A SIMPLE SYNTHESIS OF 4-THIAZOLIDINONES, TETRAHYDRO-1,3-THIAZIN-4-ONE AND HEXAHYDRO-1,3-THIAZEPIN-4-ONES FROM AMIDE-THIOLS (STUDIES ON THE SYNTHESES OF HETEROCYCLIC COMPOUNDS 749[1])

Tetsuji Kametani*

Pharmaceutical Institute, Tohoku University,

Aobayama, Sendai 980, Japan

Kazuo Kigasawa, Mineharu Hiiragi, Nagatoshi Wagatsuma,

Toshitaka Kohagizawa, and Hitoshi Inoue

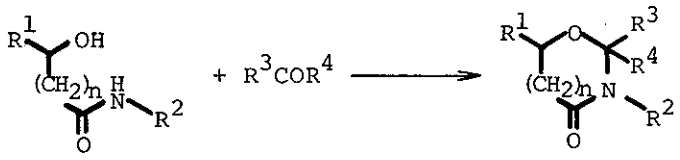
Research Laboratories, Grelan Pharmaceutical Co., Ltd.,

Sakurashinmachi, Setagaya-ku, Tokyo, Japan

Acid-catalyzed cyclisation reaction of the secondary amides (3 ∿ 10) possessing a mercapto group at α-, β- or γ-position with aldehydes gave some novel 4-thiazolidinones (11 ∿ 14), tetrahydro-1,3-thiazin-4-ones (15 ∿ 21), and hexahydro-1,3-thiazepin-4-ones (22 and 23), and the reduction of the cyclisation products 12, 16 and 23 with lithium aluminium hydride afforded thiazolidine (26), tetrahydro-1,3-thiazine (27), and hexahydro-1,3-thiazepine (28), respectively.

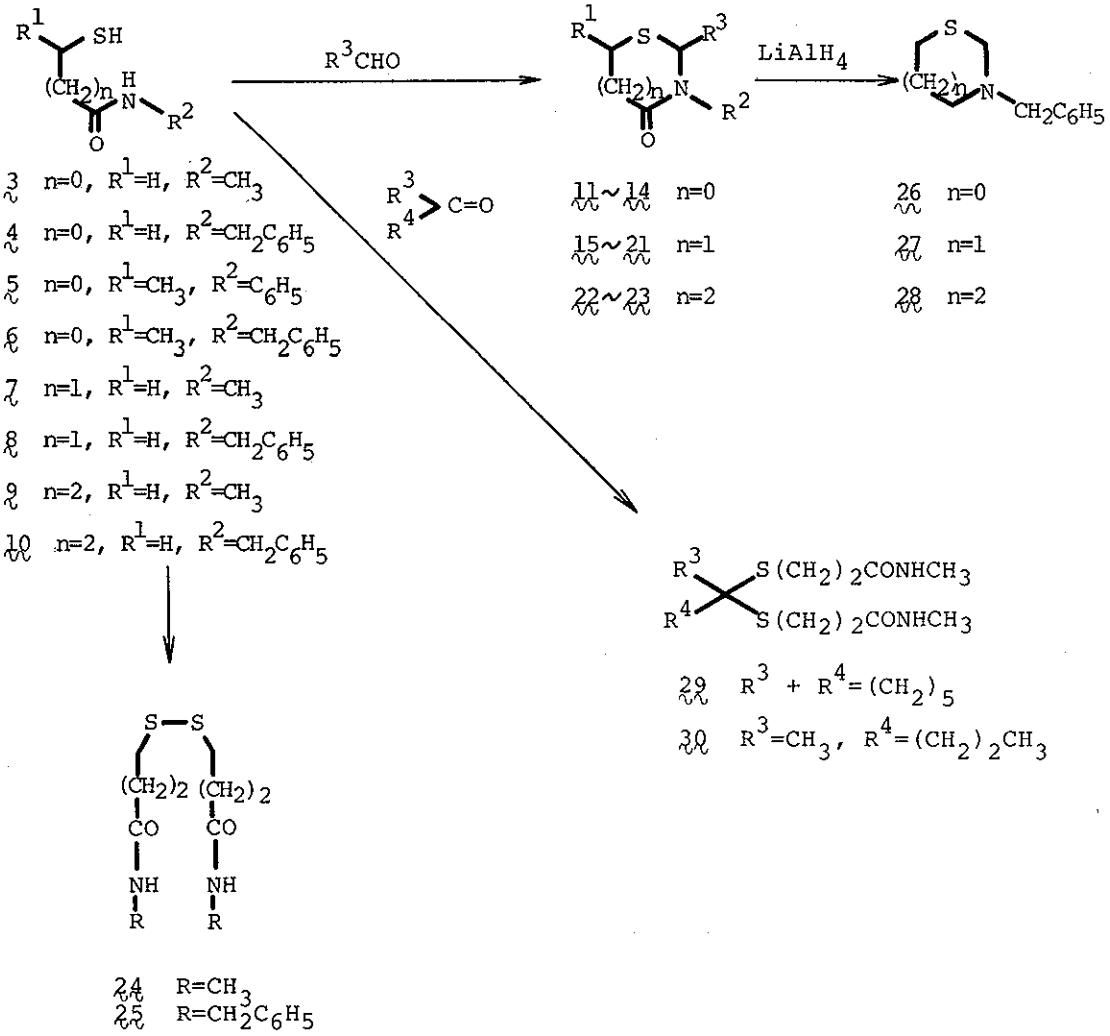
We have previously reported[2∿6] that the secondary amides possessing a hydroxyl group at α-,β- or γ-position (1) (n=0,1,2) reacted with various carbonyl compounds in the presence of acid

