m.p. 275–277° dec. Recrystallized from ethyl acetate the prisms melted at 286° dec., $[\alpha]^{22}D$ +178° ($CHCl_3$).

Anal. Calcd. for $C_{26}H_{32}O_4$: C, 76.45; H, 7.90. Found: C, 76.40; H, 7.83.

11-Ketotestosterone-propionate (XV).—A solution of 1.48 g. of 11β-hydroxytestosterone 17-propionate in 80 ml. of glacial acetic acid was treated with a solution of 0.74 g. of chromic anhydride in 4 ml. of water and 80 ml. of acetic acid at room temperature for five hours. After destroying excess oxidant with methanol the solution was concentrated *in vacuo*, the residue diluted with water and the product extracted with ether. The ether solution was processed for the neutral fraction which weighed 1.29 g. Recrystallization from a mixture of ether and Skellysolve B gave 1.13 g. (76%), m.p. 139–140°, $[\alpha]^{22}D$ +169° ($CHCl_3$).

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.70; H, 8.44. Found: C, 73.84; H, 8.64.

11-Ketotestosterone (XVI).—A solution of 1.07 g. of 11-ketotestosterone propionate in 50 ml. of 1 *N* methanolic potassium hydroxide containing 3 ml. of water was refluxed for 30 minutes. The solution was poured onto ice and the resulting mixture was slightly acidified with dilute sulfuric acid. The precipitate was recovered by filtration, washed with water and dried. It weighed 0.79 (88%), m.p. 187–188°. When the aqueous filtrate was extracted with methylene chloride an additional yield of 0.09 g. of product, m.p. 182–186° was recovered. Recrystallized from methylene chloride–ether mixture the product still melted at 187–188°, $[\alpha]^{22}D$ +224° ($CHCl_3$).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.63; H, 8.57.

The infrared spectrum in nujol of this compound showed absorption for the following functional groups: OH, 3555, 3382, 3317 $cm.^{-1}$; 11-ketone, 1704 $cm.^{-1}$, Δ^4-3-ketone, 1664 $cm.^{-1}$, conj. Δ^4-C=C, 1614 $cm.^{-1}$.

Acknowledgment.—The authors are indebted to Drs. D. H. Peterson, H. C. Murray and P. D. Meister for suggestions with regard to obtaining a supply of 11α-hydroxy-4-androstene-3,17-dione. Our thanks are due to Dr. J. L. Johnson, Mr. J. E. Stafford and Mrs. G. S. Fonken for the ultraviolet and infrared analyses, and to Mr. W. A. Struck and his associates for the optical rotations and microanalyses.

KALAMAZOO, MICHIGAN

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. L.[1] The Oxidation of Steroidal Allylic Alcohols with Manganese Dioxide. A Novel Synthesis of Testosterone[2]

BY FRANZ SONDHEIMER, C. AMENDOLLA AND G. ROSENKRANZ

RECEIVED JUNE 25, 1953

The oxidation of a number of steroidal allylic alcohols to the corresponding carbonyl compounds by means of manganese dioxide is described [Δ^4-3β-ol (I) → Δ^4-3-one (II); Δ^5-7α-ol (III) → Δ^5-7-one (IV); $\Delta^{9(11)}$-12ξ-ol (V) → $\Delta^{9(11)}$-12-one (VI) and $\Delta^{17(20)}$-21-ol (VII) → $\Delta^{17(20)}$-21-al (VIII)]. Δ^4-Androstene-3,17-dione (IX) on reduction with lithium aluminum hydride gives a mixture of Δ^4-androstene-3β,17β-diol (Xa) and the 3α,17β-diol (Xb), which on oxidation with manganese dioxide furnishes testosterone (XI)—in 90% over-all yield. Similarly progesterone (XII) is converted to Δ^4-pregnen-20β-ol-3-one (XIVa).

