the precipitate was centrifuged off. (In the case of sample H, the precipitate was centrifuged off, dissolved in a minimum amount of water and reprecipitated with alcohol.) The precipitate was dissolved in a convenient amount of water and the solution was dialyzed in a rotated Visking cellophane casing for 3 hr. (for 8.5 hr. in the case of preparation H) against running distilled water. The dialyzed solution, which had become slightly acidic, usually was adjusted to neutrality with dilute sodium hydroxide solution. The neutral solution was precipitated by the addition of three volumes of absolute alcohol, and the sirupy precipitate was separated by centrifuging. Alcohol precipitation was repeated from an aqueous solution. The sodium polyglucose sulfate was then dissolved in water and freeze-dried to give a light, stable and almost colorless powder. The properties of the resulting polyglucose sulfate sodium salts are reported in Table I.

The polyglucose sulfate can be obtained in the free acid form by passing the aqueous solution of the salt through IR-120-H Amberlite ion exchange resin. The solution (*p*H 1) can be freeze-dried to a brown sirup.

Anticoagulant Activity.—The U.S.P. assay for heparin activity was used on sheep plasma.[20] Polyglucose sulfates gave approximately the same anticoagulant activity by the assay as clinical heparin preparations, which is about one-third of the international heparin standard.

Metachromatic Activity.—Interaction with the basic thiazine dye toluidine blue was measured spectrophotometrically. Metachromatic activity was in the same order of magnitude as dextran sulfates.[21]

Acknowledgment.—We are indebted to Dr. W. C Alford for analytical determinations, and to Miss Vivian S. Williams for viscosity measurements.

[20] L. M. Tocatins. "The Coagulation of Blood." Grune and Stratton. New York, N. Y., 1955. Chapter XIII, p. 214.

[21] K. W. Walton and C. R. Ricketts, *Brit. J. Exp. Pathol.*, **35**, 227 (1954).

BETHESDA 14, MD.

[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT DIVISION OF THE SCHERING CORP.]

The Dienol–Benzene Rearrangement.[1] Some Chemistry of 1,4-Androstadiene-3,17-dione

BY MARGARET JEVNIK GENTLES, JANE B. MOSS, HERSHEL L. HERZOG AND E. B. HERSHBERG

RECEIVED JANUARY 20, 1958

1,4-Androstadiene-3ξ,17β-diol, upon treatment with weak acid or activated magnesium silicate, rearranges with loss of water to 4-methyl-1,3,5(10)-estratrien-17β-ol. The structure of the product was proved by dehydrogenation of the corresponding 17-ketone over Pd-on-carbon to the known 1-ethyl-2,8-dimethylphenanthrene.

Subsequent to the renaissance of interest in steroid 1,4-diene-3-ketones[2] we had occasion to study the chemistry of 1,4-androstadiene-3,17-dione (I) looking toward the introduction of various substituent groups at C-17. It had been shown previously that 4-androstene-3,17-dione reacts with one mole of ethylene glycol at either C-3 or C-17 depending upon the ratio of catalyst (*p*-toluenesulfonic acid) to steroid employed.[3] Under conditions most favorable for the formation of a 3-ethylene ketal it was now found that I forms only the 17-ethylene ketal II. By increasing the amount of ethylene glycol employed, an 87% yield of II was achieved. It was not possible to demonstrate the presence of either the 3-ethylene ketal of I[3a] or the 3,17-bisethylene ketal.

Since it was impossible to achieve selective protection at C-3 in this way an attempt was made to reduce the 3-carbonyl group of II. Following reaction of II with a large excess of lithium aluminum hydride[3b] in ethereal solution the excess reagent was destroyed by the addition of acetone and then a limited amount of water was added in order to afford a filterable precipitate of hydrated alumina. The reaction products were then isolated by *chromatography over Florisil* and a *ca.* 65% yield of a benzenoid, steroidal product III resulted.

