UDC 547.92/.93

193. Ken'ichi Takeda and Taichiro Komeno: Bile Acids and Steroids. XXII.[1] Thiosteroids. (7).[2] Synthesis of Some Thiazolo[5',4'-16,17]steroids[3] by the Hantzsh Reactions.

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In the previous paper[2] of this series it was reported that the Beckmann rearrangement of a mixture of the oxime-disulfide (Ia) and the oxime-thiol (Ib), which were obtained from 3β,17α-dihydroxy-16β-thiocyanatopregn-5-en-20-one 3-acetate by the action of hydroxylamine, afforded 16β,16β'-dithio bis(3β-hydroxyandrost-5-en-17-one acetate) (II) and a by-product $C_{23}H_{33}O_3NS$, m.p. 254~255° (decomp.), and that the latter was converted to an aromatic compound $C_{23}H_{31}O_2NS$, m.p. 133~135°, by dehydration with thionyl chloride and pyridine. In consideration of the reaction mechanism the aromatic compound was at that time assumed more likely to be 2'-methylthiazolo[5',4'-16,17]androsta-5,16-dien-3β-ol 3-acetate (VIIa) rather than 3'-methylisothiazolo[5',4'-16,17]androsta-5,16-dien-3β-ol 3-acetate (IVa).

For the purpose of clarifying the structures of the above mentioned by-product and the aromatic compound, the synthesis of 2'-methyl-16,17-disubstituted thiazole (VIIa) was carried out by an established method. Heating of 3β-acetoxy-16β-bromoandrost-5-en-17-one (VI) and thioacetamide in ethanol at 175° for 35 hours gave a compound $C_{23}H_{31}O_2NS$, m.p. 190~192°, in 44 % yield, which showed characteristic absorptions due to the aromatic ring in the ultraviolet and infrared spectrum (λ_{max}^{EtOH} 260 mμ, ν_{max}^{Nujol} 1512 cm^{-1}), but was different from the above aromatic compound, m.p. 133~135°.

Since this compound was prepared by the known method of 2-alkylthiazole synthesis (Hantzsch's method[4]), it must be 2'-methyl-16,17-disubstituted thiazole (VIIa). Free 3-ol (VIIb) and 4-en-3-one (VIII) were also prepared by saponification followed by Oppenauer oxidation. When they were compared with the corresponding compounds derived from the by-product in the Beckmann rearrangement, there was observed no coincidence in the physical properties among these compounds, as shown in the following table.

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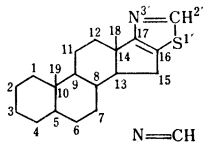
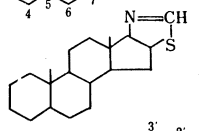
1) Part XXI. J. Kawanami: Bull. Chem. Soc. Japan, **34**, 671 (1961).

2) Part (6): T. Komeno: This Bulletin, 8, 680 (1960).

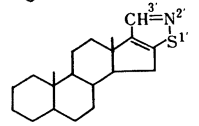
3) In this paper a simpler nomenclature and numbering system is adopted in view of the steroidal nature of the compounds, because a formal nomenclature of the fused heterocyclic system is much complicated.



