Acta Chemica Scandinavica B 34 (1980) 597–602

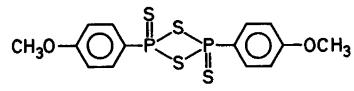
Studies on Organophosphorus Compounds. XXXIV.* Syntheses of 2,3-Dihydro-1,3,4,2-Thiadiazaphospholes and Thiohydrazides

A. A. EL-BARBARY,[a,**] S. SCHEIBYE,[a] S.-O. LAWESSON [a] and H. FRITZ [b]

[a] Department of Organic Chemistry, Chemical Institute University of Aarhus, DK-8000 Aarhus C, Denmark and [b] Ciba-Geigy AG, CH-4002 Basel, Switzerland

N'-Substituted hydrazides, *2*, react with 2,4-bis-(4-methoxyphenyl) - 1,3,2,4 - dithiadiphosphetane - 2,4-disulfide, *1*, in refluxing benzene to give 2,3-dihydro-1,3,4,2-thiadiazaphospholes, *3*; in one case also the thiohydrazide, *4e*, was isolated. Benzohydrazide, *10*, *N'*,*N'*-disubstituted hydrazides, *6*, and 4,5-dihydro-6-phenyl-3(2*H*)pyridazinone, *8*, gave the corresponding thioanalogues after reaction with *1* at 80 °C. 4-Butyl-1,2-diphenyl-3,5-pyrazolidinedione (phenylbutazone), *14*, reacts with *1* under formation of the unexpected 3,3'-dithio-bis(4-butyl-1,2-diphenyl-5-thioxo-3-pyrazoline), *15*. A mechanism for the formation of *3* is suggested.

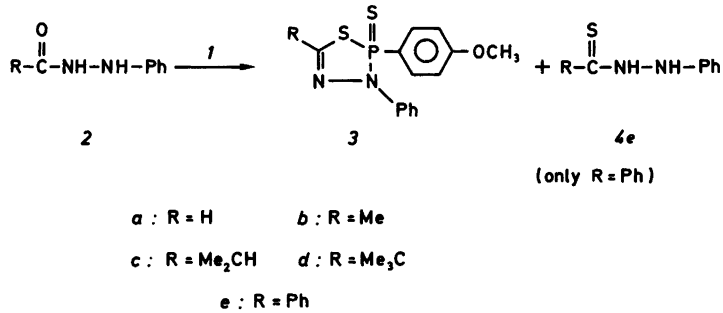
Various methods for the preparation of thiohydrazides are known, *e.g.* the reactions of dithioacids,[1] dithioesters,[2] or sodium dithioformate [3,4] with hydrazines and reactions of *N*-thiobenzoylimidazoles with hydrazines.[5] The preparation of thiohydrazides from hydrazides and P_4S_{10} has been reported in a few cases [6,7] but the yields are poor (see also a review [8] on thiohydrazides). As 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide, *1*, has been shown to be a very efficient thiation reagent for ketones,[9] carboxamides,[10–14] esters and *S*-substituted thioesters,[15,16] lactones,[17] lactams and imides [18] and enaminones,[19] the reactions of *1* with hydrazides have been studied and the results are reported in this paper.



1

RESULTS AND DISCUSSION

N'-Phenyl substituted hydrazides *2a–e* (Scheme 1) were reacted with *1* in refluxing benzene but only in one case (*2e*, R=Ph) was the corresponding thiohydrazide, *4e*, isolated. In all cases a 2,3-



2 *3* *4e* (only R = Ph)

a : R = H *b* : R = Me

c : R = Me_2CH *d* : R = Me_3C

e : R = Ph

Scheme 1. Syntheses of 2,3-dihydro-1,3,4,2-thiadiazaphospholes from hydrazides and *1*.

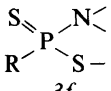
* Part XXXIII. El-Barbary, A. A., Clausen, K. and Lawesson, S.-O. *Tetrahedron 36* (1980). *In press.*

** On leave from Faculty of Science, University of Tanta, Tanta, Egypt.

0302-4369/80/080597-06$02.50

dihydro-1,3,4,2-thiadiazaphosphole, *3*, was produced in a reasonable yield. Reaction times, yields, m.p.'s and analytical data are given in Experimental.

