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SOME REACTIONS OF dl-CAMPHORIC ACID DERIVATIVES

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Amide-ester from the racemic *allo-* and *ortho-*Camphoric acid esters have now been prepared and shown to be identical with the esters prepared from α and β-camphoramic acids respectively. NMR data have been given for some reaction products of camphoric acid esters and some new products have been described.

In an earlier communication[1] some reactions of *dl. ortho-* and *allo-*camphoric acid esters were discussed, and they were shown to be *cis-* and *trans-*methyl hydrogen camphorate respectively. The NMR spectra of the *ortho-*ester taken in $CDCl_3$ solution (with TMS internal standard) gave main peak positions of the (C)-CH_3 methyls at 9.12 (3H) and 8.71 (6H)τ in addition to ester methyl peak at 6.30τ (3H). Under identical conditions *allo-*ester showed its (C)-CH_3 peaks at 9.14(3H), 8.78(3H) and 8.70 (3H)τ in addition to ester methyl at 6.30τ(3H). The additional peak at 8.78τ in case of *allo-*ester cannot be readily explained on the basis of the two esters being position isomerides, whereas, stereoisomerism as suggested earlier can explain the additional peak on the basis of environmental influence of the two carbonyl functions on the *gem-*dimethyl group on the cyclopentane ring of the camphoric acid esters. However, on esterification with diazomethane both *ortho-* and *allo-*esters give identical peak positions in their NMR spectra at 9.27 (3H), 8.81 and 8.80 (6H)τ in addition to one peak at 6.36 (6H)τ. On lithium aluminium hydride reductions *ortho-* and *allo-*esters gave dialcohols, m.p. 136°C and 134°C respectively. They did not depress each others melting point, but in the IR spectrum taken in KBr pellet a small difference in peak positions at 1021 cm^{-1} (*ortho*) and 1028 cm^{-1} (*allo*) was noted.

It was felt that the amides of the acid esters prepared under mild conditions may give conclusive evidence of stereoisomerism.

The *ortho-*esteramide, m.p. 134-36° and *allo-*esteramide, m.p. 120°, were prepared from the acid-esters through their acid chlorides under mild

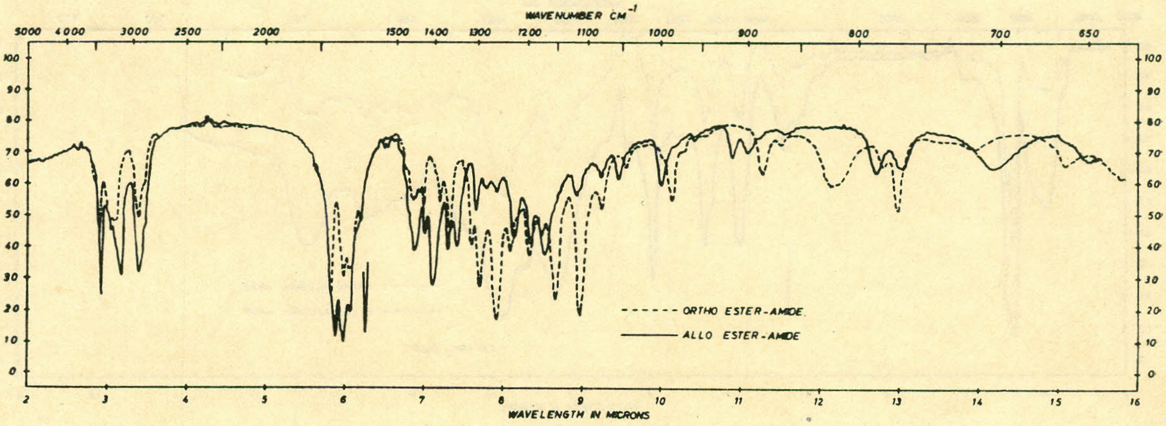


Fig. 1.—IR spectra of *ortho-* and *allo-*esteramides.

