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TERPENOIDS—XCVII

BASE CATALYSED REACTIONS WITH N-LITHIOETHYLENEDIAMINE*

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Abstract—Reaction of N-lithioethylenediamine on the 11-membered monocyclic sesquiterpenoids zerumbone (I) and zerumbol (II) has been studied. Zerumbone undergoes polymerization in the presence of the reagent whereas zerumbol via transannular cyclization–oxidation is converted to the bicyclic ketone, 2-keto-$\Delta^{5:6,4:11}$-bicyclo (6:3:0) undecane (VII). Its structure has been rigorously established by chemical degradation and spectral studies.

Two diterpenes 6-hydroxyabietic acid (XII) and 6-ketomethylabietate (XVI) have been treated with the reagent. The compound XII furnishes dehydroabietic acid (XIII) while XVI yields the phenolic acid, 6-hydroxydehydroabietic acid (XVIII), an important intermediate for the synthesis of 6-hydroxydehydroabietinol (XIV), reported to possess oestrogenic activity.

IN PREVIOUS cummunications[1,2] the use of N-lithioethylenediamine as an isomerizing and dehydrogenating agent for terpenic and non-terpenic organic compounds has been investigated. This has now been extended and applied to medium ring sesquiterpenes and diterpenes with most interesting results.

Medium ring sesquiterpenes. Both caryophyllene and humulene on treatment with lithioethylenediamine form conjugated diene and triene systems respectively, but the experiments on their structural elucidation are as yet inconclusive.[3]

Zerumbone,[4a,b] the 11-membered monocyclic ketone having a cross-conjugated dienone system, undergoes polymerization on treatment with this reagent. This ketone (I) was then reduced with LAH to the crystalline alcohol zerumbol[4b] (II) which was subsequently treated with this reagent.

It has been previously shown[1,2] that double bonds allylic to hydroxyl groups become labile in the presence of this reagent and migrate away from the hydroxyl groups. Thus geraniol[1] (III), is converted to the conjugated diene alcohol IV and dihydrogeraniol[2] (V) to citronellol (VI). Zerumbol (II) has two allylic double bonds ($\Delta^{2:3}$ and $\Delta^{10:11}$) and an isolated double bond ($\Delta^{6:7}$). On treatment with N-lithioethylenediamine, it is converted to a bicyclic ketone VII, as a result of transannular cyclization–oxidation. Acid-catalysed transannular cyclization is a characteristic feature of medium ring compounds. Transformation of germacrone

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[1] B. S. Tyagi, B. B. Ghatge and S. C. Bhattacharyya, *J. Org. Chem.* 27, 1430 (1962); *Tetrahedron* 19, 1189 (1963).

[2] B. N. Joshi, R. Seshadri, K. K. Chakravarti and S. C. Bhattacharyya, *Tetrahedron* 20, 2911 (1964).

[3] Unpublished work from our Laboratory by B. S. Tyagi and R. Seshardi.

[4] [a] V. K. Balakrishnan, R. K. Razdan and S. C. Bhattacharyya *Perf. and Ess. Oil Record* 47, 274 (1956).

[b] S. Dev, *Tetrahedron* 8, 171 (1960).

to selinanones,[5] arctiopicrin to compounds of santonin series[6] and costunolide and dihydrocostunolide to cyclocostunolide[7] and santanolides[8] may be cited as examples. The conversion of zerumbol to the bicyclic ketone VII*, however, takes place under mildly basic conditions. This may proceed in the following fashion.

The two allylic double bonds, $\Delta^{2:3}$ and $\Delta^{10:11}$, would have a tendency to migrate away from the hydroxyl group. The $\Delta^{2:3}$ double bond can conveniently do so by migrating to the $\Delta^{3:4}$ position. However, because of the presence of a *gem*-dimethyl group on C_9, the $\Delta^{10:11}$ double bond has no scope to migrate and its tendency to do so is relieved by its disappearance by cyclization, followed by rearrangement of the $\Delta^{6:7}$ double bond to give the conjugated dienone VII, the alcohol VIII, presumably being the intermediate. This oxidation of the alcohol to the ketone is reminiscent of the conversion of ionols to ionones.[2] The dienone VII is obtained in excellent yield and is more or less the exclusive product of the reaction. Its structure has been established as follows:

It corresponds to the molecular formula $C_{15}H_{22}O$ and it shows a single spot in TLC and single peak in GLC analyses. Its IR spectrum (Fig. 1) exhibits bands at 1736 (non-conjugated 5-membered ring ketone); 1665, 880 (trisubstituted double bond) and 1389, 1365 cm^{-1} (*gem*-dimethyl group).