The phosphorus heterocyclic system, *3*, has been reported once[20] but no spectroscopic data were given. The structures, *3a–e*, were confirmed by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, mass spectroscopy and elemental analyses. The ^{31}P NMR, chemical shifts of *3a–e* were found in the region δ 86.9–97.4 which is in accordance with other compounds containing the structure *3f*.[21]



3f

In the ^{1}H NMR spectrum of *3a* (R=H) H-5 absorbs at δ 7.6 and $^3J_{PH}$ is 5.6 Hz. The ^{13}C NMR data of *3a–c* are given in Table 1. The assignments of the chemical shifts can be made with the help of comparison compounds (Anisole derivatives and phenylhydrazine[22]) and are supported by the magnitude of the C,P coupling constants. In an undecoupled spectrum of *3a*, C(5) is distinguished from C(10) by its large C,H coupling constant.

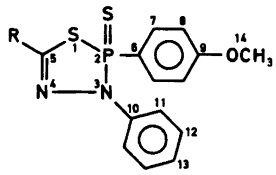
Comparing the carbon atoms C(5) in *3a–c* the same conclusion can be reached as the chemical shift value of C(5) increases with substitution whereas C(10) is unaffected. It is noted that $^4J_{PC(16)} = 2$ Hz in *3c* but no $^3J_{PC(15)}$ is observed.

Concerning the mechanism for the formation of *3*, different possibilities exist: As a thiohydrazide was isolated in one case and as treatment of *4e* with *1* gave *3e* quantitatively, reaction path A in Scheme 2 is suggested. Possibly the thiohydrazide reacts through the thiol form as has been proposed recently.[37]

The last step is supported by the fact that salts of the type R–P(S)(NHR')S$^-$ $^+$NH$_3$R' lose H_2S upon heating to 140 °C yielding the corresponding diamides.[23] An alternative mechanism (B in Scheme 2) is an attack of the nucleophilic *N'* of *2* on *1* which gives *5*. Subsequent ring closure and elimination of water gives *3*.

4-Methoxy-*N'*-methyl-N'-phenylbenzohydrazide, *6*, unable to give a phosphorus heterocycle, was reacted with *1* to give *7* in a quantitative yield and similarly *8* was transformed into *9*.

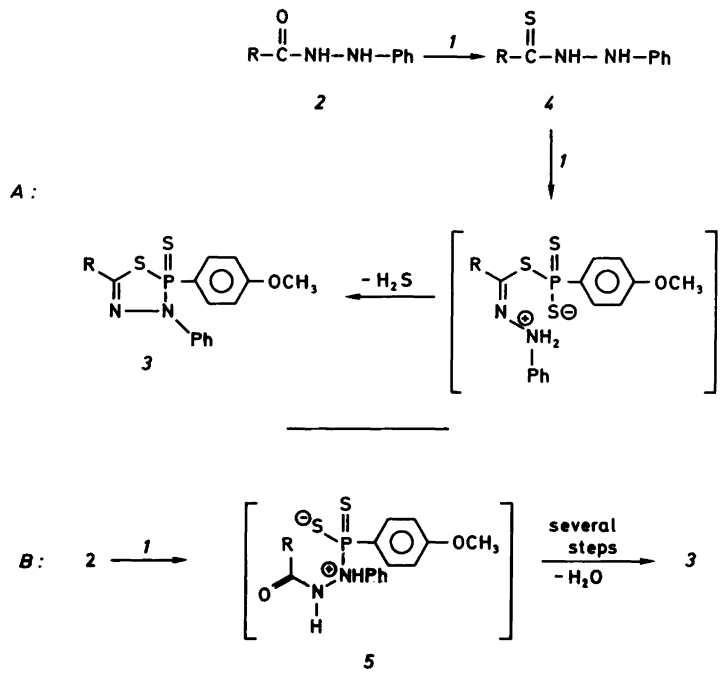
Table 1. ^{13}C NMR data of 2,3-dihydro-1,3,4,2-thiadiazaphospholes ($CDCl_3$).