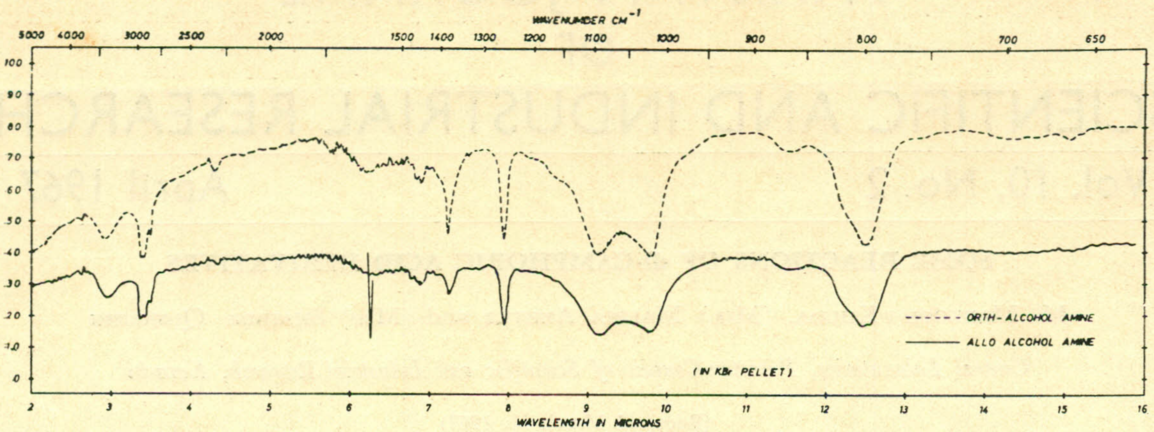


Fig. 2.—Liquid film IR spectra of amino-alcohols.

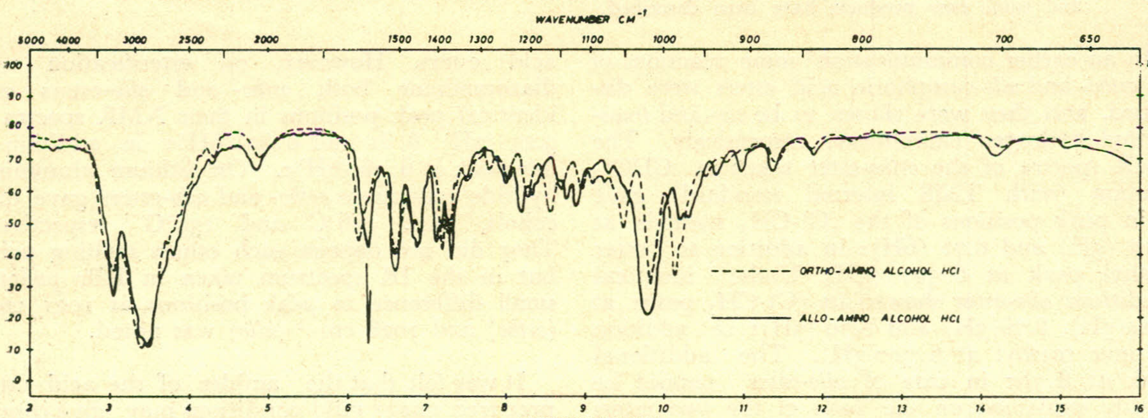


Fig. 3.—Chloroform solution IR spectra of amino-alcohols.

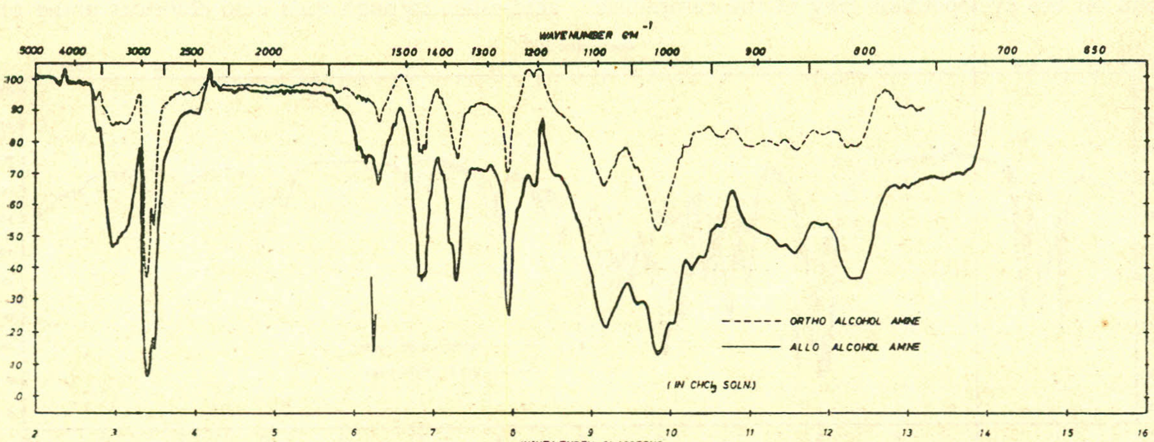


Fig. 4.—KBr peilet IR spectra of amino-alcohol hydrochlorides.

