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# TERPENOIDS—XXXIX.[1] IRESIN (PART 5)[2]

## COMPLETE STRUCTURE AND ABSOLUTE CONFIGURATION[3,4]

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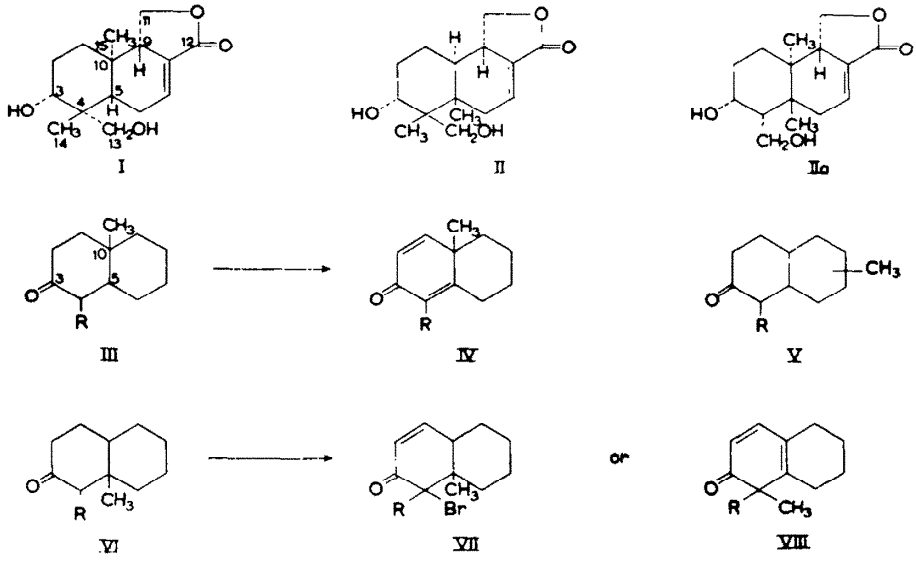
**Abstract**—The remaining uncertainty in the structure of iresin (I)—the location of the angular methyl group—has now been settled rigorously by comparing the course of tribromination–dehydrobromination experiments of its derived nor-ketone XI with steroid models. Thus it was shown that di- or tri-bromination of 4α-methyldihydrotestosterone acetate leads to 2α,6β-dibromo-4-methyltestosterone acetate, also obtainable by dibromination of 4-methyltestosterone acetate. Rotatory dispersion studies of relevant iresin and steroid model compounds demonstrate that this sesquiterpene possesses the "wrong" absolute configuration as compared to the steroids and higher terpenes.

EARLIER degradation experiments[5] from our Laboratory have shown that the sesquiterpene iresin[6] possesses structure I or II (without the absolute stereochemical implication). We should now like to report experiments[7] which establish expression I for iresin and also settle all outstanding stereochemical details.

The location of an angular methyl group in a polycyclic terpene is usually beset with considerable experimental difficulties[8] and we decided to examine a novel approach involving bromination–dehydrobromination of appropriate ketonic transformation products. The experience gained in this connection has subsequently proved also very useful in locating the angular methyl group of the diterpene cafestol.[9] In principle, the problem resolves itself to differentiating between a bicyclic (or polycyclic) ketone possessing the structural feature found in III, V or VI. Using procedures which have been studied extensively in the steroid series,[10] dibromination *cum* dehydrobromination of ketone III should lead to the cross-conjugated dienone IV, while if the angular methyl group is located at the alternate bridgehead position (VI), a mono-unsaturated ketone (e.g. VII) or a rearranged,[11] linearly conjugated dienone (VIII) should result. If the methyl group is not situated in an angular

[1] Paper XXXVIII; C. Djerassi, R. Mauli and L. H. Zalkow, *J. Amer. Chem. Soc.* **81**, in press (1959).
[2] Part 4; P. Crabbé, S. Burstein and C. Djerassi, *Bull. Soc. Chim. Belg.* **67**, 632 (1958).
[3] Supported by the Division of Research Grants (grant No. RG-3863) of the National Institutes of Health, U. S. Public Health Service.
[4] Taken from Part II of the Ph.D. thesis of Sumner Burstein.
[5] [a] C. Djerassi, W. Rittel, A. L. Nussbaum, F. W. Donovan and J. Herran, *J. Amer. Chem. Soc.* **76**, 6410 (1954); [b] C. Djerassi and W. Rittel, *Ibid.* **79**, 3528 (1957).
[6] C. Djerassi, P. Sengupta, J. Herran and F. Walls, *J. Amer. Chem. Soc.* **76**, 2966 (1954).
[7] A preliminary communication outlining these results has already appeared [C. Djerassi and S. Burstein, *J. Amer. Chem. Soc.* **80**, 2593 (1958)] as well as independent confirmation of the structure and relative configuration by X-ray analysis [M. G. Rossmann and W. N. Lipscomb, *Ibid.* **80**, 2592 (1958); *Tetrahedron* **4**, 274 (1958).
[8] Many pertinent examples can be found in J. L. Simonsen and D. H. R. Barton, *The Terpenes* Vol. III. Cambridge University Press (1952).
[9] C. Djerassi, M. Cais and L. A. Mitscher, *J. Amer. Chem. Soc.* **81**, 2386 (1959).
[10] L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene* (3rd Ed.). Reinhold, New York (1949); C. W. Shoppee, *Chemistry of the Steroids*. Academic Press, New York (1958).
[11] J. M. Beaton, F. S. Spring, R. Stevenson and J. L. Stewart, *Tetrahedron* **2**, 246 (1958).

position (e.g. V), then a phenol would be formed and all of these alternate products could be differentiated by chemical or spectroscopic means.