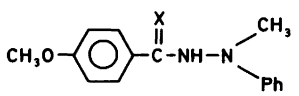
3

a: R = H
b: R = $\overset{15}{CH_3}$
c: R = $\overset{15}{CH}(\overset{16}{CH_3})_2$

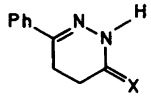
	δ			$\lvert J_{PC}\rvert$ (Hz)		
C	*3a*	*3b*	*3c*	*3a*	*3b*	*3c*
5	131.0	141.4	151.6	4.1	4.8	5.0
6	125.0	125.7	125.9	113.7	112.4	111.4
7	134.6	134.6	134.5	15.6	15.7	15.6
8	114.1	114.1	114.1	16.9	16.5	16.8
9	163.3	163.4	163.4	3.4	3.4	3.4
10	139.7	140.3	140.6	7.4	8.2	7.4
11	120.0	120.1	119.6	3.2	3.4	2.5
12	128.6	128.7	128.7	0	0	0
13	124.5	124.1	123.9	0	0	0
14	55.3	55.5	55.5	0	0	0
15	–	19.9	34.0	–	0	0
16	–	–	21.2	–	–	2.0



Scheme 2. Reaction paths for the formation of 2,3-dihydro-1,3,4,2-thiadiazaphospholes, *3*.



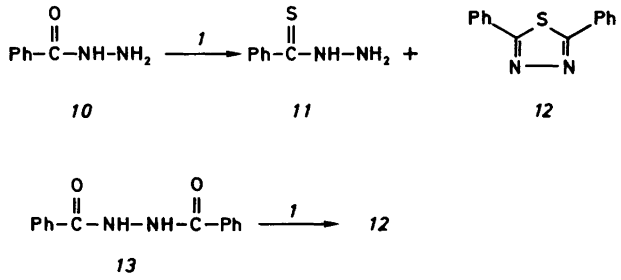
6: X = O
7: X = S



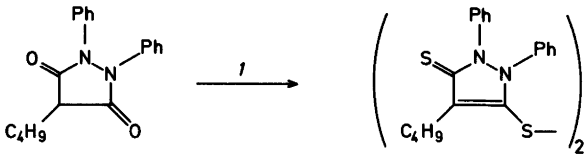
8: X = O
9: X = S

The NMR spectra of *7* show signals for two isomers in a ratio of 5.5:1, presumably the *Z* and *E* isomer with respect to the C–N bond.[24] From the spectral data no conclusion could be reached as to the preferred conformation around the N–N bond. The protons of the $N-CH_3$ group appear as two singlets at 2.86 (minor) and 3.18 ppm, and the corresponding signals in the ^{13}C spectrum are at 40.3 and 38.7 ppm. The reaction between *10* and *1* leads to *11* in 20 % yield and also to 2,5-diphenyl-1,3,4-thiadiazole, *12*, in a 9 % yield (Scheme 3).

The formation of *12* from *10* would imply an acylation or thioacylation on *N'* of *10* or *11*; it is noted that 1,2-dibenzoylhydrazine, *13*, gives *12* after reaction with P_4S_{10} [25,26] or *1*. When 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione (phenylbutazone), *14*, was allowed to react with *1* at 80 °C



Scheme 3. Thiation of benzohydrazide and 1,2-dibenzoylhydrazine.



14 *15*

for 3 h, 3,3'-dithio-bis(4-butyl-1,2-diphenyl-5-thioxo-3-pyrazoline), *15*, was isolated in 85 % yield.

The structure of *15* was determined from an X-ray crystallographic investigation.[38] The mass spectrum obtained with an inlet temperature of 160 °C showed *m/e* 340, which corresponds to ($\frac{1}{2}$ M + 1). With a probe temperature of 250 °C, M (*m/e* 678, <1 %) is detected. The noise decoupled ^{13}C spectrum of *15* shows 15 peaks of which 8 can be assigned to two nonequivalent phenyl groups. C(5) is found at δ 175.3 which is anomalous for a thiocarbonyl carbon.[10,12] C(3) and C(4) absorb at δ 142.1 and 133.3, respectively. Acylation of 15 gives $C_{21}H_{22}N_2OS_2$, *16*, which will be dealt with in coming publications.

CONCLUSION

The method described for obtaining 2,3-dihydro-1,3,4,2-thiadiazaphospholes is advantageous as the only other method for preparing compounds of this type gives mixtures of products and low yields.

EXPERIMENTAL

^1H, ^{13}C and ^{31}P NMR spectra, IR, UV and mass spectra were obtained as described earlier.[17,18] Elemental analyses were carried out by Novo Microanalytical Laboratory, Novo Industri A/S, Novo Allé, DK-2880 Bagsvaerd, supervised by Dr. R. E. Amsler. Silica gel 60 (Merck) was used for column chromatography. The b.p. of the light petroleum used was below 45 °C; m.p.'s are uncorrected.

