Triterpenoids. Part XLV. The Conversion of α-Amyrin into Phyllanthol. The Constitution of "* iso-*α-Amyradienonyl-II Acetate."*

By J. M. Beaton, J. D. Easton, M. M. Macarthur,
F. S. Spring, and Robert Stevenson.

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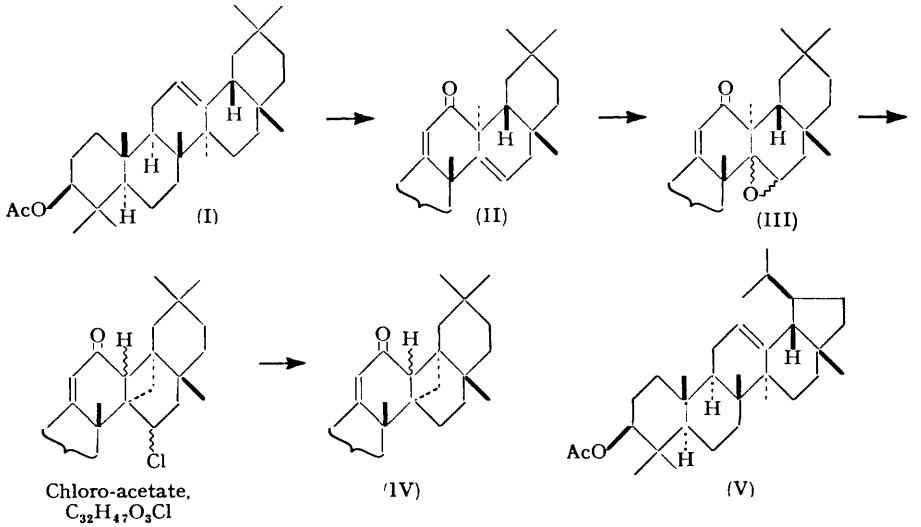
A partial synthesis of the hexacyclic triterpenoid alcohol, phyllanthol, from α-amyrin is described. The conversion of 12-oxo*iso*urs-9(11) : 14-dien-3β-yl acetate (*iso*-α-amyradienonyl acetate) (VI) into " *iso*-α-amyradienonyl-II acetate " by means of mineral acid is shown to involve a cyclisation with the formation of a *cyclo*propane ring.

During a study of the complex reactions of the pentacyclic 12-oxotaraxera-9(11) : 14-dien-3β-yl acetate (II) [formerly called *iso*-β-amyradienonyl acetate or 12-oxo*iso*oleana-9(11) : 14-dien-3β-yl acetate], Johnston and Spring (*J.*, 1954, 1556) adduced evidence that it can be converted into hexacyclic derivatives and proposed provisional structures for these compounds. In particular, it was shown that the oxo-dienyl acetate (II) gives an oxide, $C_{32}H_{48}O_4$ (III), converted by hydrochloric acid into a chloro-acetate, $C_{32}H_{47}O_3Cl$, which on reduction yields an acetate, $C_{32}H_{48}O_3$, in which the presence of an acetate and an αβ-unsaturated ketone group and a *cyclo*alkane ring was identified. For purposes of illustration these reactions were formulated as shown.

Although α-amyrin acetate (V) (Beaton, Spring, Stevenson, and Strachan, *J.*, 1955, 2610) can be converted into 12-oxo*iso*urs-9(11) : 14-dien-3β-yl acetate (VI) by a series of

* Part XLIV, *J.*, 1955, 3378.

reactions (Ruzicka, Rüegg, Volli, and Jeger, *Helv. Chim. Acta*, 1947, **30**, 140) similar to those used to convert β-amyrin acetate (I) into the analogous oxo-dienyl acetate (II), a difference has been noted in the behaviour of the isomers (II) and (VI). Whereas the former is stable to prolonged treatment with hydrochloric–acetic acid mixture (Budziarek, Johnston, Manson, and Spring, *J.*, 1951, 3019), 12-oxo*iso*ursa-9(11) : 14-dien-3β-yl acetate (VI) is thereby converted into " *iso*-α-amyradienonyl-II acetate " (Ruzicka *et al.*, *loc. cit.*) which, in contrast to the parent oxo-dienyl acetate (VI), does not contain an isolated ethylene



