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PHOTOLYSIS OF 3,5α-CYCLO-6-KETOSTEROIDS

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Abstract—The photolytic rearrangement of the steroidal 3,5-cyclo-6-keto system to give the Δ^4-6-keto system is described.

An interest in liquid phase photochemical reactions, and in steroid hormones lacking 3-oxygenation[1] led to the examination of the photolysis of 3,5α-cyclo-6-ketosteroids, and the known[2,3] androstane derivative (II; Chart I) was studied first.

For the preparation of II, known procedures[3] were followed, although it was found that direct conversion of the 3,5α-cyclo 6β-acetate (I) to the 6-ketone (II) was best accomplished using the Jones reagent[4] (chromium trioxide–sulphuric acid–acetone). This reaction presumably occurs *via* the homoallylic cation,[5] giving the 6-ol with subsequent oxidation, or conceivably by direct trapping of chromic acid by the homoallylic ion.

The oxidation procedure (chromium trioxide–acetic acid) advocated by Petrow *et al.*[3] while not, in our hands, as effective as the use of the Jones reagent was superior, in this case, to both the chromium trioxide–dimethylformamide reagent[6] and the two phase system recently described by Brown.[7]

Photolysis of the 3,5α-cyclo-6-ketone (II) in either dioxan or ethanol at 25–28°, using a 200 watt Hanovia Mercury lamp and quartz vessel led to disappearance of II and the formation of several products.[8] The major product (III) in each case (isolated in 13% and 20% yield respectively, by direct crystallization or chromatography on silica gel) had m.p. 159–164°, $[\alpha]_D$ +26°, was isomeric with (II) and contained an αβ-unsaturated ketonic grouping (λ_{max}^{MeOH} 242 mμ, $\varepsilon = 7{,}000$), evidently cisoid both from the low ε value and from the IR[9] spectrum (relative positions of C=O (5·95 μ)

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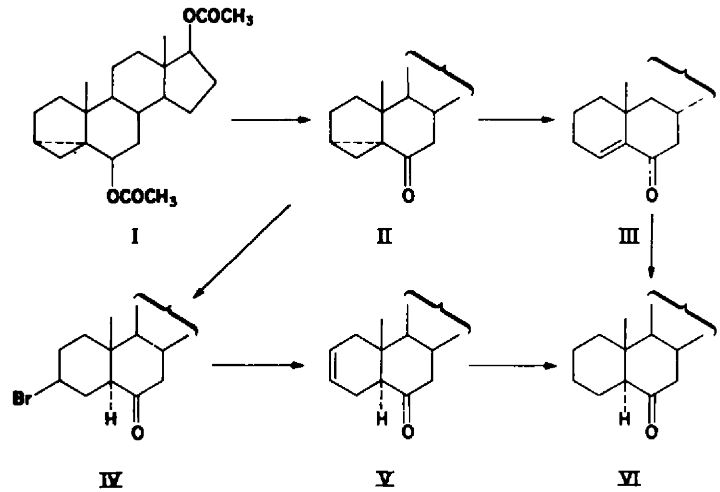
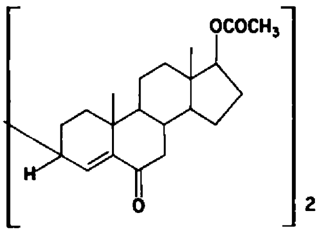
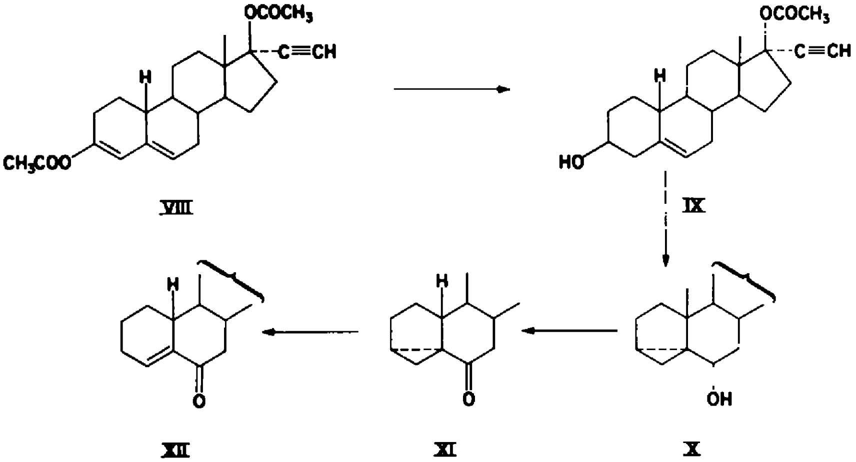
[1] For leading Ref to 3-desoxysteroid hormones, see A. Bowers, A. D. Cross, J. A. Edwards, H. Carpio, M. C. Calzada and E. Denot, *J. Med. Chem.* **6**, 156 (1963).
[2] A. Butenandt and L. A. Surányi, *Ber. Dtsch. Chem. Ges.* **75**, 591 (1942).
[3] V. Grenville, D. K. Patel, V. Petrow, I. A. Webb and D. M. Williamson, *J. Chem. Soc.* 4105 (1961).
[4] R. G. Curtis, I. M. Heilbron, E. R. H. Jones and G. F. Woods, *J. Chem. Soc.* 457 (1953).
[5] Cf. M. Simonetta and S. Winstein, *J. Amer. Chem. Soc.* **76**, 18 (1954).
[6] G. Snatzke, *Ber. Dtsch. Chem. Ges.* **94**, 729 (1961).
[7] H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.* **83**, 2952 (1961).
[8] The reaction was conveniently followed by thin-layer or paper chromatography of aliquots. Column chromatography gave, in addition to the crystalline compounds III and VII, oily mixtures which contained starting material (II), compound III, and other unidentified products in lesser amounts as shown by IR and paper chromatographic analysis (Experimental).
[9] Cf. R. L. Erskine and E. S. Waight, *J. Chem. Soc.* 3425 (1960); see also K. Noack and R. N. Jones, *Canad. J. Chem.* **39**, 2201 (1961).