catalyst to give cyclisation products (2) (n=0,1,2).



1 2

As an extension of this work, we have investigated a cyclisation



reaction of the secondary amides (3 ~ 10), possessing a mercapto group at α,β or γ-positions, with carbonyl compounds. Here we wish to report our successful result, which provides a facile synthetic route to some novel 4-thiazolidinones (11 ~ 14), tetrahydro-1,3-thiazin-4-ones (15 ~ 21), and hexahydro-1,3-thiazepin-4-ones (22 and 23).

The starting amide-thiols (3 ~ 10) were prepared by a condensation of amines with mercapto-carboxylic acid ester or γ-thiobutyrolactone, and were used in next reaction without isolation for the easy formation of the disulphides (24 and 25) by air oxidation.

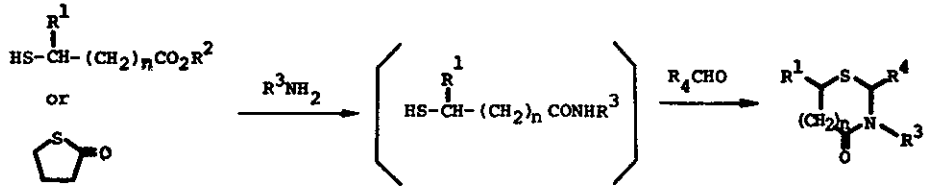
The cyclisation reaction was performed by refluxing the amide-thiols with carbonyl compounds in benzene or xylene in the presence of p-toluenesulphonic acid.

When the amide-thiols (3 ~ 10) were reacted with formaldehyde, the cyclisation reaction was proceeded smoothly and gave the thiazolidinones (11 ~ 14), tetrahydro-1,3-thiazin-4-ones (15 and 16), and hexahydro-1,3-thiazepin-4-ones (22 and 23). Furthermore the reaction of the β-mercaptopropionamides (7 and 8) with paraldehyde, benzaldehyde, capronaldehyde, 2-pentanone or cyclohexanone was examined. In these carbonyl compounds, the aldehydes were reacted with the propionamides (7 ~ 8) to form the 2-substituted thiazin-4-ones (17 ~ 21), but a reaction of ketones with N-methyl-β-mercapto-propionamide (7) gave only the unexpected mercaptals (29 and 30).

These results were summarized in Table I. In general, the reaction of amide-thiols with carbonyl compounds has completed in shorter time than that of amide-alcohols.

The structures of these compounds were confirmed by spectral data and elemental analyses as shown in Table I and II.

Table I. The Cyclization Reaction of the Secondary Amides Possessing a Mercapto Group at α-, β - or γ-Position with aldehydes.