Starting materials were prepared by known methods as follows: *1*,[9] *2a*,[3] *2b*,[27] *2c*,[28] *2d*,[29] *2e*,[30] *6*,[31] *8*,[32] *10*,[33] *13*.[34] *14* was kindly placed at our disposal by Ciba-Geigy AG, Basel, Switzerland.

General procedure for the reaction of 2a – e, 6, 8, *and* 10 *with* 1. Starting compound (10.0 mmol) and 4.04 g (10.0 mmol) of *1* were heated in 10 ml of anhydrous benzene with stirring until no more of the starting material could be detected (TLC). After cooling to room temperature the excess of *1* was filtered off. Then the reaction mixture was evaporated on silica gel under reduced pressure and applied to a silica gel column using ether – light petroleum as eluent. The reaction conditions (temperature/°C for a period of *x* h), and the physical and analytical data are given below.

Compound 3a. 25 °C, 12 h. Yield 1.15 g (36 %), m.p. 89 °C. Anal. $C_{14}H_{13}N_2OPS_2$: C, H, N, P, S. MS [*m/e* (% rel. int.)]: 320 (100, M), 232 (86), 171 (72). ^1H NMR ($CDCl_3$): δ 3.9 (3 H, s), 6.5 – 7.6 (10 H, m), 7.6 (1 H, d, J_{PH} 5.6 Hz). ^{31}P NMR ($CDCl_3$): δ 86.9.

Compound 3b. 80 °C, 10 h. Yield 3.24 g (97 %), m.p. 133 °C. Anal. $C_{15}H_{15}N_2OPS_2$: C, H, N, P. MS [*m/e* (% rel. int.)]: 334 (100, M), 284 (61), 256 (100), 132 (81), 129 (100). ^1H NMR ($CDCl_3$): δ 2.41 (3 H, d, J_{PH} 2 Hz), 3.88 (3 H, s), 6.9 – 7.4 (7 H, m), 8.08 (2 H, dd, J_{PH} 15 Hz, J_{HH} 9 Hz). ^{31}P NMR ($CDCl_3$): δ 97.4.

Compound 3c. 80 °C, 12 h. Yield 2.35 g (65 %), m.p. 80 °C. Anal. $C_{17}H_{19}N_2OPS_2$: C, H, N, P. MS [*m/e* (% rel. int.)]: 362 (100, M), 160 (74). ^1H NMR ($CDCl_3$): δ 1.33 (6 H, d, J_{HH} 7 Hz), 2.95 (1 H, br. q, J_{HH} 7 Hz), 3.82 (3 H, s), 6.8 – 7.3 (7 H, m), 8.05 (2 H, dd, J_{PH} 15 Hz, J_{HH} 9 Hz). ^{31}P NMR ($CDCl_3$): δ 91.4.

Compound 3d. 80 °C, 8 h. Yield 3.76 g (100 %), m.p. 104 °C. Anal. $C_{18}H_{21}N_2OPS_2$: C, H, N, P, S. MS [*m/e* (% rel. int.)]: 376 (55, M), 248 (18), 233 (100), 174 (47). ^1H NMR ($CDCl_3$): δ 1.4 (9 H, s), 3.8 (3 H, s), 6.8 – 7.4 (7 H, m), 8.01 (2 H, dd, J_{PH} 15 Hz, J_{HH} 9 Hz). ^{31}P NMR ($CDCl_3$): δ 92.7.

Compound 3e. 80 °C, 1.5 h. Yield 1.58 g (40 %), m.p. 114 °C. Anal. $C_{20}H_{17}N_2OPS_2$: C, H, N, P, S. MS [*m/e* (% rel. int.)]: 396 (100, M), 194 (86). ^1H NMR ($CDCl_3$): δ 3.8 (3 H, s), 6.8 – 8.2 (14 H, m). ^{31}P NMR ($CDCl_3$): δ 92.5.

Compound 4e. 80 °C, 1.5 h. Yield 0.68 g (24 %), m.p. 83 °C.[35]

Compound 7. 80 °C, 0.75 h. Yield 2.70 g (100 %), m.p. 116 °C. Anal. $C_{15}H_{16}N_2OS$: C, H, N, S. MS [*m/e* (% rel. int.)]: 272 (27, M), 167 (54), 151 (100). ^1H NMR ($CDCl_3$): δ 2.86 and 3.18 (3 H, two s, N – CH_3 of two conformers), 3.80 (3 H, s), 6.5 – 7.9 (9 H, m), 9.08 (1 H, br. s).