Since the double bond of iresin (I) would have interfered in the projected bromination experiments, it was decided to operate in the iso-dihydro series[12] and several approaches were examined for the preparation of the required key intermediate, 13-nor-3-dehydroisodihydroiresin (XI). The first method involved acid-promoted cleavage of 3-dehydroisodihydroiresin 13-trityl ether (X),[13] which was accompanied by retroaldolization and provided the desired nor-ketone XI, together with formaldehyde and triphenylcarbinol. Alternatively, the unsaturated 13-nor-ketone XIII, which had been obtained darlier[5b,13] from iresin (I), was hydrogenated to 13-nor-3-dehydrodihydroiresin (XIV)[14] and then subjected to alkaline isomerization leading again to XI.

Since neither method proceeded in satisfactory overall yield, attention was directed towards the direct oxidation[15] of isodihydroiresin (IX) with chromium trioxide in sulfuric acid–acetone.[16] Under suitable conditions, IX could be converted in 64 per cent yield into the keto aldehyde XII, which underwent a reverse Claisen condensation upon treatment with acid (or less satisfactorily with base[17]) to yield the required nor-ketone XI. It is pertinent to note that the keto aldehyde XII did not give a color

[12] The initial hydrogenation product, dihydroiresin (XXVII) can be isomerized wtih base[6] to the stable isodihydroiresin (IX).

[13] C. Djerassi, F. W. Donovan, S. Burstein and R. Mauli, *J. Amer. Chem. Soc.* **80**, 1972 (1958).

[14] This substance has already been obtained in pure form by acid-catalyzed retroaldolization[2] of naturally occurring dihydroiresone (XXVI), but since the latter is extremely rare[2] it could not be employed as starting material in the present investigation.

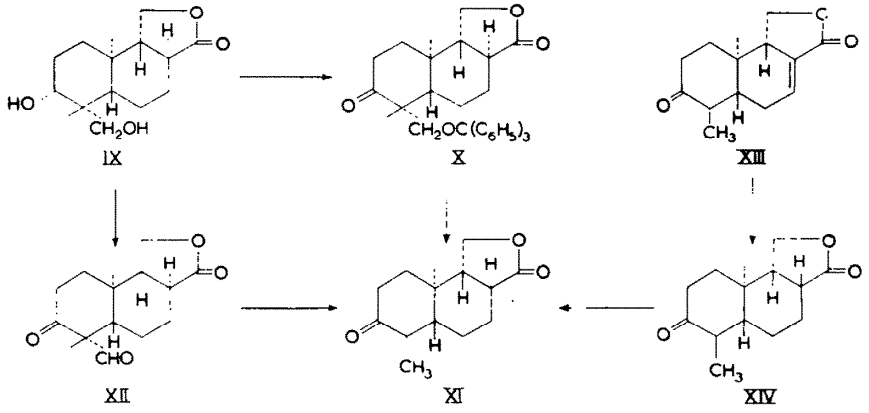
[15] Oxidation with chromium trioxide in pyridine solution does not afford[5b] the keto aldehyde XII.

[16] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946). For further references to this oxidation procedure see C. Djerassi, R. R. Engle and A. Bowers, *J. Org. Chem.* **21**, 1547 (1956).

[17] The comparative stability (see experimental) of the keto aldehyde XII towards base is remarkable in view of the known lability [see A. L. Wilds and C. Djerassi, *J. Amer. Chem. Soc.* **68**, 1715 (1946)] of such formyl ketones and may possibly be ascribed to prior opening of the lactone ring.

with ferric chloride, thus excluding a structure[18] such as IIa from consideration as a possible representation for iresin.

Monobromination of XI led to 2-bromo-13-nor-3-dehydroisodihydroiresin (XV).[19] Ultraviolet[20] and infrared[21] spectroscopic examination confirmed the equatorial orientation of the bromine atom, which represented strong indication[22,23] that the




angular methyl group of iresin was located at C-10 (I). If the nor-ketone XI were actually derived from formulation II (angular methyl group at C-5) of iresin, then the bromine atom would have been expected[22,24] to exhibit an axial orientation.

In order to provide more conclusive evidence bearing on this point, the nor-ketone XI was treated with two molar equivalents of bromine in the expectation that a 2,4-dibromo ketone (XVIII) would be formed,[25] which could then be subjected to dehydrobromination. The presence of two bromine atoms in the crystalline reaction product was demonstrated by analysis, but ultraviolet and infrared spectral examination as well as determination of the optical rotatory dispersion curve (see Fig. 1) clearly showed the presence of an $\alpha,\beta$-unsaturated carbonyl moiety. The formation of a double bond implied *in situ* dehydrobromination which in turn required three molar equivalents of bromine. That the reaction had indeed proceeded by a process of disproportionation and had involved three equivalents of bromine was shown by the isolation of the identical product in the tribromination of the nor-ketone XI. The ultraviolet absorption maximum at 262–264 m$\mu$ (log $\varepsilon$ 4·09) was suggestive of a 2,6-dibromo-$\Delta^4$-3-keto chromophore, since such steroids with an axial 6-bromine

[18] Footnote 23 in ref. 5*b*.

[19] The position of the bromine atom was not established rigorously, but since the A/B *trans* juncture of XI has been proved (*vide infra*), substitution at C-2 follows almost certainly by analogy to the known steric course of the monobromination of *trans*-9-methyl-3-decalones [B. Riniker, J. Kalvoda, D. Arigoni, A. Fürst, O. Jeger, A. M. Gold and R. B. Woodward, *J. Amer. Chem. Soc.* **76**, 312 (1954); M. Yanagita and K. Yamakawa, *J. Org. Chem.* **21**, 500 (1956); C. Djerassi and D. Marshall, *J. Amer. Chem. Soc.* **80**, 3986 (1958)].