conditions. *dl*-Camphorimide, m.p. 250° C, was also obtained during the reaction. α- and β-camphoramidic acids described in the literature [2] was prepared and the methyl esters were shown to be identical with *allo*- and *ortho*-esteramides, m.p. 120° and 134-36° respectively. The *ortho*- and *allo*-esteramides gave different IR spectra in KBr pellet, and in the NMR spectra showed the (C)-CH_3 peaks at 9.14 (3H), 8.79 (3H) and 8.71 (3H)τ in $CDCl_3$ solution (TMS internal standard) in addition to an ester methyl peak at 6.29 (3H)τ. On lithium aluminium hydride reduction the amino-alcohols obtained from the ester-amides, gave superimposable IR spectra both in their KBr pellet and chloroform solution spectra; however, the crystalline hydrochlorides, m.p. 250°C and m.p. 256°C, from the *ortho*- and *allo*-amino-alcohols respectively, showed some difference in their IR spectra taken in KBr pellets, but did not depress each others melting point.

Experimental

Unless otherwise stated IR spectra were taken in KBr pellet with a Beckmann IR-5 spectrophotometer, NMR spectra are for $CDCl_3$ solution recorded on Varian A-60 spectrophotometer. All m.ps. are uncorrected and all the compounds described below belong to the racemic (*dl*) camphoric acid series. Analyses were done by Drs. Pascher & Pascher, West Germany, and the Microanalytical Section of this Laboratory.

ortho-*Camphoryl Diol*.—An etherial (50 ml) solution of *ortho*-camphoric acid methyl ester (5 g), prepared from *dl*–camphoric acid was added slowly to a refluxing ethereal (200 ml) slurry of powdered lithium aluminium hydride (4 g). After refluxing for 3 hours the reaction mixture was cooled in ice and decomposed carefully with ice–water and 5% sulphuric acid. The ethereal layer was dried (Na_2SO_4) and the solvent evaporated off. The residue was crystallised from ether–petroleum ether (40–60°) to give ortho-*camphoryl diol*, m.p. 136°C (3 g.) (Found: C, 69.78, 69.73; H, 11.39, 11.73; O, 18.71; Active H^+, 1.183%. $C_{10}H_{20}O_2$ requires C, 69.72; H, 11.70; O, 18.58; Active H^+(two), 1.163%).

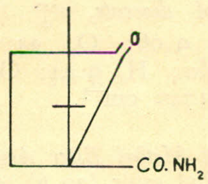
allo-*Camphoryl diol*.—*allo*-Camphoric acid methyl ester (5 g) was reduced in ether solution with lithium aluminium hydride as described above. The reaction product was crystallised from ether–petroleum ether (40–60°), to give allo-*camphoryl diol*, m.p. 134°C (4 g) (Found: C, 69.13; H, 11.53; O, 19.46; Active H^+, 0.977%. $C_{10}H_{20}O_2$ requires C, 69.72; H, 11.70; O, 18.58; Active H^+ (two), 1.163%). The diol (0.5 g) on acetylation with acetic anhydride (1 ml) and acetyl chloride (5 drops) at room temperature overnight gave after working up (extracting aqueous $NaHCO_3$ neutralised mass with ether, and washing the ether layer with dilute caustic soda solution) an oil which was distilled in a Hickmann still to give *camphoryl diol diaceate*, $n_D^{26°}$ 1.4590 (Found: C, 66.09; H, 9.06; O, 24.56%. $C_{14}H_{24}O_4$ requires C, 65.60; H, 9.44; O, 24.96%). It had ν_{max} 1245, 1740 cm^{-1}.

ortho-*Camphoric Methyl Ester Amide*.—*ortho*-Camphoric acid methyl ester (20 g) was treated with an excess of thinoyl chloride (freshly distilled; 7.4 ml). After 1 hour at room temperature the excess of thionyl chloride was slowly removed *in vacuo* at room temperature (until bubbling just ceased; vigorous removal decomposes the ester chloride to camphoric anhydride). The ester acid chloride was slowly added to an excess of cold liquor ammonia (400 ml) with stirring. The precipitated solid was filtered, washed with water and crystallised from dilute ethanol to give ortho-*camphoric methyl ester amide* (5 g), m.p. 134-6°C (Found: C, 51.86; H, 8.85; O, 22.79%. $C_{11}H_{19}O_3N$ requires C, 61.94; H, 8.98; O, 22.51 %). It had ν_{max} 1620, 1640, 1670, 1720, 3200 and 3450 cm^{-1}.

