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

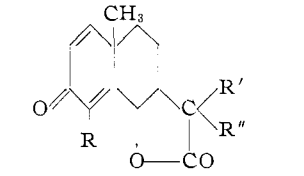
STEREOCHEMICAL CONFIGURATION OF SANTONIN ISOMERS

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*

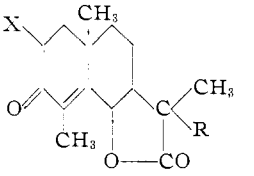
Such differences in the configuration should cause different spectra and we have undertaken to correlate structure with infrared spectra.

Experimental

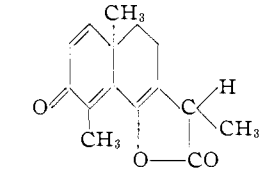
Perkin–Elmer infrared spectrometer model 21 equipped with NaCl optics was used. Fifty-four samples were examined; santonins (racemic and optically active) (I, 11 samples), 4-norsantonins (II, 2 samples), 1,2-dihydrosantonins (V, 5 samples), and their 2-bromo derivatives (VI, 3 samples), 11-carbethoxysantonins (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.



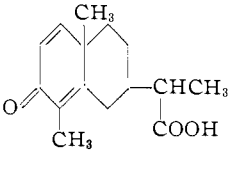
I, R = R′ = CH_3, R″ = H
II, R = R″ = H, R′ = CH_3
III, R = CH_3, R′ = R″ = H
IV, R = R′ = CH_3, R″ = $COOC_2H_5$



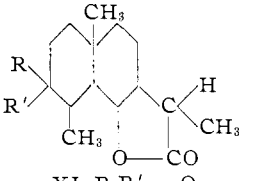
V, X = R = H
VI, X = Br, R = H
VII, X = H, R = $COOC_2H_5$
VIII, X = Br, R = $COOC_2H_5$



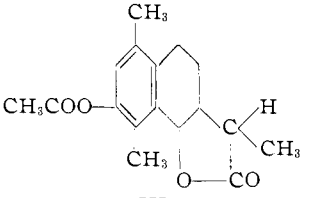
IX



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-

(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).

mers only a slight difference occurs. This may be due to the lack of an associating group in the santonin molecules by which intermolecular hydrogen bond can be formed. The following discussions are based on spectra in chloroform solution.

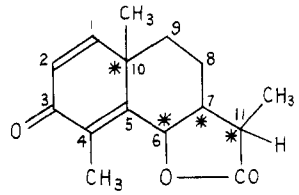


Fig. 1.—The structure of santonin.

1800–1500 Cm.$^{-1}$ Region.—The C=O absorption due to γ-lactone of santonin isomers appears near 1780 cm.$^{-1}$. Brewster and Kucera[4] have observed that in γ-lactones fused to a cyclohexane ring the C=O band occurs at a higher frequency in the *trans* isomer than in the *cis* one. Detailed measurements were conducted for santonin in this region and the results are shown in Table II, which

TABLE II

THE C=O STRETCHING VIBRATION OF γ-LACTONE IN CM.$^{-1}$

	Santonin	Dihydro-santonin	11-Carbeth-oxysantonin	11-Nor-santonin
A	1773	1773	..	..
B	1773	..	..	..
C	1769	1765	1778	1781
D	1771	1769	1789	
α	1781	1778	1785	1785
β	1781	1778	1784	

indicates that for both the santonin and dihydrosantonin (V) the correlation obtained by Brewster, *et al.*, holds though the difference in wave number between *trans*- and *cis*-lactones is about 10 cm.$^{-1}$, being smaller than the values (20–30 cm.$^{-1}$) found by those investigators. 11-Carbethoxy- and 11-norsantonin (III and IV) show the band at a frequency about 10 cm.$^{-1}$ higher than santonin and the above correlation becomes ambiguous. This fact means that a substituent at C_{11} may interact with the C=O group of the γ-lactone.