The use of manganese dioxide for the oxidation of polyene alcohols to the corresponding carbonyl compounds was first described in 1948 by Morton and collaborators,[3] who oxidized vitamin A to vitamin A aldehyde with this reagent. Since that time other polyene alcohols, both primary and secondary, have been oxidized with manganese dioxide,[4] and it has been shown that even simple singly unsaturated alcohols may be oxidized to the corresponding carbonyl compounds with the reagent (allyl alcohol → acrolein, oct-3-yn-2-ol → oct-3-yn-2-one).[5] We have investigated the manganese dioxide oxidation of a number of singly unsaturated allylic alcohols of the steroid series, and have found that oxidation to the corresponding carbonyl compounds may often be brought about smoothly and in satisfactory yield.

The first alcohol to be oxidized was Δ^4-cholesten-3β-ol, containing the Δ^4-3β-ol system I. In this and subsequent oxidations it was found that commercial manganese dioxide gave erratic and unreproducible results, and with some samples no oxidation at all was observed. The dioxide prepared from manganese sulfate and potassium permanganate,[6] however, proved to be quite satisfactory, and this material could be kept for several months in a stoppered bottle without loss of activity.[7] When Δ^4-cholesten-3β-ol was shaken at room temperature with this reagent in any one of a variety of solvents, such as benzene, chloroform, ethylene chloride or acetone, oxidation to Δ^4-cholesten-3-one (type II) proceeded rapidly, and the latter could be isolated in almost quantitative yield. Similarly the mixture of Δ^4-cholesten-3α-ol and -3β-ol (predominantly the latter[8]), obtained by the lithium aluminum hy-

(1) Steroids. XLIX, A. Sandoval, L. Miramontes, G. Rosenkranz, Carl Djerassi and Franz Sondheimer, THIS JOURNAL, **75**, 4117 (1953).

(2) Presented in part at the Los Angeles Meeting of the American Chemical Society, March, 1953. A preliminary announcement of part of this work has been published (F. Sondheimer and G. Rosenkranz, *Experientia*, **9**, 62 (1953)).

(3) S. Ball, T. W. Goodwin and R. A. Morton, *Biochem. J.*, **42**, 516 (1948).

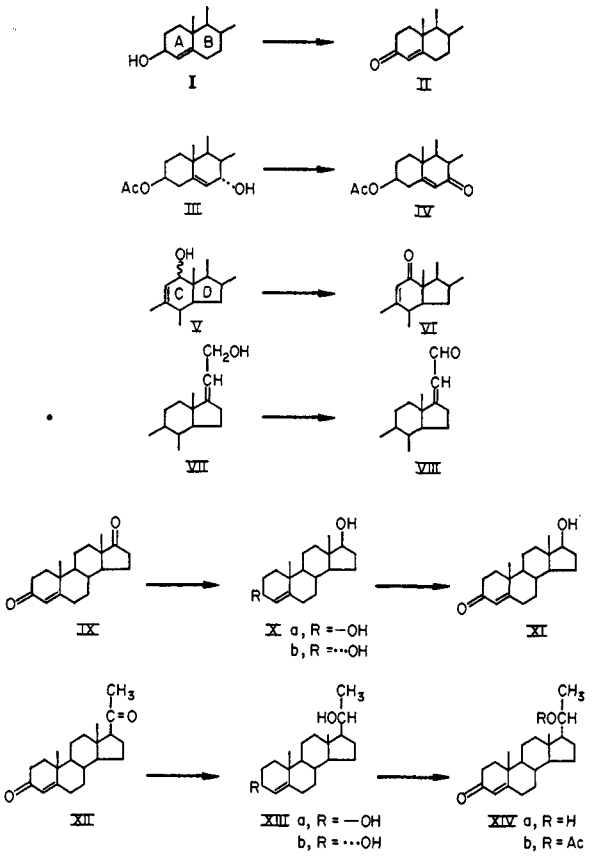
(4) *Cf.* N. L. Wendler, H. L. Slates, N. R. Trenner and M. Tishler, THIS JOURNAL, **73**, 719 (1951); E. A. Braude, *et al.*, *J. Chem. Soc.*, 1755 (1951); 1419, 1430 (1952); B. C. L. Weedon and R. J. Woods, *ibid.*, 2687 (1951); K. R. Farrar, J. C. Hamlet, H. B. Henbest and E. R. H. Jones, *ibid.*, 2657 (1952); R. Ahmad, F. Sondheimer, B. C. L. Weedon and R. J. Woods, *ibid.*, 4089 (1952); R. Ahmad and B. C. L. Weedon, *Chemistry and Industry*, 882 (1952).

