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TERPENOIDS—LVII

SYNTHESIS OF SOME GERMACRANE DERIVATIVES*

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Abstract—Both liquid and solid hexahydrocostunolides obtained by the pressure hydrogenation of costunolide (V) and solid dihydrocostunolide (VI) respectively, give the same optically active hexahydrogermacrol (IIIa), when subjected to controlled reduction with $LiAlH_4$, followed by Huang-Minlon reduction. The alcohol (IIIa) on oxidation with chromic oxide gives optically active hexahydrogermacrone (IIa). Dehydration of IIIa with $KHSO_4$ followed by catalytic hydrogenation gives the optically inactive saturated hydrocarbon, germacrane (IV). Since the total synthesis of solid dihydrocostunolide (VI) has already been achieved the preparation of IIIa, IIa and IV from VI constitutes a total synthesis of the above three compounds.

Germacrone, the crystalline constituent of Bulgarian Zdravets oil (from *Geranium macrorhyzum* L.), shown by Sorm *et al.*[1,2] to possess the structure I gives a hexahydro derivative (II) on catalytic hydrogenation. The latter is converted to an alcohol (III) on reduction with lithium aluminium hydride. Dehydration of III with potassium hydrogen sulphate, followed by catalytic hydrogenation, gives the saturated hydrocarbon, germacrane (IV). All three compounds, II, III and IV obtained from germacrone, though possessing 3 to 4 asymmetric centres are optically inactive and are probably present as a mixture of several stereoisomers. The synthetic germacrane,[3] as well as the one prepared from aristolactone[4] have been shown by GLC analysis to consist of three stereoisomers.

With a view to obtain hexahydrogermacrol, hexahydrogermacrone and the saturated hydrocarbon germacrane in stereochemically pure forms, costunolide (V) was converted into hexahydrogermacrol (IIIa).

Costunolide was hydrogenated under pressure to give liquid hexahydrocostunolide which by GLC analysis on a silicon column at 250° indicates the presence of two components in almost equal proportions. Since the partial hydrogenation of costunolide (V) is known[5] to give two dihydrocostunolides, one solid (VI; structure assigned on the basis of its conversion to santanolide ‘c’) and the other liquid (VII) it is probable that the two hexahydrocostunolides indicated by GLC analysis are the two C_{11}-epimers (VIII and IX).

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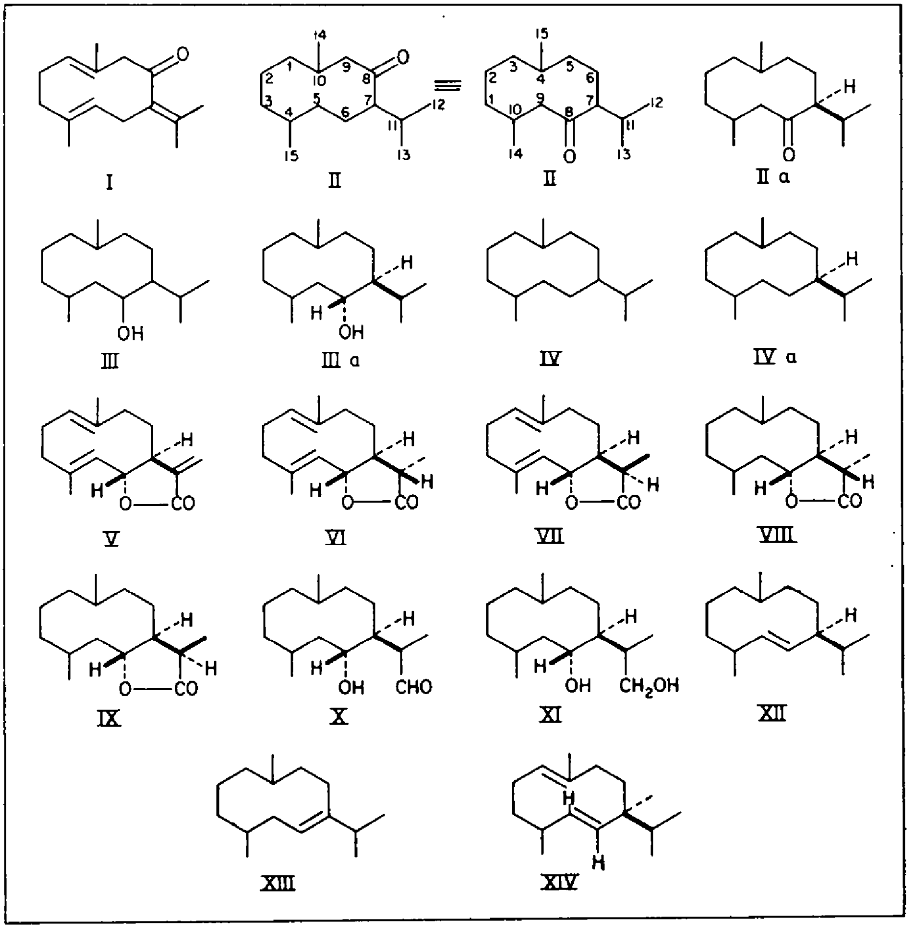
[1] I. Ognjanov, D. Ivanov, V. Herout, M. Horak, J. Pliva and F. Sorm, *Coll. Czech. Chem. Comm.* **23**, 2033 (1958).

