543. *The Chemistry of the Triterpenes. Part XI.* The Conversion of Lupeol into Germanicol* (iso*Lupeol*). *The Structure of Lupeol Hydrochloride.*

By T. G. Halsall, E. R. H. Jones, and G. D. Meakins.

*iso*Lupenyl acetate, obtained from lupeol hydrochloride by Duerden, Heilbron, McMeeking, and Spring (*J.*, 1939, 322), has been shown to be identical with germanicyl acetate. The simplest members of the lupeol and the germanicol series have thus been directly inter-related.

Lupeol hydrochloride is formulated as 19(α)-chloro-18(α)-oleanan-2"β"-ol (XIII) from a consideration of its reduction to the known 18(α)-oleanan-2"β"-ol and its dehydrochlorination by various reagents. The stereochemistry at four of the asymmetric centres of lupeol (C_{13}, C_{17}, C_{18}, and C_{19}) can now be regarded as rigidly established.

A preliminary account of part of this work has already been published (Ames, Davy, Halsall, Jones, and Meakins, *Chem. and Ind.*, 1951, 741).

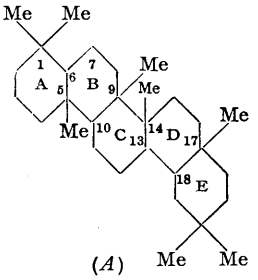
Nomenclature.—The nomenclature used in this and the following paper is as follows. The name oleanane is applied to structure (*A*) with the stereochemical orientation at $C_{(5)}$, $C_{(8)}$, $C_{(9)}$, $C_{(10)}$, $C_{(14)}$, and $C_{(17)}$ defined as that found in δ-amyrene [olean-13(18)-ene]. The orientation at $C_{(13)}$ is defined as that found in germanicol (and in β-amyranol) in which the hydrogen atom at $C_{(13)}$ has been shown to be *cis* to the methyl group at $C_{(17)}$ (Barton and Brooks, *J.*, 1951, 257). The orientation at $C_{(18)}$ is defined as that found in oleanolic acid in which the hydrogen atom at $C_{(18)}$ has been shown to be *cis* to the methyl group at $C_{(17)}$ (Barton and Holness, *J.*, 1952, 78).

Prefixes α and β have been used by Barton (*Experientia*, 1950, **6**, 316) to denote the configuration of substituents on rings A and B relative to the methyl group at $C_{(5)}$ which was arbitrarily assigned the β-configuration, *i.e.*, the $C_{(5)}$-methyl group was arbitrarily assumed to lie above the plane of the ring, as denoted by the thick bond in formula (*B*).

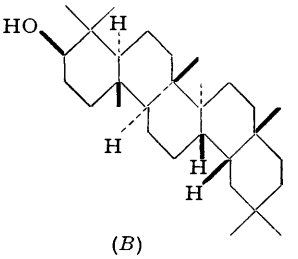
The orientation of substituents attached to rings D and E will now be provisionally related to the methyl group at $C_{(17)}$. There is evidence (Barton and Holness, *loc. cit.*; Klyne, personal communication) that this methyl group at $C_{(17)}$ lies on the same side of

* Part X, *J.*, 1951, 2702.

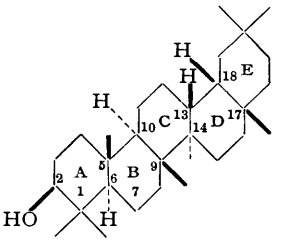
the plane of the ring system as does that at $C_{(5)}$; this relation is now accepted, but, until it is confirmed, the configurational prefixes of groups attached to rings D and E will be enclosed in parentheses; thus, the $C_{(17)}$-methyl group taken as subsidiary standard is assigned the prefix (β).



(*A*)



(*B*)



(*C*)

The 2-hydroxyl group in δ-amyrin has been considered to have the β-configuration on the former of the above conventions. Until this is finally proved or disproved, we shall denote the configuration of the hydroxyl group in these substances as " β " (in quotation marks). β-Amyrin would therefore be designated olean-12-en-2"β"-ol, and 18-*iso*-β-amyranol (Budziarek, Manson, and Spring, *J.*, 1951, 3336), in which rings D and E are *trans*-fused, would be 18(α)-oleanan-2"β"-ol (cf. Rule 5.1 of the rules for steroid nomenclature, *J.*, 1951, 3532).