(5) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(6) O. Mancera, G. Rosenkranz and F. Sondheimer, *ibid.*, 2189 (1953).

(7) These observations are essentially in agreement with those of Attenburrow, *et al.* (reference 5). We did not, however, treat our dioxide with alkali, although it was later reported by the English workers that they found it essential to do so.

(8) P. A. Plattner, H. Heusser and A. B. Kulkarni, *Helv. Chim. Acta*, **32**, 265 (1949); W. G. Dauben, R. A. Micheli and J. F. Eastham, THIS JOURNAL, **74**, 3852 (1952). Both these groups found that at least 70% of the 3β-isomer was formed in this reduction, despite an earlier report by H. McKennis and G. W. Gaffney (*J. Biol. Chem.*, **175**, 217 (1948)) that the reduction led approximately to equal amounts of the 3β- and the 3α-isomers.



dride reduction of Δ^4-cholesten-3-one, was re-oxidized readily with manganese dioxide to the Δ^4-3-one. The analogous reaction in the 22a-spirostane series proceeded with equal ease.

Other steroidal allylic alcohols investigated were Δ^5-22a-spirostene-3β,7α-diol 3-acetate[9] (III), which with manganese dioxide at room temperature furnished the corresponding Δ^5-7-one (IV)[9] and $\Delta^{9(11)}$-22a-5α-spirostene-3β,12ξ-diol (V)[10] which was oxidized to the $\Delta^{9(11)}$-12-one (VI).[11] Of special interest is the oxidation of the primary allylic alcohol $\Delta^{5,17(20)}$-pregnadiene-3β,21-diol (VII)[12] to the aldehyde, $\Delta^{5,17(20)}$-pregnadien-3β-ol-21-al (VIII) (isolated as the 3-acetate),[13] since this appears to be the most convenient method of preparation of the latter type of substance.

It was found early in this investigation that saturated alcohol groupings, such as the 17β-hydroxy function, were unaffected by manganese dioxide at room temperature (*cf.* reference 3), and this finding forms the basis of a new synthesis of testosterone. Δ^4-Androstene-3,17-dione (IX) was reduced with lithium aluminum hydride to what is presumably essentially a mixture of Δ^4-androstene-3β,17β-diol (Xa) and the 3α,17β-diol (Xb).[14] Direct oxidation of the reduction product with manganese dioxide at room temperature affected only the allylic alcohol function, and testosterone (XI) was produced in 90% over-all yield. This process compares very favorably as regards simplicity of operation and over-all yield with the previously described syntheses of the hormone.[15]

Similarly progesterone (XII) on lithium aluminum hydride reduction gave a mixture of the glycols XIIIa and XIIIb, together with some of the corresponding 20α-epimers,[16] which on manganese dioxide oxidation yielded the known Δ^4-pregnen-20β-ol-3-one (XIVa),[16b,16c,17] further characterized as the acetate (XIVb).[18]

Experimental[19]

Manganese Dioxide.—The dioxide employed for all the oxidations described in this paper was prepared from potassium permanganate and manganese sulfate, as described previously.[6]

Δ^4-Cholesten-3-one (Type II).—A solution of 1 g. of Δ^4-cholesten-3β-ol (m.p. 129–131°, $[\alpha]^{20}D$ +45°[8]) in 100 cc. of chloroform was shaken at room temperature with 10 g. of manganese dioxide. The progress of the reaction was followed by withdrawing small samples at intervals, evaporating each and determining the ultraviolet spectrum (in 95% ethanol).