The structure of III was established in the following fashion: The benzenoid nature of III was apparent from the ultraviolet [bands at 262 mμ (ε 259) and 269 mμ (ε 197)] as was the disappearance of the dienone group originally present in II. The infrared spectrum of III displayed aromatic absorption at 6.30 and 6.38 μ and lacked the bands customarily assigned to 1,4-diene-3-ketones. The loss of an atom of oxygen was clear from the carbon and hydrogen analyses of III and its transformation products. Hydrolysis of the 17-ethylene ketal group of III in aqueous acetic acid yielded IV, which had ultraviolet and infrared spectra consistent with the assigned structure. Reduction of IV with sodium borohydride or of I with lithium aluminum hydride (*with chromatography*) afforded V. Oxidation of IV or V with chromic acid in acetic acid gave a diketone VI, which contained a six-membered ring carbonyl group conjugated to the benzene ring [ultraviolet bands at 253 mμ (ε 9,000) and 299 mμ (ε 2,000)].

Recapitulation of the evidence to this point led to the logical surmise that a dienone–phenol type rearrangement had occurred during the lithium aluminum hydride step. Isolation of the lithium

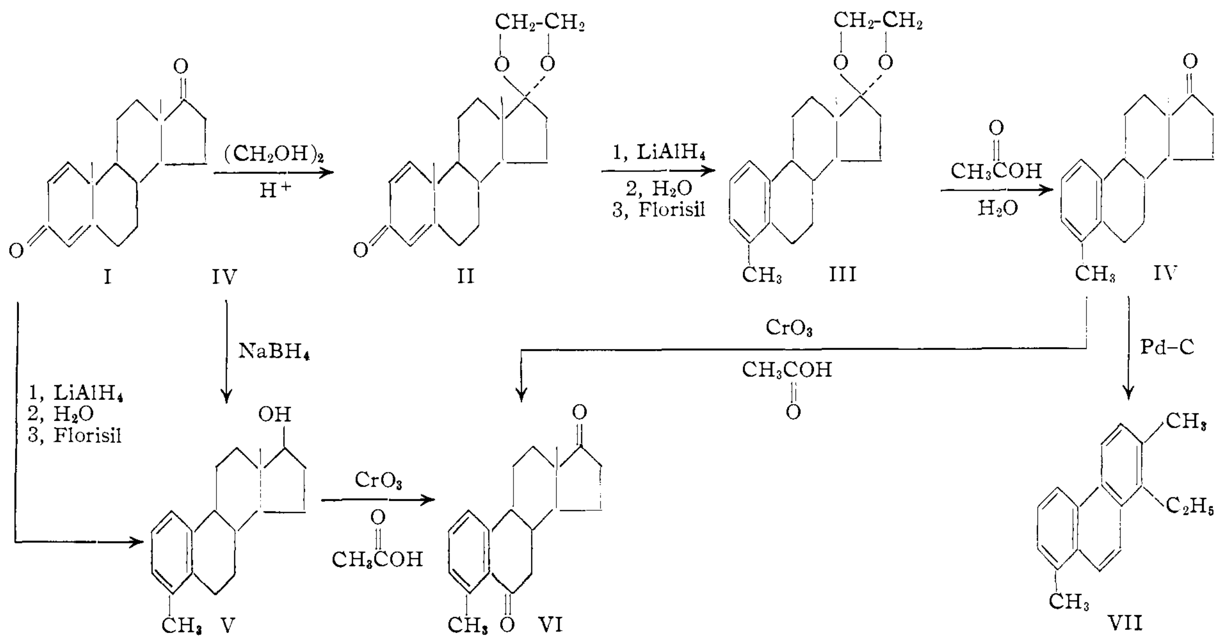
[1] The name for this rearrangement was first suggested to us by Dr. J. Meinwald of Cornell University. Since that time a preliminary communication of H. Plieninger and G. Keilich, *Angew. Chem.*, **68**, 618 (1956), has appeared in which the rearrangement of 4-trichloromethyl-4-methylcyclohexadienol to *o*-trichloromethyltoluene by the action of mineral acid is described. These authors propose that the rearrangement be designated in the same way. A related aromatization, without rearrangement, was postulated by U. Weiss, *et al.*, *Science*, **119**, 774 (1954), to account for the conversion of prephenic acid to phenylpyruvic acid.

[2] H. L. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. L. Perlman and M. M. Pechet, *ibid.*, **121**, 176 (1955).

