[Contribution from the Organic Chemistry Department, National Research Center]

Carbonyl and Thiocarbonyl Compounds. V.[1] Synthesis of Newer Unsaturated Nitriles, Carboxylic Acids, and Esters Derived from Xanthene and Thiaxanthene

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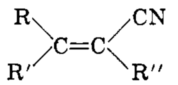
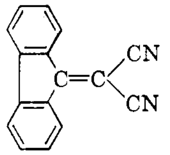
The synthesis of the unsaturated nitriles, carboxylic acids, and esters IIIa–IIIi is described and a comparative study of the methods of their preparation is stressed.

The reaction of malononitrile and ethyl cyanoacetate with *p*-benzoquinoazines with the production of unsaturated nitriles is described and a reaction mechanism is suggested.

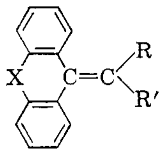
In the course of studies on the biological activity of unsaturated nitriles, the preparation of newer members derived from xanthene and thiaxanthene has been found necessary. Although several compounds of the general formula I have been prepared, little is known about the heterocyclic derivatives from this group.[1a] Unsaturated nitriles of the general formula I were generally prepared by condensing an aldehyde or a ketone with the appropriate cyano compound in a Knoevenagel reaction.[2] Von Schenk and Finken[2a] prepared several aryl substituted unsaturated dinitriles by condensing malononitrile with various ketones in the presence of a base. The ability of the carbonyl group to condense varied with different ketones. Thus, while diphenyldicyanoethylene (I. R = R′ = C_6H_5; R″ = CN) was obtained in a 36% yield from benzophenone, the diphenylene analogue II was obtained in an almost quantitative yield from fluorenone, and malononitrile.


I


II

In an attempt to prepare xanthenemalononitrile IIIa by applying this reaction to xanthone, a very poor yield of the product is obtained. However, a greater yield could be produced by using xanthione instead of xanthone, a fact which provides a further example of the weak reactivity of the carbonyl group of xanthone towards condensation.[3] It is found that IIIa can be produced in a much higher yield from xanthione by allowing the latter to react with malononitrile in presence of mercuric oxide as a desulfurizing agent instead of adding a base.[4] In trying to apply this method for the preparation of thiaxanthene-malononitrile IIIb from thiaxanthione, thiaxanthone is mainly produced and only a very small amount of the expected dinitrile is obtained. However, the yield is improved remarkably when the reaction is carried out in a nitrogen atmosphere. It is found that xanthione and thiaxanthione are oxidized easily to the corresponding ketones when boiled with mercuric oxide in alcohol. Latif and Fathy[1] have shown also that thiaxanthione is easily oxidized by the action of tetrahalo-*o*-benzoquinones. This is rather noteworthy, as it has been reported that both xanthione and thiaxanthione are stable to atmospheric oxgyen in absence of sunlight.[5] In general xanthione is more stable towards oxidizing agents than the thioanalogue.

It is found that a maximum yield is obtained when IIIa and IIIb are prepared from the corresponding keto chlorides. Thus, when 9,9-dichloroxanthene or 9,9-dichlorothiaxanthene is allowed to react with malononitrile at elevated temperatures IIIa or IIIb are produced respectively in excellent yields. 9,9-Dichloroxanthene reacts similarly with



IIIa. X = O; R = R′ = CN
IIIb. X = S; R = R′ = CN
IIIc. X = O; R = $COOC_2H_5$; R′ = CN
IIId. X = S; R = $COOC_2H_5$; R′ = CN
IIIe. X = O; R = R′ = $COOC_2H_5$
IIIf. X = O; R = COOH; R′ = CN
IIIg. X = S; R = COOH; R′ = CN
IIIh. X = O; R = H; R′ = CN
IIIi. X = S; R = H; R′ = CN

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(1) Part IV of this series, *J. Org. Chem.*, **25**, 1618 (1960).

(1) (a) Some members of this series have been prepared recently by H. Kato, T. Ogawa, and M. Ohta; *Bull. Chem. Soc. Japan*, **33**, 1468 (1960).