It shows UV absorption, λ_{max} 237 mμ (ε 13850), characteristic of conjugated diene system. It forms a semicarbazone, m.p. 123–24°, which shows UV absorption, λ_{max} 236 mμ (ε, 37509), indicating that the keto group is isolated and not in conjugation with any double bond.

Quantitative hydrogenation on Adams catalyst in alcohol medium shows the presence of two double bonds in the parent ketone. The resulting tetrahydro product does not show any UV absorption but shows IR absorption for the cyclopentanone system (1739 cm^{-1}) and forms a semicarbazone, m.p. 172–173°. In conformity with its structure VII it shows in its NMR spectrum† (Fig. 2) signals at 8·95, 8·93, 9·03, 9·05, 9·19 τ (9H, due to Me groups at C_3 and C_9); a signal at 8·3 τ (3H, due to Me group on a double bond at C_6). In the olefinic region a multiplet centred at 4·7 τ (2H) is due to the olefinic protons at C_4 and C_5.

On reduction with LAH the ketone VII is converted to the crystalline alcohol VIII, $C_{15}H_{24}O$, m.p. 92–93°; acetate ($C_{17}H_{26}O$), b.p. 125–127°/0·8 mm. Its IR spectrum (Fig. 1) exhibits bands at 3300, 1070 (secondary OH group); 1665, 880 (trisubstituted double bond); 1380, 1365 cm^{-1} (*gem*-dimethyl group). Its UV absorption is closely similar to the parent ketone, λ_{max} 239 mμ (ε 14144). This shows that the conjugated diene system of the original ketone is retained in the alcohol. This observation also clearly leads to the conclusion that none of the two double bonds is in conjugation with the carbonyl group in the original ketone. Its

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* According to the ring index (Supplement II, p. 45, American Chemical Society, 1964), the ketone VII should be named as 2-keto-3,6,9,9-tetramethyl-$\Delta^{5:6,4:11}$-bicyclo (6:3:0) undecane. It has been numbered accordingly.

† The very complex multiplet obtained for the two vinylic protons probably arises from strong allylic coupling.

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

[6] M. Suchy, V. Herout and F. Sorm *Coll. Czech. Chem. Commun.* **24**, 1542 (1959).

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

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

NMR spectrum exhibits signals at 8·93, 8·95, 9·10 τ (9H, due to Me groups at C_3 and C_9); 8·2 τ (3H, a Me group on double bond at C_8), a peak centred at 6·5 τ (H of the secondary OH group) and in the olefinic region a multiplet centred at 4·55 τ (2H) is due to two olefinic protons at C_4 and C_5. Quantitative hydrogenation of the alcohol shows the presence of two double bonds, the resultant tetrahydro product ($C_{15}H_{28}O$) is a crystalline material, m.p. 100–101°; acetate ($C_{17}H_{30}O$), b.p. 130–132°/0·7 mm, n_D^{24} 1·5105.

The alcohol VIII, on treatment with tosyl chloride and subsequent detosylation with LAH furnishes the conjugated diene IX ($C_{15}H_{24}$). Its IR spectrum (Fig. 1) exhibits bands at 1665, 880 (trisubstituted double bond) and 1389, 1365 cm^{-1} (*gem*-dimethyl group). UV absorption shows λ_{max} 239 mμ (ϵ 12570), showing the presence of conjugated diene system. The NMR spectrum (Fig. 2) shows signals at 8·99, 9·04, 9·11 τ (9H, due to Me groups at C_3 and C_9); a signal at 8·42 τ (3H, Me group on a double bond at C_8); a peak centred at 4·7 τ of a multiplet in olefinic region (2H, due to olefinic protons at C_4 and C_5). On quantitative hydrogenation over PtO_2 in alcohol, it absorbs two moles of hydrogen giving the fully saturated tetrahydro derivative, which does not show any colour reaction with tetranitromethane.

Ozonolysis of the bicyclic hydrocarbon and subsequent decomposition of the ozonide with hot water gives a crystalline diketone X ($C_{13}H_{22}O_2$), m.p. 71–71·5° and oxalic acid. The diketone gives a positive iodoform test indicating the presence of methyl ketone function. Its IR spectrum shows absorption bands at 1750 (cyclopentanone) and 1692 cm^{-1} (saturated methyl ketone). These results conclusively prove that the ketone obtained from zerumbol on treatment with N-lithioethylenediamine is represented by the structure VII, from which the structures of the other products derived from it follow.

