BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 40 579—583 (1967)

Structure of Busch's Endo-thiatriazolines[*1]

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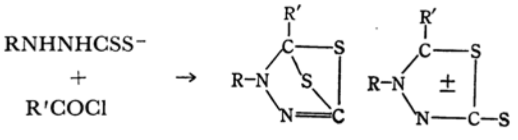
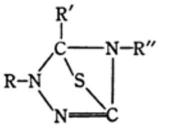
(Received May 26, 1966)

The methods of preparing 2, 4-dihydro-1, 3, 4-thiadiazole-2-thiones are discussed. The structure of the reaction products of these compounds or their methiodides with amines is determined to be 1, 3-dihydro-1, 2, 4-triazole-3-thiones.

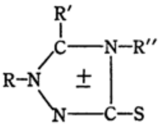
The reaction between dithiocarbazates and acyl chlorides has been extensively investigated by Busch and his collaborators,1) who have given a bridged structure (IA) for the reaction products. In view of the apparent stability of these compounds, Schönberg2) has re-interpreted the results and proposed a resonance-stabilized mono-cyclic structure (IB) for the reaction products. Baker and his collaborators3) later discussed this subject in a slightly modified form; they classified this type of compound in the "meso-ionic" family, of which sydnones are representative.



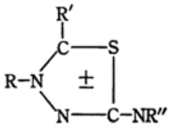
IA IB



IIA



IIB



IIC

When these compounds (IB) or their methiodides are treated with a primary amine, new bicyclic compounds (IIA) are formed, according to Busch *et al.*1e) Chemical common sense would, however, tend to reject this bicyclic structure, IIA, in favor of an alternative, IIB or IIC. Such a possibility has already been suggested by Baker and Ollis4)

[*1] Studies on Meso-ionic Compounds. XXVII. Part XXVI: M. Ohta, K. Yoshida and S. Sato, This Bulletin, **39**, 1269 (1966).

1) a) M. Busch, *Ber.*, **28**, 2635 (1895); b) M. Busch, *J. Prakt. Chem.*, **60**, 25, (1899); c) M. Busch, *ibid.*, **60**, 216, 217, 225 (1899); d) M. Busch, *ibid.*, **67**, 201 (1902); e) M. Busch, W. Kamphausen and S. Schneider, *ibid.*, **67**, 216 (1902); f) M. Busch and S. Schneider, *ibid.*, **67**, 246 (1902); g) M. Busch and E. Blume, *ibid.*, **67**, 257 (1902).

2) A. Schönberg, *J. Chem. Soc.*, **1938**, 824.

3) W. Baker and W. D. Ollis, *ibid.*, **1949**, 307; W. Baker, W. D. Ollis and V. D. Pooles, *ibid.*, **1950**, 1542; W. Baker, W. D. Ollis, A. Phillips and T. Strawford, *ibid.*, **1951**, 289.

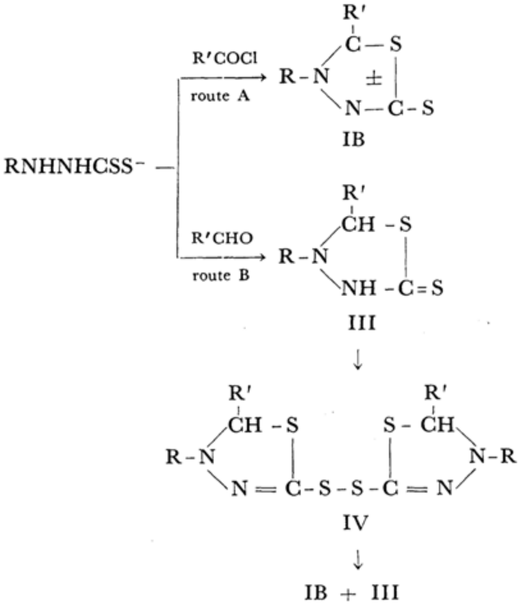
4) W. Baker and W. D. Ollis, *Quart. Revs.*, **11**, 15 (1957).

in their review of meso-ionic compounds. With this type of compound, however, a serious problem arises: which of the two hetero-atoms (*i. e.*, nitrogen and sulfur) is exo to the ring?

The purpose of the present investigation is to elucidate the structure of the products which arise from the reaction of IB and amines. Related to this main purpose is the intention to ascertain the optimum reaction conditions for the preparation of IB and related compounds.

