The Triethylamine Catalyzed Reaction of *N,N*-Disubstituted Thioamide–Bromine Adducts with Unsubstituted Thiobenzamide

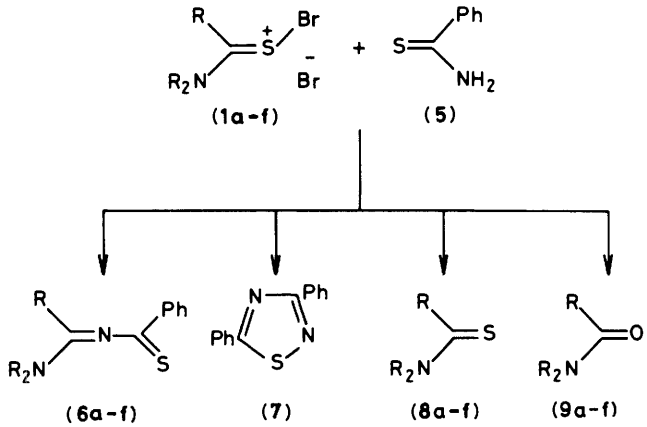
Antonino Corsaro, Anna Compagnini, Giancarlo Perrini, and Giovanni Purrello*
Department of Chemistry, University of Catania, Viale A. Doria 8, 95125 Catania, Italy

The reaction of *N,N*-disubstituted thioamide–bromine adducts with unsubstituted thioamide, followed by treatment with triethylamine, affords novel *N'*-thiobenzoylamidines along with smaller amounts of secondary products. A mechanism is proposed for the formation of the amidines. The results give an insight into the initial steps of the mechanism by which thioamides are converted into 1,2,4-thiadiazoles.

Our interest has recently focused on 1,5-electrocyclizations of conjugated thione-ylides which lead to sulphur-containing heterocyclic compounds.[1,2]

A promising approach to the general construction of these conjugated ylides is based upon the reaction of *N,N*-disubstituted thioamide–bromine adducts (**1**) with appropriate nucleophiles. Thus treatment of the adducts (**1**) with β-aminocinnamonitriles (**2**), followed by triethylamine promoted deprotonation, afforded transient imino-conjugated thione-ylides (**3**) which undergo 1,5-electrocyclization and aromatization to trisubstituted thiazoles (**4**) (Scheme 1).[2]

We now report on the reaction between the adducts (**1a—f**) and unsubstituted thiobenzamide (**5**), followed by treatment with triethylamine. Apart from the interest in the bromine displacement reaction in the adducts (**1**), this investigation has given an insight into the detailed mechanism by which aromatic thioamides are oxidized to 1,2,4-thiadiazoles by halogens.[3] Previously, detailed mechanisms have been described only for the oxidation by hydrogen peroxide.[3-5]



(**1**),(**6**),(**8**),(**9**)**a**; R = Ph; $NR_2 = NC_4H_8$
b; R = Ph; $NR_2 = NC_5H_{10}$
c; R = Ph; $NR_2 = NC_4H_8O$
d; R = *p*-$MeOC_6H_4$; $NR_2 = NC_4H_8O$
e; R = *p*-ClC_6H_4; $NR_2 = NC_4H_8O$
f; R = Me; $NR_2 = NC_4H_8O$

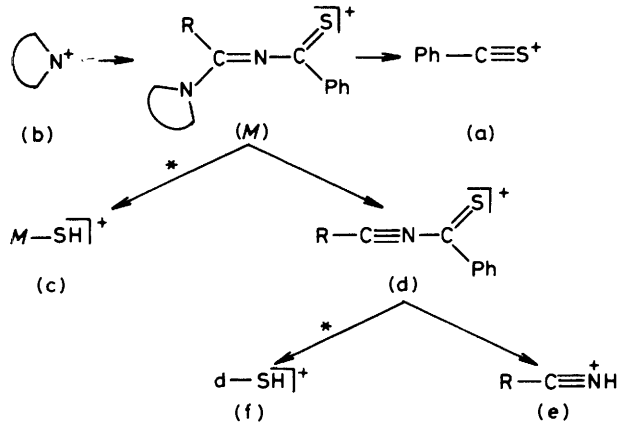
Scheme 2.

