Ring-Closure Reaction of *N*-Arylthiomethylaroylamides to 1,3-Benzothiazines [1]

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N-Arylthiomethylaroylamides substituted with an electron-donating group in the *meta* position undergo two-directional cyclization in the presence of phosphorus oxychloride to give both positional isomers of the 4*H*-1,3-benzothiazine derivative. The structures of the products were confirmed by ^1H and ^{13}C nmr spectroscopy. Mixed ring-closure reactions of several *N*-arylthiomethylaroylamides **3**, **6**, **9**, **13** have shown that these conversions are introduced by a proton-catalyzed intermolecular rearrangement.

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Introduction.

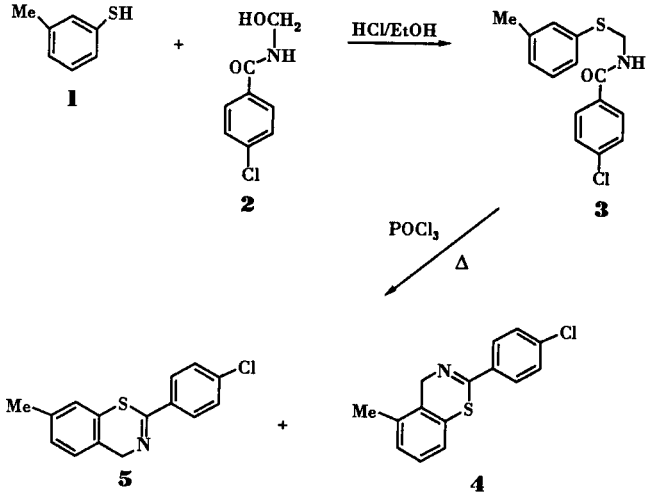
In earlier research [2] we investigated the ring-closure reactions of a number of *N*-3,4-dialkoxyphenylthiomethylaroylamides in the presence of phosphorus oxychloride, leading to 4*H*-1,3-benzothiazines. It was found that these cyclizations were introduced by an acid-catalyzed intermolecular rearrangement [3]. Besides the studied mixed cyclization [3], this conclusion was supported by effecting the ring-closure with phosphorus oxychloride in pyridine solution [4], when (on the analogy of the Bischler-Napieralski dihydroisoquinoline cyclization) the products were the isomeric 2*H*-1,3-benzothiazine derivatives. In several cases, when the cyclization of *N*-3,4-dimethoxythiomethylaroylamide derivatives was effected in acid medium with phosphorus oxychloride, the ring-closure leading to 1,3-benzothiazines occurred in two directions, and a small amount of the corresponding 2*H*-1,3-benzothiazine derivatives was also formed [5,6]. Further, it was found that unsubstituted *N*-phenylthiomethylaroylamides did not undergo cyclization to form a 1,3-benzothiazine ring [3]. This latter observation was confirmed by Ito *et al.* [7].

As a conclusion, we supposed that other *N*-arylthiomethylaroylamides are also liable to cyclization if they contain electron-donating substituents, since electrophilic substitution of the aromatic ring is then favored. This assumption was confirmed by the formation of 2-phenyl-6-methyl-4*H*-1,3-benzothiazine in the cyclization of *N*-4-methylphenylthiomethylbenzamide with phosphorus oxychloride [8]. In this case, no ring-closure to 2*H*-1,3-benzothiazine was observed.

Results and Discussion.

It was expected that 1,3-benzothiazine ring formation from *N*-3-methylphenylthiomethylaroylamides in the presence of phosphorus oxychloride would give both positional isomers of the 4*H*-1,3-benzothiazine derivatives, due to the reaction occurring in two directions. Thus, *m*-thiocresol (**1**) was condensed with *N*-hydroxymethyl-4-chlorobenzamide (**2**) in an ethanolic solution of hydrogen chloride to obtain *N*-3-methylphenylthiomethyl-4-chlorobenzamide (**3**); the ring-closure reaction of this compound gave a mixture of 5-methyl- and 7-methyl-2-(4-chlorophenyl)-4*H*-1,3-benzothiazines **4** and **5** (Scheme 1). Formation of the 2*H*-1,3-benzothiazine isomer was not observed here, either. Besides compound **5**, the presence of about 3% of the minor component, the 5-methyl derivative **4**, was detected by nmr spectroscopy after preparation of the picrates and liberation of the mixture of bases from them.