[2] V. Herout, M. Horak, B. Scheneider and F. Sorm, *Chem. & Ind.* **35**, 1089 (1959).

[3] M. Suchy and F. Sorm, *Coll. Czech. Chem. Comm.* **23**, 2175 (1958).

[4] M. Martinsmith, S. J. Smith, J. B. Stenlake and W. D. Williams, *Tetrahedron Letters* No 20, 1639 (1963).

[5] A. S. Rao, G. R. Kelkar and S. C. Bhattacharyya, *Tetrahedron* **9**, 275 (1960).



Liquid hexahydrocostunolide, when reduced with lithium aluminium hydride,[6] gives a mixture of X and XI. Huang-Minlon reduction of this mixture affords optically active hexahydrogermacrol,$C_{15}H_{30}O$ (IIIa), which was purified by chromatography (GLC, single peak). The alcohol (IIIa) on oxidation with Jones' chromic acid reagent[7] yields pure optically active ketone, $C_{15}H_{28}O$ (IIa; by GLC) identified by IR spectrum (Fig. 1) and physical constants as hexahydrogermacrone. In agreement with the structure IIa, the NMR spectrum (Fig. 2) shows signals at 0·81, 0·9, 0·98 δ (12H) due to four CH_3 groups at C_4, C_{10}, and C_{11} and a multiplet at 2·26, 2·29, 2·34, 2·45, 2·58 δ (3H) due to three protons adjacent to the carbonyl group at C_5 and C_7.

Dehydration of IIIa with potassium hydrogen sulphate gives a mixture of two hydrocarbons (XII and XIII), $C_{15}H_{28}$ in which XIII predominates as indicated by IR and NMR spectra. The mixture of hydrocarbons on catalytic hydrogenation gives

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[6] A. M. Shaligram, A. S. Rao and S. C. Bhattacharyya, *Tetrahedron* **18**, 969 (1962); G. E. Arth, *J. Amer. Chem. Soc.* **75**, 2413 (1953); see also E. Lederer, C. Asselineau and S. Bory, *Bull. Soc. Chim. Fr.* 1527 (1955).

[7] A. Bowers, T. G. Hallsall, E. R. H. Jones and (in part) A. J. Lemin, *J. Chem. Soc.* 2548 (1953).

the pure saturated optically inactive hydrocarbon $C_{15}H_{30}$, (IV; by GLC), identified by IR spectrum[8] (0·1 mm cell, Fig. 1) and physical constants as germacrane. The optical inactivity of IV is possibly due to the presence of a plane of symmetry in the molecule (drawn across C_2 and C_7) provided the dispositions of the methyl groups at C_4 and C_{10} are *cis*-symmetrical with respect to the plane.