On the above conventions it is tentatively believed that the structure of oleanan-2"β"-ol may be completely represented in the form (*B*) (Barton and Holness; Klyne, *locc. cit.*).

However, there is evidence (Klyne, *Chem. and Ind.*, 1952, 172) that the α and β conventions are used in opposite senses in the steroid and the triterpenoid field, *i.e.*, that the two reference groups—the $C_{(10)}$-methyl group in the steroids and the $C_{(5)}$-methyl group in triterpenoids—although both labelled β, lie one above and the other below the plane of the paper in the conventional representation. This will be tentatively accepted. It then becomes advisable to reconcile the two conventions. The steroid conventions are so long established that it is preferable to change the above triterpenoid conventions, and it is proposed, following a most helpful suggestion from the Editors, to do this as follows.

(1) The formulæ of triterpenoids will be turned through 180° about an axis through $C_{(1)}$ and $C_{(7)}$. (2) The prefixes α and β will be retained as previously, and they will continue to be denoted by broken and thick bonds which will denote those directed below and above the plane of the paper respectively, as hitherto. The formula for oleanan-2"β"-ol thus becomes (*C*). The effect is to retain the present prefixes, the method of denoting them in projection formulæ, and the *relative* orientations of the substituents, but to reverse the *actual* arbitrary orientations at each asymmetric centre of a triterpenoid.

In the present state of knowledge it appears probable that formula (*C*) correctly interprets the positions of substituents in oleanan-2"β"-ol relative both to each other and to the steroids.

If later Klyne's correlation of the triterpenoids and steroids should be reversed, the names, the prefixes, and the representation of the prefixes can still be retained and it will merely be necessary to revert from formulæ of type (*C*) to those of type (*B*).

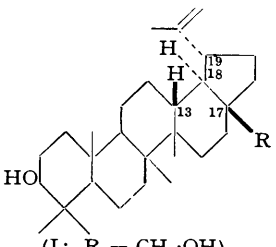
Bijvoet, Peerdeman, and van Bommel (*Nature*, 1951, **168**, 271) have shown that the absolute configuration of glyceraldehyde is correctly represented by the Fischer convention. Lardon and Reichstein (*Helv. Chim. Acta*, 1949, **32**, 2003) have tentatively concluded that the steroid conventions are the opposite of the Fischer convention and should thus be reversed in an *absolute* sense, *e.g.*, that the steroid $C_{(10)}$-methyl group (β) lies below the plane of the conventionally written rings. If Lardon and Reichstein's observation is confirmed, the prefixes, the present methods of writing ring structures, and the representations of α and β by broken and thick or normal bonds can be retained, but the convention on which the bond representation is based can be reversed: it will merely be necessary to specify that a broken bond represents one directed above the plane of the paper and a full or heavy line one directed below the plane of the paper.

Structurally the change of (*B*) to (*C*) emphasises several apparent relations between steroids and triterpenoids (both penta- and tetra-cyclic), but the realities behind these appearances remain to be established.

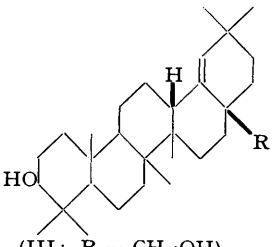
In reversing the presentation of triterpenoid formulæ we have the concurrence of Professor F. S. Spring, F.R.S., Dr. D. H. R. Barton, and Dr. W. Klyne to whom we are much indebted for discussion of the implications. We would also like to express our appreciation to the Editor for his advice and help in drawing up this statement.

Davy, Halsall, and Jones (*J.*, 1951, 2696) have described the conversion of betulin (I), a triterpene of the lupeol group, into moradiol (III), the corresponding member of the germanicol series. There is no possibility of converting the parent alcohol, lupeol (II), into germanicol (IV) by a similar method. Further, the direct isomerisation of lupeol, or one of its derivatives, into germanicol is unlikely to be satisfactory since under the acidic conditions necessary for this process further isomerisation to the δ-amyrin system (V) will occur. This desirable conversion of the parent alcohol has now been achieved following investigations in two directions. The first of these is discussed here; the second in the following paper.