VII



and C=C (6·17 μ) absorptions and abnormally strong C=C absorption). The optical rotatory dispersion curve[10] was very similar in both shape and amplitude to that recorded[11] for Δ^4-cholesten-6-one.

Structure III was established in the following way. The cyclo-propane ring in II

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[10] Measured through the courtesy of Prof. W. Klyne, to whom our best thanks are due.

[11] C. Djerassi, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **78**, 6362 (1956).

was opened with HBr-acetic acid[12] to give the 3β-bromo compound (IV), which was dehydrobrominated (quinoline) to furnish the Δ^2-compound (V). The latter proved to be stable to methanolic potassium hydroxide under reflux, and the fact that no Δ^4-6-ketone was generated would seem to confirm the absence of the Δ^3-isomer.

Hydrogenation of V over Pd–$CaCO_3$ gave in high yield the saturated 6-ketone (VI). Attempts to transform the 3-bromo compound (IV) directly to VI by, for example, Raney nickel reduction or hydrogenation with Pd–C were ineffective.

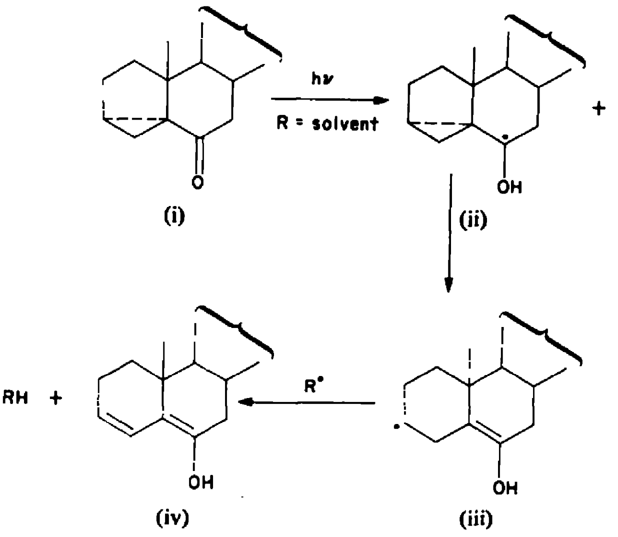
The saturated 6-ketone (VI) proved to be identical in all respects with the compound obtained by lithium–liquid ammonia reduction of the photolysis product (III).