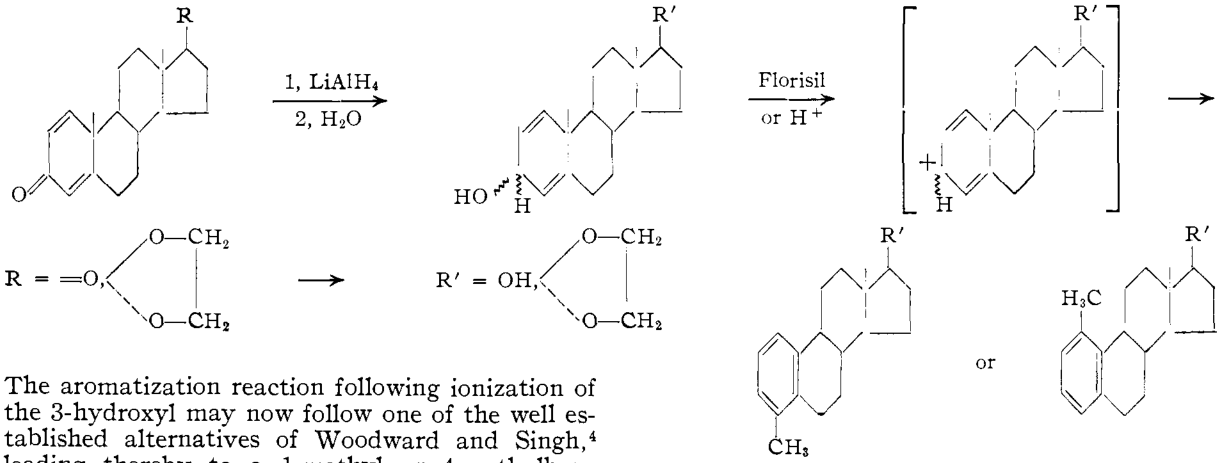
[3] H. L. Herzog, M. A. Jevnik, M. E. Tully and E. B. Hershberg, THIS JOURNAL, **75**, 4425 (1953).

[3a] *Cf.* J. A. Hogg, *et al.*, *ibid.*, **77**, 4438 (1955), who claim to have prepared the 3-cycloethylene ketal of methyl-3,11-diketo-1,4,17(20)-[*cis*]-pregnatrien-21-oate. Neither detailed procedure nor constants of the ketal are reported.

[3b] *Cf.* F. Sondheimer, *et al.*, *Chemistry & Industry*, 1482 (1954), who noted that reduction of 1,4-androstadiene-3,17-dione with sodium borohydride affords a mixture of diols containing products in which the double bond at 1- has been reduced.



aluminum hydride reduction product following the addition of water to the reaction but prior to chromatography gave a mixture of diols which was essentially free of conjugated unsaturation, either dienone or aromatic. Chromatography of this mixture on Florisil, or brief warming with aqueous acetic acid, resulted in loss of the 3-hydroxyl group and aromatization. The reaction sequence may now be written as



The aromatization reaction following ionization of the 3-hydroxyl may now follow one of the well established alternatives of Woodward and Singh,[4] leading thereby to a 1-methyl or 4-methylbenzenoid structure.

The choice for the structure of III (and V) was made unequivocally on the basis of results obtained from palladium-catalyzed dehydrogenation of IV.

Dreiding and co-workers[5] showed that 1-methoxy-4-methylestra-1,3,5(10)-triene-17-one is dehydrogenated over 5% palladium-on-charcoal catalyst at 350° to 1-ethyl-2,8-dimethylphenanthrene (VII) and other products. They proved the structure of VII by synthesis. Following their method, dehydrogenation of IV at 350° afforded VII which was identified by detailed comparison with an authentic sample synthesized according to the Dreiding–Voltman procedure. Hence, it must be concluded that the methyl group originally at C-10 in I is now at C-4 in III and its transformation products, and that the structure of III is in all respects consistent with the formulation 4-methylestra-1,3,5(10)-triene-17-one 17-cycloethylene ketal.

Because of our inability to protect the 3-carbonyl group, we attempted the selective ethination of I according to the method of Stavely.[6] In contrast to the results of the Syntex group,[7] we were able to isolate a small yield (6%) of 17α-ethinyl-1,4-androstadiene-17β-ol-3-one by this method whose structure was apparent from carbon and hydrogen analyses, infrared and ultraviolet spectra. Our constants are in good agreement with published values.[7]

We thank Dr. Hans Reimann and Mr. Lawrence Finckenor for helpful suggestions.

(4) R. B. Woodward and T. Singh, THIS JOURNAL, **72**, 494 (1950).