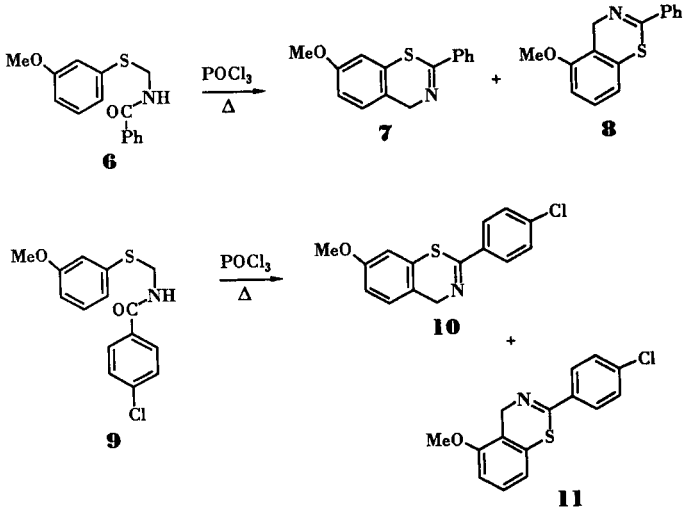
Scheme 1



Next, the phosphorus oxychloride-induced cyclization of the acid amide thioether **6** reported by Ito *et al.* [7] was investigated. In this case also, after isolation of the products as the crude picrates, ^1H nmr spectroscopy revealed the formation of isomers **7** and **8**, as expected. Recrystallization of the mixture of picrates gave pure 2-phenyl-7-

methoxy-4*H*-1,3-benzothiazine picrate, which was identical in all respects with the compound reported in the literature [7]. Thin-layer chromatography after liberation of the base from the mother liquor furnished the pure isomer **8**, whose picrate was also prepared (Scheme 2).

Scheme 2



The condensation of 3-methoxythiophenol and *N*-hydroxymethyl-4-chlorobenzamide (**2**) gave the acid amide thioether **9**; cyclization of this compound yielded the 4*H*-1,3-benzothiazine derivative **10** and about 3% of the 5-methoxy isomer **11**. The latter was characterized *via* its nmr data, and the main product **10** was isolated as a pure substance on recrystallization (Scheme 2).

The Japanese researchers [7] suggested that the cyclization of compound **6** to a 4*H*-1,3-benzothiazine involved intramolecular rearrangement; however, no evidence was given to support this assumption. On the basis of our earlier opposite observations [3], we deemed this mechanism unlikely.

In order to clarify the issue, the acid amide thioether **12** was prepared from thiophenol and *N*-hydroxymethyl-4-chlorobenzamide (**2**); attempted cyclization of **12** in the presence of phosphorus oxychloride gave no 1,3-benzothiazine derivative. Compounds **6** and **12** were subjected to a mixed ring-closure reaction; the products were compounds **7** and **10** in 45:55 percentage ratio (Scheme 3). This result is evidence that the cyclization proceeds by an intermolecular rearrangement, in contrast to the mechanism suggested by Ito *et al.*

