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Reaction of Hydrazonyl Halides with Primary Thioamides; Formation of Thiohydrazides and Hydrazonyl Sulfides

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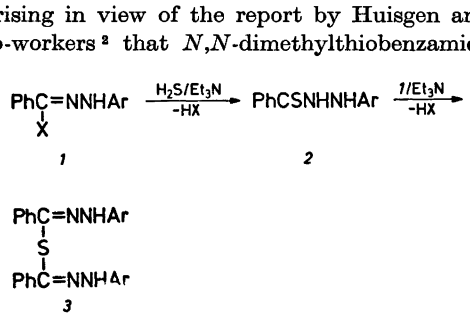
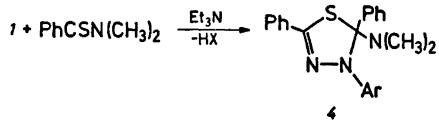
N-Aryl benzohydrazonyl halides react with primary thioamides in the presence of triethylamine to give nitriles and, depending on the relative concentrations of the reactants, thiohydrazides or hydrazonyl sulfides in excellent yields. In the absence of base no reaction is observed. *N,N*-Dimethyl benzohydrazonyl chloride reacts with thioacetamide to give almost quantitatively the hydrochloride of *N,N*-dimethylthiobenzhydrazide, while base (triethylamine) is required for reaction to take place in case of the *N,N*-diphenyl analog. Different reaction mechanisms are discussed in terms of 1,3-dipolar cycloaddition processes and displacement of the hydrazonyl halogen by the thioamide or its anion.

In a recent study [1] of the reaction of hydrazonyl halides (*1*) with hydrogen sulfide in the presence of triethylamine it was found that thiohydrazides (*2*) react with *1* to form hydrazonyl sulfides (*3*), see Scheme 1. This observation is surprising in view of the report by Huisgen and co-workers [2] that *N,N*-dimethylthiobenzamide



Scheme 1.

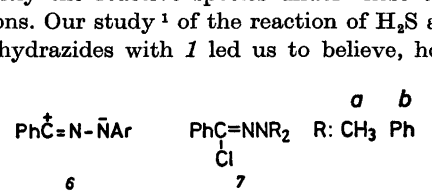
and other compounds with a C=S double bond react with *1* in the presence of triethylamine to give cyclic products such as *4* (Scheme 2). We have therefore examined in more detail



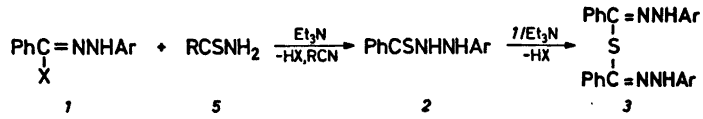
Scheme 2.

the reaction of hydrazonyl halides with various thioamides (for reactions with derivatives of thiourea and thiosemicarbazide, see Ref. 3). The present paper deals in particular with the reactions of primary thioamides ($RCSNH_2$, *5*), while those of secondary and tertiary thioamides will be described in a forthcoming paper.[4]

The thorough studies by Huisgen and collaborators on the reactions of hydrazonyl chlorides in the presence of base have established that 1,3-dipolar species, nitrilimines (*6*), are frequently the reactive species under these conditions. Our study [1] of the reaction of H_2S and thiohydrazides with *1* led us to believe, how-



ever, that nucleophilic displacement of the halogen atom in *1* might in some cases be a viable mechanistic alternative. In order to examine this further we have included in the present study experiments with *N,N*-disubstituted hydrazonyl chlorides (*7*), which are incapable of reacting as 1,3-dipolar species, and experiments with 2,5-diphenyltetrazole, which is known to generate 1,3-diphenylnitrilimine (*6*, Ar=Ph) at elevated temperatures.[6a]



Ar/X
a Ph/Cl
b 2-ClC$_6$H$_4$/Cl
c 2,4-Br$_2$C$_6$H$_3$/Br
d 2-Br-4-ClC$_6$H$_3$/Br
e 2,4,6-Cl$_3$C$_6$H$_2$/Br

R
a CH_3
b Ph
c 3-Pyridyl
d $(CH_3)_2CHO$-

Scheme 3.