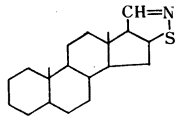
thiazolo[5',4'-16,17]-androst-16-ene



16,17-dihydrothiazolo-[5',4'-16,17]androstane



isothiazolo[5',4'-16,17]-androst-16-ene

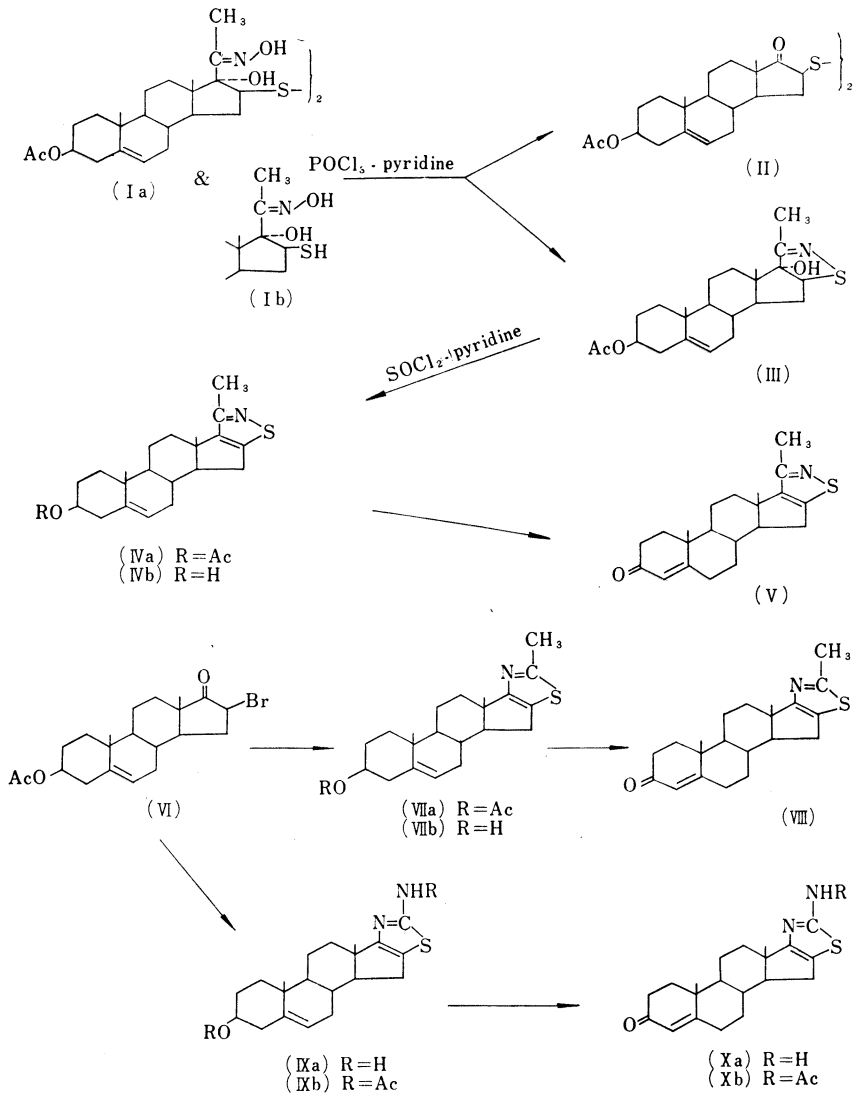


16,17-dihydroisothiazolo-[5',4'-16,17]androstane

4) A. Hantzsh: Ann., **250**, 257, 281 (1889); **259**, 228, 253 (1890).

TABLE I.

3′-Methyl-16,17-disubstituted isothiazole	3β-OAc (IVa)	3β-OH (IVb)	4-en-3-one (V)
m.p.	133～135°	183～185°	219～221° (decomp.)
$[\alpha]_D$ (in $CHCl_3$)	−73°	−73°	+87°
UV λ_{max}^{EtOH} mμ (ε)	254 (5, 740)	254.5 (5, 840)	244 (20, 300)
IR ν_{max}^{Nujol} cm^{-1}	1731, 1230 1507	3507～3497 1510	1676, 1620 1513
2′-Methyl-16,17-disubstituted thiazole	3β-OAc (VIIa)	3β-OH (VIIb)	4-en-3-one (VIII)
m.p.	190～192°	200～202° (decomp.)	203～205° (decomp.)
$[\alpha]_D$ (in $CHCl_3$)	−40°	−56°	+91°
UV λ_{max}^{EtOH} mμ (ε)	260 (5, 400)	260 (5, 480)	243 (20, 110)
IR ν_{max}^{Nujol} cm^{-1}	1736, 1242 1512	3334 1515	1679, 1622 1514



Consequently the by-product in the Beckmann rearrangement of (Ia) and (Ib) should be 3′-methyl-16,17-dihydroisothiazolo[5′,4′-16,17]androst-5-ene-3β,17-diol 3-acetate (III), and the dehydration product should now be assigned 3′-methylisothiazolo[5′,4′-16,17]androsta-5,16-dien-3β-ol acetate (IVa). Formation of this isothiazoline compound (III) may be due to the ready attack of the powerful nucleophillic sulfur anion on the nitrogen cation formed from the oxime (I) prior to the migration of the C_{17}-C_{20} bond.