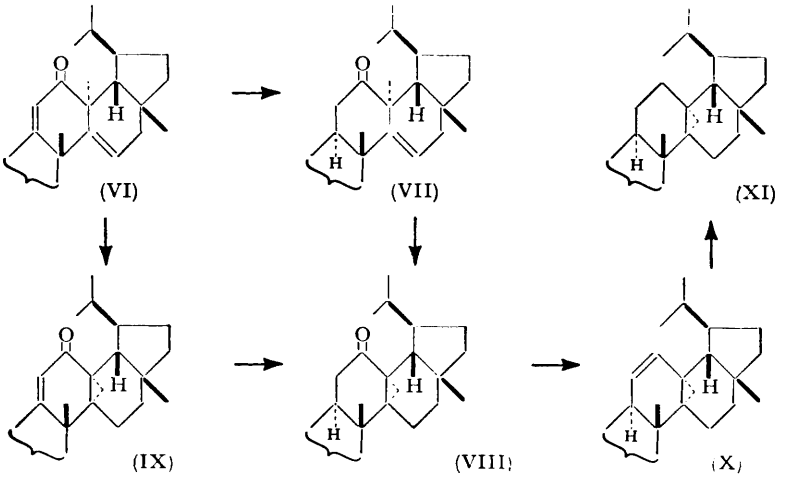
linkage. Johnston and Spring (*loc. cit.*) commented upon a resemblance between the hexacyclic acetate, $C_{32}H_{48}O_3$, derived from β-amyrin and the isomeric " *iso*-α-amyradienonyl-II acetate " and suggested that the two have analogous structures. This is equivalent to suggesting that the conversion of the acetate (VI) into " *iso*-α-amyradienonyl-II acetate " by mineral acid consists in the formation of a new *cyclo*alkane ring. This view has now been shown to be correct and, further, the precise nature of the *cyclo*alkane ring in " *iso*-α-amyradienonyl-II acetate " has been determined.

Reduction of the acetate (VI) with lithium and liquid ammonia gives 12-oxo*iso*urs-14-en-3β-ol, characterised by the preparation of its acetate (VII), which does not show the absorption spectrum of an αβ-unsaturated ketone. Its absorption in the region 2000—2200 Å and a positive reaction with tetranitromethane confirm the presence of an isolated double bond. When treated with hydrogen chloride in acetic acid, the unsaturated acetate (VII) is isomerised to 12-oxo-13 : 27-*cyclo*ursan-3β-yl acetate (VIII), the structure of which follows from the following facts. It does not give a colour with tetranitromethane in chloroform, and it does not show the ultraviolet absorption spectrum of an αβ-unsaturated ketone. Consequently its formation from (VII) consists in the formation of a new *cyclo*alkane ring. The nature of this ring was deduced from the ultraviolet absorption spectrum of (VIII) which shows a maximum at 2140 Å (ε 5500), indicating that the carbonyl group is conjugated with a *cyclo*propane ring. 12-Oxo-13 : 27-*cyclo*ursan-3β-yl acetate (VIII) was obtained also by another route. As stated above, treatment of the oxo-dienyl acetate (VI) with hydrogen chloride in acetic acid gives " *iso*-α-amyradienonyl-II acetate " which we now formulate as 12-oxo-13 : 27-*cyclo*urs-9(11)-en-3β-yl acetate (IX). Reduction of this with lithium in liquid ammonia gives, as major product, the acetate (VIII).