(5) A. S. Dreiding and A. Voltman, *ibid.*, **76**, 537 (1954); A. S. Dreiding and A. J. Tomascewski, *ibid.*, **76**, 540 (1954).

(6) H. E. Stavely, *ibid.*, **61**, 79 (1939).

(7) F. Sondheimer, M. Velasco and G. Rosenkranz, *ibid.*, **77**, 5673 (1955).

Experimental[8]

1,4-Androstadiene-3,17-dione 17-Ethylene Ketal (II).—A solution of 700 mg. of 1,4-androstadiene-3,17-dione (I) in 35 ml. of C.P. benzene was refluxed with 0.16 ml. of ethylene glycol and 7 mg. of *p*-toluenesulfonic acid for four hours with concomitant distillation of 12 ml. of benzene. The reaction mixture was cooled, made alkaline by the addition of a few drops of 10% potassium hydroxide solution and washed with water until neutral. After drying over anhydrous magnesium sulfate, a drop of pyridine was added and the solvent was removed *in vacuo*. Heptane was added to the residue and concentration *in vacuo* was repeated. The residue was taken up in hexane and chromatographed on 15 g. of Florisil. Elution with hexane afforded, after recrystallization, 280 mg. of II as needles, m.p. 171–172°, $\lambda_{\max}^{\mathrm{MeOH}}$ 244 mμ (ϵ 15,600), $[\alpha]^{25}\mathrm{D}$ 0° (dioxane); $\lambda_{\max}^{\mathrm{Nujol}}$ 6.03, 6.16 and 6.24 μ (3-keto-$\Delta^{1,4}$-diene).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.65; H, 8.65.

From later hexane fractions 85 mg. of crystalline I, m.p. 140–142°, was recovered. When the reaction was repeated with 14 mg. of *p*-toluenesulfonic acid and 0.34 ml. of ethylene glycol (other conditions as before) no chromatography was necessary to isolate II and there resulted by crystallization from heptane 700 mg. (87%) of II, m.p. 168–170°.

4-Methylestra-1,3,5(10)-triene-17-one 17-Ethylene Ketal (III).—To a mixture of 1 g. of II and 1 g. of lithium aluminum hydride was added slowly 100 ml. of dry ether while the temperature was maintained at 0–5° with the aid of mechanical agitation. The reaction mixture was then refluxed for two hours, cooled again to 0–5°, and 10 ml. of acetone was added cautiously with agitation. Then, 10 ml. of water was added dropwise with agitation. The mixture was filtered and the hydrated alumina was washed with ether. The combined filtrates were washed with water, dried and concentrated to a residue. There resulted 990 mg. of colorless oil.

The oil was taken up in hexane and chromatographed on 15 g. of Florisil. The hexane fractions were pooled and crystallized from hexane at −78°. There resulted 250 mg. of III, m.p. 115–116.5°. Recrystallization from methanol–water raised the m.p. to 116–117° $[\alpha]^{25}\mathrm{D}$ +16° (dioxane), $\lambda_{\max}^{\mathrm{MeOH}}$ 262 mμ (ϵ 259), 268–270 mμ (ϵ 197); $\lambda_{\max}^{\mathrm{Nujol}}$ 6.30 μ, 6.38 μ (aromatic unsaturation), 8.46 μ, 8.55 μ (C–O–C of ketal). The compound was unstable on long standing. After 19 months storage a band at 5.75 μ (17-carbonyl) appeared in the infrared spectrum of the ketal indicating slow hydrolysis.

Anal. Calcd. for $2C_{21}H_{29}O_2 \cdot H_2O$: C, 78.46; H, 9.01. Found: C, 78.75; H, 8.89.

4-Methylestra-1,3,5(10)-triene-17-one (IV).—A solution of 1.80 g. of III in 100 ml. of 85% aqueous acetic acid was heated to reflux for two minutes, cooled and diluted to the cloud point with water. Compound IV crystallized as needles. By successive filtration and dilution with more water a total of 1.06 g. of IV, m.p. 182–186° (68%), was obtained. Further recrystallization from ether–hexane raised the m.p. to 184.5–186°, $[\alpha]^{25}\mathrm{D}$ +146° (dioxane); $\lambda_{\max}^{\mathrm{MeOH}}$ 263 mμ (ϵ 245), 271 mμ (ϵ 195); $\lambda_{\max}^{\mathrm{Nujol}}$ 5.78 μ (17-carbonyl), 6.31 μ (aromatic saturation).