Absorption bands related to the A and B rings are almost the same as those of steroids having a similar structure. The C=O band of the 3-ketone of santonins and 11-carbethoxysantonins (IV) appears in the range 1658–1667 cm.$^{-1}$ and those of 1,2-dihydrosantonins (V and VII), 4-norsantonins (II), 11-norsantonins (III) and 1,2,4,5-tetrahydro-α-santonin (α-isomer) (XI) in the range 1665–1670, 1667–1670, 1660 and 1708 cm.$^{-1}$, respectively.[5,6] However, in deoxysantoninic acid series (*e.g.*, X), those bands shift by 5 to 10 cm.$^{-1}$ toward the lower frequency: for three compounds having the santonin-like skeleton, the absorption is observed in the range 1655–1660 cm.$^{-1}$ and for five compounds with the dihydrosantonin-like skeleton in the range 1653–1660 cm.$^{-1}$. These shifts may be the result of decreased strain in the A ring caused by the absence of the lactone ring.

The introduction of a bromine atom into the C_2 of dihydrosantonin (*i.e.*, V → VI and VII → VIII) causes a shift of the C=O band to the higher frequency (1685–1690 cm.$^{-1}$) by 20–30 cm.$^{-1}$. From this value it is reasonable to consider that the bromine atom occupies an equatorial position.[7-9] This is also supported by the consideration that there is a steric repulsion between the bromine atom and the C_{10}-methyl group as in the case of 2-bromo-4,4-dimethylcyclohexanone.[8-10]

The medium strong band in the range 1620–1640 cm.$^{-1}$ which shows somewhat higher frequency for the *trans*-lactone can be assigned to the C_1=C_2 vibration, since the spectra of 1,2-dihydro compounds (V—VIII, XI and XII) lack this band. The weak band between 1603 and 1626 cm.$^{-1}$, therefore, can be assigned to the C_4=C_5 vibration, but this band is often masked by the C_1=C_2 band.

1500–1350 Cm.$^{-1}$ Region.—Although there is no marked absorption in this region, 1,2-dihydro- and 11-norsantonin (V, VII and III) gave rise to a weak but characteristic band in the range 1410–1418 cm.$^{-1}$. These can be associated with the CH_2 bending vibration perturbed by the C=O group at the α-position and, accordingly, seem to be caused by the CH_2 at C_2, in the case of 1,2-dihydrosantonin (V and VII), and at C_{11}, in the case of 11-norsantonin (III).[11,12] A medium strong band at 1400 cm.$^{-1}$ may be due to the ethylenic CH in-plane bending vibration at C_1=C_2 in $\Delta^{1,4}$-3-keto structure.[13]

1350–650 Cm.$^{-1}$ Region.—Santonin and all its related compounds having a γ-lactone show two strong bands in this region (Fig. 2). The first appears between 1130 and 1190 cm.$^{-1}$, independent of their stereochemical configuration. Exceptionally, for the 11-carbethoxy derivatives IV the intensity of this band is relatively weak and difficult to distinguish owing to the presence of a strong absorption of carbethoxy group near this region. The intensity of this band appears to be stronger for the *cis*-lactone than for the *trans*-fused one.

As for the second band the structural correlation is much clearer. The intensity and the position of the band depend upon the mode of lactone-fusion as well as the nature of the C_6–O bond. The C_6–O equatorial *trans*-lactone (α- and β-santonins and their 1,2-dihydro and 2-bromo-1,2-dihydro compounds) and the β,γ-unsaturated lactone (*e.g.*, IX) which has a double bond between C_6 and C_7 give rise to one strong band at 1028–1035 cm.$^{-1}$ and their 11-carbethoxy derivatives at 1042–1046 cm.$^{-1}$. 1,2,4,5-Tetrahydro-α-santonin (α-isomer) (XI) and its deoxo compound XII show the band at about 1000 cm.$^{-1}$, a slightly lower frequency. The corre-

(4) J. H. Brewster and C. H. Kucera, THIS JOURNAL, **77**, 4564 (1955).

(5) R. N. Jones, P. Humphries, F. Herling and K. Dobriner, *ibid.*, **74**, 2820, 6319 (1952).

(6) R. N. Jones and F. Herling, *J. Org. Chem.*, **19**, 1252 (1954).

(7) R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, THIS JOURNAL, **74**, 2828 (1952).

(8) E. J. Corey, *ibid.*, **75**, 2301 (1953).