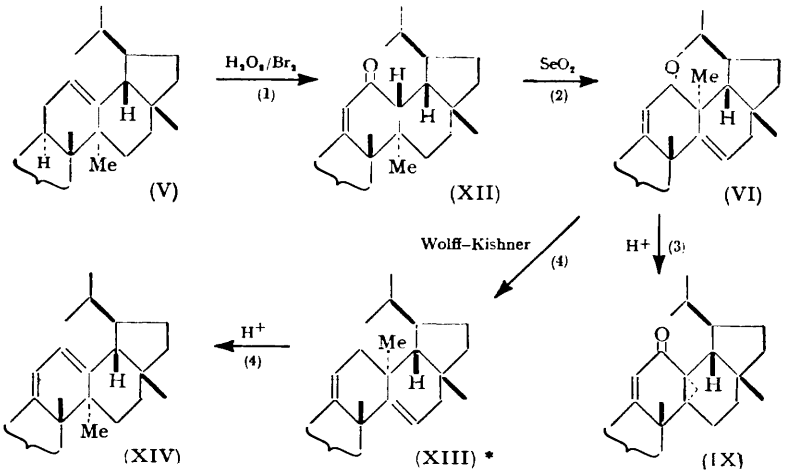
The recognition that treatment of either the oxo-dienyl acetate (VI) or the oxo-enyl acetate (VII) with mineral acid leads to the formation of a *cyclo*propane ring made possible a partial synthesis of phyllanthol, a naturally occurring triterpenoid alcohol isolated from the root bark of *Phyllanthus engleri* (Pax) by Alberman and Kipping (*J.*, 1951, 2296) and shown to be 3β-hydroxy-13 : 27-*cyclo*ursane by Barton, Page, and Warnhoff (*J.*, 1954,

2715; Barton and de Mayo, *J.*, 1953, 2178). In terms of the α-amyrin formula (V), the constitution and stereochemistry of phyllanthol are represented as in (XI).

Our first approach to a conversion of α-amyrin into phyllanthol was a modified Wolff–Kishner reduction of 12-oxo-13 : 27-*cyclo*ursan-3β-yl acetate (VIII). This reaction did



not proceed smoothly and although there was obtained, after acetylation, a low yield of a product which did not depress the m. p. of phyllanthyl acetate, this product is not homogeneous since it shows ethylenic absorption of low intensity in the ultraviolet region. The low yield did not encourage us to attempt purification. As an alternative, treatment of the acetate (VIII) with lithium aluminium hydride, followed by acetylation of the product, vielded a homogeneous acetate, $C_{32}H_{50}O_2$, which gave an orange colour with tetranitromethane and showed maximal absorption at 2250 Å (ε 4300). Because of these properties we designate this acetate 13 : 27-*cyclo*urs-11-en-3β-yl acetate (X). A related compound, 13 : 27-*cyclo*urs-11-ene-3β : 28-diol, has recently been obtained by Zürcher, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1954, **37**, 2145) by treatment of urs-12-ene-3β : 14 : 28-triol (obtained from quinovic acid) with methanesulphonyl chloride and reduction of the product



(1) Seymour, Sharples, and Spring, *J.*, 1939, 1079. (2) Ruzicka *et al.*, *loc. cit.* (3) This paper. (4) Easton and Spring, *J.*, 1955, 2120.

* It is possible that the hydrocarbon obtained by this method has the 11: 14-diene structure (Easton and Spring, *loc. cit.*).

with lithium aluminium hydride. The ultraviolet absorption spectrum of the corresponding diacetate ($\lambda_{max.}$ 2240 Å, log ε 3·64) is almost identical with that of the acetate (X).

Catalytic hydrogenation of the acetate (X) gave phyllanthyl acetate (XI), identity being confirmed by mixed m. p. and by a comparison of the infrared absorption spectra of the specimen obtained from α-amyrin and a specimen from its natural source, kindly given to us by Professor D. H. R. Barton, F.R.S. We cordially thank Dr. G. Eglinton for the infrared absorption data. This constitutes a second partial synthesis of phyllanthol from another member of the ursane group of triterpenoids, the first being a partial synthesis from quinovic acid (Zürcher, Jeger, and Ruzicka, *loc. cit.*).

In our view, the most remarkable feature of the experiments described above is the demonstration of the mobility of the carbon atom originally attached as a methyl group to $C_{(14)}$ in α-amyrin. In the requisite environment it can migrate to $C_{(13)}$ [(V) ⟶ (XII) ⟶ (VI)]. With suitable treatment, the methyl group now attached to $C_{(13)}$ will migrate back to $C_{(14)}$ [(VI) ⟶ (XIII) ⟶ (XIV)]. In different conditions the same carbon atom can be induced to bridge $C_{(13)}$ and $C_{(14)}$ [(VI) ⟶ (IX)].