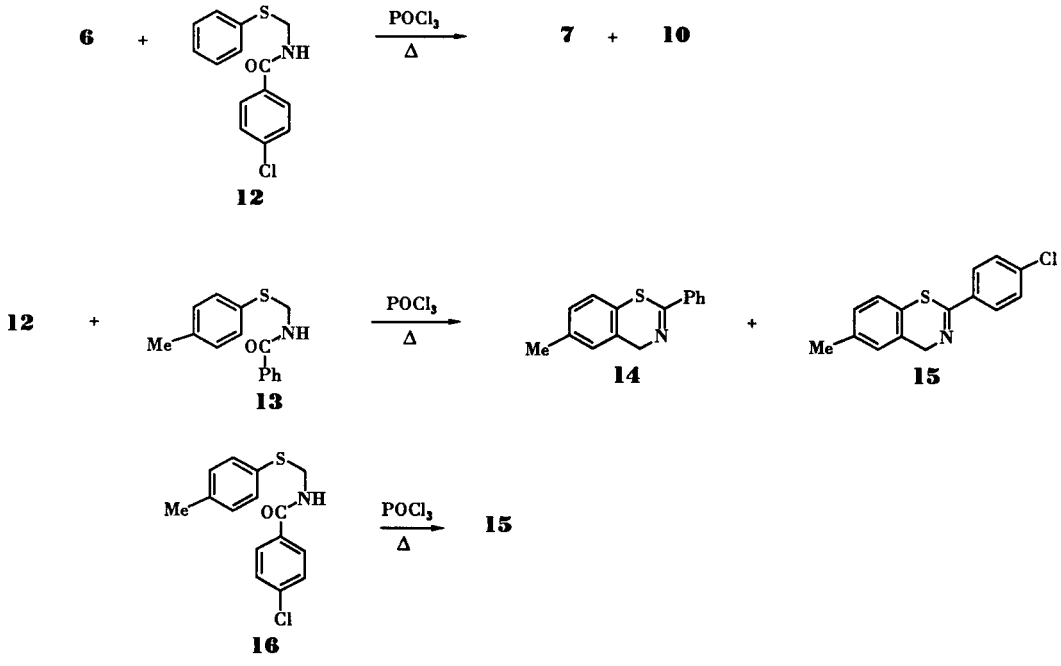
A similar result was obtained from a study of the mixed cyclization of the acid amide thioethers **12** and **13**; the products of the intermolecular rearrangement were the 4*H*-1,3-benzothiazine derivatives **14** and **15** in a ratio of 1:5. Compound **15** was also prepared in an independent way by cyclization of the acid amide derivative **16**.

In conclusion, it can be stated that the reaction mechanism of the cyclizations to 4*H*-1,3-benzothiazines involving intramolecular rearrangement, as suggested by the Japanese authors [7], is not consistent with the experimental facts.

EXPERIMENTAL

Melting points are uncorrected. The nmr spectra were recorded on a Bruker AM-400 spectrometer in deuteriochloroform at

Scheme 3



room temperature (^{1}H: 400.136 MHz; ^{13}C: 100.614 MHz; chemical shifts δ are given in ppm relative to the internal standard tetramethylsilane).

N-(3-Methylphenylthiomethyl)-4-chlorobenzamide (**3**).

m-Thiocresol (**1**) (12.4 g, 0.1 mole) and *N*-hydroxymethyl-4-chlorobenzamide (**2**) (18.6 g, 0.1 mole) were dissolved with gentle heating in a mixture of ethanol (30 ml) and a saturated solution of hydrogen chloride in ethanol (25 ml). The mixture was allowed to stand overnight. Ice (50 g) was gradually added to the solution to cause precipitation of the product (yield 83%). Recrystallization from a mixture of carbon tetrachloride and *n*-hexane gave colorless crystals, mp 75-76°; pmr (deuteriochloroform): δ 2.28 (3H, s, Me), 4.80 (2H, d, J = 6.08 Hz, H-7), 7.25 (1H, s, H-2), 7.23 (1-H, d, J = 7.95 Hz, H-4), 7.17 (1-H, t, J = 7.55 Hz, H-5), 7.04 (1H, d, J = 7.40 Hz, H-6), 7.31 (2H, d, J = 8.5 Hz, H-2',6'), 7.60 (2H, d, J = 8.5 Hz, H-3',5'), 6.97 (1H, b, NH); cmr (deuteriochloroform): 21.25 (Me), 44.50 (C-7), 128.46 (C-2', C-6'), 128.80, 128.35, 128.38, 129.08, 132.12 (Ar methine), 132.31, 133.4, 138.02, 139.08 (Ar quaternary), 166.18 (C-8).

Anal. Calcd. for $C_{15}H_{14}ClNOS$: C, 61.74; H, 4.84; N, 4.80. Found: C, 62.01; H, 5.10; N, 5.03.

2-(4-Chlorophenyl)-7-methyl-4*H*-1,3-benzothiazine (**5**) and 2-(4-Chlorophenyl)-5-methyl-4*H*-1,3-benzothiazine (**4**).