RESULTS AND DISCUSSION

Primary thioamides (*5a–c*) and *O*-alkylthiocarbamates (*5d*) react with hydrazonyl bromides and chlorides (*1*) in the presence of triethylamine to form thiohydrazides (*2*), hydrazonyl sulfides (*3*), and nitriles (or alkyl cyanates in the case of thiocarbamates) according to Scheme 3. This reaction provides an easy route to thiohydrazides as well as to hydrazonyl sulfides and compares favourably with previously reported syntheses of these compounds (see Ref. 1 and references cited therein). A thiohydrazide (*2*) is the main product when the reactants *1* and *5* are present in equimolar amounts, whereas a hydrazonyl sulfide (*3*) is formed when an excess of *1* is employed (*cf.* Table 1). The concomitant formation of a nitrile (or cyanate) in these reactions is demonstrated by the appearance of a sharp absorption in the region 2230–2250 cm^{-1} in the IR spectra [7,8] of reaction mixtures from which *3* was subsequently isolated. The nitrile has further been isolated and shown to be identical to authentic material. Nitrile formation by (formal) abstraction of hydrogen sulfide from primary thioamides has been reported to take place through the action of a variety of reagents such as imidoyl chlorides,[9] sulfenyl chlorides in the presence of pyridine,[10] the triphenylphosphine/carbon tetrahalide system,[11] or phenylpropiolamidines;[12] likewise, dehydrosulfurization of *O*-alkylthiocarbamates by mercury(II) oxide to give alkyl cyanates has been described.[13]

Table 1. Yields [a] of thiohydrazides (*2*) and hydrazonyl sulfides (*3*) obtained from PhCXNNHAr (*1*) and RCSNH$_2$ (*5*).

Reactants			Yields in $CHCl_3$		Yields in C_6H_6	
1	*5*	*1/5*	*2*	*3*	*2*	*3*
1a	*5a*	2		90		89
1a	*5b*	2				87
1a	*5c*	2				96
1a	*5d*	2				82
1b	*5a*	2				92
1c	*5a*	2			11	82
1c	*5b*	2				93
1d	*5a*	2				87
1e	*5a*	2				86[c]
1a	*5a*	1[b]	78	19	24	13
1a	*5b*	1		39		60
1c	*5a*	1	93	7	47[c]	26
1c	*5b*	1		14		29
1d	*5a*	1	90, 74[c]	7	81	13
1e	*5a*	1	96, 73[c]	1	80	14

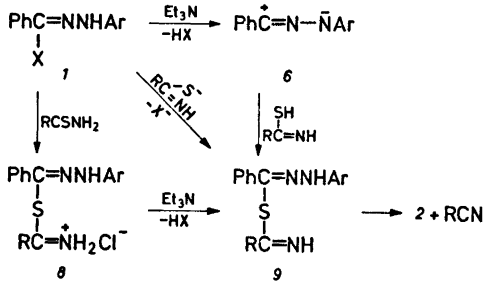
[a] Yields obtained with 5 mmol thioamide in 150 ml solvent. [b] Reaction time 12 h. [c] Crystallized once.

The formation of *2* in preference to *3* when equimolar amounts of *1* and thioacetamide are employed indicates that the thioacetyl group of thioacetamide is more reactive towards *1* (or *6*) than is the thiobenzoyl group of the thiohydrazide. This is further confirmed by the following observations: *2* rather than *3* is formed when triethylamine is added to a mixture of equimolar amounts of a hydrazonyl halide, thioacetamide and a thiohydrazide, and sulfide formation increases significantly at the expense of the thiohydrazide when employing thiobenzamide instead of thioacetamide.

Primary thioamides do not react with *N*-arylhydrazonyl halides in the absence of base; attempted reactions of various hydrazonyl halides with thioacetamide in chloroform (molar

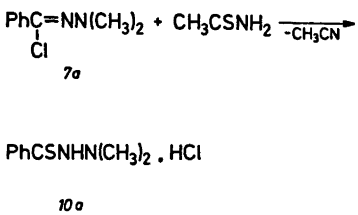
ratio *1*:5 = 1) at room temperature did not produce thiohydrazides in detectable amounts (TLC), and the starting materials were recovered almost quantitatively. Similarly, the chemical shift of the CH_3-group of thioacetamide dissolved in $CDCl_3$ is not changed upon the addition of a hydrazonyl halide to the solution, whereas subsequent addition of triethylamine causes the methyl signal to move upfield to a chemical shift value identical to that of acetonitrile.[14]

The necessity for base to be present for the reaction to proceed is, however, compatible with either of two mechanisms; the triethylamine may dehydrohalogenate *1* [5] (*1*→*6*, see Scheme 4) and the resultant nitrilimine (*6*) then add to the SH group (*6*→*9*), or the halogen atom of *1* may be displaced by the thioamide sulfur atom, in which case the triethylamine would serve to convert the thioamide to the thioamide anion prior to displacement (*1*→*9*) or to deprotonate a possible initial adduct such as *8* (*8*→*9*).