In the case of the dioxan photolysis, a second crystalline product (VII), m.p. 285°, $[\alpha]_D$ +168° was isolated in about 0·5% yield. The mol. wt. (Found: 622) and analysis argue for a photodimer, and the UV absorption (246 mμ; ε = 16,300 based on structure VII) and IR spectrum (λ_{max}^{Nujol} 5·76, 5·94, 6·18, 7·99 μ) are consistent with structure VII, which we tentatively propose. The optical rotatory dispersion curve[10] of VII was also similar to that shown by the Δ^4-6-ketone.

The NMR spectrum[13] of the photodimer (VII) showed, in accord with symmetrical structure, singlets at 0·82 ppm (18-methyl), 0·96 ppm (19-methyl) and 2·03 ppm (methyl of 17-acetate) as well as a broad peak centered at 6·25 ppm (β-olefinic hydrogen[14] of αβ-unsaturated ketone).

By comparison, the monomer (III) showed peaks at 0·83 ppm (18-methyl), 0·99 ppm (19-methyl) and 2·03 ppm (methyl of 17-acetate) as well as a broad resonance centered at 6·4 ppm (β-olefinic hydrogen of αβ-unsaturated ketone).

The generation of the Δ^4-6-keto system from the 3,5α-cyclosteroid may involve radical intermediates such as those shown in paths A or B, for example.



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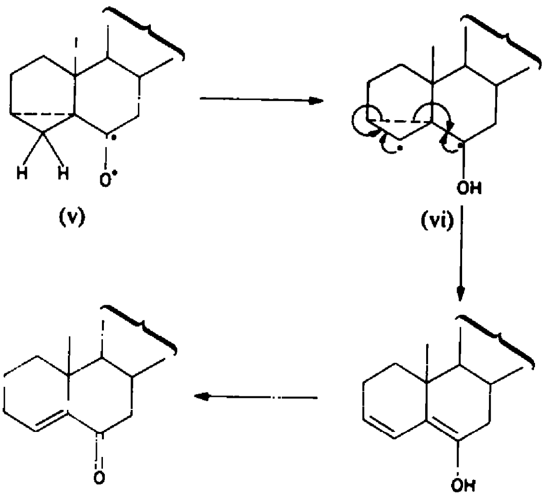
[12] Cf. A. Butenandt and L. A. Suranyi, Ref. 2.

[13] Measured at 60 Mc. in $CDCl_3$ solution, with tetramethylsilane as internal reference, using a Varian A-60 spectrometer. Positions of protons are given in parts per million (ppm) from tetramethylsilane (=0). We thank Dr. Leon Mandell, Emory University Atlanta, Georgia, for these measurements and for helpful comments.

[14] See for example M. Circumalli and D. B. MacLean, *Canad. J. Chem.* **40**, 1068 (1962).

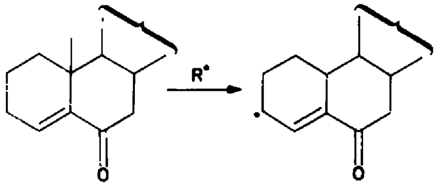
Pathway B would require hydrogen abstraction as shown, from the carbon atom β to the 6-keto group, leading to (vi), which can then collapse[15] to (vii). The intervention of charged species cannot of course, be excluded.



(v) (vi)

(III) (vii)

The formation of the symmetrical dimer (VII) can be conveniently explained by assuming combination between two radicals (viii) derived from the Δ^4-6-ketone *via* hydrogen abstraction by solvent radicals.[16]



(viii)

As an extension of the reaction we turned to the 19-norandrostene series (Chart I). A convenient starting point was the known[17] 19-nor-Δ^5 compound IX. However, the

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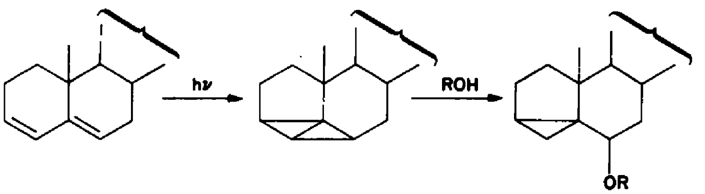
[15] It is interesting to compare such a sequence with the pathway proposed by W. G. Dauben and F. G. Willey, *Tetrahedron Letters* No. 20, 893 (1962) for the photochemical transformation of $\Delta^{3,5}$-cholestadiene to the 3,5β-cyclo-6β-ethoxy compound.