Since the Hantzsh's method was successful in the preparation of 2′-methylthiazolo compounds from the above bromoketone, it was applied to the synthesis of 2′-aminothiazolo compounds. In this case the reaction product of 16β-bromo-17-one (VI) with thiourea was obtained as an amorphous powder which showed no absorption bands characteristic of 2-aminothiazole but the amidine type absorption bands appeared at 1640 (s), 1605 (m), and 1511 (w) cm^{-1} in the infrared spectrum.[5] Saponification of this compound with alkali afforded a compound $C_{20}H_{28}ON_2S$, m.p. 262~264° (decomp.), in good yield, which was converted by acetylation to the O,N-diacetate, m.p. 291~293° (decomp.). Ultraviolet and infrared data of these two compounds are listed together with those of 2-amino and 2-acetamino thiazol in Table II.

Table II.

	2-Aminothiazole derivatives	Compound (IXa)	2-Acetaminothiazole derivatives	Compound (IXb)
IR ν_{max} cm^{-1}	1570 1634	1604	1650 1690	1694
	1493 1538	1503	1535 1550	1530
UV[a] λ_{max} mμ (ε)	259 (2,040)	270 (6,430)	273 (8,320)	287 (11,290)

a) Values of 2-amino-4-methylthiazole and its acetate were cited.

a) H. M. Randall, R. G. Fowler, N. Fuson, J. R. Dangl, "Infrared Determination of Organic Structures" Van Nostrand (1949), pp. 20.

b) S. G. Bogomolov, Yu. N. Sheinker, I. Ya. Postovskii; Doklady skad. Nauk. S. S. S. R., **93**, 277 (1953), C. A., **48**, 3143 (1954).

As is apparent from the table, there is a good coincidence between the optical data of these compounds. Hence the newly prepared compounds were assumed to be 2′-aminothiazolo[5′,4′-16-17]androsta-15,16-dien-3β-ol (IXa) and its O,N-diacetate (IXb), respectively, but the structure of the above intermediate was not determined because the presence of the hydroxyl or the ketone group was not conspicuous in its infrared spectrum. Oppenauer oxidation of (IXa) gave 2′-aminothiazolo[5′,4′-16,17]androsta-4,16-dien-3-one (Xa), which on acetylation afforded the N-monoacetate (Xb).

Experimental[*2]

3′-Methylisothiazolo[5′,4′-16,17]androsta-5,16-dien-3β-ol (IVb)——A solution of 1.47 g. of the dehydration compound (III) and 1.60 g. of K_2CO_3 in 20 cc. of MeOH and 7 cc. of H_2O was heated under reflux for 30 min. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated. The residue was crystallized from Me_2CO to give 1.26 g. of (IVb) as long plates, m.p. 182~184°, which was recrystallized twice from Me_2CO to long plates, m.p. 183~185°; $[\alpha]_D^{20}$ −73.0±2° (c=1.108, $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{29}ONS$: C, 73.42; H, 8.51; N, 4.08; S, 9.33. Found: C, 73.43; H, 8.48; N, 4.06; S, 9.13. UV: $\lambda_{max}^{95\%\ EtOH}$ 254.5 mμ (ε 5,840). IR ν_{max}^{Nujol} cm^{-1}: 3507~3497 (OH), 1666 (5-en), 1510 (aromatic).

3′-Methylisothiazolo[5′,4′-16,17]androsta-4,16-dien-3-one (V)——A solution of 1.26 g. of (IVb) in 30 cc. of toluene and 6 cc. of cyclohexanone was distilled to give 10 cc. of a distillate and then slow

*2 All melting points were determined in capillary tubes and uncorrected. Infrared spectra were measured with a Koken IR spectrophotometer, Model DS-301, and UV spectra were taken with a Hitachi Recording UV spectrophotometer, EPs-2. Optical rotations were measured with the Rudolf Photoelectronic Polarimeter, Model 200.