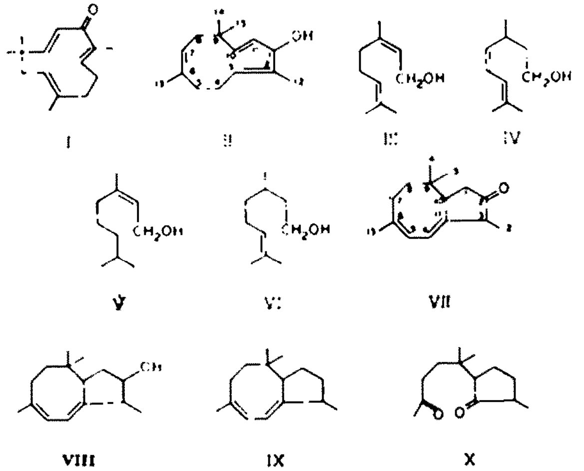


CHART 1

Diterpenes. Previously (- -)abietic acid[8] (XI) was treated with N-lithioethylenediamine to yield dehydroabietic acid (XIII). It is now shown that 6-hydroxyabietic acid (XII) on treatment with the reagent is also converted to dehydroabietic acid (XIII)

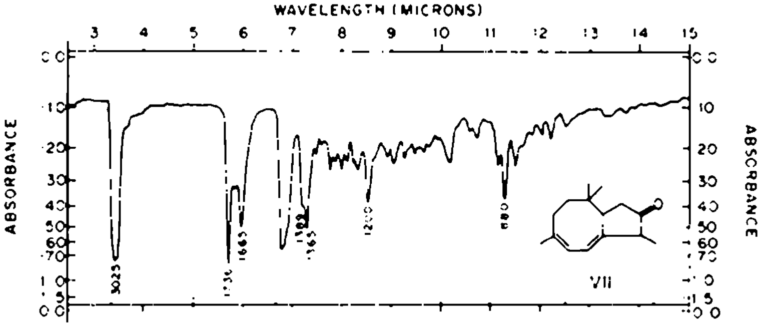


FIG. 1. I.R. Spectra of alcohol (VIII) and Hydrocarbon (IX).