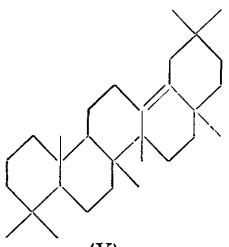
As indicated by Ames, Halsall, and Jones (*J.*, 1951, 450) evidence of rearrangement involving the double bond of lupeol was provided by Duerden, Heilbron, McMeeking, and Spring (*J.*, 1939, 322) who showed that lupeol could be converted into the acetate of an *iso*lupeol by addition of hydrogen chloride, followed by dehydrochlorination and acetylation. Inspection of the constants of the *iso*lupenyl acetate (m. p. 269—270°; $[\alpha]_D^{20}$ +25·3°) suggested the possibility of its identity with germanicyl acetate (m. p. 274—276°; $[\alpha]_D$ +18·1°) (Simpson, *J.*, 1944, 283). A reinvestigation of these reactions has therefore been carried out.



(I; R = CH_2·OH)
(II; R = CH_3)



(III; R = CH_2·OH)
(IV; R = CH_3)



(V)

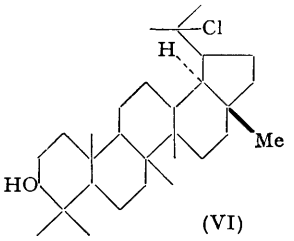
Repetition of the hydrochloride preparation by the original procedure yielded an impure product, and a modified procedure has therefore been developed. Dehydrochlorination of the hydrochloride by boiling it under reflux with acetic anhydride for 20 hours yielded an acetate (*iso*lupenyl acetate) which had the same constants as, and whose melting point was undepressed on admixture with, an authentic specimen of germanicyl acetate, kindly provided by (the late) Dr. J. C. E. Simpson. The infra-red spectra of the two acetates were identical. The constants of the alcohol and the ketone agreed with those of germanicol and germanicone. A comparison of the melting points and rotations of the compounds derived from lupeol with those of the corresponding germanicol derivatives is given in the table.

	*iso*Lupeol series		Germanicol series	
	M. p.	$[\alpha]_D$	M. p.	$[\alpha]_D$
Alcohol	180—181°	+ 7°	176—177°	+ 6° [1]
Acetate	279—280	+19°	274	+18° [1]
Ketone	188—190	+37°	186	— [2]

[1] Simpson, *J.*, 1944, 283.
[2] Dupont and Julia, *Bull. Soc. chim.*, 1947, 1071.

Although the structures of lupeol (II) (Ames, Halsall, and Jones, *loc. cit.*) and germanicol (IV) (David, *Bull. Soc. chim.*, 1947, **14**, 1071; Barton and Brooks, *J.*, 1951, 257) are known, the nature of the intermediate hydrochloride is not immediately apparent. The two basic

structures to be considered are (VI) and (VII). The former involves direct addition of hydrogen chloride, rearrangement to the six-membered ring occurring on dehydrochlorin-



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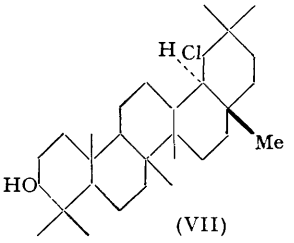

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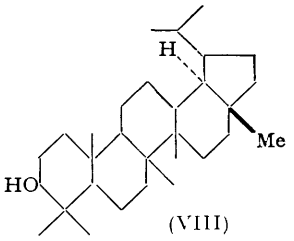
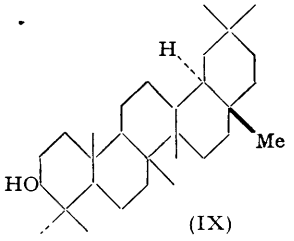


(VIII)

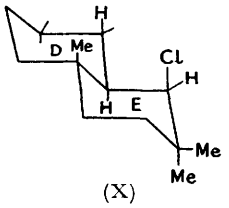


(IX)

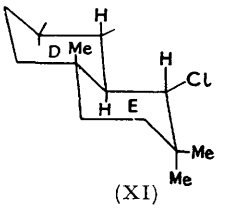
ation; structure (VII), on the other hand, envisages a ring enlargement during the addition. The latter alternative has in fact been shown to be correct.