Results and Discussion

There have been two methods[1] for the preparation of compounds IB (2, 4-dihydro-1, 3, 4-thiadiazole-2-thiones); they can schematically be represented as follows:



a) R=Ph, R'=Ph
b) R=Ph, R'=Et
c) R=Ph, R'=2-furyl
d) R=Ph, R'=Me

In order to obtain a sufficient quantity of this type of compound, our first effort was directed toward finding out the optimum conditions for the preparation of the 4, 5-diphenyl derivative (IBa). When potassium *β*-phenyldithiocarbazate was treated with benzoyl chloride in water, the desired compound was indeed obtained, but *N, N'*-dibenzoylphenylhydrazine was also formed in almost an equal amount and the yield (*ca.* 10%) was far from satisfactory. The same by-product was formed when the reaction was carried out in toluene. When ethanol was used as the solvent, an unidentified product with a high melting point was formed, and in tetrahydrofuran, the starting material was recovered unchanged. In the last three reaction media, IBa was not isolated at all. This finding is noteworthy since Kier *et al.*[5] have prepared the 4-phenyl-5-ethyl derivative from potassium *β*-phenyldithiocarbazate and propionyl chloride in toluene, though in only a yield of 5%. When triethylammonium phenyldithiocarbazate was used in place of the potassium salt, *N'*-benzoyl-*N*-phenylhydrazine was obtained as the only isolable product. Recourse was thus had to ammonium phenyldithiocarbazate; in this case, the desired product IBa was formed in 21% yield, together with some *N, N'* - dibenzoylphenylhydrazine.

Since the above-described direct-preparative method was proved ineffective, we considered the indirect method (route B) as an attractive alternative. When ammonium phenyldithiocarbazate was treated with benzaldehyde, 4, 5-diphenyl-1, 3, 4-thiadiazolidine-2-thione (IIIA) was isolated in 42% yield. Starting from propionaldehyde, furfural, and acetaldehyde, the corresponding thiazolidine-2-thiones (IIIb–d) were formed in variable yields, but not from cinnamaldehydes, in which case cinnamaldehyde phenylhydrazone was formed in almost a quantitative yield.

These thiadiazolidinethiones (III) were oxidized by iodine or by ferric chloride to give the disulfides (IV), which, upon pyrolysis, gave the desired products, IB and the thiadiazolidinethiones (III), in good yields. When the pyrolysis of IVa was attempted in chloroform at 80°C for an hour, the starting material was recovered unchanged. However, when it was heated in higher-boiling solvents, pyrolysis took place readily to give the desired product IBa in high yields. In this reaction, as is shown in the diagram, the formation of the meso-ionic compound (IB) is always accompanied by the formation of an equimolar amount of thiadiazolidinethione (III). By the use of dimethylsulfoxide or sulfur as the pyrolysis solvents, we expected that the hydrogenated product (III) could be re-dehydrogenated in these weakly-oxidizing solvents to give the disulfide (IV), which, *in situ*, could be pyrolyzed under the reaction conditions, and that, in repeating this cycle, eventually all the thione (III) could be oxidized and pyrolyzed to give the meso-ionic compound (IB) as the sole reaction product. Such attempts were, however, fruitless.

As has been described earlier, when compound IB are treated with a primary amine, or, better, when they are treated with methyl iodide, to give the methiodides, and when the latter is treated with an amine, new heterocyclic compounds of either structure, IIB or IIC, are formed. Compound II gave another methiodides, VI, when treated with methyl iodide. Two sets of reaction paths, shown in Fig. 1, may be considered.

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[5] L. B. Kier, M. C. Dodd and P. Sapko, *Nature*, **204**, 697 (1964).

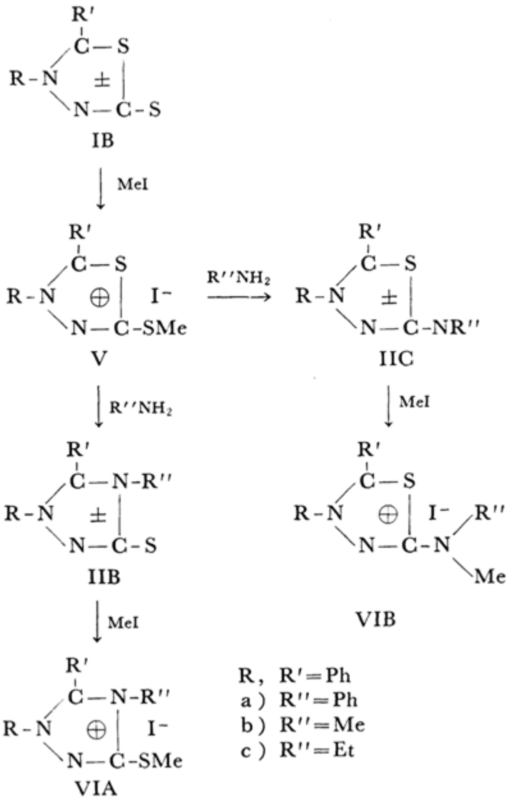
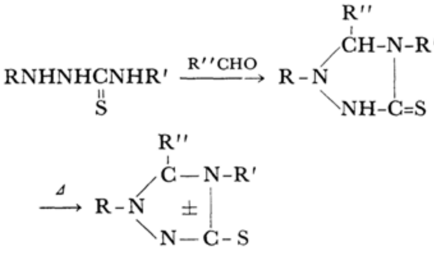