[20] R. C. Cookson, *J. Chem. Soc.* 282 (1954).

[21] R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, *J. Amer. Chem. Soc.* **14**, 2828 (1952); R. N. Jones, *Ibid.* **75**, 4839 (1953).

[22] E. J. Corey, *J. Amer. Chem. Soc.* **75**, 2301 (1953) and later papers.

[23] A similar argument has been employed [C. Djerassi, M. Cais and L. A. Mitscher, *J. Amer. Chem. Soc.* **80**, 247 (1958)] in the structure proof of cafestol.

[24] E. J. Corey and J. J. Ursprung, *J. Amer. Chem. Soc.* **78**, 5041 (1956).

[25] Under somewhat different experimental conditions, M. Yanagita and A. Tahara, *J. Org. Chem.* **20**, 959 (1955), isolated such 2,4-dibromo ketones in the tetrahydrosantonin series.

atom absorb near 250 m$\mu$[26] and the additional methyl substituent can be expected to produce a bathochromic shift of at least 10 m$\mu$.[10,27] The correctness of structure XVI as the di- or tri-bromination product of 13-nor-3-dehydroisodihydroiresin (XI) was established by the course of the dehydrobromination with collidine–dimethylformamide which led to a crystalline product to which we are assigning the 1,4,6-trienone formulation XVII. This is consistent with the analytical figures and especially with the ultraviolet absorption spectrum, which exhibited maxima at 224 and 296 m$\mu$

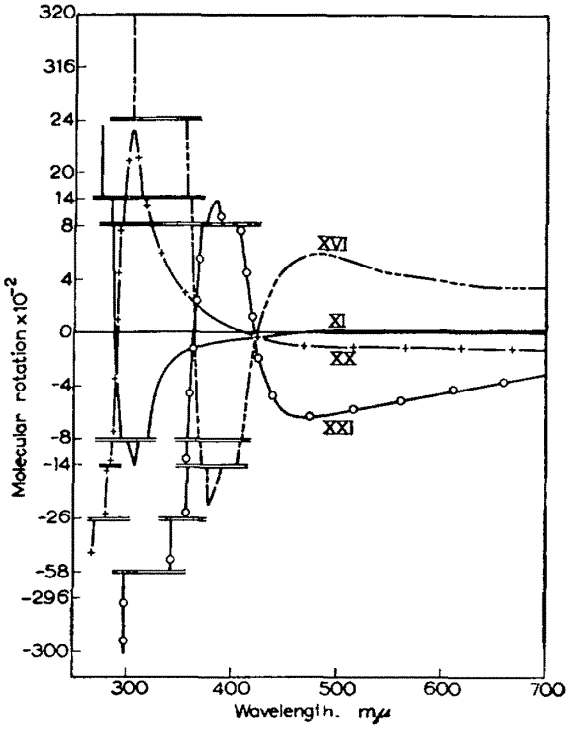



Fig. 1.

and a shoulder at 250 m$\mu$. Steroidal 1,4,6-trien-3-ones (XIX) absorb at 222, 256 and 298 m$\mu$[26a,28] and furthermore, they show three infrared bands in the double bond region between 6·0 and 6·25 $\mu$, which were also noted in the trienone XVII of the iresin series.

Even more striking support for structures XVI and XVII could be presented by model experiments in the steroid series. For this purpose, 4$\alpha$-methyldihydrotestosterone acetate (XX)[29] was tribrominated under the same conditions employed above for XI, whereupon 2$\alpha$,6$\beta$-dibromo-4$\alpha$-methyltestosterone acetate (XXI) was obtained in about 50 per cent yield. The axial ($\beta$)-orientation of the bromine atom at C-6

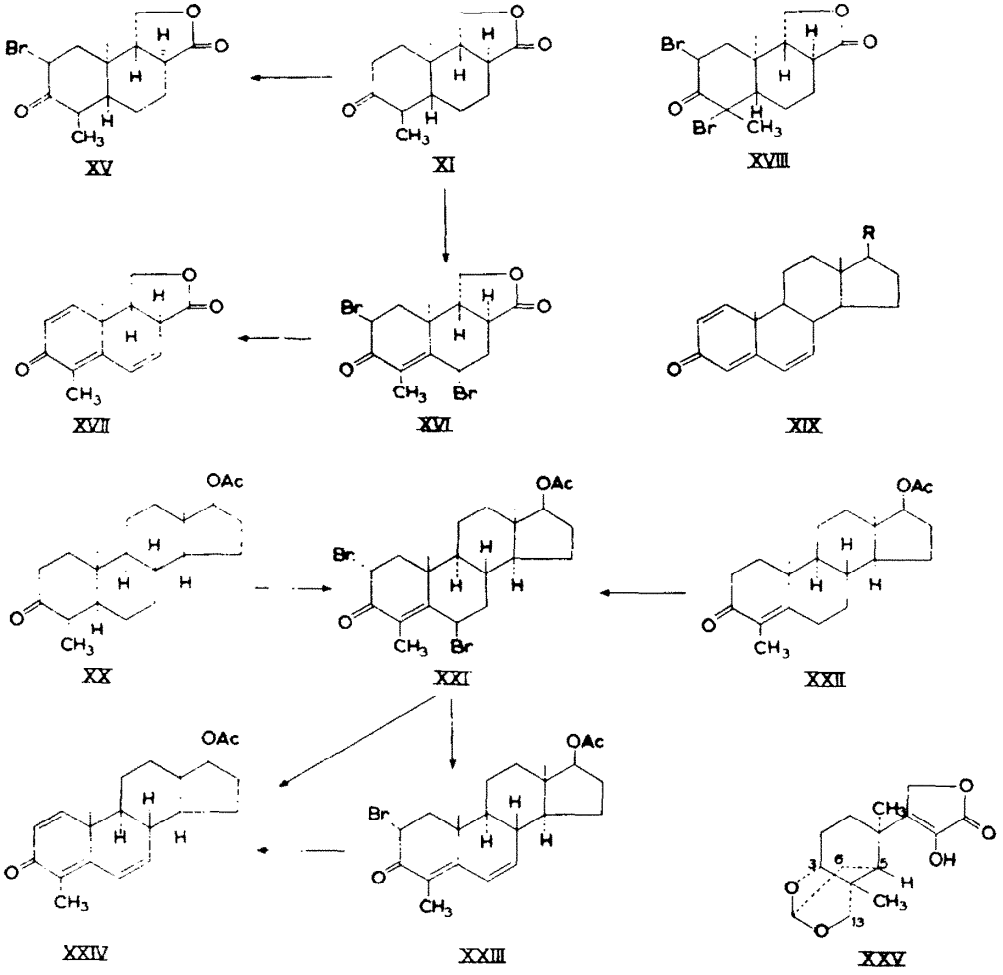
[26] [a] C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann and J. Pataki, *J. Amer. Chem. Soc.* **72**, 4534 (1950); [b] A. L. Nussbaum, O. Mancera, R. Daniels, G. Rosenkranz and C. Djerassi, *Ibid.* **73**, 3263, footnote 9 (1951); [c] M. Fieser, M. A. Romero and L. F. Fieser, *Ibid.* **77**, 3305 (1955); [d] B. Ellis and V. Petrow, *J. Chem. Soc.* 1179 (1956).