5) It was observed by W. Otting and F. Drawert (Chem. Ber. 88, 1469 (1955)) that a number of 2-substituted thiazolines show a strong absorption at 1640 cm^{-1} in the infrared spectra.

distillation was continued while a solution of 770 mg. of (iso-PrO)$_3$Al in 20 cc of toluene was added dropwise over a period of 55 min. After slow distillation for a further 1 hr., a solution of Rochelle salt was added to the reaction mixture and extracted with Et_2O. The Et_2O solution was washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was crystallized from petr. ether to give 1.10 g. of (V), m.p. 219~221°(decomp.), which was recrystallized from Me_2CO to small needles, m.p. 219~221°(decomp.); $[\alpha]_D^{19}$ +87.1±2°(c=1.044, $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{27}ONS$: C, 73.85; H, 7.97; N, 4.10; S, 9.39. Found: C, 73.83; H, 8.05; N, 3.98; S, 9.40. UV: $\lambda_{max}^{95\%\ EtOH}$ 244 mμ (ε 20,300). IR ν_{max}^{Nujol} cm^{-1}: 1676, 1620 (4-en-3-one), 1513 (aromatic). A solution of this compound in EtOH was treated with picric acid and a picrate, m.p. 182~184°(decomp.), was obtained as prisms by recrystallization from EtOH. *Anal.* Calcd. for $C_{21}H_{27}ONS \cdot C_6H_3O_7N_3$: C, 56.83; H, 5.30; N, 9.82; S, 5.62. Found: C, 56.93; H, 5.42; N, 9.60; S, 5.69.

2′-Methylthiazolo[5′,4′-16,17]androsta-5,16-dien-3β-ol 3-acetate (VIIa)——A solution of 730 mg. of 3ε-acetoxy-16β-bromoandrost-5-en-17-one (VI) and 800 mg. of thioacetamide in 20 cc. of abs. EtOH was heated at 175°(bath-temp.) in a steel bomb for 35 hr. The reaction mixture was diluted with H_2O and extracted with Et_2O. The Et_2O solution was washed with aq. Na_2CO_3 and H_2O, dried over anhyd. Na_2SO_4, and evaporated to dryness. The residue (759 mg.) was chromatographed on 20 g. of Al_2O_3. From the first eluate with petr. ether-benzene (4:1) 136 mg. of a red oil was separated and the residue (375 mg.) from the next eluates with the same solvent (4:1, 2:1, 1:1) was crystallized from MeOH to 304 mg. of (VIIa), m.p. 185~190°, which was recrystallized from MeOH to plates, m.p. 190~192°. $[\alpha]_D^{30}$ −39.5±2°(c=0.970, $CHCl_3$). *Anal.* Calcd. for $C_{23}H_{31}O_2NS$: C, 71.65; H, 8.10; N, 3.63; S, 8.32. Found: C, 71.86; H, 8.04; N, 3.69; S, 8.42. UV: $\lambda_{max}^{95\%\ EtOH}$ 260 mμ (ε 5,400). IR ν_{max}^{Nujol} cm^{-1}: 1736, 1242, 1028 (OAc), 1512 (aromatic).

2′-Methylthiazolo[5′,4′-16,17]androsta-5,16-dien-3β-ol (VIIb)——A solution of 240 mg. of (VIIa) and 300 mg. of K_2CO_3 in 10 cc. of MeOH and 3 cc. of H_2O was heated under reflux for 30 min. After dilution with H_2O, the precipitate was collected by filtration and dried to give 210 mg. of (VIIb), m.p. 197~202°(decomp.), which was recrystallized from MeOH to plates, m.p. 200~202°(decomp.). $[\alpha]_D^{30}$ −55.9±4°(c=0.606, $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{29}ONS$: C, 73.42; H, 8.51; N, 4.08; S, 9.33. Found: C, 73.72; H, 8.89; N, 3.99; S, 9.41. UV: $\lambda_{max}^{95\%\ EtOH}$ 260 mμ (ε 5,480). IR ν_{max}^{Nujol} cm^{-1}: 3334 (OH), 1515 (aromatic).