Compound **3** (29.2 g, 0.1 mole) was refluxed in phosphorus oxychloride (30 ml) for 2 hours. The mixture was poured into ice-water, neutralized with sodium carbonate, and extracted with chloroform. The extract was dried over sodium sulfate, the solvent was evaporated off, and the residue was extracted with hot ethanol (150 ml). The undissolved material was separated by filtration. The ethanolic solution was concentrated to 40 ml. A concentrated solution of picric acid in ethanol (60 ml) was added to precipitate the picrate, yellow crystals (3.24 g), mp (recrystallized from ethanol) 177-178°. The base was liberated from the picrate to give colorless crystals, mp 92-95°; **4**, pmr (deuteriochloroform): δ 2.48 (3H, s, Me), 4.79 (2H, s, H-4), 7.17 (1H, d, H-6), 7.37 (2H, d, J = 7.6 Hz, 2',6'-H), 7.94 (2H, d, J = 7.6 Hz, 4',5'-H); cmr (deuteriochloroform): 18.7 (Me), 53.9 (C-4); **5**, pmr (deuteriochloroform): δ 2.35 (3H, s, Me), 4.74 (2H, s, H-4), 7.38 (2H, d, J = 8.6 Hz, 2',6'-H), 7.93 (2H, d, J = 8.6 Hz, 4',5'-H), 7.18 (1H, s, H-8), 7.11 (1H, d, J = 7.6 Hz, H-6), 7.20 (1H, d, J = 7.6 Hz, H-5); cmr: (deuteriochloroform) 21.03 (Me), 56.32 (C-4), 126.70, 127.00, 128.55, 128.74, 129.02 (Ar methine), 128.16, 130.36, 135.49, 137.34, 137.6 (Ar quaternary), 160.62 (C-2).

According to ^{1}H nmr spectroscopy, both the picrates and the free bases consisted of a mixture of compounds **4** and **5** in a ratio of 3:97.

2-Phenyl-7-methoxy-4*H*-1,3-benzothiazine (**7**) and 2-Phenyl-5-methoxy-4*H*-1,3-benzothiazine (**8**).

Compound **6** (2.73 g, 10 mmoles) was dissolved in phosphorus oxychloride (5 ml) and the solution was maintained at 115° for 2 hours. The reaction mixture was processed as described above to obtain a mixture of the picrates (0.9 g); nmr spectroscopy revealed that, besides compound **7**, the 4*H*-1,3-benzothiazine **8** was formed in an amount of 5%. Recrystallization from ethanol gave the pure picrate of **7**, which was identical in all respects with the compound reported in the literature [7]; **7**, pmr (deuteriochloroform): δ 3.86 (3H, s, OMe), 4.91 (2H, s, H-4), 6.99 (1H, d, J = 8.88 Hz, H-5), 7.00 (1H, s, H-8), 7.30 (1H, d, J = 8.8 Hz, H-6), 8.11 (2H, d, J = 7.90 Hz, H-2',6'), 7.53 (2H, t, J = 7.90 Hz, H-3',5'), 7.67 (1H, t, J = 7.87 Hz, H-4'), 9.05 (picric acid).

The base liberated from the mother liquor was purified by chromatography on a plate of silica gel to furnish **8** as a pure compound; its picrate crystallized from ethanol as yellow crystals, mp 173-174°; **8** (picrate), pmr (deuteriochloroform): δ 3.91 (3H, s, OMe), 5.07 (2H, s, H-4), 7.00 (1H, d, J = 8.2 Hz, H-6), 7.04 (1H, d, J = 8.2 Hz, H-8), 7.41 (1H, t, J = 8.2 Hz, H-7), 7.52 (2H, t, J = 7.9 Hz, H-3',5'), 7.69 (1H, t, J = 7.9 Hz, H-4'), 8.07 (2H, d, J = 7.9 Hz, H-2',6'), 8.94 (picric acid).

Anal. Calcd. for $C_{21}H_{16}N_4O_8S$: C, 52.06; H, 3.33; N, 11.57. Found: C, 51.90; H, 3.50; N, 11.65.

N-(3-Methoxyphenylthiomethyl)-4-chlorobenzamide (**9**).

3-Methoxythiophenol (2.8 g, 20 mmoles) and *N*-hydroxymethyl-4-chlorobenzamide (3.7 g, 20 mmoles) were dissolved in ethanol (5 ml). A solution of hydrogen chloride in ethanol (2.5 ml) was added, and the mixture was gently heated. It was allowed to stand overnight, then concentrated under reduced pressure to obtain the residue as a viscous oil (97%). A small portion of the product was purified by chromatography on silica gel for analysis as a colorless viscous oil; pmr (deuteriochloroform): δ 3.74 (3H, s, OMe), 4.84 (2H, d, J = 6.1 Hz, H-7), 6.76 (1H, dd, J = 8.15, 2.15 Hz, H-6), 6.95 (1H, b, NH), 6.98 (1H, d, J = 2.12 Hz, H-2), 7.00 (1H, d, J = 8.1 Hz, H-4), 7.19 (1H, t, J = 8.0 Hz, H-5), 7.31 (2H, d, J = 8.5 Hz, H-3',5'), 7.61 (2H, d, J = 8.5 Hz, H-2',6'); cmr (deuteriochloroform): δ 44.80 (C-7), 55.94 (OMe), 128.94, 132.86, 135.65, 138.69 (Ar quaternary), 113.96, 116.86, 123.67, 129.08, 129.44, 130.66 (Ar methine), 166.80 (C-8).