Compd No.	n	R^1	R^2	R^3	R^4	Reaction solv.[a]	Conditions Refluxing Time (h)	Yield(%)	b.p. (mmHg)or m.p./Recryst. Solvent (°C)	Formula	Anal. Calcd. C	H	N
11	0	H	CH_3	H	CH_3	A	3	37.4	68-70 (1.1)	C_4H_7NOS	41.00 (41.30)	6.02 (6.10)	11.96 (11.89)
12	0	H	$CH_2C_6H_5$	H	C_2H_5	B	6	73.5	135-137(1.2)	$C_{10}H_{11}NOS$	62.15 (62.44)	5.73 (5.77)	7.24 (6.72)
13	0	CH_3	C_6H_5	H	CH_3	B	4	11.8	133-135/benzene-hexane	$C_{10}H_{11}NOS$	61.15 (61.82)	5.73 (5.68)	7.24 (7.06)
14	0	CH_3	$CH_2C_6H_5$	H	CH_3	B	4	56.2	142-144(1.5)	$C_{11}H_{13}NOS$	63.72 (63.95)	6.32 (6.28)	6.76 (6.57)
15	1	H	CH_3	H	CH_3	B	2	39.0	86-88 (0.7)	C_5H_9NOS			10.68 (10.47)
16	1	H	$CH_2C_6H_5$	H	CH_3	B	2	52.2	123-125(0.6)	$C_{11}H_{13}NOS$	63.72 (63.73)	6.32 (6.25)	6.76 (6.81)
17	1	H	CH_3	CH_3	CH_3	B	5	76.1	84-87 (0.5)	$C_6H_{11}NOS$	49.62 (49.18)	7.64 (7.85)	9.65 (9.59)
18	1	H	CH_3	C_6H_5	CH_3	B	5	31.3	90-92/benzene-hexane	$C_{11}H_{13}NOS$			
19	1	H	$CH_2C_6H_5$	CH_3	CH_3	B	5	40.8	120-121(4.0)	$C_{12}H_{15}NOS$	65.12 (65.24)	6.83 (6.74)	6.33 (6.39)
20	1	H	$CH_2C_6H_5$	$(CH_2)_4CH_3$	CH_3	B	5	21.0	155-157(0.35)	$C_{16}H_{23}NOS$			5.05 (4.83)
21	1	H	$CH_2C_6H_5$	C_6H_5	CH_3	B	6	12.2	158-160(0.6)	$C_{17}H_{17}NOS$			4.94 (4.89)
22	2	H	CH_3	H		A	3	26.4	93-95/benzene-ether	$C_6H_{11}NOS$	49.62 (49.57)	7.63 (7.65)	9.65 (9.59)
23	2	H	$CH_2C_6H_5$	H		A	3	57.3	89-90/benzene-hexane	$C_{12}H_{15}NOS$	65.12 (65.34)	6.83 (6.88)	6.33 (6.32)