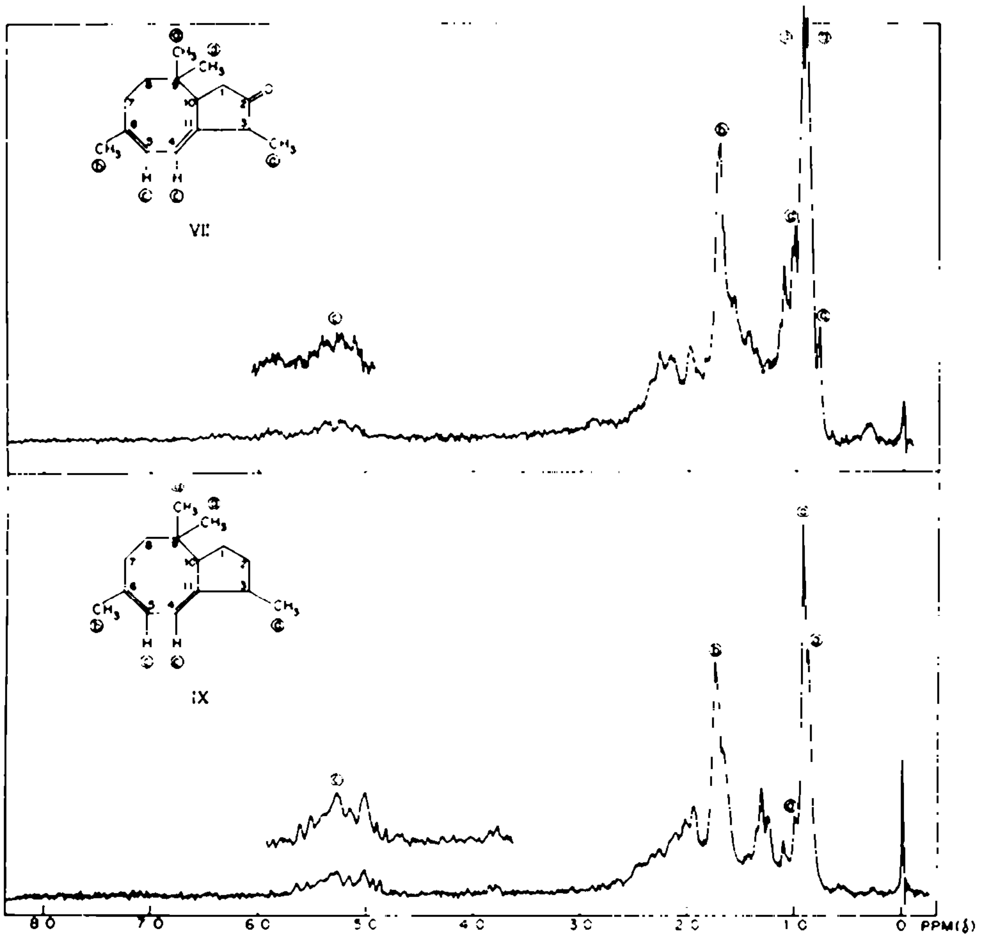


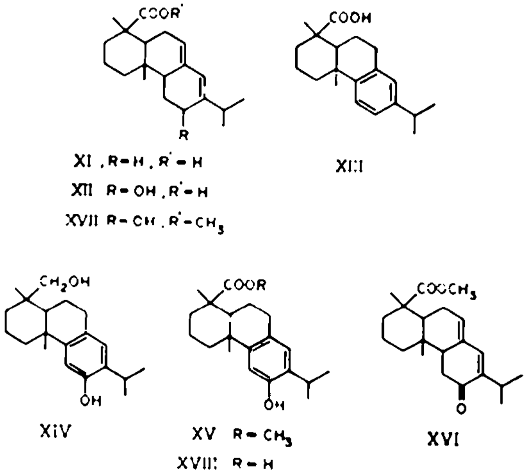
FIG. 2

Fieser and Campbell[9] investigated the utilization of dehydroabietic acid as a starting material for the synthesis of 6-hydroxydehydroabietinol (XIV), which has been reported to possess oestrogenic activity. The synthesis of 6-hydroxydehydromethylabietate (XV), an intermediate in the synthesis of XIV, has been carried out by them in five steps.

In the present case, 6-ketomethylabietate (XVI), obtained from 6-hydroxymethylabietate (XVII) on treatment with N-lithioethylenediamine is directly converted to 6-hydroxydehydroabietic acid (XVIII).

6-Ketomethylabietate (XVI) is prepared by oxidation of 6-hydroxymethylabietate (XVII). The oxidizing agents such as chromic acid in acetic acid, Sarret's reagent (chromic acid and pyridine) are not suitable, as they give only polymerized products during oxidation. With reference to the previous work of oxidation of zerumbol to zerumbone by active manganese dioxide,[4b] 6-hydroxymethylabietate (XVII) yields a mixture of 6-ketomethylabietate (XVI) and unreacted XVII.

A number of experiments was carried out with variation of time of treatment with the oxidizing agent in pet. ether solution. The maximum yield of XVI (λ_{max} 293 mμ; ϵ 10,628) was obtained when the oxidation was carried out for 48 hr. The progress of the reaction was followed by UV spectroscopy. When a mixture of 6-hydroxy and 6-ketomethyl esters was treated with lithioethylenediamine, a mixture of XIII and XVIII was obtained, and separated into the phenolic and non-phenolic constituents by treatment with alkali. The methyl ester XV is purified by crystallization from pet. ether, m.p. 162–163°; IR bands at 1725, 1176 (ester group); 3580, 1266 (phenol); 1538 (aromatic ring) and 1389, 1365 (isopropyl group); UV absorption λ_{max} 285 mμ (ϵ 1250).



XI, R = H, R' = H
XII R = OH, R' = H
XVII R = OH, R' = CH_3

XIII

XIV

XV R = CH_3
XVIII R = H

XVI

CHART 2

EXPERIMENTAL

M.ps are uncorrected. Rotations were taken in alcohol. UV spectra in alcohol soln on a Beckmann DK, recording spectrophotometer and IR spectra on a Perkin–Elmer (Model 137b) Infracord

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[9] L. F. Fieser and W. P. Campbell, *J. Amer. Chem. Soc.* **60**, 159 (1938); **61**, 2528 (1939); See also R. N. Moore and R. V. Lawrence, *Ibid.* **81**, 458 (1959).

Spectrophotometer; NMR spectra: on a A-60 Varian instrument set at 60 Mc, TMS was used as a internal standard; CCl_4 solns were used. Microanalyses were carried out in the micro-analytical section of the laboratory.