Reduction of lupeol hydrochloride with sodium and *iso*propyl alcohol or by hydrogenation with a Raney nickel catalyst under mild conditions gave an alcohol which was not lupanol (VIII), thus excluding structure (VI). From structure (VII) 18(α)-oleanan-2"β"-ol (IX) should be obtained. This compound has recently been prepared by Budziarek, Manson, and Spring (*J.*, 1951, 3336) and its constants are identical with those of the reduction product of lupeol hydrochloride (cf. Ames, Davy, Halsall, Jones, and Meakins, *Chem. and Ind.*, 1951, 741). The identity of the alcohol and its acetate with 18(α)-oleanan-2"β"-ol and 18(α)-oleanan-2"β"-yl acetate has been confirmed by mixed melting-point determinations kindly carried out by Professor F. S. Spring.

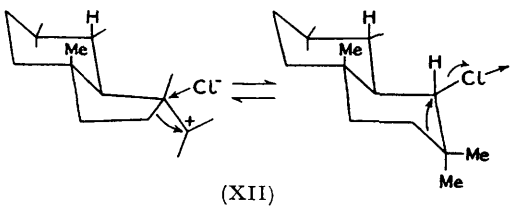
Formula (VII) having been established as the basic structure of lupeol hydrochloride, the configuration at $C_{(19)}$, carrying the chlorine atom, has to be elucidated. The two possibilities are represented by the partial formulæ (X) and (XI), with the chlorine atom polar (β) and equatorial (α), respectively.



(X)



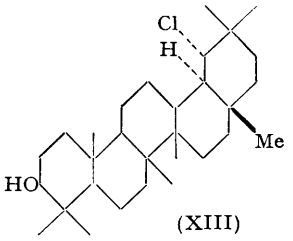
(XI)



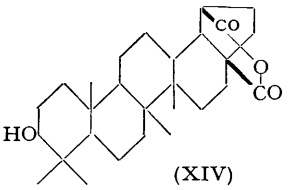
(XII)

Elimination of hydrogen chloride by an E_2 mechanism (*trans*-elimination) from (X) should lead to germanicol. An analogous reaction is the formation of moradiol diacetate by the *trans*-dehydration of 18(α)-oleanan-2"β" : 19(β) : 28-triol 2"β" : 28-diacetate (Davy, Halsall, Jones, and Meakins, *J.*, 1951, 2702). In the case of (XI) the product should be lupeol, the reaction being analogous to the formation of the five-membered ring A which occurs when elimination of the $C_{(2)}$-hydroxyl group of pentacyclic triterpenes is brought about, as in the preparation of γ-lupene from lupanol (cf. Barton, *Experientia*, 1950, **6**, 316). Duerden *et al.* (*loc. cit.*) effected dehydrochlorination of lupeol hydrochloride with silver acetate in ethanol and obtained lupeol, an observation which has been confirmed in the present work. In this reaction an E_2-type of mechanism presumably operates, attack by Ag^+ on the chlorine atom being the initial step (cf. XII). This being so, the configuration

at $C_{(19)}$ in the hydrochloride must be that represented by (XI), and the hydrochloride is to be formulated as 19(α)-chloro-18(α)-oleanan-2" β "-ol (XIII).



(XIII)



(XIV)

The dehydrochlorination to the germanicol structure which occurs on boiling under reflux with acetic anhydride is unlikely to take place by an E_2 ionic mechanism. Two possible alternatives have been considered: an E_1 ionic mechanism and a pyrolytic unimolecular *cis*-elimination. Structure (XI) fulfils the stereospecific requirements of the second mechanism. To distinguish between these possibilities lupeol hydrochloride has been heated under reflux in xylene, a non-ionising solvent of the same boiling point as acetic anhydride, and in benzonitrile, an unreactive solvent with good ionising properties. In the first case the hydrochloride was recovered unchanged, but in benzonitrile, as in acetic anhydride, germanicol was obtained. The pyrolytic mechanism is thus excluded and the E_1 ionic mechanism indicated.

The re-formation of lupeol from the hydrochloride is of considerable stereochemical significance. As the silver acetate reaction will not affect the D–E ring fusion, lupeol must have the same D–E configuration as the hydrochloride and, in turn, as 18(α)-oleanan-2"β"-ol since this is formed from the hydrochloride. The D–E ring fusion of 18(α)-oleanan-2"β"-ol is known unambiguously to be *trans* from its method of synthesis (Budziarek *et al.*, *loc. cit.*) and hence the *trans*-D–E ring fusion for lupeol, suggested by Davy, Halsall, Jones, and Meakins (*loc. cit.*), is confirmed. Further, the formation of the hydrochloride *and* its reconversion into lupeol, as represented in (XII), requires that the *iso*propenyl group should be *trans* to the $C_{(17)}$-methyl group. This conclusion differs from that previously drawn by Davy, Halsall, Jones, and Meakins (*loc. cit.*) by consideration of the conversion of betulin (I) into the anhydride (XIV) (Ruzicka and Rey, *Helv. Chim. Acta*, 1943, **25**, 2143). We believe, however, that inversion occurs at $C_{(19)}$ at some stage during the formation of (XIV). This point is now being examined.