a) A=benzene, B=xylene

Table II Spectral Data of the Cyclisation Products

Compd. No.	IR $\nu_{max.}$ ($CHCl_3$)	NMR($CDCl_3$) δ
11	1670	2.97 (3H, s, N-C<u>H</u>$_3$), 3.58 (2H, t, <u>J</u> 1 Hz, 5-H), 4.44 (2H, t, <u>J</u> 1 Hz, 2-H)
12	1670	3.60 (2H, t, <u>J</u> 1 Hz, 5-H), 4.25 (2H, t, <u>J</u> 1 Hz, 2-H), 4.53 (2H, s, N-C<u>H</u>$_2$C$_6$H$_5$), 7.26 (5H, s, aromatic protons)
13	1670	1.62 (3H, d, <u>J</u> 7 Hz, CHC<u>H</u>$_3$), 3.91 (1H, q, <u>J</u> 7 Hz, C<u>H</u>CH$_3$), 4.67, 4.81 (2H, each d, <u>J</u> 9 Hz, 2-H), 6.91-7.57 (5H, m, aromatic protons)
14	1670	1.51 (3H, d, <u>J</u> 7 Hz, CHC<u>H</u>$_3$), 3.78 (1H, q, <u>J</u> 7 Hz, C<u>H</u>CH$_3$), 4.11 (2H, s, N-C<u>H</u>$_2$C$_6$H$_5$), 4.47 (2H, s, 2-H), 7.20 (5H, s, aromatic protons)
15	1630 , 1650	2.79 (2H, t, <u>J</u> 5 Hz, 5-H or 6-H), 2.87 (2H, t, <u>J</u> 5 Hz, 5-H or 6-H), 3.02 (3H, s, N-C<u>H</u>$_3$), 4.29 (2H, s, 2-H)
16	1630 , 1650	2.91 (2H, t, <u>J</u> 4 Hz, 5-H or 6-H), 2.95 (2H, t, <u>J</u> 4 Hz, 5-H or 6-H), 4.28 (2H, s, N-C<u>H</u>$_2$C$_6$H$_5$), 4.73 (2H, s, 2-H), 7.34 (5H, s, aromatic protons)
17	1630	1.63 (3H, d, <u>J</u> 7 Hz, CHC<u>H</u>$_3$), 2.56-3.32 (4H, m, 5-H and 6-H), 3.02 (3H, s, N-C<u>H</u>$_3$), 4.51 (1H, q, <u>J</u> 7 Hz, C<u>H</u>CH$_3$)
18	1625	2.61-2.89 (4H, m, 5-H and 6-H), 2.95 (3H, s, N-C<u>H</u>$_3$), 5.49 (1H, s, C<u>H</u>C$_6$H$_5$), 7.32 (5H, s, aromatic protons)
19	1630	1.56 (3H, d, <u>J</u> 7 Hz, CHC<u>H</u>$_3$), 2.48-3.34 (4H, m, 5-H and 6-H), 4.12, 5.32 (2H, each d, <u>J</u> 15 Hz, N-C<u>H</u>$_2$C$_6$H$_5$), 4.45 (1H, q, <u>J</u> 7 Hz, C<u>H</u>CH$_3$), 7.28 (5H, s, aromatic protons)
20	1630	0.61-2.24 (11H, m, -(C<u>H</u>$_2$)$_4$C<u>H</u>$_3$), 2.48-3.52 (4H, m, 5-H and 6-H), 4.05, 5.43 (2H, each d, <u>J</u> 15 Hz, N-C<u>H</u>$_2$C$_6$H$_5$), 4.14 (1H, t, <u>J</u> 7 Hz, C<u>H</u>(CH$_2$)$_4$CH$_3$), 7.31 (5H, s, aromatic protons)
21	1635	2.30-3.14 (4H, m, 5-H and 6-H), 3.50, 5.71 (2H, each d, <u>J</u> 15 Hz, N-C<u>H</u>$_2$C$_6$H$_5$), 5.38 (1H, s, C<u>H</u>C$_6$H$_5$) 7.21, 7.25 (10H, each s, aromatic protons)
22	1630	1.79-2.25 (2H, m, 6-H), 2.60-2.99 (4H, m, 5-H and 7-H), 2.99 (3H, s, N-C<u>H</u>$_3$), 4.47 (2H, s, 2-H)
23	1630	1.88-2.25 (2H, m, 6-H), 2.70-3.02 (4H, m, 5-H and 7-H), 4.38 (2H, s, N-C<u>H</u>$_2$C$_6$H$_5$), 4.65 (2H, s, 2-H), 7.28 (5H, s, aromatic protons)

In addition, the reduction of the cyclisation products (12, 16, and 23) was carried out with lithium aluminium hydride to give 3-benzylthiazolidine (26), 3-benzyl-tetrahydro-1,3-thiazine (27), and 3-benzyl-hexahydro-1,3-thiazepine (28), respectively. The structures of these products were verified by spectral data and elemental analyses. The reductants showed no carbonyl absorption in i.r. spectrum and the n.m.r. spectral data were consistent with assigned structures.

There are a few reports[7] on a reaction of the amides possessing a mercapto group with carbonyl compounds, but the amides were limited to primary ones. Thus we could demonstrate the examples of the cyclisation reaction of the secondary amides having a mercapto group at α-,β- or γ-position with aldehydes to give 4-thiazolidinones, 1,3-thiazin-4-ones and 1,3-thiazepin-4-ones.

EXPERIMENTAL

M.p.s were determined on a Yanagimoto hot-stage apparatus. I.r. and n.m.r. spectra were recorded with Hitachi-215 spectrophotometer and JNM-PMX-60 spectrometer (tetramethylsilane as internal standard). The starting amide-thiols (3 ~ 10) were prepared by a condensation of ethyl thioglycolate, methyl thiolactate[8], methyl β-mercaptopropionate[9] or γ-thiobutyrolactone[10] with methylamine (40 % solution in methanol), benzylamine or aniline with stirring at room temperature, and were allowed to react without isolation, with the exception of 4 which was stable enough for characterisation or storage, because the exposure of 9 and 10 to air caused air oxidation and gave the disulphides (24 and 25).