TABLE I

Min.	log ϵ (λ_{max} 240 mμ)	Cholestenone, %	Min.	log ϵ (λ_{max} 240 mμ)	Cholestenone, %
0	..	..	30	4.08	72
2.5	3.70	30	45	4.13	81
5	3.81	39	60	4.18	91
10	3.91	49	90	4.21	98
15	3.97	56	120	4.22	100

After 24 hours' shaking, the maximum at 240 mμ remained essentially unchanged, but an additional maximum at 284 mμ (log ϵ 3.17) appeared.

A preparative experiment was performed as above, and the product was isolated after 3 hours of shaking. Crystallization from methanol furnished 0.93 g. (93%) of Δ^4-cholesten-3-one with m.p. 78–79°, λ_{max} 240 mμ, log ϵ 4.22, identified with an authentic specimen by mixture melting point and infrared comparison.

Nearly identical results were obtained when the above-described oxidation was carried out with the total lithium aluminum hydride reduction product of Δ^4-cholesten-3-one (consisting of the Δ^4-3β-ol (I) admixed with the corresponding Δ^4-3α-ol).[5]

Δ^4-22a-Spirosten-3-one (Type II).—A solution of 1.5 g. of a mixture of Δ^4-22a-spirosten-3β-ol and the Δ^4-3α-ol (m.p. 181–183°, no appreciable absorption in the ultraviolet) obtained by lithium aluminum hydride reduction of Δ^4-22a-spirosten-3-one[20] in 150 cc. of chloroform was shaken with

(9) H. J. Ringold, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **74**, 3318 (1952).

(10) C. Djerassi, H. Martinez and G. Rosenkranz, *J. Org. Chem.*, **16**, 1278 (1951).

(11) *Idem, ibid.*, **16**, 303 (1951).

(12) H. Heusser, K. Eichenberger and P. A. Plattner, *Helv. Chim. Acta*, **33**, 1088 (1950), and earlier references cited therein.

(13) *Idem., ibid.*, **33**, 370 (1950), and earlier references cited there.

(14) H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Hotermann and R. Robinson, *J. Chem. Soc.*, 361 (1953).

(15) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, p. 371; A. C. Ott, M. F. Murray and R. L. Pederson, THIS JOURNAL, **74**, 1239 (1952), and references cited therein.

(16) For the stereochemical course of the lithium aluminum hydride reduction of 20-ketopregnanes unsubstituted at C-17 and C-21, *cf.* (a) W. Klyne and E. Miller, *J. Chem. Soc.*, 1972 (1950); (b) J. Romo, M. Romero, C. Djerassi and G. Rosenkranz, THIS JOURNAL, **73**, 1528 (1951); (c) R. B. Turner and D. M. Voitle, *ibid.*, **73**, 2283 (1951).

(17) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1922 (1949).

(18) Similar differential oxidations of the lithium aluminum hydride reduction products of Δ^4-androstene-3,17-dione (IX) and progesterone (XII) to testosterone (XI) and Δ^4-pregnen-20β-ol-3-one (XIVa), respectively, have recently been carried out by means of Raney nickel in acetone (J. Romo, *Bol. inst. quím. univ. na. auton. Mé*, **4**, 91 (1952).

(19) Melting points are uncorrected. Rotations were measured in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are indebted to Srta. Paquita Revaque for these determinations, as well as for the infrared spectra, which were measured on a Perkin-Elmer 12C single beam spectrometer with sodium chloride prism. The microanalyses were performed by Srta. Amparo Barba.

(20) R. E. Marker, T. Tsukamoto and D. L. Turner, THIS JOURNAL, **62**, 2525 (1940).

15 g. of manganese dioxide at room temperature for 4 hours. The oxide was then removed by filtration and washed well with chloroform. Crystallization of the product from chloroform–ether furnished 1.26 g. (84%) of Δ^4-22a-spirosten-3-one, m.p. 183–185°, $[\alpha]^{20}D$ −6°, λ_{max} 240 mμ, log ε 4.24, identified with an authentic sample (m.p. 185–186°, $[\alpha]^{20}D$ −8°) by mixture melting point.