[27] R. B. Woodward, *J. Amer. Chem. Soc.* **64**, 76 (1942).

[28] S. Kaufmann, J. Pataki, G. Rosenkranz, J. Romo and C. Djerassi, *J. Amer. Chem. Soc.* **72**, 4531 (1950).

[29] Y. Mazur and F. Sondheimer, private communication. The synthesis was patterned after that reported for 4$\alpha$-methylcholestan-3-one [Y. Mazur and F. Sondheimer, *J. Amer. Chem. Soc.* **80**, 5220 (1958)].

follows from the position of the ultraviolet absorption maximum (263·5 mμ)[30] and from the fact that its rotatory dispersion curve (Fig. 1) was very similar to that[31] of 6β-bromotestosterone acetate and quite distinct from that[31] of the equatorial 6α-isomer. The direct formation of 4-methyl-2,6-dibromo-$\Delta^4$-3-ketones (XVI, XXI) by tribromination of 4-methyl-3-ketones (XI, XX) with the A/B *trans* juncture is best interpreted by assuming initial production of a 2,4-dibromo intermediate (e.g. XVIII) —typical of A/B *trans* 3-keto steroids[10]—followed by spontaneous dehydrobromination to a 2-bromo-$\Delta^4$-3-ketone and allylic bromination[26a] at C-6. The substantial correctness of this assumption was indicated by formation, in good yield, of the identical 2α,6β-dibromo-4-methyltestosterone acetate (XXI) by dibromination in ether–acetic acid solution of 4-methyltestosterone acetate (XXII).[32] These are precisely the conditions under which testosterone acetate yields 2α,6β-dibromotestosterone acetate.[26a]




[30] If the bromine atom had been equatorial, the absorption maximum would have occurred below 255 mμ.[26,27]
[31] C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **80**, 1216 (1958).
[32] F. Sondheimer and Y. Mazur, *J. Amer. Chem. Soc.* **79**, 2906 (1957). We are indebted to Syntex, S. A., Mexico City, for a generous gift of testosterone required in the synthesis of XXII.

Dehydrobromination of 2α,6β-dibromo-4-methyltestosterone acetate (XXI) with collidine–dimethyl formamide proceeded unsatisfactorily and the only pure product which was isolated represented partially dehydrobrominated material in the form of 2-bromo-4-methyl-6-dehydrotestosterone acetate (XXIII), which exhibited a single ultraviolet absorption maximum at the expected position (294 mμ). However, when the dehydrobromination was conducted with lithium carbonate and lithium bromide in dimethyl formamide,[33] there was isolated a difficultly separable mixture of the crystalline 2-bromo-$\Delta^{4,6}$-3-ketone (XXIII) and of oily 4-methyl-$\Delta^{1,4,6}$-androstatrien-17β-ol-3-one acetate (XXIV). The latter was also obtained when the 2-bromo-$\Delta^{4,6}$-ketone XXIII was refluxed for 4 hr with collidine and it did exhibit the characteristic triple ultraviolet absorption maxima[34] at 226, 255 (shoulder) and 306 mμ. Furthermore, its crystalline 2,4-dinitrophenylhydrazone had the expected ultraviolet absorption maximum at 412 mμ.

The above reactions leave no doubt about the correctness of structures XVI and XVII for the transformation products of iresin and these, in turn, are only possible if the sesquiterpene possesses structure I. The alternate expression II does not permit formation of a double bond between positions 4 and 5.

With the structural situation settled, it is now possible to examine in detail the relative and absolute stereochemistry of the molecule. The bromination experiments strongly favor a *trans* ring juncture and this is supported by the rotatory dispersion results discussed below. Using the absolute representation I, a *trans* fusion automatically defines the stereochemistry at C-3 and C-4, since it has already been pointed out earlier[35] that the internal acetal XXV, produced[5b] by ozonolysis of iresin (I), requires that the C-3 hydroxyl group, the 5-6 bond and the C-13 substituent all must be on the same side of ring A. Evidence for the equatorial nature of the C-3 hydroxyl group[36] of iresin has been presented earlier[2,13]—*viz* the formation[2] of dihydroiresin (XXVII) in the sodium borohydride reduction of dihydroiresone (XXVI)—thus defining the relative configuration of four out of the five asymmetric centers of iresin (I).