(9) E. J. Corey, *ibid.*, **76**, 175 (1954).

(10) E. J. Corey, *Experientia*, **9**, 329 (1953).

(11) R. N. Jones and A. R. H. Cole, THIS JOURNAL, **74**, 5648 (1952).

(12) R. N. Jones, A. R. H. Cole and B. Nolin, *ibid.*, **74**, 5662, 6321 (1952).

(13) R. N. Jones and C. Sandorfy, "Chemical Application of Spectroscopy (Technique of Organic Chemistry, Vol. IX)," Interscience Publishers, Inc., New York, N. Y., 1956, p. 382.

sponding absorption of the C_6–O equatorial *cis*-lactone (santonins A and B) appears at 1028 cm.$^{-1}$ with medium intensity, while the C_6–O axial *cis*-lactones (santonins C and D series) show a strong absorption near 950 cm.$^{-1}$ and their 11-carbethoxy derivatives almost at the same position with somewhat weaker intensity. The relative intensity of the first and the second bands also has some correlation with stereochemical configuration. The first band is weaker than the second for compounds with a C_6–O equatorial *trans*-lactone, while this relation is reversed for those with a C_6–O equatorial *cis*-lactone. In the case of a C_6–O axial *cis*-lactone, the intensity of the two bands is nearly equal. To illustrate this relation, portions of the spectra of santonin isomers are given in Fig. 2, in which the bands in question are indicated by an arrow. In the figure, the second band of santonins C and D is assigned as a doublet. The reason for splitting of the band is not clear, but since all the other isomers have an absorption of medium intensity at 950 cm.$^{-1}$, the possibility exists that the latter interacts with the second band of santonins C and D and causes it to split into two strong bands. The assumption is further supported by the fact that 1,2-dihydrosantonins C and D and their 2-bromo compounds exhibit only a single strong band, while the spectra of their C_6–O equatorial isomers are transparent in this region. This consideration also makes it reasonable to choose the absorption at 1028 cm.$^{-1}$ of santonins A and B as their second band rather than the absorption near 955 cm.$^{-1}$. There is some ambiguity in identifying the first band of α- and β-santonins, but the strongest band in this region is tentatively adopted.

The above generalization on the position and the intensity of the two bands should be useful for determining the stereochemical feature of a γ-lactone fused to a cyclohexane ring.[14]

Previously, Thompson, *et al.*,[15] assigned the two strong bands of esters in the range 1185–1250 and 1000–1200 cm.$^{-1}$ to the stretching vibration of O–CO and C–OCO bonds, respectively. This assignment may be applied to the absorption of γ-lactone in santonin. Thus, it is possible to say that the first band (1130–1190 cm.$^{-1}$) is due to the O–CO stretching vibration and the second (944–971 or 1028–1046 cm.$^{-1}$) to the C–OCO vibration of the alcohol residue. The fact that the position of the former band is not so sensitive to the stereochemical configuration of the lactone ring, while that of the latter is considerably influenced by the configurational change can be explained as follows:

When the C_6–O bond is equatorial, it lies approximately in the same plane as the A and B rings of santonin skeleton. Therefore, the C_6–O stretching vibration will couple with the B-ring vibration and, consequently, increase its absorption frequency. This is similar to the observation in 3-hydroxysteroids.[16,17] On the other hand, the axial C_6–O bond causes little interaction with the B-ring vibration so that absorption remains at a lower frequency. With regard to the O–CO bond it has no