The aqueous ammonia solution on acidification and extraction with ether was separated into two parts by shaking with soldium bicarbonate solution. The acidic material from the bicarbonate layer was collected in ether after acidification. The acidic fraction, separated through dissolution in bicarbonate solution and on fractional crystallisation from dilute methanol gave unchanged *ortho*-camphoric acid methyl ester, m.p. and mixed m.p. with authentic sample 83°C (5.76 g). From the second crop a small quantity of camphoric anhydride, m.p. 220–21°C, was obtained.

The portion remaining in ether after shaking with $NaHCO_3$ on repeated fractional crystallisation from ether-petroleum ether gave a small amount of crystals, m.p. 245° (0.285 g), from the less soluble fractions, which was identified as camphorimide by m.p. and mixed m.p. with camphorimide described in the later experiment.

The rest of the neutral mass (3.38 g) was sublimed at atmoshpheric pressure at 240°C. It was resublimed at 3.5 mm and the sublimate deposited upto 150°C was collected separately. This had a comphoraceous odour and had m.p. 172°C (0.353 g). It anaylsed for 1,1,5-*trimethyl*-2,5-*bicyclobutane*-6-*one*-2-*carbamide* (V). (Found: C, 66.11, 65.93; H, 8.13, 7.90; O, 17.2; N-CH_3, 0.00; Active H^+, 0.789%. $C_{10}H_{15}O_2N$ requires C, 66.27; H, 8.35; O, 17.66; N-CH_3, 0.00; Active H^+ (two), 1.111%). The higher temperature sublimate at 165°/3.5 mm was camphoric anhydride, m.p. 222°C (2.862 g). The bicycloketo-amide had ν_{max} 1680, 1760, 3100, 3200 cm^{-1}.

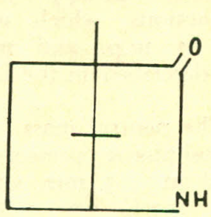


1,1,5-Trimethyl- 2, 5-*bicyclo*- butane-6-one-2-carbamide (V)

allo-*Camphoric Methyl Ester Amide.*—*allo*-Camphoric acid methyl ester (20 g) was converted into its acid chloride as described above and the ester acid chloride added on to liquor ammonia solution. On working up as described above it gave after two crystallisations from dilute ethanol, allo-*camphoric methyl ester amide*, m.p. 120°C (4.5 g) (Found: C, 61.86; H, 8.85; N, 6.14, 6.60; O, 23.31%. $C_{11}H_{19}O_3N$ requires C, 61.94; H, 8.98; N, 6.57 ; O, 22.51%). It had ν_{max} 1675, 1700, 1720i, 3190, 3450 cm^{-1}.

The acidic fraction on repeated cyrstallisation from dilute methanol gave *camphorimide*, m.p. 250°C (5.3 g) (Found: C, 66.30, 66.31; H, 8.79; 8.86; N, 7.70,7.80, 7.75, 7.54%. $C_{10}H_{15}O_2N$ equires C, 66.27; H, 8.35; N, 7.73%). It had ν_{max} 1695, 1775, 3100, 3200 cm^{-1}.

The *allo*-camphoric ester amide (5 g) underwent a Hoffmann rearrangement in alkaline hypobromite solution (1.41 ml Br_2 in 47 ml water and 5.6 g NaOH), at room temperature for 20 min followed by warming on water bath, cooled, and extracted with ether to give 3.49 g of a compound which on repeated crystallisation from petroleum ether (40–80°) gave a *cycloamide* VI, m.p. 209–10 °C. (Found: C, 70.20; H, 10.23; N, 9.42; O, 11.54%. $C_9H_{15}NO$ requires C, 70.55; H, 9.87; N, 9.14; O, 10.44%). It had ν_{max} 1700, 3275 cm^{-1}.



Cyclo amide (IV)

α-*Camphoramidic Acid.*—Finely powdered camphoric anhydride (2 g) was added to 35% liquor ammonia solution (50 ml) and slightly warmed to give a clear solution. After filtration the filtrate is acidified with hydrochloric acid and the crystalline solid collected by filtration and crystalised from hot water to give α-camphoramidic acid, m.p. 192°C (Found: C, 60.37; H, 8.77; N, 6.78; O, 24.44%. Calc. for $C_{10}H_{17}O_3N$, C, 60.28; H, 8.60; N, 7.03; O, 24.09%). It had ν_{max} 1610, 1660, 1700, 3150 and 3400 cm^{-1}.