(2) (a) R. von Schenk and H. Finken, *Ann.*, 462, 272 (1928). (b) A. C. Cope, *J. Am. Chem. Soc.*, **59**, 2327 (1937). (c) F. S. Prout, *J. Org. Chem.*, **18**, 928 (1953).

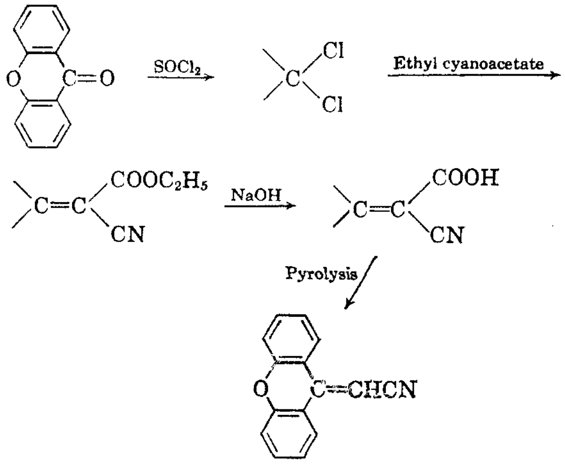
[3] *Cf.* N. Campbell, S. R. McCallum, and D. J. Mackenzie, *J. Chem. Soc.*, 1922 (1957); E. H. Rodd, *Chemistry of Carbon Compounds*, Elsevier, New York, vol. IVB, 1959, p. 977.

[4] *Cf.* R. B. Ashworth, A. E. Growther, F. H. S. Curd, J. A. Hendry, and D. N. Richardson, *J. Chem. Soc.*, 475 (1949).

[5] A. Schönberg and A. Mustafa, *J. Chem. Soc.*, 275 (1943).

ethyl cyanoacetate and ethyl malonate giving the unsaturated esters IIIc and IIIe, respectively. IIId is similarly obtained from 9,9-dichlorothiaxanthene and ethyl cyanoacetate. In general the yields of the xanthene derivatives are much higher than the corresponding thianalogues. In each case the greatest yield is obtained when malononitrile is used followed by the cyano ester.

In order to obtain the ethylene IIIh, IIIc is preferentially hydrolyzed by dilute alcoholic alkali giving the corresponding acid IIIf together with xanthone. On heating the acid above its melting point under reduced pressure, IIIh is produced in good yield as is illustrated in scheme "A." The corresponding thiaxanthene derivative IIIi could be similarly obtained. However, the yield of the acid IIIg obtained by the alkali hydrolysis of IIId is much lower than its corresponding xanthene derivative, as most of the ester is cleaved during hydrolysis giving thiaxanthone. The easy cleavage of the ethylenic double bond by alkali in these compounds is also illustrated by the fact that xanthone and thiaxanthone are produced respectively when boiling IIIa or IIIb with a 10% solution of sodium hydroxide.

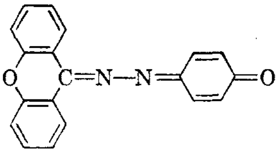


IIIh
"A"

Various xanthenes have been prepared through the intermediate formation of 9,9-dichloroxanthene, but, as far as we are aware, the latter has not been separated or described. It could be obtained in a crystalline form by the action of thionyl chloride on xanthone and crystallizing the crude reaction product from low boiling petroleum ether at low temperature. Microanalysis could not be carried out, however, as the substance decomposes readily to give xanthone. 9,9-Dichlorothiaxanthene could be obtained in good yield by following a similar procedure.