The proof that "*iso*-α-amyradienonyl-II acetate" is 12-oxo-13 : 27-*cyclo*urs-9(11)-en-3β-yl acetate (IX) and the similarity between this compound and the acetate, $C_{32}H_{48}O_3$, obtained from β-amyrin suggest that the provisional formulation (IV) for the acetate $C_{32}H_{48}O_3$ (Johnston and Spring, *loc. cit.*) may require revision to 12-oxo-13 : 27-*cyclo*olean-9(11)-en-3β-yl acetate, *i.e.*, that the acetate, $C_{32}H_{48}O_3$, and its congeners may contain a *cyclo*propane ring.

Experimental

Rotations were measured in chloroform and ultraviolet absorption spectra in ethanol solutions. Grade II alumina and light petroleum (b. p. 60—80°) were used for chromatography.

12-*Oxo*-13 : 27-cyclo*urs*-9(11)-*en*-3β-*yl Acetate* (IX) ("iso-α-*Amyradienonyl*-II *Acetate*") (cf. Ruzicka, *et al.*, *loc. cit.*; Easton and Spring, *loc. cit.*).—A solution of 12-oxo*iso*ursa-9(11) : 14-dien-3β-yl acetate (3·0 g.; m. p. 221—222°, $[\alpha]_D$ +8°) in glacial acetic acid (600 c.c.) was treated with a rapid stream of dry hydrogen chloride for 40 min. and the mixture kept for 4 days and then evaporated under reduced pressure. The residue crystallised from *n*-hexane–benzene to give 12-*oxo*-13 : 27-cyclo*urs*-9(11)-*en*-3β-*yl acetate* (1·2 g.) as needles, m. p 269—270°, $[\alpha]_D$ +160°, +157° (*c*, 0·8, 1·3), $\lambda_{max.}$ 2370 Å (ε 11,000). It gives a very pale yellow colour with tetranitromethane in chloroform (Found : C, 80·2; H, 10·3. $C_{32}H_{48}O_3$ requires C, 79·95; H, 10·1%).

12-*Oxo*-13 : 27-cyclo*urs*-9(11)-*en*-3β-*ol* was obtained by hydrolysis of the acetate in the usual manner. It separates from *n*-hexane–acetone as needles, m. p. 215—216°, $[\alpha]_D$ +154°, +157° (*c*, 0·6, 1·0) (Found : C, 82·0; H, 10·6. $C_{30}H_{46}O_2$ requires C, 82·1; H, 10·6%). Acetylation of the alcohol in the usual way and crystallisation from *n*-hexane–benzene refurnished the acetate (IX) as needles, m. p. 268—269°, $[\alpha]_D$ +158° (*c*, 1·7).

12-*Oxo*iso*urs*-14-*en*-3β-*yl Acetate* (VII) *from* 12-*Oxo*iso*ursa*-9(11) : 14-*dien*-3β-*yl Acetate* (VI).—The acetate (VI) (8·0 g., m. p. 221—222°, $[\alpha]_D$ +7°) in dry ether (1·5 l.) was added during 7 min. with stirring to a solution obtained by adding lithium (750 mg.) to liquid ammonia (1·5 l.), and the mixture stirred for 10 min. After the addition of ammonium chloride, the product was isolated in the usual manner and refluxed for 2 hr. with 3% ethanolic potassium hydroxide. Crystallisation of the product gave 12-*oxo*iso*urs*-14-*en*-3β-*ol* (1·1 g.) as needles, m. p. 233—234°, $[\alpha]_D$ −39°, −40° (*c*, 0·8, 0·9) (Found : C, 81·3; H, 11·1. $C_{30}H_{48}O_2$ requires C, 81·7; H, 11·0%). Light absorption : ε_{2100} 2900, ε_{2150} 1600, ε_{2200} 1000. The compound gives a yellow colour with tetranitromethane. Acetylation of the alcohol gave 12-*oxo*iso*urs*-14-*en*-3β-*yl acetate* as needles (from chloroform–methanol), m. p. 227—228°, $[\alpha]_D$ −27°, −28° (*c*, 1·3, 1·1) (Found : C, 79·3; H, 10·4. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·4%). Light absorption : ε_{2100} 2700, ε_{2150} 1300, ε_{2200} 800. The acetate gives a yellow colour with tetranitromethane.