Fig. 1. Possible reaction routes of compounds IB with amines.

The appearance of two NMR peaks of the methyl groups of VIb at 6.24 and 7.20 τ gives support to the structure VIAb. The appearance of the *S*-methyl group of V at 7.14 τ suggests that the 7.20 peak of VIAb is due to the *S*-methyl group. This assignment is further supported by the available NMR data on the *S*-methyl group at 7.5, 7.53, and 6.90 τ of 2-methylthio-4-methylpyridine,⁶⁾ phenyl methyl sulfide⁶⁾ and 3-methylthio-5-phenyl-1, 2-dithiolium perchlorate⁷⁾ respectively, the ring of the last compound being positively charged. The remaining peak, that at 6.24 τ, can then be assigned to the ring *N*-methyl group. The value of the *N*-methyl group of the aromatic ring extends over a wide range,⁶⁾ and difficulties are encountered in the choice of an ideal model compound for comparison. Taking sydnones as a typical meso-ionic compound, the NMR peak of the methyl group of 3-methyl-sydnone⁸⁾ appears at 5.90 τ, while that of *N*-acetyl-3-methylsydnoneimine⁹⁾ is at 5.76 for the base and at 5.52 τ for the hydrochloride. As to the structure of IIb, its NMR peak at 6.33 τ, very close to the value of the ring *N*-methyl group of VIAb, is suggestive of the structure IIBb.¹⁰⁾ Further, a slight shift of this peak to a higher magnetic field than with VIAb is in agreement with the case of the sydnoneimine derivatives. All the compounds IB and IIB show a strong infrared absorption around 1350 cm^{-1}; this band is absent with the methiodies, V and VI; this infrared band may be said to be characteristic of a compound with a thione group.¹¹⁾ From these spectral data, it may be concluded that the structure of II is IIB.

Identical compound, IIBa and b, have been prepared by Busch and his collaborators¹⁴⁾ by heating benzaldehyde with 1, 4-diphenyl- and 1-phenyl-4-methyl - thiosemicarbazide respectively. From the results of the present investigation, it may safely be concluded that all the products formed by the reaction of 1, 4-disubstituted thiosemicarbazides and aldehydes have the structure IIB.



Experimental

All melting points were determined on a micro hot stage, and are not corrected. Infrared spectra were taken on KBr tablets. NMR spectra were taken on a Japan Electron Optics Lab., Model C-60 Spectrometer (60 megacycle) on a deuterochloroform solution, containing tetramethylsilane as an internal standard; they are represented by τ values. All the compounds reported in the literature gave satisfactory elemental analyses. They are not recorded unless there is a considerable discrepancy in the melting points.

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6) "NMR Spectra Catalog," Vols. I and II, Varian Associates, Palo Alto, Calif. (1962, 1963).

7) E. Campaigne and R. D. Hamilton, *J. Org. Chem.*, **29**, 2877 (1964).

8) K. D. Lawson, W. S. Brey, Jr., and L. B. Kier, *J. Am. Chem. Soc.*, **86**, 463 (1964).

9) H. U. Daeniker and J. Druey, *Helv. Chim. Acta*, **45**, 2441 (1962).

10) It is regretable that we could not find any NMR data on *N*-methyl ketimine type compounds.

11) Although this absorption may seem to be in a frequency a little too high for a C=S absorption,¹²⁾ there have been several reports¹³⁾ where the strong absorption in the 1300—1350 cm^{-1} range is assigned to the thione group of five-membered heterocyclic rings. For further examples and discussion, see Ref. 13c.

12) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London (1958); A. R. Katritzky, "Physical Methods in Heterocyclic Chemistry," Vol. II, Academic Press, New York (1963).

13) a) C. Ainsworth, *J. Am. Chem. Soc.*, **78**, 4475 (1956); b) E. Lieber, C. N. Pillai, J. Ramachandran and R. D. Hites, *J. Org. Chem.*, **22**, 1750 (1957); c) E. Lieber, C. N. R. Rao, C. N. Pillai, J. Ramachandran and R. D. Hites, *Can. J. Chem.*, **36**, 801 (1958).