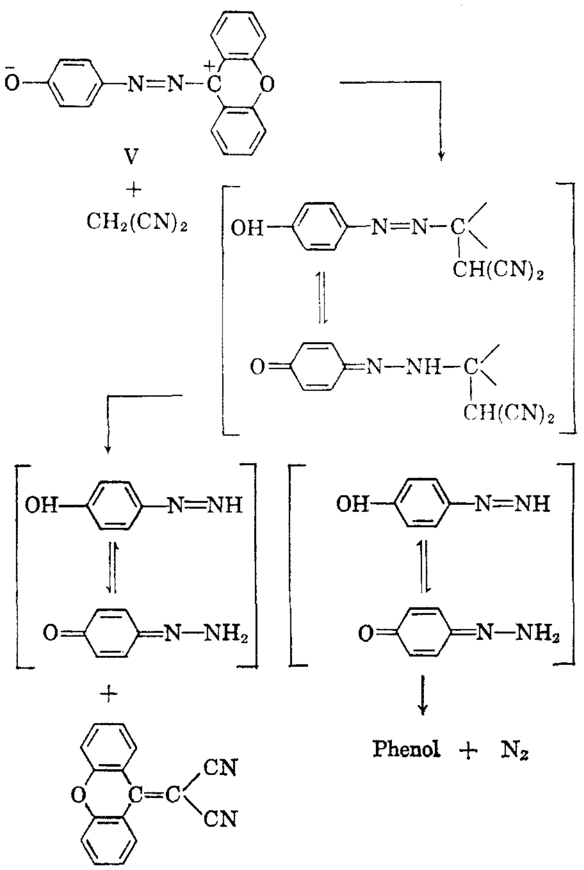
Reaction of N^1-p-benzoquinonylidene-N^2-xanthonylideneazine(IV) *with malononitrile and ethyl cyanoacetate.*

In a previous article,[6] the synthesis of *p*-benzoquinoazines of the general formula $R_2 = C{=}N{-}N = R'{=}O$ and their reaction with nucleophilic reagents have been described. It has been shown that IV is prepared by condensing *p*-benzoquinone with xanthone hydrazone in dry benzene. It is cleaved by hydrazine hydrate giving xanthone hydrazone and xanthone azine together with phenol.



IV

In the present investigation, it is found that IV reacts readily with malononitrile and with ethyl cyanoacetate in boiling alcohol giving the unsaturated dinitriles IIIa and IIIc, respectively. The yield of IIIa in this reaction is much higher than IIIc Attempting to prepare IIIe by the action of ethyl malonate on IV, the product is obtained only in traces. It appears that the difference in the yield with the different active methylene compounds goes parallel with their nucleophilic character;



IIIa "B"

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[6] N. Latif and I. Fathy, *J. Org. Chem.*, **25**, 1614 (1960).

the greater yield is obtained in the case of malononitrile followed by ethyl cyanoacetate then with ethyl malonate. It is believed that structure V contributes largely to the actual state of the quinoazine molecule, and the reaction proceeds by the nucleophilic attack of the active methylene compound on the quinoazine. A mechanism illustrated by scheme "B" should be taken into consideration, among other possibilities, to explain the production of the unsaturated nitriles in this reaction. The isolation of phenol among the reaction products is in favor of the suggested mechanism.

EXPERIMENTAL

Redistilled ethyl cyanoacetate (Merck) and ethyl malonate (B.D.H.), which was distilled over anhydrous sodium carbonate, were used.

Preparation of 9,9-dichloroxanthene. In a 50-ml. round bottom flask fitted with a reflux condenser and a calcium chloride tube, a solution of xanthone (2. g.) in thionyl chloride (10 ml.) was heated for 3 hr. The thionyl chloride was then driven off under reduced pressure and the oily residue was left to cool in vacuum. The crystalline product obtained was washed with a few milliliters of ice cold petroleum ether (b.p. 40–60°) and then crystallized from the same solvent using a vessel protected from moisture. Concentration of the solution during crystallization was carried out under reduced pressure in the cold. 9,9-Dichloroxanthene was obtained as colorless crystals which melt at about 103° (yield about 80%). It is soluble in most organic solvents and it turns brown when exposed to air.

Preparation of 9,9-dichlorothiaxanthene. A solution of thiaxanthone in thionyl chloride was refluxed as above for 6 hr. The keto chloride was obtained as colorless crystal which melt at about 130°. It is soluble in most organic solvents, and it turns brown red when exposed to air.

Preparation of Δ^9, *α-xanthenemalononitrile* (IIIa).[7] 9,9-Dichloroxanthene (from 2 g. of xanthone) and malononitrile (1 g.) were mixed well together in a dry 50-ml. round bottom flask fitted with a calcium chloride tube. The mixture was then heated at 100° (bath temperature) for 1 hr., when a vigorous reaction with evolution of hydrogen chloride took place. The reaction mixture was left to cool and the green solid mass obtained was washed with cold acetone and recrystallized from benzene to give IIIa as green yellow crystals m.p. 244–245° (yield almost quantitative). It gives deep yellow-green color with concentrated sulfuric acid.