Results and Discussion

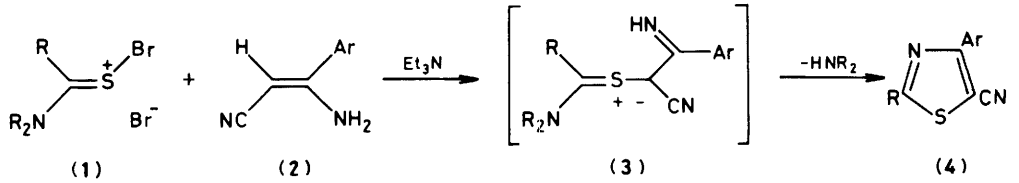
The dropwise addition of the thioamide (**5**) in chloroform to a stirred ice-cooled solution of the adducts (**1a—f**) in the same solvent, followed by treatment with triethylamine, afforded *N'*-thiobenzoylamidines (**6a—f**) (*ca.* 60%) along with smaller amounts of sulphur, 3,5-diphenyl-1,2,4-thiadiazole (**7**), the thiobenzamides (**8a—f**), and the benzamides (**9a—f**) (Scheme 2).

The structures of the amidines (**6a—f**) (Table) were assigned on the basis of elemental analysis, spectroscopic data, and chemical transformations. ^{1}H N.m.r. spectra showed the signals of aromatic protons in the range δ 7.2—8.5 and those of amino protons in the range δ 3.5—4.1. Besides intense molecular ions, mass spectra, run at 70 eV, contained four major fragments which can be accounted for in terms of simple fissions and hydrogen migrations in molecular ions (Scheme 3).

Simple α- and γ-fission with respect to the thiocarbonyl function leads to the common thiobenzoyl (a) and amine (b) cations respectively. Two initial migrations of a hydrogen atom must be involved for the formation of ions (c) and (d). Hydrogen migration from the α-carbon of a radical of a carbon-nitrogen double bond to a sulphur atom and subsequent loss of



Scheme 3.



Scheme 1.

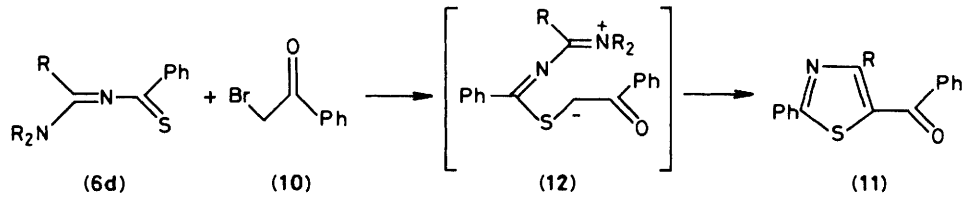
Table. Analytical data for *N'*-thiobenzoylamidines (**3a–f**)

Compd.	Yield (%)	M.p. (°C)	Formula	Analysis (%)[b]		
(6a)	58	126—127[c]	$C_{18}H_{18}N_2S$	73.45 (73.30)	6.1 (6.31)	9.5 (9.55)
(6b)	63	139—140[c]	$C_{19}H_{20}N_2S$	74.0 (74.22)	6.5 (6.35)	9.1 (9.16)
(6c)	65	135—136[c]	$C_{18}H_{18}N_2OS$	69.65 (69.32)	5.8 (5.94)	9.05 (9.21)
(6d)	67	149—151[c]	$C_{19}H_{20}N_2O_2S$	67.05 (67.32)	5.9 (5.79)	8.25 (8.10)
(6e)	57	145[c]	$C_{18}H_{17}ClN_2OS$	62.7 (62.53)	4.9 (4.72)	8.1 (8.31)
(6f)	43	*d*	$C_{13}H_{16}N_2OS$	62.9 (62.74)	6.45 (6.51)	11.3 (11.42)

[a] Yields after chromatography followed by one recrystallization, based on the starting amounts of thioamide (**5**). [b] Found values; required values in parentheses. [c] Red-orange needles. [d] Dense reddish oil.

a sulphydryl radical leads to (c). Hydrogen migration from the α-carbon of the amine moiety to the nitrogen atom bound to the thiocarbonyl group and loss of unsaturated amine leads to (d). Two other abundant ions, (e) and (f), arise from fission of the thiocarbonyl carbon-nitrogen bond and a loss of a sulphydryl radical respectively in fragment (d).