There remains only the stereochemistry of C-9 and this can be established by considering the course of the catalytic hydrogenation of iresin (I) and its naturally occurring[2] double bond isomer, isoiresin (XXVIII). It has already been noted[12] that the initial product of the catalytic hydrogenation of iresin (I) is dihydroiresin and by assuming entrance of hydrogen from the side opposite to the C-10 angular methyl group, we arrive at stereo-formula XXVII for dihydroiresin. Any remaining doubt is dissipated by the course of the catalytic hydrogenation of isoiresin (XXVIII) which also yielded[2] dihydroiresin (XXVII)[37] and it is inconceivable that in this case adsorption on the catalyst surface and hence entry of hydrogen occurred from the same side of the molecule as the angular methyl group. Dihydroiresin upon treatment with

[33] R. Joly and J. Warnant, *Bull. Soc. Chim. Fr.* 367 (1958).

[34] These values are almost identical with those observed[9] with 4-ethyl-$\Delta^{1,4,6}$-cholestatrien-3-one, which also was noncrystalline, but differ slightly from those observed with the trienone XVII of the iresin series. This slight hyposchromic shift may be due to the lactone ring.

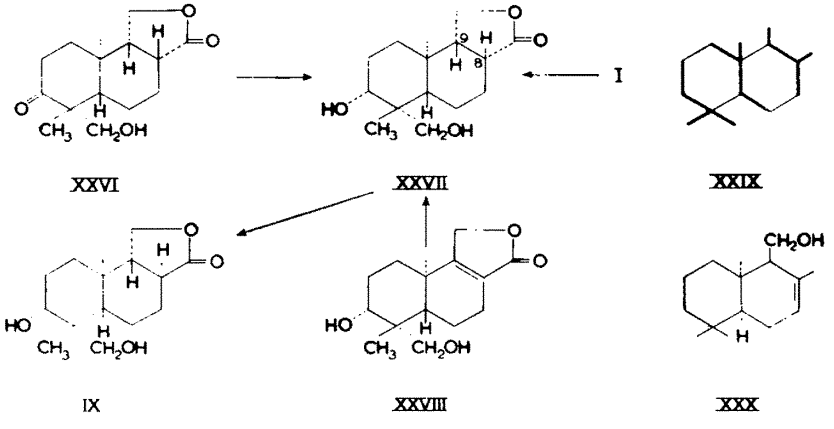
[35] Footnote 26 in ref. 5*b*.

[36] In the internal acetal XXV, this hydroxyl group must, of course, be axial in order to permit construction of a six-membered ring through *meta* substituents of a cyclohexane ring. This requirement is easily accommodated by "flipping" of the ring from one chair conformation into the alternate one, a conformational change which is possible only after ring B has been opened in the ozonolysis of I.

[37] This experiment was actually conducted on the corresponding diacetates.

base at room temperature is isomerized[6] irreversibly in excellent yield to isodihydroiresin. Since it has been shown[5b] that this isomerization involves only inversion of configuration at C-8, then if one accepts expression XXVII for dihydroiresin, IX follows automatically for isodihydroiresin. Inspection of these structures immediately offers a rationalization for the driving force in this isomerization, since in the unstable dihydroiresin (XXVII), the carboxyl group of the lactone is axially oriented. In the stable isomer, isodihydroiresin (IX), this is now equatorial thus relieving the strong 1,3-interaction between the axial angular methyl group and the carboxyl group in dihydroiresin (XXVII). This inversion appears to occur prior to opening of the lactone ring, since it has been observed[38] that some isodihydroiresin can be isolated by direct chloroform extraction of the aqueous, alkaline solution before acidification.

We can turn now to a consideration of the absolute configuration of iresin, which was settled entirely by rotatory dispersion measurement.[39] In Fig. 1, there are reproduced the rotatory dispersion curves of 13-nor-3-dehydroisodihydroiresin (XI) and of its bromination product XVI together with those of 4α-methyldihydrotestosterone acetate (XX) and of 2α,6β-dibromo-4-methyltestosterone acetate (XXI). The latter two compounds represent standards of known absolute configuration and the relative configurations of the two pairs (XI vs. XX; XVI vs. XXI) are identical as far as the bicyclic systems are concerned. As has been demonstrated by us in a great number of examples,[39,40,41] this condition is sufficient—barring unusual conformational distortion—to produce identical signs and similar shapes of the rotatory dispersion curves if the relative and absolute configurations are identical. On the other hand, if the relative configurations are identical but the absolute configurations are opposite, then mirror image curves will be obtained and this is exactly the situation which is observed in Fig. 1. This is supported further by the rotatory dispersion data (see experimental) of 4-methyl-$\Delta^{1,4,6}$-androstatrien-17β-ol-3-one acetate (XXIV) and of the corresponding trienone XVII of the iresin series where Cotton effects of opposite sign are again observed. Other relevant rotatory dispersion curves are given in our earlier paper[2] and the entire rotatory dispersion evidence is overwhelmingly in favor




[38] Footnote 28 in ref. 5b.
[39] See C. Djerassi, *Bull. Soc. Chim. Fr.* 741 (1957) for earlier references to work carried out in our Laboratory on the relation of structure and rotatory dispersion of cyclic ketones.
[40] C. Djerassi and D. Marshall, *J. Amer. Chem. Soc.* **80**, 3986 (1958).
[41] C. Djerassi, D. Marshall and T. Nakano, *J. Amer. Chem. Soc.* **80**, 4853 (1958).

of the absolute representation I, which is the mirror image of that found among the steroids and most of the higher terpenoids.