Scheme 4.

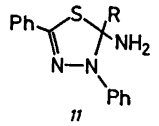
To test the possibility of a displacement mechanism the reaction of *N*,*N*-disubstituted hydrazonyl chlorides (*7*) with thioacetamide was examined. The dimethyl compound (*7a*) gives an almost quantitative yield of the hydrochloride of *N*,*N*-dimethylthiobenzhydrazide (*10a*, see Scheme 5), and the reaction of the diphenyl hydrazonyl chloride (*7b*) with thioacetamide and triethylamine leads, similarly, to *N*,*N*-diphenylthiobenzhydrazide. Base (triethylamine) is not required for the former reaction to take place, since the dimethylamino group of *10a* (or *7a*) in itself is sufficiently basic to serve as proton acceptor. These reactions must occur by nucleophilic displacement of the



Scheme 5.

hydrazonyl halogen atom, 1,3-dipole formation being precluded by the presence of two substituents at the terminal nitrogen atom, and a similar mechanism may indeed be an alternative to reaction *via* 1,3-dipolar species (nitrilimines) for *1*.

To shed light on the possible intermediacy of nitrilimines in these reactions attempts were made to react primary thioamides (*e.g.* thioisonicotinamide) with 2,5-diphenyltetrazole in refluxing bromobenzene, with 1-hexanol added to trap [2,4] any 5-aminothiadiazoline (*11*) formed by addition of the nitrilimine across the C=S double bond of the thioamide.[2]



However, considerable decomposition of the reactants took place and the only identifiable products were ammonia, sulfur and small (4 %) amounts of the corresponding thioanilide (thioisonicotinanilide), presumably formed *via* partial reduction of the tetrazole or the nitrilimine to aniline and subsequent transamidation. These experiments are not regarded as conclusive, because of the rather drastic conditions compared to the reactions described above. Although neither the tetrazole experiment nor the reactions of *1* in the presence of triethylamine gave rise to cyclic compounds such as *11*, nor to possible hydrolysis (or alcoholysis) products formed herefrom, it remains possible that the nitrilimine, if formed from *1*, adds to the thiol form of the thioamide to give *9* (see Scheme 4) in analogy with the reactions of nitrilimines with phenol and thiophenol.[6]

The relative yields of *2* and *3* vary somewhat with the solvent employed, with sulfide (*3*)

formation more favoured in benzene than in chloroform (see Table 1). The reason for this may be that the acidity of thioamides exhibits a significant solvent dependence.[15]

EXPERIMENTAL

Materials

The thioacetamide used was reagent grade (BDH AnalaR). All other thioamides were prepared by literature procedures: thiobenzamide,[16] thionicotinamide,[16] thioisonicotinamide,[16] and *O*-isopropylthiocarbamate.[17] The hydrazonyl halides and the *N,N*-disubstituted hydrazonyl halides were prepared as described previously.[18,20] *N*-(2,4,6-Trichlorophenyl)benzohydrazonyl bromide (*1e*) was prepared according to Chattaway and Walker[21] from benzaldehyde 2,4,6-trichlorophenylhydrazone and bromine in 66 % yield after crystallization from acetic acid as white needles, m.p. 89–90 °C (lit.[22] m.p. 98 °C). (Anal. $C_{13}H_8BrCl_3N_2$: C, H, N). 2,5-Diphenyltetrazole was prepared according to Huisgen *et al.*[6a]

Preparation of thiohydrazides (*2*)

N'-Thiobenzoyl-N-(2-bromo-4-chlorophenyl)-hydrazine (2d). Triethylamine (10.7 mmol) was added to a stirred solution of *1d* (5.0 mmol) and thioacetamide (5.0 mmol) in chloroform (50 ml). After 4 h the solution was washed with aqueous acetic acid and water and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue extracted with boiling ethanol, leaving the sparingly soluble sulfide *3d* (7 %), m.p. 190–192 °C (lit.[19] 188–190 °C). Evaporation of the ethanolic solution yielded the crude thiohydrazide in 90 % yield. (Anal. $C_{13}H_{10}BrClN_2S$: C, H, N, S), m.p. 115–116 °C (benzene–hexane).