The preparation of anhydrous ethylenediamine, treatment of the various compounds with the lithio derivative and subsequent processing of the reaction products were essentially the same as described in previous communications.

Isolation of zerumbone (I). Zerumbone was isolated from the oil of *Zingiber zerumbet* (Smith) and purified by crystallization from pet. ether, m.p. 66–67°; λ_{max} 245 mμ (ε 8415); 325 mμ (ε 1105); TLC single spot; VPC single peak; IR bands at 1667, 1266 (α,β-unsaturated ketone); 970 (*trans* disubstituted double bond); 3030; 1667, 825 (trisubstituted double bond); 1379, 1361 cm^{-1} (*gem*-dimethyl group).

Preparation of zerumbol (II). Zerumbol was prepared by reduction of zerumbone with LAH and crystallizing from pet. ether, m.p. 77–78°; TLC single spot; IR bands at 3300, 1300 (secondary OH group); 1670, 980 (*trans* disubstituted double bond) and 1389, 1365 cm^{-1} (*gem*-dimethyl group).

Preparation of ketone VII. Zerumbol (15 g) was treated with lithioethylenediamine (Li 4·5 g, ethylenediamine 250 ml) and refluxed with stirring for 12 hr to give a product which on purification by chromatography over alkaline alumina (grade II, 450 g) followed by vacuum distillation gave the liquid VII (10·05 g) showing TLC single spot; VPC single peak; b.p. 135–137°/0·7 mm; n_D^{26} 1·4940; IR (Fig. 1), UV, NMR (Fig. 2) data discussed in the theoretical part. (Found: C, 82·81; H, 10·42. $C_{15}H_{22}O$ requires: C, 82·51; H. 10·16%.) semicarbazone, m.p. 123–124°. (Found: C, 69·70; H, 9·41; N, 14·80. $C_{16}H_{25}ON_3$ requires: C, 69·78; H, 9·15; N, 15·26%.)

Hydrogenation of the bicyclic ketone VII. The bicyclic ketone (0·6910 g), dissolved in EtOH (75 ml) was stirred in an atm of H with pre-reduced Adams' catalyst (70 mg). The equivalent of 1·88 moles H was absorbed. The catalyst was filtered off and the solvent removed under vacuum to furnish the tetrahydro derivative (0·6805 g), which on chromatography over alkaline alumina (grade II, 25 g) followed by distillation gave the pure product, TLC single spot, GLC single peak; b.p. 140–142°/0·8 mm; n_D^{24} 1·5015. (Found: C, 81·55; H, 11·40. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%.) Semicarbazone; m.p. 172–173°. (Found: C, 68·9; H, 11·01; N, 14·81. $C_{16}H_{29}ON_3$ requires: C, 68·77; H, 10·46; N, 15·04%.)

Preparation of the bicyclic alcohol VIII. The ketone VII (5 g) was reduced with LAH to VIII, which on crystallization from EtOH gave the pure product, m.p. 92–93°. (Found: C, 81·55; H, 11·01. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%.) IR (Fig. 1) UV and NMR data of the alcohol already discussed in theoretical part; acetate, b.p. 125–127°/0·8 mm; n_D^{24} 1·5085. (Found: C, 77·55; H, 10·5. $C_{17}H_{26}O$ requires: C, 77·82; H, 9·99%.)

Hydrogenation of the bicyclic alcohol VIII. The alcohol (0·300 g) dissolved in EtOH (25 ml) was stirred in an atm. of H with prereduced PtO_2 catalyst (45 mg). The equivalent of 1·95 moles H was absorbed. The catalyst was filtered and the solvent removed *in vacuo* to yield the tetrahydro derivative (0·298 g) which was crystallized from EtOH, m.p. 100–101°. (Found: C, 80·24; H, 12·12. $C_{15}H_{28}O$ requires: C, 80·29; H, 12·58%.) Acetate; b.p. 130–132°/0·7 mm; n_D^{24} 1·5105. (Found: C, 80·97; H, 11·79. $C_{17}H_{30}O$ requires: C, 81·53; H, 12·08%.)

Preparation of the bicyclic hydrocarbon IX. The alcohol VIII (5 g) was tosylated by tosyl chloride (7·5 g) in pyridine (25 ml). The product (4·85 g) was detosylated by reduction with LAH (0·950 g) in ether (100ml). The resulting hydrocarbon was further purified by chromatography over neutral alumina (grade I, 200 g) followed by vacuum distillation; TLC single spot, GLC single peak; b.p. 95–97°/0·7 mm; n_D^{24} 1·4905. (Found: C, 86·57; H, 13·61. $C_{15}H_{28}$ requires: C, 86·46; H, 13·54%.) Spectral data (Fig. 1, Fig. 2) discussed earlier.

