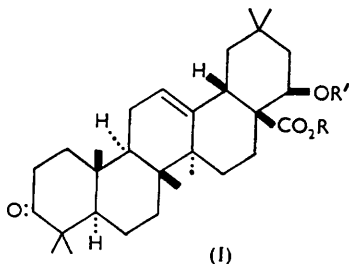


803. Triterpenoids. Part XXIII.* The Nature of Lantadene A.

By D. H. R. BARTON, P. DE MAYO, and J. C. ORR.

Lantadene A has again been isolated from *Lantana camara*. By a comparison of purified lantadene A and its derivatives with rehmannic acid and its corresponding derivatives their identity has been established. This conclusion has been confirmed by degradation.

In a previous Part ¹ of this series the constitution of lantadene B was established as (I; R = H, R' = $\beta\beta$ -dimethylacryloyloxy). The more interesting, physiologically active lantadene A, isolated and studied by Louw,² has not hitherto been available to us for investigation. From a specimen of *Lantana camara* of Australian origin, we have recently been able to isolate again lantadene A. The present paper is our report on its constitution.



Louw² stated that lantadene A formed a methyl ester, a 2:4-dinitrophenylhydrazone, and an acetate. For convenience of exposition the physical constants found by Louw² are summarised in the Table. The lantadene A isolated in our own work had constants also as summarised in this Table in reasonable agree-

ment with those of Louw. Through the courtesy of Dr. O. Jeger (Zürich) in forwarding to us small authentic specimens of lantadene A and its 2:4-dinitrophenylhydrazone, obtained originally from Dr. P. G. J. Louw, we have been able to confirm the authenticity of our material. By the criteria summarised in the Experimental section the homogeneity of lantadene A, as now described, was established. The identity of lantadene A with rehmannic acid³ (I; R = H, R' = angeloyloxy), first suggested by the physical constants

* Part XXII, *J.*, 1956, 4150.

¹ Barton, de Mayo, Warnhoff, Jeger, and Perold, *J.*, 1954, 3689.

² Louw, *Onderstepoort J. Vet. Sci.*, 1943, 18, 197; 1948, 23, 233; 1949, 22, 321, 329; see also Sanders, *J. Amer. Vet. Med. Assoc.*, 1946, 139.

³ Barton and de Mayo, *J.*, 1954, 887, 900.

summarised in the Table, was confirmed by all the usual criteria. However, in view of the importance of lantadene A and the fact that m. p. depressions are not always observed¹ in such closely related compounds, we deemed it advisable to repeat on lantadene A the degradation previously applied³ to rehmannic acid. The identical

| Acid | Lantadene A (authentic) ² | | Lantadene A (this paper) | | Rehmannic acid ³ | | Lantadene B ¹ | |
|------------------------------|---|--------------|-----------------------------|--------------|--------------------------------|--------------|--------------------------|--------------|
| | M. p. | $[\alpha]_D$ | M. p. | $[\alpha]_D$ | M. p. | $[\alpha]_D$ | M. p. | $[\alpha]_D$ |
| Acid | 276—280° | +81° | 282—286° | +89° | 282—287° | +84° | 293—294° | +85° |
| | 282—287°* | | | | | | | |
| Me ester | 125 | — | 137—139 | +86 | 140 | +86 | 234—236 | +89 |
| 2 : 4-Dinitrophenylhydrazone | 268 | +35 | 271—272 | +35 | 273—274 | +27 | 264—265 | +48 |

* After several recrystallisations.

results obtained confirm beyond question that lantadene A and rehmannic acid are the same compound. The acetate² of lantadene A must, of course, be a mixed anhydride of the same type that we prepared earlier¹ from lantadene B.

Our experiences with *Lantana camara* have shown that this plant is very variable in its triterpenoid content. Material examined previously¹ contained only lantadene B. The Queensland *L. camara*, from which we isolated lantadene A, had only traces of lantadene B. A specimen of South African origin, which recently came to hand, contained no crystallisable triterpenoid material.

Now that the constitutions of the (indirectly) photosensitising triterpenoids icterogenin^{3,4} and lantadene A (rehmannic acid) have been elucidated, the way is clear for studies on the relation between physiological activity and molecular structure.

EXPERIMENTAL

For general experimental conditions see Part VII.⁵ Rotations were determined in CHCl_3 solution. Ultraviolet absorption spectra were taken in EtOH solution with the Unicam S.P. 500 Spectrophotometer. Infrared spectra were kindly determined by Dr. G. Eglinton and his associates. Silica gel for chromatography was obtained from Messrs. Hopkin and Williams Ltd. Light petroleum of b. p. 40—60° was used throughout unless stated to the contrary. The m. p.s of lantane A and rehmannic acid were determined as follows: the sample was inserted at 220° and heated at about one degree per 3.5 sec. to 260° and then at one degree per 15 sec. until melted.