Compound 9. 80 °C, 1.75 h. Yield 1.87 g (100 %), m.p. 160 °C. Anal. $C_{10}H_{10}N_2S$: C, H, N, S. MS [*m/e* (% rel. int.)]: 190 (100, M), 130 (12), 103 (18), 77 (21). ^1H NMR (DMSO-d_6): δ 2.78 – 3.10 (4 H, m), 7.1 – 7.9 (5 H, m), 10.57 (1 H, br. s).

Compound 11. Solvent: toluene 110 °C, 3 h. Yield 0.30 g (20 %), m.p. 71 °C.[2]

Compound 12. Solvent: toluene, 110 °C, 3 h. Yield 0.22 g (9 %), m.p. 140 °C.[36]

Reaction of 4e *with* 1. 0.11 g (0.5 mmol) of *4e* and 0.20 g (0.5 mmol) of *1* were refluxed with stirring in 10 ml of anhydrous benzene for 6 h. Working up as above. Yield: 0.1 g (85 %) of *3e*. M.p. and mixed m.p. with an authentic sample 114 °C.

Reaction of 13 *with* 1. The genral procedure was followed with the following exceptions: 8.08 g (20.0 mmol) of *1* was used instead of 4.04 g (10.0 mmol). 80 °C, 8 h. Yield 2.15 g *12* (91 %).

Reaction of 14 *with* 1. As above. 80 °C, 3 h. Yield 2.89 g (85 %), *15*, m.p. 139–141 °C. Anal. $C_{38}H_{38}N_4S_4$: C, H, N, S.

Compound 15. MS [*m/e* (% rel. int.)]: 340 (70, M), 307 (100), 86 (100), 84 (95). ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.98 (3 H, t, J_{HH} 7.0 Hz), 1.43 (2 H, m), 1.72 (2 H, m), 2.75 (2 H, t, J_{HH} 7.5 Hz), 6.84 (2 H, m, aromatic *ortho* protons), 7.24–7.37 (8 H, m, aromatic). IR (film): 3060 (m), 2940 (m), 2880 (m), 2220 (w), 1600 (s) cm^{-1}. UV (EtOH) [nm (log ε)]: 222 (4.21), 307 (3.91).

Acetylation of 15. 0.68 g (2.0 mmol) of *15* and 0.21 g (2.1 mmol) of triethylamine were dissolved in 4 ml of CH_2Cl_2. 0.16 (2.0 mmol) of acetyl chloride was added drop by drop to the stirred reaction mixture. After reflux for 30 min the reaction mixture was evaporated on silica gel and applied to a column using 75 % ether–light petroleum (v/v) as eluent. Yield 0.38 g (50 %) of compound *16*. 0.28 g (41 %) of the starting material was regenerated.

Compound 16. M.p. 141 °C (ether). MS [*m/e* (% rel. int.)]: 382 (58, M), 339 (100), 307 (72). ^{1}H NMR ($CDCl_3$): δ 0.93 (3 H, t, J_{HH} 6.9 Hz), 1.12–2.00 (4 H, m), 2.28 (3 H, s), 2.70 (2 H, t, J_{HH} 7.3 Hz), 6.83–7.50 (10 H, m). IR ($CHCl_3$): 2940 (s), 1740 (s), 1600 (m). UV (EtOH) [nm (log ε)]: 228 (5.64), 350 (5.46). Anal. $C_{21}H_{22}N_2OS_2$: C, H, N, S.

Acknowledgement. Thanks are expressed to DANIDA for a grant to one of us (A.A.E.-B.).