Experimental

(M.p.s were determined on a Kofler block and are corrected. Rotations were determined in chloroform. Light petroleum refers to the fraction with b. p. 40—60°. The alumina used for chromatography had an activity of I—II.)

Lupeol Hydrochloride (cf. Duerden *et al.*, *loc. cit.*).—Dry ethanol (800 c.c.) was saturated with hydrogen chloride at 0° and added gradually to a solution of lupeol (10 g.) in ethanol (500 c.c.) with periodic cooling. After 5 days at 20°, dilution with water and extraction with chloroform yielded the hydrochloride, which crystallised from ethanol containing a little chloroform as a felted mass of needles (4·1 g.), m. p. 204—206°, $[\alpha]_D^{20}$ −26° (*c*, 1·0). Further purification was effected by adsorption of the hydrochloride (0·82 g.) from benzene–light petroleum (1 : 4; 85 c.c.) on a column of alumina (60 g.), and elution with benzene–ether (1 : 1; 500 c.c.), whereupon a fraction (0·74 g.) was obtained which crystallised from ethanol as needles (0·63 g.), m. p. 211—212°, $[\alpha]_D^{20}$ −31° (*c*, 1·1) (Found : C, 77·6; H, 10·9; Cl, 7·75. Calc. for $C_{30}H_{51}OCl$: C, 77·8; H, 11·0; Cl, 7·7%). Duerden *et al.* (*loc. cit.*) report the following constants for lupeol hydrochloride : m. p. 195—196°, $[\alpha]_D$ −10° (*c*, 0·9).

Germanicyl Acetate (iso*Lupenyl Acetate*).—Lupeol hydrochloride (3·2 g.) in acetic anhydride (50 c.c.) was boiled under reflux for 22 hours. The crystalline material (2·4 g.) which separated on cooling was washed with alcohol, dried, adsorbed from light petroleum–benzene (9 : 1; 70 c.c.) on a column of alumina (250 g.), and eluted with the same solvent (2 × 1500 c.c.). The second fraction (1·95 g.) was crystallised from chloroform–ethanol, giving lustrous plates of germanicyl acetate (*iso*lupenyl acetate) (1·6 g.), m. p. 274—275°, $[\alpha]_D^{20}$ +18° (*c*, 0·99). Repeated recrystallisation raised the m. p. to 279—280° (undepressed on admixture of the specimen with

authentic germanicyl acetate), $[\alpha]_D^{20}$ +19° (*c*, 0·95) (Found: C, 82·05; H, 11·3. Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%).

Germanicol (iso*Lupeol*).—*iso*Lupenyl acetate (275 mg.) in benzene (3 c.c.) was heated under reflux for 2 hours with 5% ethanolic potassium hydroxide (20 c.c.). The product (259 mg.), isolated in the usual manner, was adsorbed from light petroleum–benzene (9 : 1) on a column of alumina (20 g.). The fraction (220 mg.) eluted with benzene–ether (4 : 1) was crystallised from methanol, giving germanicol (*iso*lupeol) as small needles (200 mg.), m. p. 180—181° (undepressed on admixture of the specimen with an authentic sample of germanicol), $[\alpha]_D^{20}$ +7° (*c*, 1·0) (Found: C, 84·3; H, 11·8. Calc. for $C_{30}H_{50}O$: C, 84·45; H, 11·8%).

Germanicone (iso*Lupenone*).—*iso*Lupeol (410 mg.) in acetic acid (70 c.c.)–chloroform (18 c.c.) was added to chromic acid (150 mg.) in 95% acetic acid (15 c.c.), and the mixture kept at 20° for 2 days. The product, isolated in the usual manner, was adsorbed from light petroleum on a column of alumina (50 g.). Elution with light petroleum–benzene afforded germanicone (*iso*lupenone) (320 mg.), which was twice crystallised from methanol–chloroform giving thin lustrous plates (265 mg.), m. p. 188—190°, $[\alpha]_D^{20}$ +37° (*c*, 1·0) (Found: C, 85·1; H, 11·4. Calc. for $C_{30}H_{48}O$: C, 84·8; H, 11·4%).