[16] The formation of dioxanyldioxan on irradiation of dioxan has been noted by K. Pfordte, *Liebigs Ann.* **625**, 30 (1959).

[17] J. Iriarte, C. Djerassi and H. J. Ringold, *J. Amer. Chem. Soc.* **81**, 436 (1961).

yield for the sequence VIII → IX (using sodium borohydride–tetrahydrofuran) is less than 1·0%.[18] We were finally able to increase the yield for the conversion of VIII to IX to about 50% by using the sodium borohydride–dimethylformamide–water system[19] for ten minutes at steam bath temperature.

The Δ^5-3β-hydroxy compound (IX) was then converted, *via* the 3β-toluenesulphonate ester, to the 3,5α-cyclosteroid (X). Oxidation of the latter with Jones reagent gave the 6-ketone (XI) which was irradiated, in dioxan, as for compound II. By chromatography of the mixture on Florisil, there was obtained, in approximately 10% yield, the Δ^4-6-ketone (XII) which showed the expected spectroscopic properties and analytical data.

EXPERIMENTAL

M.ps were taken on the Kofler block. Rotations were measured at 25° in dioxan solution at about 1% concentration, UV spectra were measured in MeOH, and IR data refer to Nujol mulls unless otherwise stated. We are indebted to the Physical Chemistry Department, Schering Corporation, for these measurements. Microanalyses were performed by Mr. E. Conner, Microanalytical Laboratory, Schering Corporation.

3,5α-Cycloandrostane-17β-ol-6-one 17β-acetate (II)

To a cooled (10°) solution of (I; 19·4 g) in acetone (1 l.) was added dropwise, with swirling, CrO_3–H_2SO_4 reagent (8 N with respect to 0; 30 ml). The mixture was kept overnight at 5°, and was then poured into iced water, and the resulting suspension filtered. The residue on the filter was washed with water and dried giving 14·63 g crude product with m.p. 108°–114°. Crystallization from MeOH raised the m.p. to 116–118°, and the product (II) then showed $[\alpha]_D$ +20°, λ_{max}^{Nujol} 5·76, 5·92, 8·05μ. (Petrow *et al.* Ref. 3 report m.p. 114–116°.)

Photolysis of 3,5α-cycloandrostan-17β-ol-6-one 17β-acetate (II)

A solution of II (4·0 g) in dioxan (150 ml) was irradiated, at 25–28°, in a quartz vessel by a Hanovia 200 watt Hg-lamp (654A-36). (Similar results were obtained when EtOH was substituted for dioxan except that the photodimer (VII) was not isolated.)

After 2 hr, the solution was evaporated to dryness *in vacuo* and the residue was crystallized twice from MeOH, then twice from isopropyl ether, to give III (313 mg) m.p. 159–164°, $[\alpha]_D$ +26°. λ_{max}^{MeOH} 242 mμ (= 7,000) λ_{max}^{Nujol} 5·76, 5·95, 6·17, 8·05 μ. (Found: C, 75·93; H, 8·90. Calc. for $C_{21}H_{30}O_3$: C, 76·32; H, 9·15%).

The mother liquors from the above crystallizations were combined, evaporated and chromatographed on Florisil. Elution with hexane–benzene (3:1) gave non-crystallizable oils (IR absorptions at 5·76, 5·92–5·95, 6·17, 8·05 μ; paper chromatography showed presence of starting material (II), Δ^4-6-ketone (III) and other substances in smaller amounts).

Further elution with hexane–benzene (3:1), with hexane–benzene (1:1) and with benzene gave a further quantity of III (200 mg) identified by m.p., mixed m.p., IR and paper chromatographic comparison.

Elution with ether gave crystalline VII which after 2 crystallizations from isopropyl ether had m.p. 280–285°, $[\alpha]_D$ +168°. λ_{max}^{MeOH} 246 mμ (= 16,300 based on mol. wt. of 659·9). λ_{max}^{Nujol} 5·76, 5·94, 6·18, 7·99, 8·05 μ. (Found: C, 76·42; H, 8·78; mol. wt. 622. Calc. for $C_{42}H_{58}O_6$: C, 76·56; H, 8·87%; mol. wt. 658·9.)