12-*Oxo*-13 : 27-cyclo*ursan*-3β-*yl Acetate* (VIII).—(*a*) A solution of 12-oxo*iso*urs-14-en-3β-yl acetate (220 mg.) in glacial acetic acid (50 c.c.) was treated with a stream of dry hydrogen chloride for 40 min. and the mixture kept for 3 days at room temperature, then evaporated under reduced pressure. The residue crystallised from chloroform–methanol to give 12-*oxo*-13 : 27-cyclo*ursan*-3β-*yl acetate* (150 mg.) as needles, m. p. 259—261°, $[\alpha]_D$ +60° (*c*, 1·6), $\lambda_{max.}$ 2140 Å (ε 5500) (Found : C, 79·6; H, 10·7. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·4%). This acetate does not give a colour with tetranitromethane in chloroform.

(*b*) 12-Oxo-13 : 27-*cyclo*urs-9(11)-en-3β-yl acetate (1·0 g.) in ether (150 c.c.) was added during

2 min. to a solution obtained by adding lithium (300 mg.) to liquid ammonia (200 c.c.). Stirring was continued for 3 min., and the excess of reagent decomposed by acetone. The product was isolated in the usual manner and acetylated by warm pyridine and acetic anhydride. A solution of the acetylated product in light petroleum (400 c.c.) was chromatographed on alumina (30 g.). Elution with light petroleum–benzene (9 : 1; 300 c.c.) gave fractions of m. p. 259—261° to 250—253°, which were combined (190 mg.) and recrystallised from chloroform–methanol to give an *acetate* as needles, m. p. 259—261°, $[\alpha]_D$ +47° (*c*, 1·8), ε 3100 at 2060 Å (Found: C, 76·6; 76·6, 76·6; H, 10·2, 10·1, 10·3%). The acetate gives a pale yellow colour with tetranitromethane and when it is mixed with 12-oxo-13 : 27-*cyclo*urs-9(11)-en-3β-yl acetate (m. p. 259—261°, $[\alpha]_D$ +60°) its m. p. is strongly depressed.

Continued elution of the alumina with light petroleum–benzene (9 : 1, 400 c.c.; 1 : 1, 100 c.c.) furnished fractions (284 mg.) which after crystallisation from chloroform–methanol gave 12-oxo-13 : 27-*cyclo*ursan-3β-yl acetate (155 mg.) as needles, m. p. 259—261° (no depression *), $[\alpha]_D$ +59° (*c*, 1·6), ε 4700 at 2150 Å.

The final fractions from the chromatogram were eluted with light petroleum–benzene (1 : 1, 300 c.c.) and benzene (400 c.c.). They were crystallised repeatedly from chloroform–methanol to give an *acetate* (80 mg.) as needles, m. p. 318—320°, $[\alpha]_D$ −15°, −15·5° (*c*, 1·6, 1·7), ε 4900 at 2110 Å (Found: C, 79·5; H, 10·1. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·4%). The acetate gives a faint yellow colour with tetranitromethane in chloroform.

12-*Oxo*-13 : 27-cyclo*ursan*-3β-*ol*.—A solution of 12-oxo-13 : 27-*cyclo*ursan-3β-yl acetate (100 mg.) in 3% methanolic potassium hydroxide (50 c.c.) was refluxed for 1 hr. The product, which partly separated from the hot solution, was completely precipitated by the addition of water and crystallised from chloroform–methanol to give 12-*oxo*-13 : 27-cyclo*ursan*-3β-*ol* as needles, m. p. 319—321°, $[\alpha]_D$ +51° (*c*, 0·22) (Found: C, 81·3; H, 11·25. $C_{30}H_{48}O_2$ requires C, 81·8; H, 11·0%). Acetylation of the alcohol in the usual manner furnished 12-oxo-13 : 27-*cyclo*ursan-3β-yl acetate as needles from chloroform–methanol, m. p. and mixed m. p. 261—263°, $[\alpha]_D$ +57° (*c*, 1·0).