Tosylation of IIIa followed by reduction of the tosylate with lithium aluminium hydride gives mainly a mixture of unsaturated hydrocarbons, $C_{15}H_{28}$, the IR spectra of which resemble that of the $KHSO_4$—dehydration product (XII and XIII). Catalytic hydrogenation of the mixture of unsaturated hydrocarbons gives again germacrane (IV), $C_{15}H_{30}$. Huang-Minlon reduction of the ketone (IIa) was unsuccessful.

Subsequently, costunolide was partially hydrogenated to solid dihydrocostunolide (VI) which was further hydrogenated under pressure to give solid hexahydrocostunolide* (VIII), m.p. 62–63° (IR spectrum, Fig. 1). This was subjected to the same series of reactions as the liquid hexahydrocostunolide to yield the alcohol, ketone and the hydrocarbon (IIIa, IIa and IV). The identity of the two series was established by IR spectra, physical constants and GLC analysis and proves that liquid hexahydrocostunolide is essentially a mixture of two C_{11}-epimeric hexahydrocostunolides, (VIII and IX).

Even though any assumption about the dispositions of the methyl groups at C_4 and C_{10} cannot be made at this stage, it is clear that the isopropyl group at C_7 in the compounds IIa and IIIa is β-oriented.

In an earlier communication,[9] the preparation of the hydrocarbon XIV, $C_{15}H_{26}$, from costunolide has been described. This was hydrogenated first in ethyl acetate and then in ethyl acetate-acetic acid mixture using Adams catalyst to yield the saturated hydrocarbon, $C_{15}H_{30}$ (IVa) (90% by GLC), identified by IR spectrum and physical constants as germacrane.

It differs as regards the rotation from the germacrane obtained from IIIa via $KHSO_4$-dehydration. The C_7 side chain in the germacrane from XIV is necessarily β-oriented. Its NMR spectrum (Fig. 2) is in agreement with the structure IVa.

Since the total synthesis of solid dihydrocostunolide (VI) has already been reported,[10] the preparation of compounds IIa, IIIa and IV from solid dihydrocostunolide via the solid hexahydrocostunolide, constitutes the total synthesis of the above compounds. The total synthesis of germacrane (IV) has been described earlier by Sorm *et al.*[3]

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Rotations were determined in $CHCl_3$ solution. The IR spectra (solids in nujol and liquids as liquid films, unless otherwise stated) were recorded on an Infracord spectrophotometer (Model 137 B) using NaCl optics, by Mr. K. G. Deshpande. The NMR spectra were taken in CCl_4 solution, using TMS as internal reference by Dr. P. M. Nair and colleagues. GLC analyses were carried on a Griffin and George apparatus (MK IIA model), employing polyester column