Hydrogenation of the bicyclic hydrocarbon IX. The hydrocarbon (1·05 g) dissolved in EtOH (75 ml) was stirred in an atm. of H with pre-reduced PtO_2 catalyst (150 mg). The equiv of 1·98 moles H was absorbed. The tetrahydro deriv (1·01 g) was subjected to chromatography over neutral alumina (grade I, 30 g) followed by vacuum distillation to give the pure product, colourless to tetranitromethane; TLC single spot, GLC single peak; b.p. 110–112°/0·5 mm; n_D^{24} 1·5108. (Found: C, 84·48; H, 14·84. $C_{15}H_{32}$ requires: C, 84·81; H, 15·19%.)

Ozonolysis of the bicyclic hydrocarbon IX. The hydrocarbon (1·05 g) dissolved in pure, dry chf (25 ml) was ozonized in Tower's ozonizer (1·5 hr). The ozonide after removal of solvent under moderate vaccum was decomposed with hot water. The ozonolytic product was extracted with ether and the solid residue after crystallization from EtOH afforded X, m.p. 71–71·5°. (Found: C, 74·51;

H, 10·41; $C_{13}H_{22}O_2$ requires: C, 74·24; H, 10·53%.) It showed positive iodoform test for the presence of methyl ketone. The aqueous portion (5 ml) after oxidation with 30% H_2O_2 (1 ml) followed by neutralization with ammonium hydroxide gave a ppt of calcium oxalate on treatment with $CaCl_2$aq

6-Hydroxyabietic acid (XII). 6-Hydroxyabietic acid was prepared by SeO_2 oxidation of XI[9] and had m.p. 154–155°; $[\alpha]_D^{24}$ −123·56° (alcohol, c, 1·28). (Found: C, 75·60; H, 9·80; $C_{20}H_{30}O_3$ requires: C, 75·43; H, 9·50%.)

The reaction mixture of 6-hydroxyabietic acid (2·5 g), Li (1·5 g) in ethylenediamine (30 ml) was refluxed for 18 hr. Excess ethylenediamine was removed by distillation under red. press. The residual amide was hydrolyzed by refluxing for 15 hr with 15% alcoholic KOH (30 ml). The final product yielded dehydroabietic acid (2·07 g) which was crystallized from a mixture of dry ether and pet. ether m.p. 174–175°; $[\alpha]_D^{24}$ +67·2° (alcohol, *c*, 2·67). (Found: C, 80·23; H, 9·52. $C_{20}H_{28}O_2$ requires: C, 80·00; H, 9·33%.)

6-Ketomethylabietate (XVI). 6-Ketomethylabietate was prepared by oxidation of 6-hydroxymethylabietate with active MnO_2 in pet. ether (40–60°) for 48 hr. Final oxidation product had UV absorption λ_{max} 239 mμ (ε 10628); IR spectrum bands at 3400, 1053 (secondary OH) and 1695, 1270 cm^{-1} (carbonyl) showing the mixture of 6-hydroxy and 6-keto-methylabietate.

A mixture of the esters (5 g), Li (1·5 g) in ethylenediamine (75 ml) was refluxed for 18 hr. Further working up yielded a mixture of dehydroabietic acid and 6-hydroxy-dehydroabietic acid (4·27 g). The ether soln of the acid mixture (25 ml) was esterified by diazomethane. The soln of ester was shaken with 2% KOH (25 ml) twice. The K-salt of the phenolic ester in the alkaline soln (45 ml) was acidified with 2% HCl (50 ml), extracted with ether, followed by treatment with 2% $NaHCO_3$aq and water and dried over Na_2SO_4. After removal of ether the crude 6-hydroxy-dehydromethyleneabietate obtained was crystallized from MeOH m.p. 162–163°, $[\alpha]_D^{20}$ +74° (alcohol; *c*, 2·45). UV absorption λ_{max} 283 mμ (ε 1250); IR bands at 1725, 1176 (ester group); 3580; 1266 (phenol); 1538 (aromatic ring) and 1389, 1360 cm^{-1} (isopropyl group). (Found: C, 76·74; H, 9·45. $C_{21}H_{30}O_3$ requires: C, 76·63; H, 9·15%.)