Therefore, most of the structures of the thiol-smides were confirmed as the disulphides by the comparison of the physical constants with the references[11~14] or from the spectral data and elemental analyses for the novel ones.

N-Benzylthioglycolamide (4). m.p. 152 - 153°(from ethanol) (Found: C, 59.80; H, 5.63; N, 7.68; S, 18.01. $C_9H_{11}NOS$ requires C, 59.63; H, 6.11; N, 7.73; S, 17.69 %), $\nu_{max.}$ (KBr) 3300 (NH) and 1640 cm^{-1} (C=O), δ [$(CD_3)_2SO$] 3.26 (1H, s, SH), 3.54 (2H, s, S-CH_2CO), 4.30 (2H, d, J 5 Hz, N-$CH_2C_6H_5$), 7.27 (5H, s, aromatic protons), 8.53 (1H, broad, NH).

3-Methylthiazolidin-4-one (11). A mixture of ethyl thioglycolate (2.0 g) and 40 % methylamine in methanol solution (1.5 g) was stirred at room temperature for 3 h in a current of nitrogen. The excess of reagent and solvent were evaporated in vacuo to leave a pale yellow oil, to which were added p-toluenesulphonic acid (0.5 g), paraformaldehyde (1.5 g) and benzene (50 ml). After the mixture had been refluxed for 3 h with stirring under the azeotropic removal of the water formed by using the water-separator, the solvent was evaporated under reduced pressure. The residue was dissolved in chloroform (50 ml) and washed with aqueous sodium hydrogen carbonate and water. The organic layer was dried over sodium sulphate and filtered. After evaporation of the solvent, distillation of the residue gave the thiazolidinone (11).

All the compounds listed in Table I were obtained in a similar way as above by using the appropriate carbonyl compounds (1.5 - 2 molar equiv. with the exception of the paraformaldehyde) and amide-thiols (3 ~ 10), if necessary, with the additional operation of the

silica gel column chromatography in chloroform as an eluent.

Bis(N-methylcarbamoyl-4-propyl)disulphide (24). m.p. 104 - 106° (from benzene-hexane) (Found: C, 45.18; H, 7.64; N, 10.56; S, 23.90. $C_{10}H_{20}N_2O_2S_2$ requires C, 45.42; H, 7.62; N, 10.60; S, 24.25 %), $\nu_{max.}$ (KBr) 3300 (NH) and 1635 cm^{-1} (C=O), δ ($CDCl_3$) 1.75 - 2.69 (12H, m, $-(CH_2)_3-$ x 2), 2.79 (6H, d, J 5 Hz, $N-CH_3$ x 2), 7.16 (2H, NH x 2).

Bis(N-benzylcarbamoyl-4-propyl)disulphide (25). m.p. 122 - 125° (from methanol-benzene) (Found: C, 63.42; H, 6.94; N, 6.73; S, 15.27. $C_{22}H_{28}N_2O_2S_2$ requires C, 63.12; H, 7.22; N, 6.69; S, 15.32 %), $\nu_{max.}$ (KBr) 3300 (NH) and 1635 cm^{-1} (C=O), δ [$(CD_3)_2SO$, $CDCl_3$] 1.72 - 2.77 (12H, m, $-(CH_2)_3-$ x 2), 4.38 (4H, d, J 6 Hz, $N-CH_2C_6H_5$ x 2), 6.29 (2H, broad NH x 2), 7.27 (10H, s, aromatic protons).