The other thiohydrazides were prepared similarly in nearly quantitative yield (see Table 1) and shown to be identical to authentic material (Ref. 1).

N'-Thiobenzoyl-N-(2,4,6-trichlorophenyl)hydrazine (2e) has not been described before; it was prepared as given above from *1e* in 96 % yield. (Anal. $C_{13}H_9Cl_3N_2S$: C, H, N, S), m.p. 139–141 °C (benzene–hexane).

It should be noted that the thioacetamide must be completely dissolved before the addition of triethylamine; otherwise the yield of sulfide increases at the expense of the thiohydrazide. Use of benzene instead of chloroform caused the yields of sulfide to increase (see Table 1). When the thiohydrazide was prepared in larger scale (50 mmol) the chloroform solution was always flushed through with nitrogen before the addition of triethylamine to avoid air oxidation to the corresponding hydrazonyl disulfide.[23]

Attempted reactions with hydrazonyl halides and thioacetamide in the absence of base. Compound *1a* (2.5 mmol) and thioacetamide (2.5 mmol) were dissolved in chloroform (25 ml) and left overnight. TLC of the solution did not show any presence of thiohydrazide (*2a*) and compound *1a* was recovered almost quantitatively, m.p. 127–129 °C. Similarly, *1c* (2.5 mmol) and thioacetamide (2.5 mmol) resulted in 93 % recovery of starting material *1c*.

Compound *1a* or *1e* (*ca.* 15 mg) was added to a solution of thioacetamide (*ca.* 5 mg) in deuteriochloroform (0.50 ml). The addition did not change the chemical shift value (δ 2.57) of the methyl group of thioacetamide; subsequent addition of triethylamine caused the appearance of a new absorption at δ 1.95 (lit.[14] for CH_3 in acetonitrile δ 2.00).

Preparation of hydrazonyl sulfides (*3*)

Bis[α-(phenylhydrazono)benzyl]sulfide (3a). Triethylamine (21 mmol) was added to a stirred suspension of *1a* (10.0 mmol) and thioacetamide (5.0 mmol) in dry benzene (50 ml). After 20 h at room temperature the solution was heated to boiling and filtered to remove precipitated triethylammonium chloride. The sulfide precipitated upon cooling, yield 89 %, m.p. 159–160 °C (lit.[1] 158–160 °C). IR spectrum and R_F-value (TLC) identical to those of an authentic[1] sample. TLC of the mother liquor showed the presence of *2a*.

Compounds *1a*, *1c* and *1d* reacted in a similar manner with other primary thioamides such as thiobenzamide, thionicotinamide, and *O*-isopropyl thiocarbamate to produce the sulfides *3a*, *3b* (m.p. 193–195 °C, lit.[19] 200–202 °C), and *3d* (m.p. 192–194 °C, lit.[19] 188–190 °C) in 80–95 % yield (see Table 1). *3e* was prepared similarly from *1e*, thioacetamide and triethylamine in 85 % yield after recrystallization from benzene. M.p. 183–185 °C (decomp.). (Anal. $C_{26}H_{16}Cl_6N_4S$: C, H, N, Cl).

The yield of *3* may further be increased by reduction of the volume of solvent below that necessary for complete dissolution of the thioamide.

Identification of nitriles

Benzonitrile. (i) Triethylamine (10 mmol) was added to a stirred solution of *1a* (5.0 mmol) and thiobenzamide (2.5 mmol) in chloroform (25 ml). An IR spectrum recorded after 20 h showed a sharp absorption at 2235 cm^{-1}. (ii) An IR spectrum of a mixture of triethylamine (5 mmol), thiobenzamide (5.0 mmol) and triethylamine hydrochloride (5.0 mmol) in chloro-

form (25 ml) showed no absorption after 20 h in the region 2 200 – 2 300 cm^{-1}.