Conversion of Lupeol Hydrochloride into Lupenyl Acetate.—Lupeol hydrochloride (300 mg.) was dissolved in hot ethanol (30 c.c.) and boiled under reflux with silver acetate (400 mg.) for 18 hours. During this time the suspended solid became dark and a silver mirror formed on the surface of the flask. Dilution with water followed by ether-extraction yielded a product, which was heated under reflux with acetic anhydride (3·5 c.c.) for 1 hour. The solution was then poured into water, and the product, isolated with ether, was crystallised from ethanol–chloroform, forming plates (230 mg.), m. p. 204—208°. Further recrystallisation afforded lupenyl acetate as small plates (200 mg.), m. p. 215—216° (undepressed on admixture of the specimen with an authentic sample), $[\alpha]_D^{20}$ +46° (*c*, 0·93).

18(α)-*Oleanan-2"β"-yl Acetate.*—(a) *Reduction of lupeol hydrochloride with sodium and iso-propyl alcohol.* Sodium (7—8 g.) was added in small pieces during 2 hours to a boiling solution of lupeol hydrochloride (300 mg.) in dry *iso*propyl alcohol (50 c.c.). Destruction of excess of sodium with ethanol, and dilution of the solution with water and extraction with chloroform yielded a discoloured solid (245 mg.) which was acetylated at 20° for 12 hours with pyridine (4 c.c.)–acetic anhydride (3 c.c.) and then adsorbed from light petroleum–benzene on a column of alumina (30 g.). Elution with light petroleum–benzene (9 : 1; 700 c.c.) yielded 18(α)-oleanan-2"β"-yl acetate which crystallised from chloroform–methanol as plates (65 mg.), m. p. 286° {undepressed on admixture of the specimen with an authentic sample [m. p. 280—282°; $[\alpha]_D$ +43°]}, $[\alpha]_D^{20}$ +42° (*c*, 1·1) (Found: C, 81·3; H, 11·4. Calc. for $C_{32}H_{54}O_2$: C, 81·65; H, 11·6%).

(b) *Hydrogenolysis of lupeol hydrochloride.* Lupeol hydrochloride (500 mg.) in ethanol (230 c.c.) was shaken with hydrogen in the presence of Raney nickel for several hours at 20°. After filtration and evaporation of the solution the amorphous residue was acetylated with acetic anhydride (10 c.c.)–pyridine (10 c.c.) for 2 hours at 100°. The product, treated as above, yielded 18 (α)-oleanan-2"β"-yl acetate as plates (395 mg.), m. p. 283—284°, $[\alpha]_D^{20}$ +39° (*c*, 1·2).

18(α)-*Oleanan-2"β"-ol.*—18(α)-Oleanan-2"β"-yl acetate (206 mg.) in benzene (20 c.c.) was heated under reflux with 4% ethanolic potassium hydroxide (40 c.c.) for 2 hours. Dilution with water followed by ether extraction yielded a discoloured solid (170 mg.) which was adsorbed from light petroleum–benzene (1 : 1) on a column of alumina (10 g.). Elution with benzene–ether (4 : 1) yielded 18(α)-oleanan-2"β"-ol which, after three recrystallisations from chloroform–methanol, gave lustrous prisms (125 mg.), m. p. 230—231° with softening from 224° {undepressed on admixture of the specimen with an authentic sample, m. p. 229—230°, $[\alpha]_D$ +36°}, $[\alpha]_D^{20}$ +38° (*c*, 0·92).

Dehydrochlorination of Lupeol Hydrochloride in Benzonitrile.—The hydrochloride (0·5 g.) in purified benzonitrile (50 c.c.) was heated under reflux for 4 hours with nitrogen bubbling slowly through the solution. The solvent was then evaporated under reduced pressure, ethanol was added and also evaporated off, and the residue was adsorbed from light petroleum–benzene (9 : 1) on a column of alumina (50 g.). The fraction eluted with benzene–ether (4 : 1) was crystallised twice from chloroform–methanol, giving germanicol as small needles (250 mg.), m. p. 173—176° undepressed on admixture of the specimen with an authentic sample.

Thanks are due to Mr. E. S. Morton and Mr. H. Swift for microanalyses.

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