Δ^5-22a-Spirosten-3β-ol-7-one Acetate (IV).—A solution of 0.50 g. of Δ^5-22a-spirosten-3β,7α-diol 3-acetate (m.p. 190–193°, $[\alpha]^{20}D$ −155°)[9] in 50 cc. of benzene was shaken with 5 g. of manganese dioxide for 24 hours at room temperature. The crystalline residue, after removal of the dioxide and solvent, showed λ_{max} 234 mμ, log ε 4.10, indicating the reaction to have proceeded to 83% completion. Crystallization from methanol furnished 0.29 g. (58%) of Δ^5-22a-spirosten-3β-ol-7-one acetate with m.p. 198–199°, $[\alpha]^{20}D$ −158°, λ_{max} 234 mμ, log ε 4.18, $\nu_{max}^{CHCl_3}$ 1726 and 1674 cm.$^{-1}$, identified with an authentic specimen (m.p. 197–198°, $[\alpha]^{20}D$ −163°[9]) by mixture melting point and infrared comparison.

$\Delta^{9(11)}$-22a,5α-Spirosten-3β-ol-12-one (VI).—A solution of 0.50 g. of $\Delta^{9(11)}$-22a,5α-spirostene-3β,12ξ-diol (V) (m.p. 200–203°)[10] (most probably a mixture of C-12 stereoisomers) in 50 cc. of chloroform was shaken with 5 g. of manganese dioxide for 10 hours at room temperature. The total product showed λ_{max} 238 mμ, log ε 4.07, indicating 81% oxidation. Crystallization from chloroform–acetone yielded 0.38 g. (76%) of the $\Delta^{9(11)}$-12-one (VI) with m.p. 221–223°, λ_{max} 238 mμ, log ε 4.16, $\nu_{max}^{CHCl_3}$ 1670 cm.$^{-1}$ and free hydroxyl band, identified with an authentic specimen (m.p. 223–225°)[11] by mixture melting point and infrared comparison.

$\Delta^{5,17(20)}$-Pregnadien-3β-ol-21-al Acetate (VIII).—A solution of 0.80 g. of $\Delta^{5,17(20)}$-pregnadiene-3β,21-diol (m.p. 193–196°)[12] in 80 cc. of chloroform was shaken with 8 g. of manganese dioxide for 5 hours at room temperature. The crystalline residue with λ_{max} 244 and 284 mμ, log ε 4.25 and 3.54, respectively, was acetylated (pyridine–acetic anhydride, room temperature, 24 hours), and the product was crystallized from methanol. In this manner 0.50 g. of the 21-aldehyde VIII with m.p. 183–186° was obtained, raised on further crystallization from chloroform–methanol to 186–187°, $[\alpha]^{20}D$ −58°, λ_{max} 244 mμ, log ε 4.36, $\nu_{max}^{CHCl_3}$ 1718 and 1670 cm.$^{-1}$ (reported[13] m.p. 184–185°, $[\alpha]^{20}D$ −60°, λ_{max} 244 mμ, log ε 4.44). A further small quantity of VIII could be obtained by chromatography of the mother liquors.

Testosterone (XI) from Δ^4-Androstene-3,17-dione (IX).—A solution of 50 g. of Δ^4-androstene-3,17-dione in 300 cc. of dry tetrahydrofuran was added with stirring and ice cooling to 15 g. of lithium aluminum hydride in 1.5 l. of tetrahydrofuran during 30 minutes, and the mixture was then heated under reflux for 1 hour. The excess reagent was decomposed by the careful addition of ethyl acetate, and concentrated aqueous sodium sulfate was then added until the precipitate began to adhere to the sides of the flask. Finally *ca.* 100 g. of solid sodium sulfate was added, the salts were removed by filtration and washed well with tetrahydrofuran. Evaporation of solvent yielded 50.4 g. of a mixture of Δ^4-androstene-3β,17β-diol (Xa) and the 3α,17β-diol (Xb) as a white powder with m.p. 165–171°, no appreciable absorption in the ultraviolet.