REFERENCES

1. Jensen, K. A. and Jensen, C. L. *Acta Chem. Scand.* 6 (1952) 957.
2. Holmberg, B. *Ark. Kemi Mineral. Geol. A 17* (1944) No. 23.
3. Baker, W., Ollis, W. D. and Poole, V. D. *J. Chem. Soc.* (1950) 3389.
4. Sato, T. and Ohta, M. *Bull. Chem. Soc. Jpn.* 27 (1954) 624.
5. Walter, W. and Radke, M. *Justus Liebigs Ann. Chem. 739* (1970) 201.
6. Profft, E., Schneider, F. and Beyer, H. *J. Prakt. Chem. 2* (1955) 147.
7. Jensen, K. A. and Pedersen, C. *Acta Chem. Scand. 15* (1961) 1097.
8. Walter, W. and Reubke, K. J. In Zabicky, J., Ed., *The Chemistry of Amides*, Interscience, London 1970, p. 477.
9. Pedersen, B. S., Scheibye, S., Nilsson, N. H. and Lawesson, S.-O. *Bull. Soc. Chim. Belg. 87* (1978) 223.
10. Scheibye, S., Pedersen, B. S. and Lawesson, S.-O. *Bull. Soc. Chim. Belg. 87* (1978) 229.
11. Scheibye, S., Pedersen, B. S. and Lawesson, S.-O. *Bull. Soc. Chim. Belg. 87* (1978) 299.
12. Fritz, H., Hug, P., Lawesson, S.-O., Logemann, E., Pedersen, B. S., Sauter, H., Scheibye, S. and Winkler, T. *Bull. Soc. Chim. Belg. 87* (1978) 525.
13. Clausen, K., Pedersen, B. S., Scheibye, S., Lawesson, S.-O. and Bowie, J. H. *Org. Mass Spectrom. 14* (1979) 101.
14. Clausen, K., Pedersen, B. S., Scheibye, S., Lawesson, S.-O. and Bowie, J. H. *Int. J. Mass Spectrom. Ion Phys. 29* (1979) 223.
15. Pedersen, B. S., Scheibye, S., Clausen, K. and Lawesson, S.-O. *Bull. Soc. Chim. Belg. 87* (1978) 293.
16. Pedersen, B. S. and Lawesson, S.-O. *Tetrahedron 35* (1979) 2433.
17. Scheibye, S., Kristensen, J. and Lawesson, S.-O. *Tetrahedron 35* (1979) 1339.
18. Shabana, R., Scheibye, S., Clausen, K., Olesen, S. O. and Lawesson, S.-O. *Nouv. J. Chim. 4* (1980) 47.
19. Shabana, R., Rasmussen, J. B., Olesen, S. O. and Lawesson, S.-O. *Tetrahedron 36* (1980) *In press.*
20. Italinskaya, T. L., Shvetsov-Shilovskii, N. I., Khludova, A. I. and Melńikov, N. N. *J. Gen. Chem. USSR* (1971) 1980; *Chem. Abstr. 76* (1972) 46143w.
21. Newallis, P. E. In Mark, V., Dungan, C. H., Crutchfield, M. M. and van Wazer, J. R., Eds., *Topics in Phosphorus Chemistry*, Interscience, New York 1967, Vol. 5, p. 374.
22. Johnson, L. F. and Jankowski, W. C. *Carbon-13 NMR Spectra*, Wiley-Interscience, New York 1972.
23. Clausen, K., El-Barbary, A. A. and Lawesson, S.-O. *Tetrahedron 36* (1980). *In press.*
24. Daunis, J., Follet, M. and Gelize, M. *Recl. Trav. Chim. Pays-Bas 98* (1979) 503.
25. Jensen, K. A. and Pedersen, C. *Acta Chem. Scand. 15* (1961) 1124.
26. Eilingsfeld, H. *Chem. Ber 98* (1965) 1308.
27. Alphen, J. v. *Recl. Trav. Chim. Pays-Bas 43* (1924) 823.
28. Jacobson, M. and Acree, F., Jr. *J. Am. Chem. Soc, 67* (1945) 1621.
29. Biquard, D. and Grammaticakis, P. *Bull. Soc. Chim. Fr. 6* (1939) 1599.
30. Autenrieth, W. and Thomae, G. *Ber. Dtsch. Chem. Ges. 57* (1924) 423.

31. Bamberger, E. and Pemsel, W. *Ber. Dtsch. Chem. Ges. 36* (1903) 359.
32. Elkaschef, M. A. F., Mokhtar, K. M. and Abdel-Moti, F. M. *Indian J. Chem. 7* (1969) 1098.
33. Naegeli, C. and Stefanovitsch, G. *Helv. Chim. Acta 11* (1928) 609.
34. Frey, P. R. and Gilbert, E. C. *J. Am. Chem. Soc. 59* (1937) 1344.
35. Bock, H., Baltin, E. and Kroner, J. *Chem. Ber. 99* (1966) 3337.
36. Holmberg, B. *Ark. Kemi 9* (1956) 65.
37. Heindel, N. D., Friedrich, G. and Tsai, M. C. *J. Heterocycl. Chem. 17* (1980) 191.
38. *To be published.*

Received March 31, 1980.