The acid catalyzed hydrolysis of (**6c**) yielded *N'*-thiobenzoylbenzamide.[6] The alkaline catalyzed hydrolysis of (**6d**) yielded benzoic and *p*-methoxybenzoic acids. Furthermore the triethylamine-promoted reaction of (**6d**) with α-bromoacetophenone (**10**) afforded 2-phenyl-4-(*p*-methoxyphenyl)thiazole (**11**) (Scheme 4). An analogous reaction is reported for *N'*-thioaroylformamidines and a 1,5-electrocyclization of a ylide of type (**12**) is proposed for thiazole formation.[7]



(6d) (10) (12) (11)

Scheme 4.

Two different mechanisms can be formulated to account for formation of the amidines (**6a—f**) as the major product (Scheme 5). Path A involves attack by the sulphur atom of the thioamide (**5**) on the sulphur atom of the adduct (**1**) to give the disulphide cation (**13**) which then undergoes a 1,5-electrocyclic ring closure to (**14**). Upon treatment with triethylamine the cyclic cation (**14**) generates the unstable 3-amino-1,2,4-dithiazoline (**15**) which decomposes to the amidine (**6**) by loss of sulphur.

An alternative path B involves attack of the nitrogen atom of thioamide (**5**) on the sulphur atom of the adduct (**1**) to give the cation (**16**) which generates the transient ylide (**17**) by deprotonation. The latter undergoes a 1,3-electrocyclic closure to the thiazirane (**18**) which extrudes sulphur to yield the amidine (**3**).* Similar sulphur extrusions are well known in the analogous thiiranes.[8]

This latter mechanism (path B) can be ruled out however on the basis of the following observations. When the reaction mixture of (**1c**) and (**5**) was treated with perchloric acid instead of triethylamine, 1,2,4-dithiazolium perchlorate (**19**)[5] separated in 76% yield by cooling of the inorganic phase. Treatment of an ethanolic suspension of the salt (**19**) with pyrrolidine, piperidine, and morpholine afforded thiobenzoylamidines (**6a—c**) respectively. The production of (**6a—c**) from (**19**) parallels that of 3-aminoprop-2-enethiones from 1,2-dithiolium salts upon treatment with secondary amines.[10]

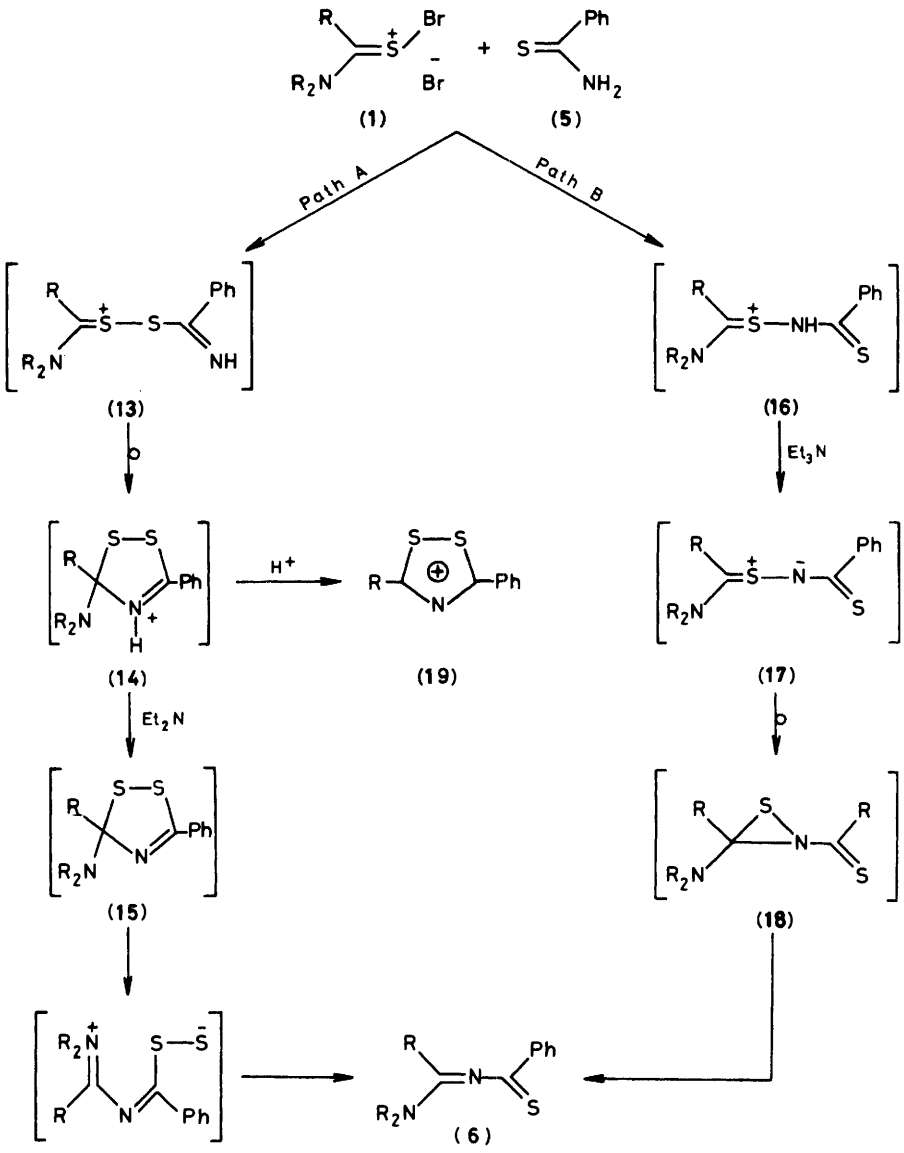
Isolation of the perchlorate (**19**) clearly supports the intermediacy of the cyclic cation (**14**) (path A), from which it originates by acid-promoted elimination of a secondary amine.