Anal. Calcd. for $C_{19}H_{24}O$: C, 85.02; H, 9.01. Found: C, 84.91; H, 9.05.

4-Methylestra-1,3,5(10)-triene-17β-ol (V).—To a suspension of 1.06 g. of IV in 75 ml. of methanol was added 530 mg. of sodium borohydride in 10 ml. of water. The mixture was refluxed for five minutes and allowed to stand overnight. A crystalline precipitate developed which upon filtration afforded 860 mg. of V, m.p. 109–112°. Recrystallization of V from methanol at −78° resulted in the formation of needles, m.p. 113–114°, $[\alpha]^{25}\mathrm{D}$ +64° (dioxane); $\lambda_{\max}^{\mathrm{Nujol}}$ 3.04 μ (OH), 6.31 μ (aromatic unsaturation). No satisfactory analysis for carbon was obtained. The analyses were consistent with three samples from different batches and all were low. However, the analysis of the hemiphthalate derivative was satisfactory.

Anal. Calcd. for $C_{19}H_{26}O$: C, 84.39; H, 9.69. Found: C, 83.63, 83.47, 83.51; H, 9.63, 9.45, 9.45.

The 17-hemiphthalate of V was prepared by refluxing a solution of 263 mg. of V and 137 mg. of phthalic anhydride in 12 ml. of anhydrous pyridine for 7 hours and then storing the mixture at 60° for ten days. The solvent was removed at room temperature and the residue was taken up in acetone. Crystallization of the crude hemiphthalate was induced by addition of hexane, 152 mg. of needles, m.p. 195–205°, resolidification and remelting 225–235° resulting thereby. Recrystallization from aqueous acetone afforded 76 mg., m.p. 237–240°. The analytical sample melted at 242–243°, $[\alpha]^{25}\mathrm{D}$ +53° (dioxane).

Anal. Calcd. for $C_{27}H_{30}O_4$: C, 77.48; H, 7.23. Found: C, 77.20; H, 7.41.

V from I. Isolation of 1,4-Androstadiene-3ξ,17β-diol.—A solution of 500 mg. of 1,4-androstadiene-3,17-dione in 70 ml. of anhydrous ether was reduced with 1 g. of lithium aluminum hydride at reflux for 0.5 hour. The mixture was treated first with 10 ml. of acetone (dropwise) and then 100 ml. of water. The ethereal layer was separated and the aqueous layer was extracted thoroughly with ether. The combined ethereal extracts were washed with water, dried and concentrated *in vacuo*. There resulted 490 mg. of oil which upon trituration with a mixture of acetone, ether and hexane afforded 260 mg. of a colorless powder, whose m.p. varied between 162–167° and 182–185° depending on the temperature of insertion. A second crop of 40 mg. was isolated by concentration of the filtrate. Recrystallization could not be effected successfully. Following trituration of the powder with cold acetone, the following constants were observed: $\lambda_{\max}^{\mathrm{MeOH}}$ 240 mμ (ϵ 346); $\lambda_{\max}^{\mathrm{Nujol}}$ 2.97 μ (OH), 5.90 μ (acetone of solvation).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.02; H, 9.81. (Sample dried 18 hr. 60°, *in vacuo*.)

When the reduction was carried out at 0° for five minutes, the product, isolated in the same way, possessed an infrared spectrum identical with that of the aforedescribed diol. The same was true for an experiment conducted at reflux for five hours.

Rearrangement of the Diol to V. (1) **By Acetic Acid.**—Fifty milligrams of diol from the preceding experiment were dissolved in 9 ml. of acetic acid and 2 ml. of water. The reaction mixture was heated to reflux for one minute, cooled and allowed to stand. Long needles of V precipitated. Upon further dilution with water, additional precipitate formed. By filtration 40 mg. of V, m.p. 109–113°, was obtained, possessing an infrared spectrum identical with that described previously.

(2) **By Florisil.**—A solution of 100 mg. of diol in 10 ml. of methylene chloride was chromatographed over 7 g. of Florisil. From elution with 25% ether-in-hexane there resulted 70 mg. of V, m.p. 109–113°. In the 100% ether fractions 15 mg. of material, m.p. 85–143°, was obtained, whose infrared spectrum revealed the presence of some unrearranged diol together with V.