Anal. Calcd. for $C_{16}H_8ON_2$: C, 78.68; H, 3.27; N, 11.47. Found: C, 78.66; H, 3.24; N, 11.39.

Reaction of xanthione with malononitrile. Method A. A suspension of xanthione (1 g.), malononitrile (0.4 g.), and yellow mercuric oxide (1 g.) in absolute alcohol (20 ml.) was heated under reflux for 6 hr. The reaction mixture was filtered while hot, and the filtrate was concentrated and then left to cool. The crystals separated were shown to be IIIa (melting point and mixed m.p.). A further amount of the product was obtained by extracting the black residue with boiling benzene and concentrating the benzene extracts (total yield about 60%).

Method B. A suspension of xanthione (1 g.), malononitrile (0.4 g.), and diethylamine (0.5 ml.) in dry benzene (20 ml.) was heated under reflux for 6 hr., and then left to cool. The yellow mass which separated was filtered off and dissolved in boiling benzene. The benzene solution was filtered while hot, concentrated, and left to cool. The crystals separated were recrystallized from the same solvent to give IIIa; yield about 20%.

Action of alkali on IIIa. Half a gram of IIIa was added to mixture of 10% aqueous solution of sodium hydroxide (20 ml.), and alcohol (20 ml.). The reaction mixture was heated under reflux for 4 hr. and cooled in ice. The colorless crystalline product which separated was filtered off, washed with water several times, and dried. It was crystallized from alcohol to give xanthone in colorless crystals (melting point and mixed melting point), (yield about 80%).

Preparation of Δ^9,*α-xantheneacetic acid, α-cyanoethyl ester* (IIIc). A mixture of 9,9-dichloroxanthene (3 g.) and ethyl cyanoacetate (4 ml.) was heated as above for 3 hr. at 100° (bath temperature). The reaction mixture was left to cool, and the solid separated was washed several times with cold petroleum ether (b.p. 40–60°), then dissolved in the least amount of boiling methyl alcohol and left to cool. The crystals obtained were recrystallized from the same solvent to give IIIc as yellow crystals, m.p. 117–118° (yield about 80%). It gives an orange-red color with concentrated sulfuric acid.

Anal. Calcd. for $C_{18}H_{13}O_3N$: C, 74.22; H, 4.46; N, 4.81. Found: C, 74.07; H, 4.54; N, 4.91.

Method B. A suspension of xanthione (2 g.), ethyl cyanoacetate (2.5 ml.), and yellow mercuric oxide (2 g.) in absolute alcohol (30 ml.) was heated under reflux for 3 hr. The reaction mixture was filtered while hot, and the black residue was extracted several times with ethanol. The combined alcoholic solutions were concentrated, filtered while hot, and then left to cool to give IIIc in yellow crystals, m.p. 117–118° (undepressed when admixed with an authentic sample prepared by method A); (yield about 60%).

Reaction of xanthione with mercuric oxide. A suspension of xanthione (1 g.) and yellow mercuric oxide (1 g.) in absolute alcohol (15 ml.) was refluxed for 3 hr. The reaction mixture was filtered while hot and the filtrate was concentrated and left to cool. The crystals separated were shown to be xanthone (melting point and mixed melting point); yield about 90%. When thioxanthione was treated similarly, thiaxanthone was produced.

Preparation of Δ^9,*α-cyano-α-xantheneacetic acid* (IIIe). The ester IIIc (2 g.) was dissolved in a mixture of alcohol (30 ml.) and 5% aqueous solution of sodium hydroxide (30 ml.). The reaction mixture was refluxed gently on the water bath for 3 hr. and then cooled in ice. The colorless crystalline product which separated was filtered off and extracted with boiling water. The water insoluble material was crystallized from ethanol to give xanthone (yield about 0.9 g.). The water extracts were cooled, acidified with dilute hydrochloric acid, and the yellow precipitate which formed was filtered off, washed with water, and dried. It was crystallized from benzene to give IIIe as canary yellow crystals (0.6 g.) which melt at about 180° with vigorous decomposition.