The results of our study allow us to define more clearly the initial steps of oxidative conversion of thioamides into 1,2,4-thiadiazoles by halogens. Thus, on the basis of our findings, it can be assumed that the reaction course proceeds *via* initial formation of a bromine adduct (**20**) which yields a disulphide cation (**21**) by bromine exchange with a further molecule of thioamide. In agreement with a newly formulated mechanism for thioamide oxidation by hydrogen peroxide,[5] production of 1,2,4-thiadiazole can then involve the electrocyclization of the cation (**21**) followed by deprotonation to the dithiazoline (**22**), and the loss of hydrogen sulphide from the amidine (**23**) (Scheme 6).

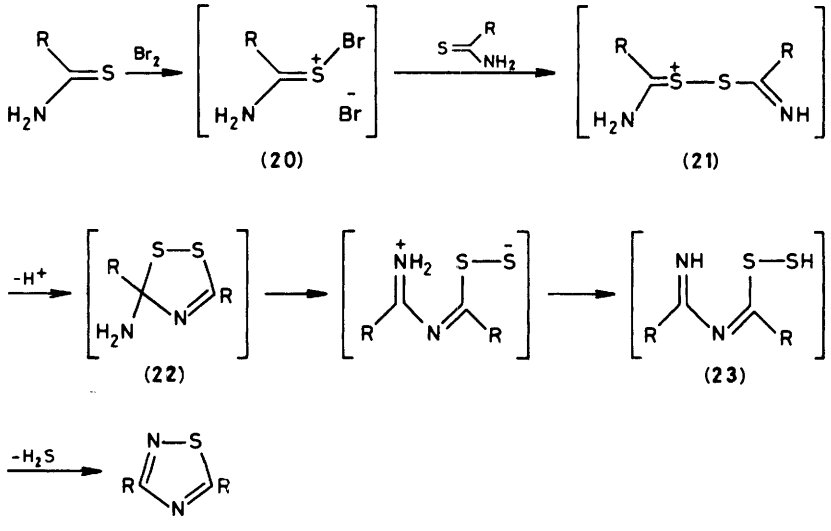
The different decay of the dithiazoline (**22**) with respect to that of (**15**) (see Scheme 5), is clearly due to the presence of the two hydrogen atoms which permit the elimination of hydrogen sulphide after attack of the nucleophilic nitrogen atom on the S–S bond.[11]

Formation of the thiadiazole (**7**) in our experiments is attributable to the action of free bromine present in the starting solutions of the bromine adducts. Our earlier investigations showed that the adducts (**1**) are formed in 80—90% yield by mixing equimolar amounts of the corresponding thioamides (**8**) and bromine in chloroform solution at ice-bath temperature[2] (see also Experimental section). The same evidence has been also obtained from the C^{13} n.m.r. spectra of the adducts (**1a—**

* The production of (**6**) from the decomposition of a 2-amino-1,3,4-dithiazoline, deriving by a 1,5-electrocyclization of the ylide (**17**), has been excluded on the basis of the behaviour of the corresponding 2-amino-1,3-dithioles.[9]



Scheme 5.