14) M. Busch, E. Opfermann and H. Walter, *Ber.*, **37**, 2318 (1904); M. Busch and H. Holzmann, *ibid.*, **34**, 320 (1901).

TABLE 1. PREPARATION OF 4,5-DIPHENYL-2,4-DIHYDRO-1,3,4-THIADIAZOLE-2-THIONE (IBa) FROM β-PHENYLDITHIOCARBAZATE AND BENZOYL CHLORIDE

Salt	Reaction media, condition	Yield of IBa	Other products
K	Water (20°C; 30°C)	10%	*N*,*N*′-Dibenzoylphenylhydrazine
K	EtOH (20°C; 0°C/K_2CO_3)	—	Unidentified; mp above 330°C
K	THF (room temp./$CaCl_2$; K_2CO_3)	—	Starting material
K	Toluene (60°C)	—	*N*,*N*′-Bibenzoylphenylhydrazine
Et_3NH	Et_3N (room temp.)	—	*N*′-Benzoylphenylhydrazine
NH_4	Water (room temp.)	21%	*N*,*N*′-Dibenzoylphenylhydrazine

TABLE 2. PREPARATION OF 4,5-DISUBSTITUTED 1,3,4-THIAZOLIDINE-2-THIONES (III)

R	Time	Characteristics	mp (reported), °C	Yield, %	IR (C=S) (cm⁻¹)
Ph	4 hr	Yellow amorph.	130 (154—155)[14]	42	
Et	4 hr	Greenish amorph.	129.5—130 (125)[1a]	40	1478
2-Furyl	18 hr	Greenish yellow prism	122—123 (123.5—124.5)**	3.5	1485
PhCH=CH	20 hr	Cinnamaldehyde phenylhydrazone*			

* Sole reaction product. ** E. Taeger and Z. El-Hewehi, *J. Prakt. Chem.*, **[4]18**, 256 (1962)

TABLE 3. PREPARATION OF 2,4-DIHYDRO-1,3,4-THIADIAZOLE-2-THIONES (IB) BY PYROLYSIS OF IV

R	Time min	Yield %	Mp °C	Characteristics	IR (C=S) cm⁻¹	Anal Found/Calcd % C	H	N
Ph	120	100	232—233[d]	Orange yellow prisms[a]	1350			
Et	60	55	193—194	Pale orange plates[b]	1340	54.17 54.05	4.52 4.50	12.58 12.61
2-Furyl	90	80	212--213	Orange yellow silky needles[c]	1330	54.53 55.38	3.21 3.08	10.94 10.77
Me	20	78	223—224[e]	Pale green leaflets[c]	1360	52.19 51.90	3.97 3.85	13.69 13.46

Recrystallized from a) ethylcellosolve; b) *n*-butanol; c) ethanol
Reported mp: d) 231—232°C[1e]; e) 216°C[1a]

4,5-Diphenyl-2,4-dihydro-1,3,4-thiadiazole-2-thione (IBa). Freshly prepared β-phenyldithiocarbazate was dissolved or suspended in the specific reaction medium. Into this mixture under vigorous stirring, there was added an equimolar amount of benzoyl chloride. The reaction mixture was separated by suitable methods and was recrystallized from suitable solvents. The known compounds were identified by elemental analyses and by admixed melting points with authentic specimens. The results are listed in Table 1.

4,5-Disubstituted-1,3,4-thiadiazolidine-2-thiones (III). To a vigorously stirred aqueous solution of ammonium β-phenyldithiocarbazate, there was slowly added a 1.5 molar equivalent of aldehyde at a temperature of about 60°C; the mixture was stirred at the same temperature for a specific period of time. The results are listed in Table 2.

Disulfides (IV). To a solution of 5 g of 4,5-diphenyl-1,3,4-thiadiazolidine-2-thione in 300 m*l* of ethanol, there was added a solution of 3 g of iodine in ethanol; this mixture was then allowed to stand overnight. Water was added to the mixture, and the resulting precipitate was collected to give 5 g of a brownish-yellow powder. Recrystallization from ethanol-ether afforded fine orange needles, mp 122°C; reported mp 138°C.[1a]

Found: C, 61.45; H, 4.10; N, 10.50%. Calcd for $C_{28}H_{22}N_4S_4$: C, 61.99; H, 4.09; N, 10.33%.

Similar results could be obtained when the oxidation was effected with ferric chloride.