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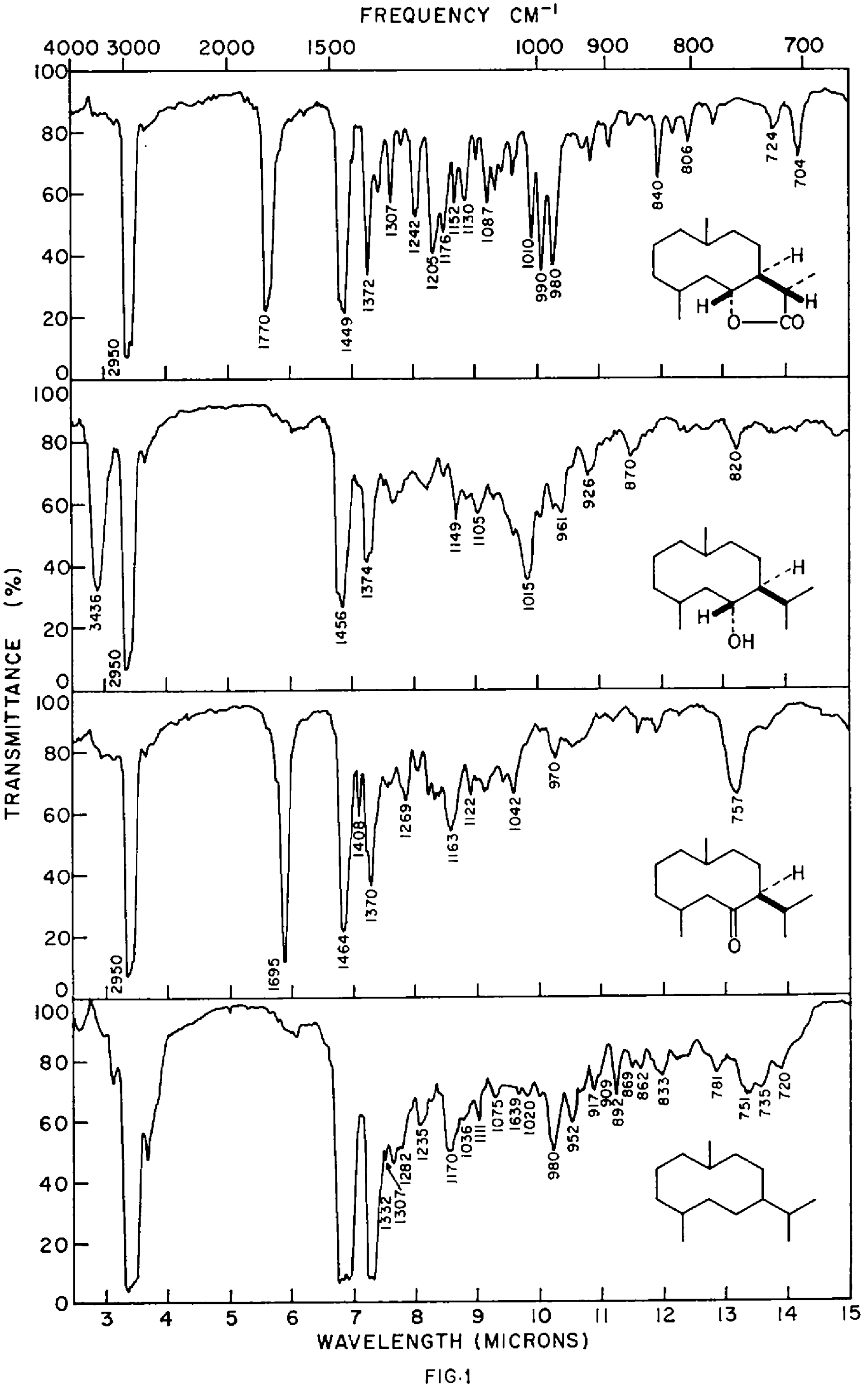
* Unpublished work by A. S. Bawdekar of our Laboratory.

[8] J Pliva, M. Horak, V. Herout and F. Sorm, *Sammlung der Spektren und Physikalischen Konstanten* Teil I; Sesquiterpene S 38, S 41.

[9] G. H. Kulkarni, G. R. Kelkar and S. C. Bhattacharyya, *Tetrahedron* **20**, 1301 (1964).

[10] E. J. Corey and Alfred G. Hortmann, *J. Amer. Chem. Soc.* **85**, 4033 (1963).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1152
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1010
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980
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O
CO
3436
2950
1456
1374
1149
1105
1015
961
926
870
820
H
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2950
1695
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1282
1235
1170
1036
1111
1075
1639
1020
980
952
917
909
892
869
862
833
781
751
735
720
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