Scheme 6.

e)[12] and from the C^{13}-proton n.m.r. coupling constants for dimethylaminothioacetamide.[13]

Trace amounts of the benzamides (**9**) are always isolated whenever the adducts (**1**) were employed. The former were shown to be formed by hydrolysis of (**1**) as a result of traces of water being present in the solvents.[2]

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. I.r. spectra (KBr discs) were taken on a Perkin-Elmer 281 spectrophotometer. ^{1}H N.m.r. spectra were recorded on a Varian A60 instrument with deuteriochloroform as solvent, unless otherwise indicated, and tetramethylsilane as internal standard. Mass spectra were obtained with a LKB 9000S spectrometer. Elemental analysis was performed on a Carlo Erba 1006 elemental analyzer. Column chromatography and t.l.c. were performed with silica gel H and GF_{254} (Merck) respectively.

N,N-Disubstituted thiobenzamides (**8a—e**)[14] were prepared by the Willgerodt-Kindler reaction. 4-Thioacetylmorpholine (**8f**)[14] was made by the reaction of 4-acetylmorpholine with phosphorus pentasulphide in boiling carbon disulphide.

In no case were bromine–thioamide adducts (**1a—f**) isolated because of their rapid decomposition both upon exposure to moisture and storage at room temperature. They were generated in solution by adding dropwise a solution of bromine (0.02 mol) in chloroform (10 ml) to a stirred ice-cooled solution of the corresponding *N,N*-disubstituted thioamide (**8a—f**) (0.02 mol) in the same solvent (40 ml).[2]

General Procedure for Reaction of the Adducts (**1a—f**) *with the Thioamide* (**5**).—To a stirred ice-cooled solution of the adducts (**1a—f**), prepared as above reported from (**8a—f**) and bromine, the thioamide (**5**) (0.02 mol) in chloroform (30 ml) was added dropwise. The mixture was stirred for an additional 15 min and then treated with an excess of triethylamine. After being stirred for a further 15 min, the solution was washed repeatedly with water and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue chromatographed. Elution with ethyl acetate–cyclohexane (9:1) gave *N'*-thiobenzoylamidines (**6a—f**), as orange reddish needles, unless otherwise stated, along with sulphur, 3,5-diphenyl-1,2,4-thiadiazole (**7**), the original thiobenzamides (**8a—f**), and the benzamides (**9a—f**). Analytical data for (**6a—f**) are listed in the Table. ^{1}H N.m.r. spectra of (**6a—f**) showed two multiplets at δ 3.5—4.1 (amino radical protons) and at δ 7.2—8.5 (ArH). The thiadiazole (**7**) (*ca.* 4% in all runs), m.p. 90 °C, was identical (mixed m.p. and superimposed i.r. spectra) with a specimen prepared according to the literature.[15] The benzamides (**9a**),[16] (**9b**),[17] (**9c**),[18] (**9d**),[19] (**9e**),[20] and (**9f**)[21] were isolated in very poor amounts and were identical (mixed m.p. and/or superimposed i.r. spectra) with samples obtained according to the literature.

Acid Catalyzed Hydrolysis of the Amidine (**6c**).—A solution of (**6c**) (3 mmol) in ethanol (15 ml) containing 10% HCl (3 ml) was stirred and kept at room temperature overnight. After dilution with water and extraction with chloroform, the extracts were dried (Na_2SO_4) and evaporated to give *N*-thiobenzoylbenzamide which formed reddish rhombs from ethanol (84%), m.p. 118—119 °C (lit.,[6] m.p. 119 °C).

Alkaline Catalyzed Hydrolysis of the Amidine (**6d**).—A solution of (**6d**) (3 mmol) in ethanol (15 ml) containing 10% NaOH (3 ml) was refluxed for 1 h. After acidification and extraction with chloroform, the extracts were dried (Na_2SO_4) and evaporated to give benzoic acid, m.p. 122 °C and *p*-methoxybenzoic acid, m.p. 183 °C, identical (mixed m.p. and superimposed i.r. spectra) with commercially available samples.

5-Benzoyl-2-phenyl-4-(p-methoxyphenyl)thiazole (**11**).—To a stirred solution of stoicheiometric amounts (3 mmol) of the amidine (**6d**) and α-bromoacetophenone (**10**) in benzene (20 ml) an excess of triethylamine was added at room temperature. The mixture was kept for 3 h after which the triethylamine hydrochloride was filtered off and the filtrate evaporated under reduced pressure to leave a residue. Crystallization from ethanol afforded the thiazole (**11**) (43%) as colourless needles, m.p. 178—180 °C (Found: C, 74.45; H, 4.85; N, 3.65. $C_{23}H_{17}NO_2S$ requires C, 74.58; H, 4.77; N, 3.77%); $\nu_{max.}$(KBr) 1 685 cm^{-1} (C=O); δ($CDCl_3$) 3.9 (s, 3 H, OCH_2), 6.9—7.4 (m, 14 H, ArH); *m/z* 371 (M^+) and 105 ($PhCO^+$).