4-Methylestra-1,3,5(10)-triene-6,17-dione (VI).—To a solution of 270 mg. of V in 5 ml. of glacial acetic acid was added 375 mg. of chromic acid in 1 ml. of water. The resulting solution was stirred for two hours at 50°, whereupon 1 ml. of ethanol was added. The solution was then concentrated *in vacuo* to a volume of 2 ml. and 20 ml. of water was added. The oils, which had precipitated after the mixture stood overnight, were taken up in methylene chloride, washed with water, dried and chromatographed on 15 g. of Florisil. The 50% ether-in-hexane fractions afforded 20 mg. of needles, m.p. 129–133°. Recrystallization from ether–hexane gave VI, m.p. 132–133°, $[\alpha]^{25}\mathrm{D}$ +85° (dioxane); $\lambda_{\max}^{\mathrm{MeOH}}$ 253 mμ (ϵ 8,960), 299 mμ (ϵ 2,030); $\lambda_{\max}^{\mathrm{Nujol}}$ 5.77 μ (17-carbonyl), 5.96 μ (6-carbonyl), 6.28 and 6.36 μ (aromatic unsaturation).

Anal. Calcd. for $C_{19}H_{22}O_3$: C, 80.81; H, 7.85. Found: C, 80.53; H, 7.68.

By oxidation of IV by the same procedure (270 mg. of IV, 500 mg. of chromium trioxide) there was obtained 55 mg. of VI, m.p. 133–135°, identical in infrared spectrum with the sample obtained by oxidation of V.

Dehydrogenation of IV to VII.—A mixture of 0.2 g. of IV and 0.2 g. of 5% palladium-on-charcoal (Baker and Co. Platinum Works) was heated under nitrogen at 350 ± 5° for ten minutes. The cooled residue was taken up in benzene, filtered and concentrated to an orange, glassy residue, which was taken up in hexane–benzene (5:1) and chromatographed on 12 g. of activated alumina. From the hexane–

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[8] All melting points are corrected. Analyses and optical data were obtained by the Physical Chemistry Department of these laboratories and by the Galbraith Laboratories, Knoxville, Tenn.

benzene (5:1) eluates was obtained 90 mg. of colorless platelets which, on recrystallization from methanol, gave 20 mg. of VII as plates, m.p. 113–114°; λ_{max}^{MeOH} 217, 255, 262, 283, 294, 307 mμ (ε 38,900, 53,500, 65,600, 15,700, 14,900, 17,500); λ_{min}^{MeOH} 234, 257, 278, 288, 298 mμ (ε 9,200, 51,200, 14,000, 10,900, 7,900); λ_{max}^{Nujol} 3.24, 6.22, 6.31, 6.53, 12.20, 12.62, 13.56 μ.

From the mother liquor of crystallization a **trinitrobenzene complex** was prepared, m.p. 168.5–170°.

An authentic sample of VII was prepared according to Dreiding and Voltman[5] at 350°. The resulting product melted at 117–118°, possessed the same ultraviolet maxima and minima as VII from IV, and possessed the same infrared spectrum as VII from IV. A mixture of VII from the two sources melted at 114.5–116.5°.

The trinitrobenzene complex prepared from VII according to Dreiding and Voltman melted at 171–173°. A mixture of VII trinitrobenzene from the two sources melted at 170–172°.

BLOOMFIELD, N. J.

[CONTRIBUTION FROM THE RESEARCH LABORATORY ATTACHED TO TAKEDA PHARMACEUTICAL INDUSTRIES, LTD.]

Infrared Spectra of Santonin Isomers[1]

BY TOKUNOSUKE KANZAWA, HIDEO KAMIO, MASAO SUMI AND MASAO NISHIKAWA

RECEIVED FEBRUARY 13, 1958

Infrared spectra of santonins and related compounds (54 samples) were examined. Some correlation was found between structure and spectra. The absorption of the γ-lactone is discussed in considerable detail. Two characteristic bands appear in the 1200–900 cm.$^{-1}$ region and combination of their position and intensity serves to determine the stereochemical configuration of the lactone ring.