3β-Bromo-5α-androstan-17β-ol-6-one 17β-acetate (IV)

A solution of II (1·0 g) in glacial acetic acid (50 ml) and 30% HBr–acetic acid (8·0 ml) was left at room temp for 30 hr. The reaction mixture was then poured into water, and the resulting precipitate filtered off, washed with water and dried. Two crystallizations from isopropyl ether gave the pure

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[18] The 64% yield reported in ref. 19 is clearly a misprint and should be 0·64%. The latter figure agrees exactly with the actual weights of product reported, and is also consistent with the yields obtained on duplicating the described procedure.

[19] D. Taub, R. D. Hoffsommer and N. L. Wendler, *J. Amer. Chem. Soc.* 81, 3291 (1959).

IV (927 mg), m.p. 184–186°, $[\alpha]_D$ −21°. λ_{max}^{Nujol} 5·77, 5·85, 8·0 μ. (Found: C, 61·00; H, 7·65; Br. 19·76. Calc. for $C_{21}H_{30}O_3$ Br: C, 61·31; H, 7·60; Br, 19·43%.)

Δ^2-*Androsten*-17β-*ol*-6-*one* 17β-*acetate* (V)

A solution of IV (3·5 g) in freshly distilled quinoline (10 ml) was maintained at 150°–155° (oil bath temp) for 2 hr. The reaction mixture was then cooled, poured into water and extracted with ether. The ethereal extract was washed twice with 1 N HCl and was then washed 3 times with water, dried (Na_2SO_4) and evaporated *in vacuo.* The residue was crystallized from isopropyl ether, and then from MeOH to give V (415 mg.) m.p. 162–166°. The analytical sample (from MeOH) had m.p. 166–170°, $[\alpha]_D$ +5°. λ_{max}^{Nujol} 5·76, 5·86, 6·04, 8·04 μ. (Found: C, 75·92; H, 8·89. Calc. for $C_{21}H_{30}O_3$: C, 76·32; H, 9·15.)

5α-*Androstan*-17β-*ol*-6-*one* 17β-*acetate* (VI)

A. *By hydrogenation of the* Δ^2-*compound* (V). A solution of V (120 mg) in EtOH (10 ml) containing 15% Pd-$CaCO_3$ (120 mg) was hydrogenated at 24° for 1·75 hr. (Absorption of H_2 then ceased). The usual work-up and crystallization from MeOH gave VI (77 mg), m.p. 133–134°, $[\alpha]_D$ −31°. λ_{max}^{Nujol} 5·76, 5·83, 8·0 μ. (Found: C, 75·81; H, 9·80. Calc. for $C_{21}H_{32}O_3$: C, 75.86; H, 9·70.)

B. *By lithium-liquid ammonia reduction of the* Δ^4-6-*ketone* (III). A solution of III (300 mg) in ether (150 ml) was added quickly to a stirred solution of Li (300 mg) in liquid ammonia (150 ml). When all the steroid had been added, excess Li was destroyed by addition of solid NH_4Cl, and the mixture was then worked up in the usual way. The crude product was re-acetylated (at C-17) using pyridine acetic anhydride at room temp for 18 hr, and the acetylated product was chromatographed in Florisil. Elution with mixtures ranging from hexane–benzene (1 : 3) to neat benzene gave a series of crystalline fractions. These were combined (on the basis of paper and thin-layer chromatographic data) and crystallized from MeOH to give VI (55 mg), m.p. 129–133°, $[\alpha]_D$ −31°. Recrystallization raised the m.p. to 133–134°, undepressed on admixture with the product obtained by procedure A above. Identity was further confirmed by comparison of IR spectra which were superimposable and by paper and thin-layer chromatography.