3,5-Diphenyl-1,2,4-dithiazolium Perchlorate (**19**).—To a stirred ice-cooled solution of the adduct (**1c**), prepared as reported above, the thioamide (**5**) (0.02 mol) in chloroform (30 ml) was added dropwise. The mixture was stirred for an additional 15 min and then treated with 70% perchloric acid (30 ml). The mixture was stirred for a further 15 min after which the inorganic phase was separated and allowed to stand overnight at 0 °C. From the perchloric acid solution the salt (**19**) was deposited as a yellow powder (76%), m.p. 265 °C (from nitromethane–ether) (lit.,[5] m.p. 266—267 °C).

Reaction of the Perchlorate (**19**) *with Secondary Amines.*—To a stirred suspension of the perchlorate (**19**) (5 mmol) in ethanol (10 ml) morpholine (0.01 mol) was added at room temperature. The reddish mixture was stirred for 4 h and then diluted with water and extracted with chloroform. The extracts were dried (Na_2SO_4) and evaporated to give *N'*-thiobenzoylamidine (**6c**). Upon addition of pyrrolidine and piperidine, instead of morpholine, the amidines (**6a,b**) were isolated. The amidines (**6a—c**) which were obtained in *ca.* 80% yield, were identical with authentic samples obtained upon treatment of admixtures of the adducts (**1a—c**) and thioamide (5) with triethylamine.

Acknowledgements

We are grateful to Professor P. Caramella for helpful discussions and the Italian M.P.I. for financial support.

References

1 A. Corsaro, M. Tarantello, and G. Purrello, *Tetrahedron Lett.*, 1981, 3305.
2 A. Corsaro, A. Compagnini, M. Tarantello, S. Barbaro, and G. Purrello, *Synth. Commun.*, 1982, **12**, 865.
3 R. M. Hurd and G. De La Mater, *Chem. Rev.*, 1961, 68.
4 F. Kurzer, *Adv. Heterocycl. Chem.*, 1965, **5**, 123.
5 J. Liebscher and H. Hartmann, *Liebigs Ann. Chem.*, 1977, 1005.
6 J. Goerdeler and H. Porrmann, *Chem. Ber.*, 1962, **95**, 627.
7 J. C. Meslin and H. Quiniou, *Tetrahedron*, 1975, **31**, 3055.
8 A. V. Fokin and A. F. Kolomiets, *Russ. Chem. Rev.*, 1976, **45**, 71.
9 N. Lozac'h and M. Stavaux, *Adv. Heterocycl. Chem.*, 1980, **27**, 220.
10 N. Lozac'h and M. Stavaux, *Adv. Heteorcycl. Chem.*, 1980, **27**, 175.
11 R. A. Olofson, J. M. Landesberg, R. O. Berry, D. Leaver, W. A. H. Robertson, and D. M. McKinnon, *Tetrahedron*, 1966, **22**, 2119.
12 A. Corsaro and G. Purrello, unpublished data.
13 R. J. Niedzielsky, R. S. Drago, and R. L. Middaugh, *J. Am. Chem. Soc.*, 1964, **86**, 1694.
14 D. A. Peak and F. Stanfield, *J. Chem. Soc.*, 1952, 4070.
15 A. W. Hofmann and S. Gabriel, *Chem. Ber.*, 1892, **25**, 1578.
16 L. Knorr, *Liebigs Ann. Chem.*, 1898, **301**, 1.
17 J. V. Braun, *Chem. Ber.*, 1903, **36**, 3524.
18 J. V. Braun and E. Beschke, *Chem. Ber.*, 1906, **39**, 4122.
19 E. Kasztreiner, J. Borsy, and L. Vargha, *Biochem. Pharmacol*, 1962, **11**, 651.
20 L. Turbanti, G. Cerbai, G. Bramati, P. Bianchini, and N. Tellini, *Chim. Ther.*, 1967, **2**, 354 (*Chem. Abstr.*, 1968, **69**, 36048).
21 L. Médar, *Bull. Soc. Chim. Fr.*, 1936, **3**, 1343.

Received 15*th August* 1983; *Paper* 3/1425