Abe and his collaborators[2] have successfully synthesized the naturally occurring (−)-α- and (−)-β-santonins as well as the other stereoisomers. Santonin has four asymmetric carbons and their positions are indicated by asterisks in the formula (Fig. 1). Of the sixteen optically active isomers required by theory, however, only twelve exist, since four isomers having a *trans*-lactone in the diaxial configuration at C_6 and C_7 cannot be constructed. These twelve are tentatively called *d*- and *l*-santonins A, B, C and D and *d*- and *l*-α- and β-santonins. Abe, *et al.*, have further elucidated that the skeleton of santonin isomers corresponds to the A and B rings of $\Delta^{1,4}$-3-ketosteroids and the stereochemical configuration of these isomers is summarized in Table I.

TABLE I

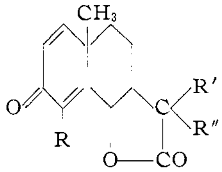
STEREOCHEMICAL CONFIGURATION OF SANTONIN ISOMERS

Santonin	C_6–O	C_7–C_{11}	Lactone	C_7–H, C_{11}–H
A	Equat.	Axial	*Cis*	*Cis*
B	Equat.	Axial	*Cis*	*Trans*
C	Axial	Equat.	*Cis*	*Trans*
D	Axial	Equat.	*Cis*	*Cis*
α	Equat.	Equat.	*Trans*	*Trans*
β	Equat.	Equat.	*Trans*	*Cis*

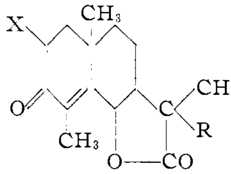
Such differences in the configuration should cause different spectra and we have undertaken to correlate structure with infrared spectra.

Experimental

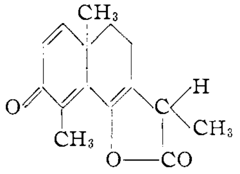
Perkin-Elmer infrared spectrometer model 21 equipped with NaCl optics was used. Fifty-four samples were examined; santonins (racemic and optically active) (I, 11 samples), 4-norsantonins (II, 2 samples), 1,2-dihydrosantonins (V, 5 samples), and their 2-bromo derivatives (VI, 3 samples), 11-carbethoxysantonins (IV, 4 samples), 11-carbethoxy-1,2-dihydrosantonins (VII, 3 samples) and their 2-bromo derivatives (VIII, 2 samples), 11-norsantonins (III, 2 samples), santonene series (*e.g.*, IX, 5 samples),[3] deoxysantoninic acid derivatives (*e.g.*, X, 10 samples), desmotroposantonin series (*e.g.*, XIII, 2 samples), tetrahydrosantonin (XI) and its deoxo compound XII, 3-octalone series (3 samples). They were all synthesized by Abe and his collaborators and their purity was confirmed by elementary analysis. Spectra were taken between 2 and 15 μ in Nujol mull and in 5% chloroform solution. The wave numbers in the double bond region were checked by the absorption of polystyrene film as a standard.



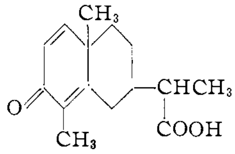
I, R = R′ = CH_3, R″ = H
II, R = R″ = H, R′ = CH_3
III, R = CH_3, R′ = R″ = H
IV, R = R′ = CH_3,
R″ = $COOC_2H_5$



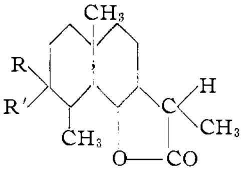
V, X = R = H
VI, X = Br, R = H
VII, X = H,
R = $COOC_2H_5$
VIII, X = Br,
R = $COOC_2H_5$



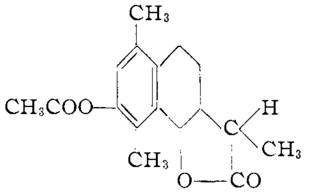
IX



X



XI, R,R′ = O
XII, R = R′ = H



XIII

Results and Discussion

The spectrum of a racemic compound in the crystalline state generally differs from that of the optically active one. In the case of santonin iso-

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(1) Presented at the Annual Meeting on Infrared and Raman Spectroscopy held at the Osaka University, Oct. 5, 1956.

(2) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi and T. Toga, THIS JOURNAL, **75**, 2567 (1953); **78**, 1416, 1422 (1956).

(3) These samples were kindly supplied by Dr. Nishikawa, to whom we are much indebted; *cf. J. Pharm. Soc. Japan*, **75**, 1199, 1202 (1955).