Nicotinonitrile. (*i*) Triethylamine (40 mmol) was added to a stirred suspension of *1b* (20.0 mmol) and thionicotinamide (10.0 mmol) in dry benzene (100 ml). After 12 h at room temperature the solution was heated to boiling and filtered. An IR spectrum showed a sharp absorption at 2230 cm^{-1}. The solution was evaporated under reduced pressure and the crude sulfide *3b* was washed carefully with ethanol, yield 92 %, m.p. 169 – 171 °C (lit.[19] 167 – 168 °C). The ethanolic solution was evaporated to dryness, the residue dissolved in ether and washed with aqueous sodium hydroxide and water, dried over Na_2SO_4 and the ether removed *in vacuo*. The resulting oil was sublimated to give white crystals, m.p. 48 – 50 °C (mixed m.p. 48 – 50 °C). A mass spectrum showed the molecular ion (*m/e* 104, base peak). (*ii*) Triethylamine (1 mmol) was added to a stirred suspension of thionicotinamide (1.0 mmol) and triethylamine hydrochloride (1.0 mmol) in dry benzene (10 ml). After 20 h the solution was filtered and 93 % thionicotinamide was recovered. An IR spectrum showed no absorption in the region 2200 – 2300 cm^{-1}.

Isopropyl cyanate. Triethylamine (2.0 mmol) was added to a stirred solution of compound *1a* (1.0 mmol) and *O*-isopropylthiocarbamate (0.5 mmol) in chloroform (2.5 ml). An IR spectrum recorded after 15 min showed a weak but distinct absorption at 2250 cm^{-1}. After 30 min the intensity had increased, but a new absorption appeared at 2150 cm^{-1}; this absorption (medium intensity) and a weak one at 1700 cm^{-1} were the only important ones in the region 1700 – 2300 cm^{-1} after 4 h.

Pure isopropyl cyanate [24] (kindly donated by Dr. E. Huge-Jensen) and triethylamine were dissolved in chloroform; and IR spectrum recorded after 24 h showed absorptions at 2150 and 1700 cm^{-1} as in the above experiment. These absorptions are probably due to decomposition of the cyanate to a mixture of isopropyl isocyanate and triisopropyl isocyanurate.[24]

Competition experiments with thioamides and thiohydrazides in presence of hydrazonyl halide. Compound *1c* (2.50 mmol), thioacetamide (2.50 mmol) and *2c* (2.50 mmol) were stirred together in chloroform (75 ml) until all thioacetamide had dissolved, whereupon triethylamine (7.5 mmol) was added. After 4 h the solution was washed with aqueous acetic acid and water, and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue was extracted with boiling ethanol leaving the sparingly soluble sulfide *3c* (8 %), m.p. 191 – 194 °C. Evaporation of the ethanolic solution to dryness yielded the crude thiohydrazide *2c* in 82 % yield (in excess of added *2c*).

A similar experiment conducted in benzene (75 ml) gave *2c* (71 % in excess) and *3c* (11 %).

Similarly, *1a* (5.00 mmol), *2a* (5.00 mmol), thiobenzamide (5.00 mmol) and triethylamine (15.0 mmol) in chloroform (150 ml) afforded after 24 h a 66 % yield of the sulfide *3a*.

N,N-Disubstituted thiobenzhydrazides (10). N,N-Dimethylthiobenzhydrazide (10a). Compound *7a* (5.0 mmol) and thioacetamide (10 mmol) were mixed together in chloroform (25 ml) at room temperature. After 1 h the reaction mixture was cooled, followed by filtration to give yellow crystals (92 %). Crystallization from ethanol gave the pure hydrochloride of *10a* (82 %), m.p. 145 – 150 °C. (Anal. $C_9H_{12}N_2S.HCl$: C, H, N). Treatment of the hydrochloride with aqueous Na_2CO_3 gave the free *10a*, m.p. 107 – 109 °C (benzene – hexane, 1:1) (lit.[25] 106 – 107 °C).

N,N-Diphenylthiobenzhydrazide (10b). Compound *7b* (2.0 mmol), thioacetamide (4.0 mmol) and triethylamine (8.0 mmol) were refluxed together for 20 h in chloroform (10 ml). Work-up as for thiohydrazides (*2*) gave crude *10b* (57 %). Crystallization from benzene – light petroleum (1:1) gave m.p. 134 – 135 °C (lit.[26] 132 – 133 °C).

Reaction with 2,5-diphenyltetrazole. Thioisonicotinamide (5.0 mmol) and 2,5-diphenyltetrazole (5.0 mmol) were refluxed together in bromobenzene (25 ml) and 1-hexanol (1 ml) for 5 h at 160 °C. The solvent was removed *in vacuo* and the residue treated with ethanol to give thioisonicotinanilide (4 %, after crystallization from benzene), m.p. 180 – 183 °C (lit.[27] m.p. 181 – 182 °C). A control experiment with thioisonicotinamide alone showed that this was stable under the conditions employed.