Iresin (I)[6] and its naturally occurring relatives[2] dihydroiresone (XXVI), dihydroiresin (XXVII) and isoiresin (XXVIII) represent the first group of sesquiterpenes which follow the isoprene skeleton XXIX. This particular bicyclofarnesol skeleton XXIX is found in virtually all of the di- and tri-terpenes and in demethylated form in the steroids. The discovery of iresin has thus afforded a missing link between the lower (mono- and sesqui-terpenes) and the higher ones. Subsequently, another sesquiterpene, drimenol (XXX), has been described[42] which also follows this isoprenoid pattern (XXIX), but it should be noted that its absolute configuration bears an antipodal relationship to iresin (I). The recent isolation of farnesiferol A[43] adds still another sesquiterpene to the iresin class and we have already speculated in another paper[9] on the possible biogenetic significance of this observation.

## EXPERIMENTAL[44]

*13-Nor-3-dehydroisodihydroiresin* (XI)

(a) *From* 3,13-*bisdehydroisodihydroiresin* (XII). To a rapidly stirring solution of 2·74 g of isodihydroiresin (IX)[6] in 160 cc of acetone (distilled from permanganate) was added at room temp. 6·06 cc of an 8 N chromium trioxide–sulfuric acid solution.[16] After standing for a few min, 1 l. of water was added and the product extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated to dryness. Recrystallization of the residue from hexane–acetone afforded 1·72 g of the *keto aldehyde* XII, m.p. 184–189°, $[\alpha]_D$ +48°, $\lambda_{max}^{CHCl_3}$ 5·60, 5·75 and 5·85 $\mu$. The substance gave no color with alcoholic ferric chloride. (Found: C, 68·26; H, 7·85; O, 23·78. $C_{15}H_{20}O_4$ requires: C, 68·16; H, 7·63; O, 24·21%).

The above keto aldehyde XII (1·72 g) was heated under reflux for 46 hr with 210 cc of conc HCl, 1 l. of water and 140 cc of ethanol and the volume was then reduced to one-half under reduced pressure. Extraction with chloroform, washing, drying and evaporating yielded an oily residue, which was dissolved in benzene and filtered through a short column (5·0 g) of alumina. Evaporation of the benzene solution and recrystallization from hexane–acetone furnished 710 mg of *13-nor-3-dehydroisodihydroiresin* (XI), m.p. 149–155. The analytical sample exhibited m.p. 153–155°,[45] $[\alpha]_D$ −8°, $\lambda_{max}^{CHCl_3}$ 5·61 and 5·84 $\mu$, R.D. (Fig. 1) in methanol (*c*, 0·08): $[\alpha]_{700}$ −4·9°, $[\alpha]_{589}$ +4·9°, $[\alpha]_{308}$ −605°, $[\alpha]_{275}$ +1000°. (Found: C, 71·06; H, 8·56; O, 20·54. $C_{14}H_{20}O_3$ requires: C, 71·16; H, 8·53; O, 20·31%).

When 227 mg of the keto aldehyde XII was left at room temp for 30 hr with 1 N NaOH, the reaction mixture acidified and processed as above, there was isolated 36 mg of the desired nor-ketone XI, m.p. 150–154°. Chromatography of the mother liquors on either neutral or basic (pH 8–9) alumina yielded only recovered keto aldehyde.[17]

(b) *From* 3-*dehydroisodihydroiresin* 13-*trityl ether* (X). A solution of 500 mg of the trityl ether X[13] in 60 cc of dioxane and 50 cc of 20% $H_2SO_4$ was heated under reflux for 48 hr. The volume was reduced under diminished pressure, the dimedone derivative of formaldehyde (m.p. 190–192°) being isolated from the distillate, diluted with water and extracted with chloroform. Thorough washing of the chloroform solution with 1 N KOH removed all lactonic material, thus furnishing triphenyl carbinol upon drying and evaporating. The alkaline washes were acidified, extracted with chloroform, washed with water, dried and evaporated, leaving 180 mg of solid residue. Repeated recrystallization from hexane–acetone provided ca. 15% of the nor-ketone XI.

[42] C. J. W. Brooks and K. H. Overton, *Proc. Chem. Soc.* 322 (1957).
[43] L. Caglioti, H. Naef, D. Arigoni and O. Jeger, *Helv. Chim. Acta* **41**, 2278 (1958).
[44] Melting points were determined on the Kofler block. Unless otherwise noted, rotations were measured in chloroform solution. We are indebted to Miss B. Bach for the infrared spectra and to Mrs. T. Nakano for the rotatory dispersion measurements. The microanalyses were carried out by Dr. A. Bernhardt, Mülheim (Ruhr), Germany.
[45] At times, the melting point was 139–141° and we have found that this is not as satisfactory a criterion of purity as the very characteristic infrared absorption spectrum.

(c) *From 13-nor-3-dehydroiresin* (XIII).[46] A 56 mg sample of the nor-ketone XIII[5b,13] was hydrogenated in 20 cc of ethyl acetate at room temp and atmospheric pressure in the presence of 50 mg of 5% palladized charcoal catalyst. Filtration of the catalyst after 1 hr, and evaporation to dryness left the crystalline 13-nor-3-dehydrodihydroiresin (XIV).[2] This was equilibrated without further purification by keeping at room temp for 20 hr in 7 cc of methanol containing 50 mg of KOH. Dilution with water, acidification with HCl, extraction with chloroform and evaporation left 33 mg of crystalline 13-nor-3-dehydroisodihydroiresin (XI), which exhibited m.p. 139–141°[2,45] after recrystallization from pentane–acetone. Identity was established by coincidence of the infrared spectra and rotatory dispersion curves with those of a specimen prepared according to procedure (a).