Anal. Calcd. for $C_{16}H_9NO_3$: C, 73.00; H, 3.42; N, 5.32. Found: C, 73.16; H, 3.23; N, 5.50.

Preparation of Δ^9,*α-xantheneacetonitrile* (IIIh). A 0.5-g. sample of IIIe was heated for 2 hr. at 220–240° (bath temperature) in a test-tube shaped vessel (Pyrex glass) which was connected during pyrolysis to a working vacuum oil pump. The reaction vessel was then allowed to cool in a vacuum. The crystalline product which collected on the upper parts of the reaction vessel was recrystallized from methyl alcohol to give IIIh in almost colorless crystals m.p. 132–133°.

Anal. Calcd. for $C_{15}H_9NO$: C, 82.1; H, 4.1; N, 6.4. Found: C, 82.2; H, 4.24; N, 6.49.

Preparation of Δ^9,*α-thiaxanthenemalononitrile* (IIIb). *Method A.* A mixture of 9,9-dichlorothiaxanthene (from 3 g. of thiaxanthone) and malononitrile (2 g.) was heated, as in the case of IIIa, for 3 hr. and then left to cool. The crystalline mass obtained was washed several times with boiling methyl alcohol and then recrystallized from benzene to give IIIb in orange yellow crystals, m.p. 300–301° (yield about 65%). It gives a brown red color with concentrated sulphuric acid.

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(7) This experiment was carried out by (Miss) N. Mishriky.

Anal. Calcd. for $C_{16}H_8SN_2$: C, 73.84; H, 3.07; S, 12.3; N, 10.76. Found: C, 73.63; H, 3.11; S, 12.32; N, 10.59.

Method B. A suspension of thiaxanthione (1 g.), malononitrile (0.4 g.), and yellow mercuric oxide (1 g.) in absolute alcohol (15 ml.) was heated under reflux on the water bath for 3 hr. while passing a stream of dry nitrogen. The reaction mixture was then filtered while hot and the black residue was extracted several times with boiling benzene. The benzene extracts were filtered while hot, concentrated, and then cooled to give IIIb (yield about 50%).

When the reaction was carried out in air, thioxanthone was mainly produced.

Preparation of Δ^9,*α-thiaxantheneacetic acid, α-cyanoethyl ester* (IIId). 9,9-Dichlorothiaxanthene (from 2 g. of thiaxanthone), and ethyl cyanoacetate (3 ml.) were heated together as in the case of IIIc, and the reaction mixture was left to cool. The solid product obtained was extracted several times with boiling petroleum ether (b.p. 40–60°). The petroleum extracts were filtered while hot, concentrated, and then left to cool. The crystals obtained were recrystallized from methyl alcohol to give IIId in yellow crystals, m.p. 129–130°; yield about 60%. It is soluble in ether, acetone, and benzene and gives a blood red color with concentrated sulfuric acid.

Anal. Calcd. for $C_{18}H_{14}O_2SN$: C, 70.1; H, 4.54; S, 10.38; N, 4.54. Found: C, 69.92; H, 4.39; S, 9.96; N, 4.45.

Preparation of Δ^9,*α-cyano-α-thiaxantheneacetic acid* (IIIg). The ester IIId was boiled with an alcoholic sodium hydroxide solution as in the case of IIIc. The reaction mixture was then cooled in ice, and the solid separated was filtered off and extracted with boiling water several times. The water-insoluble material was filtered off, dried, and crystallized from methyl alcohol to give thiaxanthone (undepressed when admixed with an authentic sample prepared according to Davis and Smiles[8]). The water extracts were left to cool, and acidified with dilute hydrochloric acid. The yellow precipitate formed was filtered off, dried and crystallized from benzene to give IIIg in orange crystals which melt with vigorous decomposition at about 187°. It dissolves readily in acetone, difficultly soluble in alcohol or ether. It gives a red color with concentrated sulfuric acid; (yield about 50%).

Anal. Calcd. for $C_{16}H_9O_2SN$: C, 68.81; H, 3.22; S, 11.46; N, 5.01. Found: C, 68.27; H, 3.79; S, 11.93; N, 5.00.