FIG.1

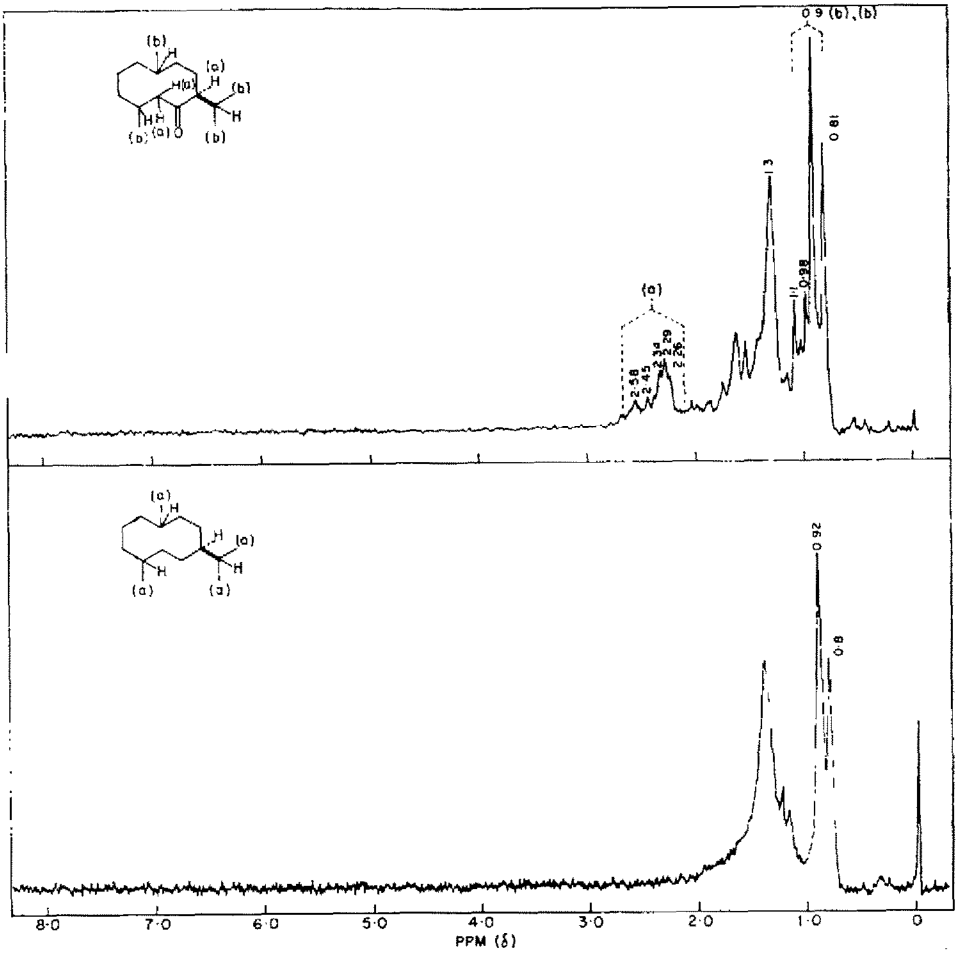

FIG 2

and H_2 as carrier gas, by Mr. Bapat and Mr. Sankpal. Microanalyses were carried out by Mr. Pansare and colleagues.

Liquid hexahydrocostunolide (VI and VII). Costunolide, m.p. 106–107°, $(\alpha)_D$ +125° (20 g) dissolved in alcohol (300 ml) was hydrogenated (1000 lbs/sq. inch press.) using Adams catalyst initially at room temp (6 hr) and then at 40–50° (6 hr). Alcohol was removed under suction and the residue after dilution with water was extracted with ether. The ether layer was washed with $NaHCO_3$ aq to remove acid (formed due to hydrogenolysis). The liquid hexahydrocostunolide obtained after removal of ether was purified by distillation to give VI and VII (18 g, b.p. 130–135°/0·6 mm, d_{28}^{28} 1·007, $(\alpha)_D$ − 25°, n_D^{28} 1·4880. (Found: C, 75·50; H, 11·0. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·0%).

Hydroxy aldehyde from VI *and* VII. Liquid hexahydrocostunolide (18 g) was reduced by gradual addition of an ethereal solution of $LiAlH_4$ (0·75 g in 250 ml) under cooling at − 10°. The reaction mixture was stirred for 3 hr at the same temp and for another 3 hr at room temp. It was then decomposed by alcohol and water and worked up to give a mixture of X and XI containing a little unreacted lactone (IR spectrum).