2-*Bromo*-13-*nor*-3-*dehydroisodihydroiresin* (XV)[19]

To a solution of 95 mg of the nor-ketone XI in 1·5 cc of glacial acetic acid containing a trace of hydrogen bromide was added dropwise a solution of 64 mg of bromine in 0·66 cc of acetic acid, the temperature being maintained around 40°. The colorless solution was diluted with 100 cc of water and the product was extracted with ether. Careful evaporation of the dried ether solution afforded an oil which solidified upon trituration with pentane. Leaching with ether and one recrystallization from hexane–acetone yielded 40 mg of the *bromo ketone* XV, m.p. 125–128°, $[\alpha]_D$ + 10°. The equatorial nature of the bromine atom was demonstrated by ultraviolet ($\lambda_{max}^{EtOH}$ 292 mμ, log ε 2·12) and infrared ($\lambda_{max}^{CHCl_3}$ 5·60 and 5·75 μ) measurements when compared[20,21] with the corresponding values ($\lambda_{max}^{EtOH}$ 293–295 mμ, log ε 1·49; $\lambda_{max}^{CHCl_3}$ 5·61 and 5·84 μ) of 13-nor-3-dehydroisodihydroiresin (XI). (Found: C, 52·83; H, 5·77. $C_{14}H_{19}BrO_3$ requires: C, 53·35; H, 6·08%).

2,6-*Dibromo*-$\Delta^4$-13-*nor*-3-*dehydroisodihydroiresin* (XVI)

(a) *By dibromination.* The nor-ketone XI (200 mg) was dissolved in 3 cc of redistilled glacial acetic acid containing a small amount of hydrogen bromide and to this solution was added dropwise with vigorous stirring at room temp over a period of 1 hr 270 mg of bromine dissolved in 31 cc of acetic acid. After 3 hr at room temp, water was added to incipient cloudiness and the resulting precipitate was collected, washed well with water and dried; yield, 180 mg, m.p. 160° (dec), undepressed upon admixture with the material prepared according to (b), $\lambda_{max}^{Nujol}$ 5·62 and 5·94 μ.

(b) *By tribromination.* The reaction was conducted with 472 mg of nor-ketone XI in 5 cc of glacial acetic acid (containing a small amount of hydrogen bromide) at 15°, the bromine solution (964 mg of bromine in 10 cc of acetic acid) being added rapidly with stirring. After standing for 1 hr at room temp, the bromine color still persisted and most of the dibromo ketone XVI had crystallized. Filtration, washing with water and careful drying at room temp *in vacuo* provided 427 mg of the *dibromo ketone* XVI, m.p. 154–157° (dec), $[\alpha]_D$ − 126° (dioxane), $\lambda_{max}^{EtOH}$ 262–264 mμ, log ε 4·09, R.D. (Fig. 1) in dioxane (*c*, 0·10): $[\alpha]_{700}$ +96°, $[\alpha]_{589}$ +122°, $[\alpha]_{495-470}$ +174° (broad peak), $[\alpha]_{380}$ −650°, $[\alpha]_{305}$ +8295°. (Found: C, 43·51; H, 4·03; Br, 41·49. $C_{14}H_{16}Br_2O_3$ requires: C, 42·88; H, 4·11; Br, 40·75%).

$\Delta^{1,4,6}$-13-*Nor*-3-*dehydroisodihydroiresin* (XVII)

A solution of 619 mg of the dibromo ketone XVI in 20 cc of freshly distilled γ-collidine (Schweizerische Teerindustrie, Pratteln, Switzerland) and 10 cc of distilled dimethyl formamide was heated under reflux for 15 min, during which time the solution became dark colored and long needles appeared. After cooling, benzene was added and the precipitate of water-soluble collidine hydrobromide (562 mg, 88% yield for 2 molar equivalents) was filtered. The benzene–collidine filtrate was washed well with dilute HCl, dried and evaporated leaving 262 mg of a dark glass. Chromatography on 10 g of neutral alumina and elution with benzene provided 121 mg of crystalline solid (infrared spectrum practically identical with that of the analytical specimen), which was recrystallized to constant melting point from hexane–acetone; m.p. 164–168°, $\lambda_{max}^{EtOH}$ 224, 250 (shoulder) and 296 mμ, log ε 4·16, 3·96 and 4·12, $\lambda_{max}^{CHCl_3}$ 5·60 (s), 6·01 (s), 6·09 (m), 6·16 (s), and 6·23 μ (w).[47] R.D.

[46] This experiment was performed by Dr. A. L. Nussbaum.

[47] For comparison, the infrared spectrum of $\Delta^{1,4,6}$-androstatrien-17β-ol-3-one acetate[26a] was measured under the same conditions and the following bands were noted in the relevant region: 6·00 (s), 6·08 (m), 6·15 (s) and 6·25 (shoulder).

in dioxane (*c*, 0·04): $[\alpha]_{700}$ −317°, $[\alpha]_{589}$ −568°, $[\alpha]_{398}$ −4368°, $[\alpha]_{388}$ −4477°, $[\alpha]_{353}$ −1605°, $[\alpha]_{333}$ −3182°. (Found: C, 73·25; H, 6·05. $C_{14}H_{14}O_3$ requires: C, 73·02; H, 6·13%).