On esterification with diazomethane in ether it gave crystals of α-*camphoramidic methyl ester*, m.p. 120°. (Found: C, 62.38; H, 8.68; N, 6.59; O, 22.80%. $C_{11}H_{19}O_3N$ requires C, 61.94; H, 8.98; N, 6.57; O, 22.51%). It had identical IR spectra with *allo*-camphoric ester amide, m.p. 120°C, and the mixed m.p. with the latter was undepressed.

β-*Camphoramidic Acid.*—Camphorimide (1 g) was dissolved in 5% caustic soda solution (50 ml) and the mixture refluxed for 1 hr. It was cooled, acidified, taken up in ether, and the ethereal layer shaken with sodium carbonate solution. The alkaline solution was acidified and extracted with ether. The residue obtained after removal of ether from the Na_2SO_4-dried extract was crystallised twice from dilute alcohol to give β-camphorimidic acid, m.p. 175.°(C, 60.29; H, 8.61; N, 7.09; O, 24.39%. Calc. for $C_{10}H_{17}O_3N$ C, 60.28; H, 8.60; N, 7.03; O, 24.09%). It had ν_{max} 1650, 1700, 3200, 3320 and 3410 cm^{-1}.

On esterification with diazomethane in ether it gave crystals of β-*camphoramidic methyl ester*, m.p. 135–36°C. (Found: N, 6.75; O, 23.30%. $C_{11}H_{19}O_3N$ requires N, 6.57; O, 22.51%). It had identical IR spectrum with *ortho*-camphoric ester amide, m.p. 134–36°C, and the mixed m.p. with the latter was undepressed.

ortho-*Camphoramine Alcohol.*—*ortho*-Camphoric ester amide (2.5 g) was dissolved in dry THF (25 ml) and added dropwise to a refluxing slurry of lithium aluminium hydride (3.7 g) in dry ether (250 ml). After 3-hr refluxing, the reaction mixture was cooled in ice bath and decomposed with water and 10% caustic soda. The ethereal layer was dried (Na_2SO_4) and the solvent removed to give colourless free amine-alcohol (1.54 g) which was converted to its hydro-chloride and crystallised from methanol-ether to give ortho-*camphoramine alcohol hydrochloride*, m.p. 250°C. (Found: N, 6.48; 7.28; O, 8.35; Cl, 16.56, 17.59%. $C_{10}H_{22}NOCl$ requires N, 6.74; O, 7.70; Cl, 17.06%).

The *ortho*-camphoramine alcohol (0.5 g) was reacted overnight with acetic anhydride (1 ml) containing few drops of acetyl chloride and the excess solvents evaporated off *in vacuo*. On distillation at 180-190°C/2-0 mm viscuous distillate was obtained as the ortho-*camphoramino alcohol* *diacetate.* (Found: N, 4.74%. $C_{14}H_{25}O_3N$ requires N, 5.16%). It had ν_{max} 1660, 1750, 3100, 3320 cm^{-1}.

allo-*Camphoramine Alcohol.*—*allo*-Camphoric ester amide (5 g) was reduced under conditions described above. The free amino-alcohol (4.13 g) obtained was converted into its hydrochloride and crystallised from methanol-ether to give allo-*camphoramine alcohol hydrochloride* m. p. 256°C. (Found: C, 57.75; H, 10.55; N, 6.99; O, 8.08; Cl, 17.01%. $C_{10}H_{20}$ NOCl requires C, 57.80; H, 10.67; N, 6.74; O, 7.70; Cl, 17.06%).

The *allo*-camphoramine alcohol gave a diacetate, b.p. 215-220°C/4 mm (Found: N, 4.83%. $C_{14}H_{25}O_3N$ requires N, 5.16%). It had ν_{max} 1660, 1750, 3100, 3320 cm–1.

Camphorimine.—Camphorimide (10 g) on reduction with lithium aluminium hydride under above conditions gave an oil which was converted to its hydrocholoride and crystallised from methanol–ether to give *camphorimine hydrocloride*, m.p. 282–88°C. (Found: C, 63.02, 62.8; H, 10.58, 10.37; N, 7.50, Cl, 19.19%. $C_{10}H_{20}NCl$ requires C, 63.30; H, 10.63; N, 7.38; Cl, 18.69%).

References

1. M. Manzoor-i-Khuda and M. Qudrat-i-Khuda, Pakistan J. Sci. Ind. Res., **5**, 74 (1962).
2. J. L. Simonsen, The Terpenes (1949), vol. 2, second edition, p. 478.