2′-Methylthiazolo[5′,4′-16,17]androsta-4,16-dien-3-one (VIII)——A solution of 155 mg. of (VIIb) in 10 cc. of toluene and 1 cc. of cyclohexanone was treated with a solution of 100 mg. of (iso-PrO)$_3$Al in 5 cc. of toluene as described above for (V). The product was recrystallized from Me_2CO to give 105 mg. of (V) as plates, m.p. 203~205°(decomp.). $[\alpha]_D^{30}$ +90.6±2°(c=1.044, $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{27}ONS$: C, 73.85; H, 7.97; N, 4.10; S, 9.39. Found: C, 73.94; H, 8.23; N, 3.98; S, 9.20. UV: $\lambda_{max}^{95\%\ EtOH}$ 243 mμ (ε 20,110). IR ν_{max}^{Nujol} cm^{-1}: 1679, 1622 (4-en-3-one), 1514 (aromatic).

2′-Aminothiazolo[5′,4′-16,17]androsta-5,16-dien-3β-ol (IXa)——A solution of 6.00 g. of 3β-acetoxy-16β-bromoandrost-5-en-17-one and 2.25 g. of $NH_2CS \cdot NH_2$ in 30 cc. of abs. EtOH was warmed under reflux for 27 hr. To the reaction mixture H_2O was added and the precipitates were collected by filtration, washed with H_2O, and dried. This substance showed slight shoulders at 240 and 275 mμ in the UV spectrum. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3566, 3448, 3222 (w), 1729, 1640, 1605 (sh), 1590 (sh), 1511 (w). These precipitates were warmed with 7 g. of KOH in 70 cc. of MeOH for 30 min. To the reaction mixture H_2O was added and the doposited crystalline product was collected by filtration, washed with H_2O, and dried. Recrystallization from $CHCl_3$-EtOH gave 4.27 g. of (IXa) as fine needles, m.p. 268~270°(decomp.). $[\alpha]_D^{29}$ −35.3±2°(c=1.003, pyridine). *Anal.* Calcd. for $C_{20}H_{26}ON_2S$: C, 69.72; H, 8.19; N, 8.13; S, 9.31. Found: C, 69.63; H, 8.33; N, 8.38; S, 9.35. UV: $\lambda_{max}^{95\%\ EtOH}$ 270 mμ (ε 6,430). IR ν_{max}^{Nujol} cm^{-1}: 3394, 3302, 3234, 3124, 1629 (s), 1513 (s), 1054. $\nu_{max}^{CHCl_3}$ cm^{-3}: 3660, 3618, 3442, 1604, 1503. Acetylation of (IXa) with Ac_2O, followed by recrystallization from $CHCl_3$-MeOH, gave the O,N-diacetate (IXb) as needles, m.p. 291~293°(decomp.). $[\alpha]_D^{27}$ −41.4±2°(c=0.980, pyridine). *Anal.* Calcd. for $C_{24}H_{32}O_3N_2S$: C, 67.27; H, 7.53; N, 6.54; S, 7.48. Found: C, 66.94; H, 7.44; N, 6.52; S, 7.55. UV: $\lambda_{max}^{95\%\ EtOH}$ 287 mμ (ε 11,290). IR ν_{max}^{Nujol} cm^{-1}: 3270, 3246, 3080, 1729, 1689, 1550, 1270, 1034. $\nu_{max}^{CHCl_3}$ cm^{-1}: 3472, 3286, 1729, 1694, 1530, 1250, 1030.