Hexahydrogermacrol (IIIa). The mixture of X and XI (17 g) dissolved in diethylene glycol (150 ml) in a 4-necked flask, fitted with a Hg-sealed mechanical stirrer, a condenser, a thermometer and an inlet for N_2. Nitrogen was allowed to bubble through and KOH (18 g) and hydrazine hydrate (13 ml) were introduced. The contents were heated to 200–220° and maintained at that temp for 4 hr with stirring. After cooling the reaction product was diluted with water and extracted with ether. Removal of ether furnished (13·5 g) of a liquid which was chromatographed on alumina (grade II, 700 g) and eluted as follows:

Fraction no.	Solvent	Vol. in ml	Wt. in g
1	Pet. ether	500	0·7
2	Pet. ether-benzene 2:1	1000	7·3
3	Benzene	500	0·5
4	Ether	500	1·5

Fraction 2 which was essentially IIIa was purified further by chromatography and distillation and showed a single peak on GLC analysis; b.p. 120–140° (bath)/0·7 mm, n_D^{22} 1·4840, $(\alpha)_D$ $-6°$ (*c*, 7·4) (Found: C, 80·05; H, 13·21. $C_{15}H_{30}O$ requires: C, 79·57; H, 13·36%). (Lit.[1] records for hexahydrogermacrol (III), $(\alpha)_D$ ±0°). The IR spectrum of IIIa is shown in Fig. 1. Fraction 4 contained the diol (XI) which was not critically examined.

Hexahydrogermacrone (IIa). Hexahydrogermacrol (IIIa; 2·1 g) was dissolved in acetone (20 ml) and Jones' reagent was added drop by drop until a brown colour persisted. It was kept at room temp for 30 min and then worked up to give the crude ketone, which was purified by chromatography and distillation to give IIa in pure form (GLC) b.p. 115–120° (bath)/0·9 mm, n_D^{24} 1·4726, $(\alpha)_D$ $+83°$ (*c*, 3·6), (Found: C, 80·95; H, 12·7. $C_{15}H_{28}O$ requires: C, 80·29; H, 12·58%). The IR and NMR spectra are shown in Figs. 1 and 2 (Lit. records for hexahydrogermacrone, n_D^{20} 1·4770, $(\alpha)_D$ ±0°).

Dehydration of (IIIa). Hexahydrogermacrol (1·3 g) was heated with $KHSO_4$ (2 g) in an atm. of N_2 at 180° for 2 hr. The product after taking up in pet. ether was filtered through a column of alumina (gr. I, 50 g). The pet. ether eluted portion was purified by distillation to give mostly XIII, indicated by IR and NMR spectra, b.p. 100–120° (bath)/1 mm, n_D^{30} 1·4711, $(\alpha)_D$ $+3°$ (*c*, 5·4), (Found: C, 86·92; H, 13·41. $C_{15}H_{28}$ requires: C, 86·46; H, 13·54%). The hydrocarbon mixture containing mostly XIII (1·03 g) was hydrogenated in acetic acid using Pt catalyst. The volume of H_2 absorbed (116 ml) at NTP) corresponded to slightly more than one double bond. The hydrogenated product was worked up and purified by chromatography and distillation to give IV in pure form (GLC), b.p. 110–120° (bath)/1 mm, n_D^{30} 1·4660, $(\alpha)_D$ ±0°, (Found: C, 85·7; H, 14·27. $C_{15}H_{30}$ requires: C, 85·63; H, 14·37%). The IR spectrum taken in 0·1 mm cell (Fig. 1) is in agreement with that of IV obtained from germacrone.[8] The NMR spectrum is identical with that of IVa shown in Fig. 2.