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REFERENCES

1. Wolkoff, P., Hammerum, S., Callaghan, P. D. and Gibson, M. S. *Can. J. Chem. 52* (1974) 879.
2. Huisgen, R., Grashey, R., Seidel, M., Knupfer, H. and Schmidt, R. *Justus Liebigs Ann. Chem. 658* (1962) 169.
3. Wolkoff, P., Nemeth, S. T. and Gibson, M. S. *Can. J. Chem. 53* (1975) 3211.
4. Wolkoff, P. and Hammerum, S. *Acta Chem. Scand. B. 30* (1976) 837.
5. Huisgen, R. *Angew. Chem. Int. Ed. Engl. 2* (1963) 565; *cf.* Hegarty, A. F., Cashman, M. P. and Scott, F. L. *J. Chem. Soc. Perkin Trans. 2* (1972) 44.
6. a. Huisgen, R., Sauer, J. and Seidel, M. *Chem. Ber. 94* (1961) 2503; b. Hegarty,

A. F., Kearney, J. A. and Scott, F. L. *J. Chem. Soc. Perkin Trans. 2* (1973) 1422; Elliott, A. J., Gibson, M. S., Kayser, M. M. and Pawelchak, G. A. *Can. J. Chem. 51* (1973) 4115; Elliott, A. J., Callaghan, P. D., Gibson, M. S. and Nemeth, S. T. *Can. J. Chem. 53* (1975) 1484.
7. Kitson, R. E. and Griffith, N. E. *Anal. Chem. 24* (1952) 334.
8. Groving, N. and Holm, A. *Acta Chem. Scand. 19* (1965) 443.
9. Ishikawa, S. *Sci. Pap. Inst. Phys. Chem. Res. (Jpn.) 2* (1925) 229; Hurd, R. N. and DelaMater, G. *Chem. Rev. 61* (1961) 45; Walter, W. and Voss, J. In Zabicky, J., Ed., *The Chemistry of Amides*, Interscience, New York 1970, p. 445.
10. Walter, W. and Hell, P.-M. *Justus Liebigs Ann. Chem. 727* (1969) 22.
11. Appel, R., Kleinstück, R. and Ziehn, K.-D. *Chem. Ber. 104* (1971) 1030.
12. Fujita, H., Endo, R. and Murayama, K. *Bull. Chem. Soc. Jpn. 45* (1972) 1582.
13. Jensen, K. A. and Holm, A. *Acta Chem. Scand. 18* (1964) 2417.
14. Bovey, F. A. *Nuclear Magnetic Resonance Spectroscopy*, Academic, New York 1969.
15. Walter, W., Meyer, H.-W. and Lehmann, A. *Justus Liebigs Ann. Chem.* (1974) 765.
16. Schöberl, A. and Wagner, A. In Houben-Weyl, *Methoden der organischen Chemie 9* (1955) 762.
17. Holmberg, B. *Sven. Kem. Tidskr. 41* (1929) 249.
18. Wolkoff, P. *Can. J. Chem. 53* (1975) 1333.
19. Barnish, I. T. and Gibson, M. S. *J. Chem. Soc. C* (1970) 854.
20. Conde, S., Corral, C. and Madronero, R. *Tetrahedron 30* (1974) 195.
21. Chattaway, F. D. and Walker, A. J. *J. Chem. Soc. 127* (1925) 975.
22. Humphries, J. E., Humble, H. and Evans, R. *J. Chem. Soc. 127* (1925) 1304.
23. Wuyts, M. H. and Lacourt, A. *Bull. Soc. Chim. Belg. 48* (1939) 193; Scherowsky, G. *Chem. Ber. 107* (1974) 1092; Barton, D. H. R., Ducker, J. W., Lord, W. A. and Magnus, P. D. *J. Chem. Soc. Perkin Trans. 1* (1976) 38.
24. Jensen, K. A., Due, M. and Holm, A. *Acta Chem. Scand. 19* (1965) 438.
25. Jensen, K. A., Baccaro, H. R., Buchardt, O., Olsen, G. E., Pedersen, C. and Toft, J. *Acta Chem. Scand. 15* (1961) 1109.
26. Wuyts, M. H. and Lacourt, A. *Bull. Soc. Chim. Belg.* 42 (1933) 1.
27. Emmert, B. and Holz, A. *Chem. Ber. 87* (1954) 676.

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