Preparation of Δ^9*α-thiaxantheneacetonitrile.* Pyrolysis of the acid IIIg was carried out as in the case of IIIf. The crystalline product collected on the upper parts of the reaction vessel were crystallized from alcohol to give IIIi in pale yellow crystals, m.p. 158°. It is soluble in ether and acetone, and gives a blood red color with concentrated sulfuric acid; yield about 70%.

Anal. Calcd. for $C_{15}H_9SN$: C, 76.59; H, 3.82; S, 13.61; N, 5.95. Found: C, 76.20; H, 4.16; S, 13.43; N, 5.96.

Reaction of N^1*-p-benzoquinonylidene-*N^2*-xanthonylideneazine* (IV) *with malononitrile.* A suspension of IV (2 g.) and malononitrile (0.5 g.) in absolute alcohol (50 ml.) was refluxed for 2 hr. The reaction mixture was cooled in ice, and the solid separated was filtered off and extracted with boiling acetone. The acetone extracts were filtered while hot, concentrated and left to cool. The yellow green crystals which separated (0.6 g.) were shown to be IIIa (melting point and mixed melting point). The residue left after acetone extraction was crystallized from xylene and was shown to be xanthone azine (undepressed when admixed with an authentic sample prepared according to Schönberg and Stolpp[9]). The alcoholic filtrate from the reaction mixture was poured onto a 2.5% sodium hydroxide solution (30 ml.), and the alkaline solution was acidified with dilute hydrochloric acid and extracted with ether. The ethereal extract was evaporated to dryness, and the oily residue was extracted with boiling water. The aqueous extracts were left to cool and then bromine water was added. The crystalline solid which separated was filtered off, dried, and recrystallized from petroleum ether (b.p. 40–60°) to give tribromophenol m.p. 95° (undepressed when admixed with an authentic sample).

Reaction of IV *with ethyl cyanoacetate.* A mixture of IV (1 g.) and ethyl cyanoacetate (2 ml.) in absolute alcohol (20 ml.) was heated under reflux for 10 hr. The reaction mixture was filtered while hot, and the filtrate was evaporated to dryness under reduced pressure. The oily residue was extracted several times with boiling petroleum ether (b.p. 40–60°), and the combined petroleum extracts were evaporated to dryness. The residue was recrystallized from methyl alcohol to give IIIc in yellow crystals, m.p. 117° (undepressed when admixed with an authentic sample prepared from 9,9-dichloroxanthene and ethyl cyanoacetate). The residue left after the petroleum ether extraction was dissolved in methyl alcohol, and the solution then poured onto a 2.5% sodium hydroxide solution. Phenol was isolated from the alkaline solution and identified as above.

DOKKI, CAIRO

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(8) Davis and Smiles, *J. Chem. Soc.*, **97**, 1290 (1910).

(9) A. Schönberg and Th. Stolpp, *Ber.*, **63**, 3102 (1930).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY AND NEUROLOGY, COLUMBIA UNIVERSITY]

Synthesis of a Series of Organophosphorus Esters Containing Alkylating Groups[1]

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A series of bifunctional organophosphorus esters with alkylating groups in their side-chains was synthesized. These compounds differed in the number of atoms between phosphorus and the electrophilic carbon atom, in the nature of the leaving group, and in the identity of the electronegative group attached to the phosphorus atom. The compounds were: ethyl 2-iodoethyl phosphorofluoridate (I), ethyl 4-iodo-1-butyl phosphorofluoridate (II), ethyl 2-brosyloxyethyl phosphorofluoridate (III), ethyl 2-brosyloxyethyl phosphoric anhydride (IV), and ethyl iodomethylphosphonic anhydride (V).

The reaction of certain organophosphorus compounds, such as diisopropyl phosphorofluoridate and tetraethyl pyrophosphate, with a variety of enzymes has led to their use in the investigation of the active sites of these enzymes.[2–8] In the hope of producing

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[1] This work was supported by a Special Fellowship BT-484 from the National Institute of Neurological Diseases and Blindness, Public Health Service.

[2] H. S. Jansz, C. H. Posthumus, and J. A. Cohen, *Biochim. Biophys. Acta*, **33**, 387, 396 (1959).