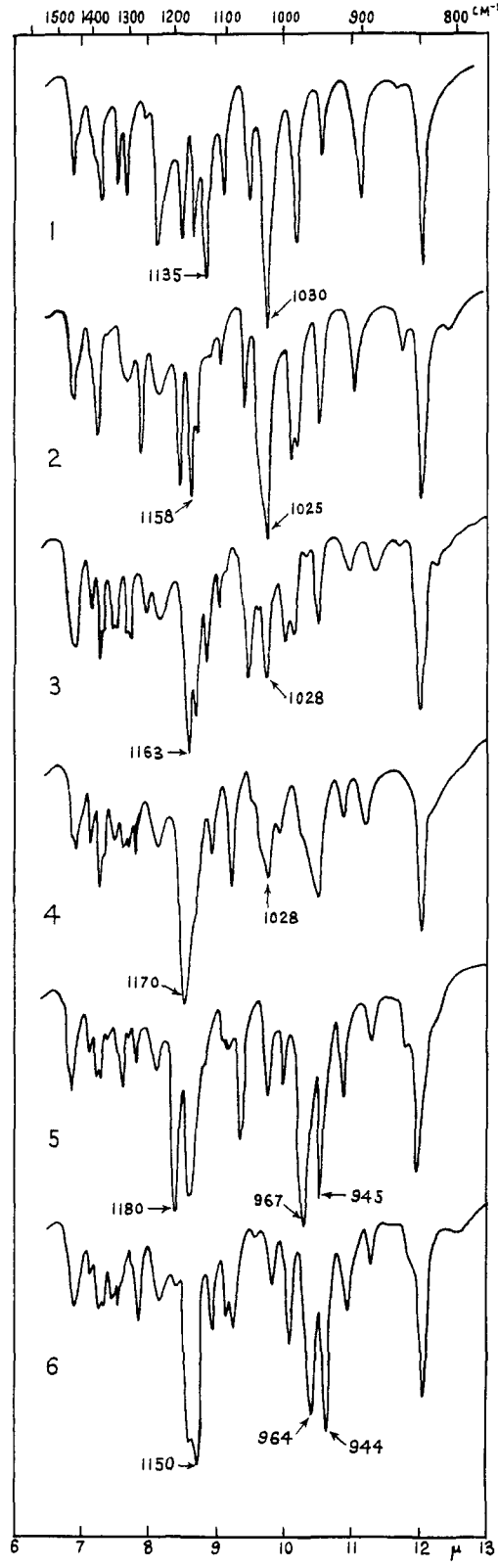


Fig. 2.—Infrared spectra of santonin isomers in $CHCl_3$ solution; 1, α-santonin; 2, β-santonin; 3, santonin A; 4, santonin B; 5, santonin C; 6, santonin D.

(14) K. Tsuda, K. Tanabe, I. Iwai and K. Funakoshi (THIS JOURNAL, **79**, 5721 (1957)) have recently applied this correlation to the determination of the lactone structure of tetrahydroalantolactones.

(15) H. W. Thompson and P. Torkington, *J. Chem. Soc.*, 640 (1945).

(16) A. R. H. Cole, R. N. Jones and K. Dobriner, THIS JOURNAL, **74**, 5571 (1952).

(17) A. R. H. Cole, *J. Chem. Soc.*, 4969 (1952).

direct relationship with the bond orientation around C_6 and C_7 atoms. Accordingly, this band is independent of the stereochemical configuration.

The absorption of the C–H out-of-plane bending vibration of ethylenic bond between C_1 and C_2 is very similar to that of corresponding steroids. 4-Norsantonins (II) possess this absorption as a doublet at the exact position of "G-band" of $\Delta^{1,4}$-3-ketosteroid,[18] but santonins themselves absorb in the range 831–833 cm.$^{-1}$ because of the C_4-methyl group.

In addition to the above results it is seen from Fig. 2 that each pair of santonin isomers epimeric at C_{11} shows some similar absorptions, for instance, at 1370 and 900 cm.$^{-1}$. These bands cannot be satisfactorily utilized for the determination of lactone structure since this feature is not common among their derivatives. As for the spectral difference between the C_{11}-epimers there was found no systematic correlation.

JUSO, OSAKA, JAPAN

(18) R. N. Jones, F. Herling and E. Katzenellenbogen, THIS JOURNAL, **77**, 651 (1955).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Insecticidal Principles of *Haplophyton cimicidum*. III. The Nature of the Acidic Function of Haplophytine[1]

BY H. R. SNYDER, H. F. STROHMAYER AND R. A. MOONEY[2]

RECEIVED FEBRUARY 10, 1958

On the basis of spectral evidence, the acidic function of haplophytine has been determined to be a phenolic hydroxyl group. A partial structure I is proposed as a working model for the alkaloid, and the preparation of O-methylhaplophytine is described.