Examination of Australian Lantana camara.—The material examined (C.S.I.R.O. sample number 5384) was worked up essentially according to the directions of Louw.² The powdered leaves and terminal branchlets (1.7 kg.) were extracted with methanol (7 l.) at room temperature (occasional stirring) for 2 days. The green solution was filtered and concentrated *in vacuo* to 3 l. Chlorophyll was removed by stirring with charcoal (3 × 25 g.), and the resultant brown solution evaporated to dryness, on a steam-bath, *in vacuo*. The residue was dissolved in hot methanol (200 ml.), diluted with benzene (1.5 l.), and left for 2 days at room temperature. The benzene solution was decanted from precipitated tar (water-soluble glycosides), and evaporated to dryness, on a steam-bath, *in vacuo*. Benzene (3 × 100 ml.) was added and removed in the same way to ensure that no methanol remained. The residue was taken up in benzene (200 ml.) and chromatographed over silica gel (230 g.). Elution with benzene-ether with proportions of ether increasing up to 100% gave 13 fractions of crystalline (from benzene or methanol) material with m. p.s ranging from 224—244° to 267—270°. The highest-melting fractions were combined and recrystallised from chloroform-methanol to constant m. p., to furnish *lantadene A* (prisms; 1.5 g.), m. p. 282—286°, $[\alpha]_D + 89°$ (*c* 1.41), λ_{max} 209 and 280 μ (ϵ 13,900 and 130 respectively) (Found: C, 75.9; H, 9.45. $\text{C}_{35}\text{H}_{52}\text{O}_5$ requires C, 76.05; H, 9.5%). The homogeneity of this material was established by extensive crystallisation and by further chromatography over silica gel. Lantadene A crystallises in two forms, prisms (see above) and needles. The two forms have identical physical constants and can be interconverted by seeding.

Lantadene A was undepressed on admixture with authentic lantadene A, m. p. 276—280°, provided by Dr. Louw, and with rehmannic acid, m. p. 282—287°. The higher m. p. (295—300°)

⁴ Rimington, Quin, and Roets, *Onderstepoort J. Vet. Sci.*, 1937, 9, 225.

⁵ Barnes, Barton, Fawcett, and Thomas, *J.*, 1952, 2339.

recorded for the last substance earlier³ refers to insertion at 260° and rapid heating. Since the m. p.s vary so much it is recommended that all comparative m. p.s should be taken simultaneously. Lantadene A was, however, slightly depressed in m. p. on admixture with lantadene B. Authentic lantadene A, lantadene A as described in the present paper, and rehmmanic acid, all had identical infrared spectra in Nujol.

Methylation with diazomethane gave *lantadene A methyl ester*, m. p. (solvated needles from methanol) 137—139°, $[\alpha]_D + 86^\circ$ (*c* 2.15) (Found: C, 75.7; H, 10.15. $C_{36}H_{54}O_5 \cdot \frac{1}{2}CH_4O$ requires C, 75.25; H, 9.7%). A non-solvated form, m. p. 149—150°, was obtained by crystallisation from benzene—light petroleum; further recrystallisation from methanol gave the solvated form.

In order to confirm the homogeneity of lantadene A, material (m. p. 280—282°) (256 mg.) was methylated with diazomethane and chromatographed over alumina (20 g.) in light petroleum. Elution with light petroleum—benzene mixtures up to 100% benzene content (19 fractions) gave only lantadene A methyl ester. Elution with 1 : 9 ether—benzene furnished lantadene B methyl ester (m. p. and mixed m. p.; 3 mg.). Lantadene A methyl ester was undepressed in m. p. (solvated form) on admixture with methyl rehmmanate.

Lantadene A was converted into its 2 : 4-dinitrophenylhydrazone in the usual way. Recrystallised from methanol this had m. p. 271—272°, $[\alpha]_D + 35^\circ$ (*c* 1.07) (Found: C, 67.45; H, 7.55; N, 7.3. Calc. for $C_{41}H_{56}O_8N_4$: C, 67.2; H, 7.7; N, 7.65%). It was undepressed in m. p. on admixture with authentic material, m. p. 268°, $[\alpha]_D + 35^\circ$ (*c* 0.23), from Dr. Louw and with rehmmanic acid 2 : 4-dinitrophenylhydrazone, m. p. 273—274°, $[\alpha]_D + 27^\circ$ (*c* 0.34). The authentic 2 : 4-dinitrophenylhydrazone, that from lantadene A as described in the present paper, and the corresponding rehmmanic acid derivative, had identical infrared spectra in Nujol. Lantadene B 2 : 4-dinitrophenylhydrazone¹ had $[\alpha]_D + 48^\circ$ (*c* 0.42).

Pyrolysis of Lantadene A Methyl Ester.—The methyl ester (89.2 mg.) was pyrolysed at 530°/0.15 mm. under the conditions used by Barton and de Mayo.³ The acid eliminated (0.87 mol.) was identified as angelic acid by m. p. and mixed m. p. (liquefied on admixture with tiglic acid). The neutral portion of the pyrolysate was chromatographed over alumina (4 g.) in light petroleum. Elution with 1 : 1 benzene—light petroleum gave oils (46.4 mg.). Elution with benzene afforded unchanged lantadene A methyl ester (m. p. and mixed m. p.). The oily fractions, on hydrogenation in "AnalaR" acetic acid over platinum for 20 hr. (uptake, 2 mols. of hydrogen), and acetylation with pyridine—acetic anhydride overnight at room temperature, gave methyl oleanolate acetate (m. p., mixed m. p., and rotation). The identity was confirmed by alkaline hydrolysis to methyl oleanolate (m. p., mixed m. p., and rotation) and by benzylation (pyridine—benzoyl chloride overnight at room temperature) to methyl oleanolate benzoate (m. p., mixed m. p., and rotation).

Hydrolysis of Lantadene A.—Lantadene A (127 mg.) was refluxed for 8 hr. with ethanolic potassium hydroxide (4%; 10 ml.). Chromatography of the product over silica gel (5 g.) in 1 : 1 benzene—light petroleum (b. p. 60—80°) gave (13 fractions), on elution with 1 : 1 benzene—ether, 22 β -hydroxyoleanonic acid (m. p. and mixed m. p.). The identity was confirmed by methylation to give methyl 22 β -hydroxyoleanonate (m. p., mixed m. p., and rotation).

Examination of South African Lantana camara.—The powdered leaves and branchlets (1.52 kg.) were extracted and processed as described above. However, even repeated chromatography afforded no crystalline ketonic (to the Zimmermann reagent) fraction.

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