Tosylation of IIIa *and reduction of the tosylate.* The alcohol (IIIa, 1·0 g) dissolved in pyridine (15 ml) was mixed with tosyl chloride (2 g) and kept at room temp for 48 hr. The product was diluted with ice cold water and extracted with ether. The ether layer was washed with dil HCl aq followed by water and dried (Na_2SO_4). Removal of ether furnished the tosylate (1·3 g) which was reduced with $LiAlH_4$ (1·5 g) in ether solution in the usual way. The hydrocarbon obtained was purified by chromatography and distillation b.p. 110–120° (bath)/0·7 mm, n_D^{25} 1·4710, $(\alpha)_D$ $+1·2°$ (*c*, 5·4) (Found: C, 86·5; H, 13·87. $C_{15}H_{28}$ requires: C, 86·46; H, 13·54%). The IR spectrum taken in 0·1 mm cell was almost identical with that of the product obtained by the $KHSO_4$-dehydration of IIIa which by GLC analysis was shown to contain about 20% saturated hydrocarbon. The component occurring to the extent of 80% corresponded to the $KHSO_4$-dehydration product from IIIa (confirmed by mixed GLC).

The hydrocarbon mixture, $C_{15}H_{28}$, obtained above (0·492 g) absorbed (50·9 ml at NTP) H_2 on hydrogenation in acetic acid using Pt catalyst corresponding to 0·95 double bond. The hydrogenated product worked up in the usual way had the following constants, b.p. 110–120° (bath)/1 mm, n_D^{25} 1·4670, $(\alpha)_D$ ±0° (Found: C, 85·90; H, 14·40. $C_{15}H_{30}$ requires: C, 85·63; H, 14·37%). The IR spectrum was identical with that of germacrane.[8]

Solid hexahydrocostunolide (VIII). Solid dihydrocostunolide (28 g) m.p. 76–77°, $(\alpha)_D$ $+114°$ was hydrogenated in alcohol solution, using Pt catalyst (1000 lbs/sq. inch press) in the manner described for liquid hexahydrocostunolide. The product was distilled, b.p. 130–40°/0·7 mm and the distillate cooled in pet. ether solution at $-18°$ for a day, yielded the crude lactone, m.p. 55–56° which after 3 crystallizations from pet. ether gave the pure lactone (VIII), m.p. 60–61°, $(\alpha)_D$ $-5·2°$ (*c*, 4·4) (Found: C, 75·50; H, 10·95. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·00%). IR spectrum is shown in Fig. 1.

Solid hexahydrocostunolide was reduced with $LiAlH_4$ followed by Huang-Minlon reduction in the manner previously described to give hexahydrogermacrol (IIIa, GLC Pure), b.p. 120–130° (bath)/0·7 mm, n_D^{28} 1·4825, $(\alpha)_D$ $-4·4°$ (Found: C, 79·80; H, 13·40. $C_{15}H_{30}O$ requires: C, 79·57; H, 13·36%). Hexahydrogermacrol (IIIa) obtained above was oxidized by Jones' reagent to the ketone (IIa, GLC pure) b.p. 110–120° (bath)/0·9 mm, n_D^{28} 1·4720, $(\alpha)_D$ +83·8° (Found: C, 80·6; H, 12·63. $C_{15}H_{28}O$ requires: C, 80·29; H, 12·58%). The compounds IIIa and IIa from both solid and liquid hexahydrocostunolides were identical in physical constants, IR spectra and GLC retention periods.

Catalytic hydrogenation of (XIV) *to germacrane* (IVa). The hydrocarbon (XIV; 0·3246 g) was hydrogenated initially in ethyl acetate and then in ethyl acetate–acetic acid using Pt catalyst. The volume of H_2 absorbed (73 ml at NTP) corresponded to the presence of the two double bonds. The hydrogenated product (IVa) worked up in the usual manner had the following constants, b.p. 110–130° (bath)/0·7 mm, n_D^{33} 1·4655, $(\alpha)_D$ +7° (Found: C, 86·12; H, 14·13. $C_{15}H_{30}$ requires: C, 85·63; H, 14·37%). GLC analysis indicated it to be about 90% pure. (The other component occurring to the extent of 10%, possibly a C_{10} epimer was not distinctly resolved from the main peak.) The IR spectrum is in agreement with that of germacrane.[8] The NMR spectrum shown in Fig. 2 is in agreement with the structure IVa.