Haplophytine, the main alkaloid of *Haplophyton cimicidum*, has the empirical formula $C_{27}H_{31}O_5N_3$. The alkaloid shows amphoteric properties. Earlier investigations[3] indicated the presence of two basic nitrogen atoms. The nature of the acidic group, however, was not understood.

The acidity could be due to the presence of one of these various groups: a carboxylic acid, a phenol, an enolizable ketone, an α- or γ-pyridone, or an easily hydrolyzable lactone or lactam. A carboxylic acid group can be ruled out because unchanged haplophytine is recovered on evaporation of ammoniacal or barium hydroxide solutions of haplophytine.[3] Chloroform removes the alkaloid from 0.2 N aqueous sodium hydroxide, while aqueous 1 N alkali extracts haplophytine from chloroform. On attempted titration of the alkaloid with 0.1 N sodium hydroxide, with phenolphthalein as indicator, no alkali was consumed at room temperature or under reflux.[4] However, haplophytine was shown to be soluble in the 0.1 N sodium hydroxide. This result would make the presence of a carboxylic acid, a lactone or a lactam doubtful. An enolizable ketone can be ruled out on the ground that no carbonyl group is reduced on catalytic hydrogenation, as shown by the infrared spectrum of the reduction product.[3] Furthermore, dihydrohaplophytine still contains the acidic group. The acidic properties can best be explained by the presence of a cryptophenolic hydroxyl group. As in the case of certain other phenols, for example *o*-hydroxyacetophenone,[5] vomicine[6] and demethylaspidospermine,[6] haplophytine shows no band in the OH or NH region of the infrared spectrum, as a consequence of strong hydrogen bonding of the phenolic hydroxyl with a carbonyl group.

It is interesting to compare the ultraviolet spectrum of haplophytine in ethanol with that in 0.02 N ethanolic sodium hydroxide. The maximum at 265 mμ in neutral solution shifts to 306 mμ under alkaline conditions. The newly formed peak in basic solution probably is caused by formation of a phenoxide ion. A similar shift, but in the opposite direction, is observed with α- or γ-pyridones, while β-hydroxypyridine, as a typical phenolic substance, gives a bathochromic shift.[7] The ultraviolet spectrum of haplophytine in 0.02 N ethanolic hydrochloric acid shows only a slight hypsochromic shift of the 265 mμ band to 260 mμ.

Since the evidence suggested the presence of a cryptophenolic group, the methylation of haplophytine was reinvestigated. Attempted methylation with dimethyl sulfate and sodium hydroxide in a nitrogen atmosphere failed,[4] as did attempted reaction of the alkaloid with methyl iodide and potassium carbonate in boiling acetone. However, contrary to previous observations, diazomethane reacted, although very slowly, with the alkaloid, and O-methylhaplophytine could be isolated in fair yields. Later it was found more convenient to prepare O-methylhaplophytine by reaction of haplophytine with trimethylphenylammonium ethoxide according to the procedure of Rodionow.[8]

The methyl ether is not amphoteric and contains only one of the two active hydrogen atoms found in haplophytine. The ultraviolet spectrum is identical in neutral and alkaline solution and is very similar to that of haplophytine (Fig. 1) in neutral or acidic solution. A slight hypsochromic shift is

(1) Grateful acknowledgment is made of the support of this research by a grant from the National Science Foundation (G 580).

(2) American Cyanamid Co. Fellow, 1957–1958.

(3) E. F. Rogers, H. R. Snyder and R. F. Fischer, THIS JOURNAL, **74**, 1987 (1952); H. R. Snyder, R. F. Fischer, J. F. Walker, H. E. Els and G. A. Nussberger, *ibid.*, **76**, 2819 (1954); **76**, 4601 (1954).

(4) R. J. Leary, Ph.D. Thesis, University of Illinois, 1957.

(5) H. L. Hergert and E. F. Kurth, THIS JOURNAL, **75**, 1622 (1953).

(6) B. Witkop and J. B. Patrick, *ibid.*, **76**, 5603 (1954).

(7) R. C. Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 435–443.

(8) W. Rodionow, *Bull. soc. chim. France*, **39**, 305 (1926).