17α-*Ethynyl*-19-*nor*-$\Delta^{5(10)}$-*androstene*-3β,17β-*diol* 17*a-cetate*[19] IX

To a solution of VIII (7·0 g) in dimethylformamide (252 ml) was added a solution of $NaBH_4$ (4·13 g) in water (63 ml) and the mixture heated on the steam bath for 10 min. The reaction mixture was then cooled and poured into water, and the aqueous mixture neutralized with acetic acid. Filtration gave the crude product which was washed with water, dried and crystallized from EtOH to give IX (3·31 g), 140–145°, $[\alpha]_D$ −64° ($CHCl_3$). (Recrystallization from EtOH raised the m.p. to 145–148°, but the material obtained by one crystallization was suitable for use in subsequent reactions.) Iriarte *et al.* Ref. 17, gave m.p. 145–150–, $[\alpha]_D$ −62° ($CHCl_3$).

17α-*Ethynyl*-19-*nor*-3, 5α-*cycloandrostane*-6β,17β-*diol* 17-*acetate* X

To a solution of IX (7·75 g) in pyridine (40 ml) was added *p*-toluenesulphonyl chloride (10·87 g) at 0°. The solution was kept at 0° for 30 min and was then stored at 5° for 18 hr. The reaction mixture was then poured into iced water, and the precipitated solid was filtered off, washed with water and dried *in vacuo* at room temp. The crude 3β-toluene-sulphonate ester thus obtained showed λ_{max}^{Nujol} 3·10, 4·75, 5·72, 6·72, 7·34, 7·41, 8·0, 8·5 μ. The IR absorptions at 7·34, 7·41 and 8·5 μ are attributed to the *p*-toluenesulphonate group.[20] Although this substance migrated as one spot on thin-layer chromatography (less polar than the 3β-ol) it was not possible to crystallize it, and the crude material was immediately solvolysed in a refluxing solution of acetone (155 ml) and water (155 ml) containing potassium acetate (12·4 g). After 5 hr under reflux the reaction mixture was cooled and poured into water. The resulting suspension was filtered, and the residue was washed with water, dried (6·8 g) and subjected to partition chromatography on Chromosorb W, using the ligroin-propylene glycol system. After some initial oily fractions, a series of crystalline fractions resulted, and these were combined and crystallized from either–hexane to give X (3·33 g), m.p. 154–156°, $[\alpha]_D$ −30° ($CHCl_3$) λ_{max}^{Nujol} 2·88, 3·03, 5·79, 7·87, 8·08 μ. (Found: C, 77·04; H, 9·22. Calc. for $C_{22}H_{30}O_3$: C, 77·15; H, 8·83.)

[20] L. J. Bellamy, *The Infra-red Spectra of Complex Molecules* p. 364. J. Wiley, New York, N.Y. (1958).

17α-*Ethynyl*-19-*nor*-3,5α-*cycloandrostan*-17β-*ol*-6-*one* 17-*acetate* XI

To a solution of X (330 mg) in acetone (20 ml), at 0°–5°, was added with swirling a solution of Jones reagent (8 N with respect to O) until a permanent orange colour persisted. The mixture was left at room temp for 30 min, and was then diluted with water and filtered. The product was washed with water, dried and subjected to partition chromatography on Chromosorb W using the ligroin–propylene glycol system. The crystalline fractions which resulted were combined and crystallized from ether–hexane to give XI (208 mg), m.p. 160–163°, $[\alpha]_D$ −57°. λ_{max}^{Nujol} 3·07, 5·73, 5·96, 7·93, 8·02 μ. (Found: C, 77·52; H, 8·35. Calc. for $C_{22}H_{28}O_3$: C, 77·61; H, 8·29%.)

17α-*Ethynyl*-19-*nor* Δ⁴-*androsten*-17β-*ol*-6-*one* 17-*acetate* (XII)

A solution of XI (1·0 g) in dioxan (150 ml) was irradiated, in a quartz cell at 26°, with a 200 watt Hanovia Hg lamp for 2 hr, under N_2 The solution was then evaporated *in vacuo*, and the residue was chromatographed on Florisil. Elution with hexane:benzene (4:1) gave solids which were combined and crystallized from acetone–ethyl acetate–hexane, to give the analytical sample of XII (112 mg), m.p. 208–215°, $[\alpha]_D$ −60°, λ_{max}^{MeOH} 245 mμ (ε = 7,200) λ_{max}^{Nujol} 3·03, 4·72, 5·72, 5·92, 6·17, 8·03 μ. (Found: C, 77·65; H, 8·36. Calc. for $C_{22}H_{28}O_3$: C, 77·61; H, 8·29.)

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