dibromobicyclo[4.1.0]heptan-3-one (7,7-Dibromonorcaran-3-one) \pm (15).—The product from the addition of dibromocarbene to the acetal (7) (7.13 g) (see above) was added to acetone (500 ml) containing toluene-*p*-sulphonic acid (2.05 g) and the mixture was kept overnight. Work-up as for (2) gave an oil (8.3 g), which decomposed when distillation in bulk was attempted. A small quantity previously eluted from silica with hexane-ether (7 : 3)

distilled at 89° and 1 mmHg; ν_{max} (liquid film) 1 712 cm^{-1} , τ 8.5–7.0 (8 H, m), δ_{C} 208.87 (C=O) (p.p.m. from Me_4Si).

(+)-Nopinone (3).—The diol (5)¹⁶ (1.7 g) obtained from (–)- β -pinene [$[\alpha]_{\text{D}}^{22} - 19^\circ$ (*c* 0.2 in EtOH)] was stirred at 50 °C with sodium bismuthate⁴ (3.1 g) in glacial acetic acid (30 ml) for 6 h. Usual work-up gave (+)-nopinone (0.9 g), b.p. 88–90° at 15 mmHg, $[\alpha]_{\text{D}}^{22} + 22^\circ$ (*c* 0.2 in EtOH), λ_{max} (MeOH) 277 nm ($\log \epsilon$ 1.46), $\tau(\text{CDCl}_3)$ 9.14 and 8.65 (6 H, 2 s, Me_2C), and 8.55–7.26 (8 H, m) (*cf.* ref. 3).

1-Oxa-4-thiaspiro[4.5]dec-7-ene (17) and 7-(2-Hydroxyethylthio)-1-oxa-4-thiaspiro[4.5]decane (18).—Freshly distilled boron trifluoride-ether complex (3.5 ml) was added in portions over 3 h to a refluxing mixture of cyclohex-3-enone (2.6 g),¹³ 2-mercaptoethanol (2 ml), and ether (27 ml). The mixture was refluxed for a further 1 h and then poured into water. The ether layer was separated and the aqueous layer extracted twice with ether. The combined extracts were washed with sodium hydrogen carbonate (5%; 2 \times 100 ml) and saturated sodium chloride solution (100 ml) and then evaporated to give an oil, which on distillation afforded the monothioacetal (17) (2.03 g), b.p. 92–92.5° at 15 mmHg. Preparative g.l.c. (Carbowax; 125 °C) gave a pure specimen, ν_{max} (liquid film) 1 645 and 750 cm^{-1} (CH=CH), $\tau(\text{CCl}_4)$ 8.25–7.85 (m, CH_2), 7.85–7.6 (m, CH_2), 7.49 (m, CH_2), 6.91 (2 H, t, J 6 Hz, CH_2S), 5.8 (2 H, t, J 6 Hz, CH_2O), and 4.6–4.0 (2 H, m, HC=CH) (Found: C, 61.5; H, 8.0; S, 20.3. $\text{C}_8\text{H}_{12}\text{OS}$ requires C, 61.5; H, 7.75; S, 20.5%).

The residue from the distillation of (17) was a viscous oil (0.48 g). This was eluted from silica (60 g) with ethyl acetate-hexane (60 : 40) giving 7-(2-hydroxyethylthio)-1-oxa-4-thiaspiro[4.5]decane (18) as a viscous oil, b.p. 142° at 0.08 mmHg; ν_{max} (liquid film) 3 400 (OH) and 1 060 (C-O), $\tau(\text{CCl}_4)$ 9.0–7.4 (9 H, m, cyclohexane H), 7.57 (exchangeable, OH), 7.24 (1 H, t, J 6 Hz, chain CH_2S), 6.96 (1 H, t, J 6 Hz, ring CH_2S), 6.94 (1 H, t, J 6 Hz, ring CH_2S), 6.19 (2 H, t, J 6 Hz, CH_2OH , displaced to 6.28 with D_2O), 5.88 (1 H, t, J 6 Hz, ring CH_2O), and 5.81 (1 H, t, J 6 Hz, ring CH_2O) (Found: C, 51.2; H, 7.6; S, 27.3. $\text{C}_{10}\text{H}_{16}\text{O}_2\text{S}_2$ requires C, 51.3; H, 7.75; S, 27.3%).

(\pm)-7-endo-Bromo-7-exo-methylbicyclo[4.1.0]heptan-3-one (2; $\text{R}^1 = \text{Br}$, $\text{R}^2 = \text{Me}$) is obtained as major product with \pm (2) when (8) is treated with lithium dimethylcuprate(II) in pentane and the product treated with toluene-*p*-sulphonic acid. Its configuration is deduced from the similarity of its lanthanide shifts with those of (12). The ketone has ν_{max} (liquid film) 1 709 cm^{-1} , τ 8.14 (3 H, s, 7-Me) and 8.8 (2 H, m, cyclopropyl H) (Found: C, 47.4; H, 5.6; Br, 39.4. $\text{C}_8\text{H}_{11}\text{BrO}$ requires C, 47.3; H, 5.5; Br, 39.55%).

We thank the Department of Education of the Republic of Ireland for a Post-Doctoral Fellowship (to D. H. G.) and a Maintenance Award (to N. W. A. G.).

¹⁶ G. Wagner, *Ber.*, 1894, 27, 2274.