The relative insolubility of this alcohol was utilised to facilitate later preparations of 12-oxo-13 : 27-*cyclo*ursan-3β-yl acetate. The mixture of products obtained by reduction of 12-oxo-13 : 27-*cyclo*urs-9(11)-en-3β-yl acetate with lithium in liquid ammonia, as described above, was warmed with ether. The insoluble fraction readily gave 12-oxo-13 : 27-*cyclo*ursan-3β-ol (yield, 43%) on recrystallisation from chloroform–methanol. Acetylation of the alcohol, in the usual manner, gave 12-oxo-13 : 27-*cyclo*ursan-3β-yl acetate as needles (from chloroform–methanol), m. p. 260—261° (no depression), $[\alpha]_D$ +60° (*c*, 0·9), λ_{max} 2150 Å (ε 4700) (Found: C, 79·6; H, 10·7%).

Wolff–Kishner Reduction of 12-*Oxo*-13 : 27-cyclo*ursan*-3β-*yl Acetate* (VIII).—12-Oxo-13 : 27-*cyclo*ursan-3β-yl acetate (200 mg.) was added to a solution obtained by adding sodium (600 mg.) to freshly distilled diethylene glycol (30 c.c.), and the mixture was heated to 170—180°. Anhydrous hydrazine was distilled (in nitrogen) into the mixture until it refluxed gently at 174°. After refluxing at this temperature for 24 hr., the mixture was distilled until the temperature rose to 216°, whereafter refluxing was continued for 18 hr. Solution was not complete during the reaction. The product was isolated in the usual manner and acetylated by using pyridine and acetic anhydride. The acetylated product in light petroleum (100 c.c.) was chromatographed on alumina (7 g.). Elution with light petroleum (200 c.c.) gave a fraction (39 mg.) which was thrice crystallised from chloroform–methanol to give blades, m. p. 264—266°, $[\alpha]_D$ +36·5° (*c*, 1·2), ε_{2040} 1700. This acetate gives a pale yellow colour with tetranitromethane in chloroform, and its mixture with phyllanthyl acetate (m. p. 268—270°) had m. p. 263—268°. A mixture with (VIII) had m. p. 253—260°. In our opinion this acetate is phyllanthyl acetate contaminated with an ethylenic component. The small amount of material available did not permit its further purification. It is probable that the efficiency of the reduction is impaired by the precipitation of 12-oxo-13 : 27-*cyclo*ursan-3β-ol.

13 : 27-cyclo*Urs*-11-*en*-3β-*yl Acetate* (X) *from* 12-*Oxo*-13 : 17-cyclo*ursan*-3β-*yl Acetate* (VIII).—Lithium aluminium hydride (200 mg.) was added to a solution of the oxo-acetate (200 mg.) in dry ether (150 c.c.). After 1 hr. at room temperature, the mixture was cooled to 0° and the excess of hydride decomposed by the addition of crushed ice. The product, isolated in the usual manner, was acetylated by treatment with acetic anhydride and pyridine at room temperature for 18 hr. The acetylated product was isolated in the usual manner, and its solution in light petroleum chromatographed on alumina. Elution with light petroleum yielded a

* Here and elsewhere these words refer to a mixed m. p. with an authentic specimen.

fraction (76 mg.) which crystallised from chloroform–methanol to give 13 : 27-cyclo*urs*-11-*en*-3β-*yl acetate* (44 mg.) as plates, m. p. 224—226°, $[\alpha]_D$ +25° (*c*, 0·8), $\lambda_{max.}$ 2250 (ε 4300) (Found : C, 82·05; H, 10·8. $C_{32}H_{50}O_2$ requires C, 82·3; H, 10·8%). It gives an orange colour with tetranitromethane.

Catalytic Hydrogenation of 13 : 27-cyclo*Urs*-11-*en*-3β-*yl Acetate* (X).—A solution of 13 : 27-*cyclo*urs-11-en-3β-yl acetate (100 mg.) in glacial acetic acid (120 c.c.) was shaken with platinum (from 100 mg. of PtO_2) and hydrogen for 2 hr. The product was isolated in the usual way and crystallised from chloroform–methanol to give phyllanthyl acetate (67 mg.) as blades, m. p. 268—272°, $[\alpha]_D$ +50°, +49° (*c*, 0·8, 1·4); this has no ultraviolet absorption and gives a pale yellow colour with tetranitromethane in chloroform. A specimen of phyllanthyl acetate, $[\alpha]_D$ +48° [from *Phyllanthus engleri* (Pax.)], separated from chloroform–methanol as blades, m. p. 268—270°; a mixture of this with the sample obtained from α-amyrin was undepressed in m. p.

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