The above solid was finely ground in a mortar, then suspended in 1250 cc. of chloroform, and stirred with 250 g. of manganese dioxide for 10 hours at room temperature. The dioxide was removed by filtration, washed thoroughly with hot chloroform, and the combined chloroform solutions were evaporated to dryness. Crystallization from acetone–hexane furnished 38.2 g. of testosterone with m.p. 152–153°, $[\alpha]^{20}D$ +108°, λ_{max} 240 mμ, log ε 4.23, as first crop, and 6.9 g. with m.p. 150–152° as second and third crops (total over-all yield 45.1 g. or 90%). Identity of the combined crops with an authentic sample was established by mixture melting point determination and infrared comparison.

Essentially identical results were obtained when the initial reduction was carried out with sodium borohydride in boiling aqueous alcohol.

Δ^4-Pregnen-20β-ol-3-one (XIVa) from Progesterone (XII).—Progesterone (5.0 g.) was reduced with lithium aluminum hydride, as described above for Δ^4-androstene-3,17-dione. The total reduction product (5.0 g.) with m.p. 162–172°, no appreciable absorption in the ultraviolet, in 500 cc. of chloroform, was stirred with 50 g. of manganese dioxide for 24 hours at room temperature. Crystallization of the product from ether–pentane furnished 3.3 g. (66%) of Δ^4-pregnen-20β-ol-3-one (XIVa) with m.p. 166–168°, raised on further crystallization to 174–175°, $[\alpha]^{20}D$ +86°, λ_{max} 240 mμ, log ε 4.23, $\nu_{max}^{CHCl_3}$ 1660 cm.$^{-1}$ and free hydroxyl band[21] (reported m.p. 171–172°, $[\alpha]^{24}D$ +84°[17]; m.p. 169–171°, $[\alpha]^{20}D$ +83°[16b]; m.p. 174–175°, $[\alpha]D$ +90°[16c]).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.48; H, 10.22.

The acetate XIVb was crystallized from acetone–hexane, and exhibited m.p. 161–162°, $[\alpha]^{20}D$ +134°, λ_{max} 240 mμ, log ε 4.22, $\nu_{max}^{CHCl_3}$ 1718 and 1660 cm.$^{-1}$ (reported m.p. 159–159.5°, $[\alpha]^{25}D$ +140°[17]; m.p. 159–161°, $[\alpha]^{20}D$ +137°[16b]; m.p. 161–162°, $[\alpha]D$ +129°[16c]).

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.83; H, 9.76.

(21) The lower melting 20α-isomer of XIVa[16c,17] which presumably was formed to some extent,[16] was probably present in the mother liquors, but no attempt at isolation was made.

MEXICO CITY, D. F.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. LI.[1] $\Delta^{4,6}$-Dien-3-ones[2,3]

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RECEIVED JUNE 25, 1953

Both Δ^4-3-ones (II) and Δ^5-3β-ols (IV) are oxidized by means of manganese dioxide to the corresponding $\Delta^{4,6}$-dien-3-ones (III). The conversion of IV to III is a useful preparative method for the latter, and the generality of this type of oxidation is demonstrated by its application to a number of different Δ^5-3β-ols (IV). The intermediate in the oxidation of IV to III is shown to be almost certainly the Δ^5-3-one (V).

In the previous paper of this series[1] it was shown that steroidal Δ^4-3β-ols (I) were oxidized smoothly to the corresponding Δ^4-3-ones (II) by means of manganese dioxide at room temperature. It was found, however, in one experiment in which the oxidation was allowed to proceed for an unusually long time (24 hours) that a new ultraviolet absorption maximum at 284 mμ of low intensity, in addition to the expected one at 240 mμ, appeared in the product. Since it had been shown that the Δ^4-3-one (II) was the primary product, it follows that this system must slowly be further attacked by the manganese dioxide, and indeed when an authentic Δ^4-3-one (Δ^4-22a-spirosten-3-one) was shaken with manganese dioxide at room temperature for 24

(1) Steroids. L. F. Sondheimer, C. Amendolla and G. Rosenkranz, THIS JOURNAL, **75**, 5930 (1953).

(2) Presented in part at the Los Angeles Meeting of the American Chemical Society, March, 1953.

(3) A preliminary announcement of part of this work has been published (F. Sondheimer and G. Rosenkranz, *Experientia*, **9**, 62 (1953)).