2′-Aminothiazolo[5′,4′-16,17]androsta-4,16-dien-3-one (Xa)——A solution of 2.74 g. of (IXa) and 2 g. of (iso-PrO)$_3$Al in a mixture of 50 cc. of dioxane, 50 cc. of toluene, and 15 cc. of cyclohexanone was refluxed for 4 hr. After cooling the reaction mixture was treated with a saturated solution of Rochelle salt and steam-distilled for 1 hr. The precipitates were collected by filtration, washed with H_2O, and dried. Recrystallization from $CHCl_3$-EtOH gave 2.38 g. of (Xa) as yellow needles, m.p. 271~273° (decomp.). (This color seemed to be produced by a trace of impurity and could not be removed by chromatography on Al_2O_3). $[\alpha]_D^{24}$ +119.3±2°(c=1.060, pyridine). *Anal.* Calcd. for $C_{20}H_{26}ON_2S$: C, 70.13; H, 7.65; N, 8.18; S, 9.36. Found: C, 69.69; H, 7.84; N, 8.27; S, 9.32. UV: $\lambda_{max}^{95\%\ EtOH}$ 242 mμ (ε 19,360). IR ν_{max}^{Nujol} cm^{-1}: 3452, 3290, 3202, 3178, 1676, 1622, 1540, 1517, 864. $\nu_{max}^{CHCl_3}$ 3662, 3548, 3428, 1663, 1605, 1506, 863.

Acetylation of 2.38 g. of (Xa) with pyridine and Ac_2O, followed by recrystallization from MeOH,

gave 2.46 g. of the N-acetate (Xb) as colorless needles, m.p. 282~284°(decomp.). $[\alpha]_D^{23.5}$ +113.2±2° (c=1.023, pyridine). *Anal.* Calcd. for $C_{22}H_{28}O_2N_2S$: C, 68.72; H, 7.34; N, 7.29; S, 8.34. Found: C, 68.71; H, 7.46; N, 7.38; S, 8.55. UV $\lambda_{max}^{95\%\ EtOH}$ mμ (ε): 241 (18,800), 287 (11,430). IR ν_{max}^{Nujol} cm^{-1}: 3230, 3068, 1694, 1665, 1616, 1552.

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Summary

2′-Methylthiazolo[5′,4′-16.17]androsta-15,16-dien-3β-ol (Ⅷ) was prepared by an established method from 3β-acetoxy-16β-bromoandrost-5-en-17-one (Ⅵ) and thioacetamide. Consequently the aromatic compound (Ⅳ) which was obtained by dehydration of the by-product (Ⅲ) of the Beckmann rearrangement of the oxime-mixture (Ia) and (Ib) of 3β-acetoxy-17α-hydroxy-16β-thiocyanatopregn-5-en-20-one and which was assigned an uncorrect thiazol structure (Ⅷ) in the previous paper, should be 3′-methylisothiazolo[5′,4′-16,17]androsta-5,16-dien-3β-ol acetate. 2′-Amino-16,17-disubstituted thiazolo-compound was also prepared from (Ⅵ) and thiourea.

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194. Katsumi Tanabe and Ryozo Hayashi: Steroid Series. IX.[1] A New Route to 6-Nitrosteroid Derivatives.

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Although many examples of the addition of nitrosyl chloride to the carbon-carbon double bond of a large variety of compounds are reported in the literature, there has been no report of such a reaction in the steroid field. In this paper the authors wish to describe the addition of nitrosyl chloride to the steroidal double bond at the 5,6-position and the conversion of the adducts to 6-nitrosteroid derivatives.

Cholesterol acetate (Ia) was treated in carbon tetrachloride solution with excess of nitrosyl chloride to give a crystalline product (Ⅱa) of m.p. 140~141° in a high yield, which showed a positive Beilstein test and exhibited a characteristic absorption band for a nitro alkane group at 1553 cm^{-1} in the infrared region.[2] Its analytical values correctly corresponded with the composition of $C_{29}H_{48}O_4NCl$. On treatment with either pyridine or alumina, (Ⅱa) was smoothly converted into the known 6-nitrocholesterol acetate (Ⅲa) of m.p. 102~104°, $[\alpha]_D$ −78.4°. When treated with zinc dust in acetic acid-ether, the compound (Ⅱa) was found to eliminate readily the chloro-nitro group to regenerate cholesterol acetate (Ia) in an almost quantitative yield. From these observations the structure 5-chloro-6β-nitro-5α-cholestan-3β-ol acetate was assigned to the product, the stereochemical assignment being based on the following considerations.

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1) Part Ⅷ: This Bulletin, **10**, 445 (1962).

2) L. J. Bellamy: "The Infrared Spectra of Complex Molecules," 298 (1958). John Wiley & Sons, Inc., New York.