The corresponding disulfide (IVd) was similarly prepared in a quantitative yield from IIId, mp 138—140°C, reported mp 140°C.[1a]

Resinous products were formed when IIIb and IIIc were treated with ferric chloride or iodine. These compounds were submitted to the pyrolysis reaction directly, without further purification.

2,4-Dihydro-1,3,4-thiadiazole-2-thiones (IIB) Obtained by the Pyrolysis of IV. Disulfide (IVa) (0.5 g) was heated in variable solvents for two hours. The following results were obtained: *n*-butanol (117°C), Y. 100%; dioxane (101°C), Y. 96%; dimethylsulfoxide (117°C), Y. 96%; Trichlene (114°C), Y. 72%; sulfur (130°C), Y. 80%; chloroform (80°C, one hour), no reaction.

After a solution of disulfide (IV) in *n*-butanol had been heated for a variable period of time, the reaction products were recrystallized from suitable solvents. The thiadiazolidinethione (III) usually separated out when the solvents of recrystallization was allowed to stand for a longer period of time. The results are summarized in Table 3.

1, 4, 5-Triphenyl-1, 3-dihydro-1, 2, 4-triazole-3-one (IIBa). A mixture of 1 g of 4, 5-diphenyl-2, 4-dihydro-1, 3, 4-thiadiazole-2-thione and 1 g of aniline was heated at 155°C for twelve hours. After that period, the evolution of hydrogen sulfide was no longer observed. After cooling, a small amount of acetic acid was added to remove the excess aniline; the resinous product, which soon solidified, was collected and was recrystallized from *n*-butanol to give 0.55 g (47%) of pale yellow needles, mp 317°C, reported mp 316°C.[1e] IR: 1350 cm^{-1}.

5-Methylmercapto-2, 3-diphenyl-1, 3, 4-thiadiazolium Iodide (V). To a suspension of 5 g of 4, 5-diphenyl-2, 4-dihydro-1, 3, 4-thiadiazole-2-thione in 25 m*l* of ethanol, 3 m*l* of methyl iodide was added; this mixture was refluxed for thirty minutes on a water bath. After cooling, the crystals which separated out were collected to give 7 g (90%) of crystals, mp 180—185°C. Reported mp 188°C.[1e] NMR: 2.1—2.6 τ (multiplet; 10H), 7.14 τ (singlet; 3H).

1, 5-Diphenyl-4-methyl-1, 3-dihydro-1, 2, 4-triazole-3-thione (IIBb). A mixture of 0.5 g of 5-methylmercapto-2, 3-diphenyl-1, 3, 4-thiadiazolium iodide, 2 m*l* of ethanol, and 4 m*l* of 30% aqueous methylamine was allowed to stand overnight; the crystals which separated out were then collected and recrystallized from *n*-butanol to give 0.31 g (97%) of pale yellow needles. This substance melted at 280°C on a micro hot stage, but melted at variable temperatures (250—269°C) in a capillary tube, depending on the rate of heating. Reported mp 242—234°C.[1e] IR: 1340 cm^{-1}. NMR: 2.50τ (singlet; 5H), 2.74τ (singlet; 5H), and 6.33τ (singlet; 3H).

Found: C, 67.47; H, 4.98; N, 15.79%. Calcd for $C_{15}H_{13}N_3S$: C, 67.42; H, 4.87; N, 15.73%.

Similarly, with ethylamine, the corresponding 4-ethyl derivative (IIBc) was obtained in 100% yield. Colorless prisms (from ethanol), mp 233—233.5°C; reported mp 232°C.[1e] IR: 1335 cm^{-1}.

1, 5-Diphenyl-4-methyl-3-methylmercapto-1, 2, 4-triazolium Iodide (VIAb). Methyl iodide was added to a suspension of 1, 5-diphenyl-4-methyl-1, 3-dihydro-1, 2, 4-triazole-3-thione in a small amount of ethanol. The whole mass rapidly went into solution. Ether was added to the solution, and the precipitate which separated out was collected and recrystallized from ethanol-ether. Mp 170—170.5°C. NMR: 1.95—2.75 τ (multiplet; 10H), 6.24 τ (singlet; 3H), and 7.20 τ (singlet; 3H).

Found: C, 46.60; H, 4.28; N, 10.50%. Calcd for $C_{16}H_{16}N_3SI$: C, 46.94; H, 3.91; N, 10.27%.

Similarly, from the 4-ethyl derivative (IIBc), the corresponding methiodide (VIAc) was obtained in a quantitative yield, mp 190—191°C.

Found: N, 10.13%. Calcd for $C_{17}H_{18}N_3SI$: N, 9.93%.