*2α,6β-Dibromo-4-methyltestosterone acetate* (XXI)

(a) *From 4-Methyltestosterone acetate* (XXII). 4-Methyltestosterone acetate (XXII)[32] (100 mg) was dissolved in 3·5 cc of anhydrous ether containing one drop of acetic acid saturated with hydrogen bromide and cooled to 0°. A solution of 93 mg of bromine in 1·0 cc of acetic acid was added very rapidly with stirring and the colorless solution was concentrated immediately *in vacuo* without external heating. When the volume had been reduced about 70%, a colorless solid precipitated, which was filtered and washed well with ethanol; yield, 102 mg, m.p. 167–170° (dec), $\lambda_{max}^{EtOH}$ 263·5 mμ, log ε 4·14, R.D. (Fig. 1) in dioxane (*c*, 0·09): $[\alpha]_{700}$ −52°, $[\alpha]_{589}$ −90°, $[\alpha]_{500-475}$ −121° (broad trough), $[\alpha]_{355}$ +283°, $[\alpha]_{300}$ −6072°. (Found: C, 52·23; H, 6·21; Br, 31·56. $C_{22}H_{30}Br_2O_3$ requires: C, 52·61; H, 6·02; Br, 31·83%).

(b) *From 4α-methyldihydrotestosterone acetate* (XX). A solution of 100 mg of 4α-methyldihydrotestosterone acetate (XX)[29,48] in 1·5 cc of glacial acetic acid and 0·5 cc of a saturated hydrogen bromide–acetic acid solution was cooled to just above the freezing point and 128 mg of bromine in 1·2 cc of acetic acid was added in less than 1 min with stirring. After 1 hr at room temp, there was still present some bromine color and dilution with aqueous methanol precipitated the white dibromo ketone XXI. Filtration and recrystallization from ethanol–chloroform led to 70 mg of colorless crystals, m.p. 165–167°, undepressed upon admixture with material prepared according to (a); the respective infrared spectra were also identical.

*Dehydrobromination of 2α,6β-dibromo-4-methyltestosterone acetate* (XXI)

(a) *With collidine–dimethyl formamide.* A solution of 1·03 g of the dibromo ketone XXI in 20 cc of γ-collidine and 15 cc of dimethyl formamide was heated under reflux for 15 min. Dilution with ether and filtration gave 520 mg (1·25 molar equivalents) of collidine hydrobromide and the filtrate was processed as described above for XVII, except that no chromatographic purification was required. Several recrystallizations of the crude dehydrobromination product from ethanol produced 100 mg of *2α-bromo-4-methyl-Δ⁴,⁶-androstadien-17β-ol-3-one acetate* (XXIII), m.p. 148°, then resolidifying and decomposing at 158–160°, $\lambda_{max}^{EtOH}$ 294 mμ, log ε 4·26, $\lambda_{max}^{CHCl_3}$ 5·75, 5·96 (s), 6·14 (s), 6·28 (m), and 7·95 μ. R.D. in dioxane (*c*, 0·13): $[\alpha]_{700}$ +91°, $[\alpha]_{589}$ +152°, $[\alpha]_{390}$ +1850°, $[\alpha]_{333}$ −1230°, $[\alpha]_{328}$ −1110°. (Found: C, 62·28; H, 6·95; O, 11·18. $C_{22}H_{29}BrO_3$ requires: C, 62·72; H, 6·93; O, 11·40%).

(b) *With lithium carbonate and lithium bromide.*[33] A mixture of 350 mg of the dibromo ketone XXI, 10 cc of redistilled dimethyl formamide, 0·3 g of anhydrous lithium carbonate and 320 mg of fused lithium bromide was heated under reflux for 24 hr in an atmosphere of nitrogen. Dilution of the mixture with water precipitated a gum which was extracted with ether. After washing with water and drying, the ether was removed and all volatile material was distilled at 50° and 1 mm. The resulting tan-colored glass (150 mg) was dissolved in benzene and chromatographed on 15 g of neutral alumina. Elution with benzene afforded a small amount (ca. 10 mg) of the 2α-bromo-Δ⁴,⁶-3-ketone XXIII, while elution with 9:1 benzene–ether led to the desired *Δ¹,⁴,⁶-4-methyl-androstatrien-17β-ol-3-one acetate* (XXIV), which resisted all attempts at crystallization; $\lambda_{max}^{EtOH}$ 226, 255 (shoulder) and 306 mμ,[34] log ε 4·10, 3·84 and 4·04, $\lambda_{max}^{CHCl_3}$ 5.79 (s), 6.04 (m), 6.13 (m) and 6.23 μ (s); R.D. in dioxane (*c*, 0·137 at 700–397·5 mμ; 0·027 at 395–360 mμ; 0·013 at 355–342·5 mμ): $[\alpha]_{700}$ +1·4°, $[\alpha]_{589}$ +8·7°, $[\alpha]_{390}$ +710°, $[\alpha]_{342.5}$ −1353°. (Found: C, 76·00; H, 8·30. $C_{22}H_{28}O_3$ requires: C, 77·61; H, 8·29%).

Since the analytical results were not very satisfactory—as had also been observed[9] with the oily Δ¹,⁴,⁶-4-ethylcholestatrien-3-one—a sample was converted into the 2,4-*dinitrophenylhydrazone* using an ethanol–sulfuric acid solution of 2,4-dinitrophenylhydrazine. Passage of its benzene solution through a small column of alumina and recrystallization from ethanol gave ruby-red crystals, m.p. 247–249°; the ultraviolet absorption maximum ($\lambda_{max}^{CHCl_3}$ 412·5 mμ, log ε 4·52) occurred at the expected[9] position. (Found: C, 64·11; H, 6·24. $C_{28}H_{32}N_4O_6$ requires: C, 64·60; H, 6·20%).

[48] This sample showed m.p. 174–176°, $\lambda_{max}^{CHCl_3}$ 5·74, 5·80 and 7·92 μ, R.D. (Fig. 1) in methanol (*c*, 0·12): $[\alpha]_{700}$ −28°, $[\alpha]_{589}$ −28°, $[\alpha]_{305}$ +655°, $[\alpha]_{270}$ −1500°.