3-Benzyl-hexahydro-1,3-thiazepine (28). To a suspension of lithium aluminium hydride (0.8 g) in anhydrous ether (50 ml), 3-benzyl-hexahydro-1,3-thiazepin-4-one (23) (4.0 g) in dioxane (30 ml) was added dropwise with stirring under ice cooling and the stirring was continued for 2 h at room temperature. After decomposition of the excess of lithium aluminium hydride by addition of 30 % aqueous sodium hydroxide, the organic layer was dried over sodium sulphate. Evaporation of the solvent and then distillation of the residue gave a colourless oil which was purified by silica gel column chromatography in chloroform as an eluent. Redistillation of the residue gave the thiazepine (28) (2.4 g, 64.0 %) as a colourless oil, b.p. 120° (0.6 mmHg) (Found: C, 69.90; H, 8.30; N, 6.80. $C_{12}H_{17}NS$ requires C, 69.51; H, 8.26; N, 6.76 %), δ ($CDCl_3$) 1.5 - 2.2 (4H, m, 5-H and 6-H), 2.5 - 3.1 (4H, m, 4-H and 7-H), 3.68 (2H, s, 2-H), 4.13 (2H, s, $N-CH_2C_6H_5$), 7.27 (5H, s, aromatic protons).

3-Benzylthiazolidine (26). 3-Benzylthiazolidin-4-one (12) (0.65 g) and lithium aluminium hydride (0.15 g) was reacted as the same way as the reduction of 23 to give the thiazolidine (26) (0.25 g, 41.5 %) as a colourless oil, b.p. 97 - 98° (0.6 mmHg) (Found: C, 66.80; H, 7.44; N, 7.77. $C_{10}H_{13}NS$ requires C, 66.99; H, 7.31; N, 7.81 %), δ ($CDCl_3$) 2.7 - 3.3 (4H, m, 4-H and 5-H), 3.54 (2H, s, 2-H), 4.03 (2H, s, N-$CH_2C_6H_5$), 7.30 (5H, s, aromatic protons).

3-Benzyl-tetrahydro-1,3-thazine (27). 3-Benzyl-tetrahydro-1,3-thiazin-4-one (16) (0.5 g) was treated with lithium aluminium hydride (0.1 g) as above to give the thiazine (27) (0.21 g, 45 %) as a colourless oil, b.p. 114 - 116° (0.4 mmHg), δ ($CDCl_3$) 1.5 - 2.0 (2H, m, 5-H), 2.5 - 3.1 (4H, m, 4-H and 6-H), 3.91, 3.99 (4H, each s, 2-H and N-$CH_2C_6H_5$), 7.25 (5H, s, aromatic protons).

REFERENCES

1 T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, T. Kohagizawa, and H. Inoue, Heterocycles, 1978, 9, 819.

2 T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, T. Kohagizawa, and T. Nakamura, Heterocycles, 1977, 6, 305.

3 T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, T. Kohagizawa, and T. Nakamura, J. Pharm. Soc. Japan, 1977, 97, 519.

4 T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, T. Kohagizawa, and H. Inoue, Heterocycles, 1977, 7, 919.

5 T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, T. Kohagizawa, and H. Inoue, J. Pharm. Soc. Japan, in press.

6 T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, T. Kohagizawa, and H. Inoue, Heterocycles, in press.

7 a) M. Ishidate and Y. Hashimoto, J. Pharm. Soc. Japan, 1956, 76, 73; b) F. C. Pennington, W. D. Celmer, W. M. McLamore, V. V. Bogert, and I. A. Solomons, J. Amer. Chem. Soc., 1953, 75, 109.

8 C. H. Eugster and K. Allner, Helv. Chim. Acta, 1962, 45, 1750.

9 B. R. Baker, M. V. Querry, S. Bernstein, S. R. Safir, and Y. Subbarow, J. Org. Chem., 1947, 12, 167.

10 N. Kharach and R. B. Langford, J. Org. Chem., 1963, 28, 1901.

11 J. W. Haefele and R. W. Broge, Proc. Sci. Sect. Toilet Goods Assoc., 1959, 32, 520. (Chem. Abs., 1960, 54, 543c).

12 R. N. Misra and S. S. Guha-Sircar, J. Indian Chem. Soc., 1956, 33, 523 (Chem. Abs., 1955, 49, 15606d).

13 G. E. Frandkin, Khim. Zashchita Organizma Ioniziruyushchikh Izlucheni, 93 (1960) (Chem. Abs., 1961, 55, 27649c).

14 I. L. Knunyants, N. D. Kuleshova, and M. G. Linkova, Izvest. Akad. Nauk S.S.S.R., Ser. Khim., 1081 (1965) (Chem. Abs., 1965, 63, 8192h).

Received, 6th May, 1978