Anal. Calcd. for $C_{15}H_{14}ClNO_2S$: C, 58.53; H, 4.58; N, 4.55; Cl, 11.52. Found: C, 58.80; H, 4.70; N, 4.70; Cl, 11.80.

2-(4-Chlorophenyl)-7-methoxy-4*H*-1,3-benzothiazine (**10**) and 2-(Chlorophenyl)-5-methoxy-4*H*-1,3-benzothiazine (**11**).

The crude compound **9** (3.08 g, 10 mmoles) was dissolved in phosphorus oxychloride (6 ml) and the solution was refluxed for 2 hours. It was then poured into ice-water, neutralized with sodium carbonate and extracted with chloroform. The extract was dried over sodium sulfate and the solvent was evaporated. The residue was extracted with hot ethanol (50 ml) and the mixture of the picrates of **10** and **11** (0.7 g) was precipitated with picric acid. Spectroscopic analysis (nmr) showed that the crude base liberated from the picrates contained about 3% of the isomer **11** besides the main product **10**. Recrystallization of the crude base from ethanol gave **10** as colorless crystals, mp 98-99°; pmr (deuteriochloroform): δ 3.77 (3H, s, OMe), 4.70 (2H, s, 4-H), 6.86 (1H, dd, J = 8.3 Hz, 2.4 Hz, H-6), 6.92 (1H, d, J = 2.44 Hz, H-8), 7.22 (1H, d, J = 2.32 Hz, H-5), 7.39 (2H, d, J = 8.6 Hz, H-2',6'), 7.93 (2H, d, J = 8.6 Hz, H-3',5'); cmr (deuteriochloroform): δ 56.10 (C-4), 56.61 (OMe), 112.26, 114.46, 128.17, 129.30, 129.56 (Ar methine), 123.74, 128.94, 132.26, 136.09, 137.84 (Ar quaternary), 160.4 (C-2).

Compound **11** had pmr (deuteriochloroform): δ 3.77 (3H, s, OMe), 4.88 (2H, s, 4-H).

Anal. Calcd. for $C_{15}H_{12}ClNOS$: C, 62.17; H, 4.18; N, 4.83; Cl, 12.24. Found: C, 62.30; H, 4.35; N, 5.00; Cl, 12.03.

The picrate prepared from the base **10** consisted of yellow crystals, mp 165-166° dec.

Anal. Calcd. for $C_{21}H_{15}ClN_4O_8S$: N, 10.80; Cl, 6.83. Found: N, 11.05; Cl, 6.79.

N-Phenylthiomethyl-4-chlorobenzamide (**12**).

Compound **12** was prepared from thiophenol (11 g, 0.1 mole) and *N*-hydroxymethyl-4-chlorobenzamide (18.6 g, 0.1 mole) in the same way as described for compound **3**. The product was crystal-

lized from ethanol, mp 92-94° (91%); pmr (deuteriochloroform): δ 4.85 (2H, d, J = 6.3 Hz, 7-H), 6.55 (1H, b, NH), 7.61 (2H, d, J = 8.5 Hz, 3',5'-H), 7.36 (2H, d, J = 8.5 Hz, 4',6'-H), 7.25-7.47 (5H, m, aromatic H); cmr (deuteriochloroform): δ 44.48 (C-7), 127.63, 128.40, 128.92, 129.32, 131.49 (Ar methine), 132.33, 133.64, 138.2 (Ar quaternary), 166.0 (CO).

Anal. Calcd. for $C_{14}H_{12}ClNOS$: C, 60.55; H, 4.36; N, 5.04. Found: C, 60.40; H, 4.45; N, 5.23.

Mixed Ring-closure Reaction of *N*-3-Methoxyphenylthiomethylbenzamide (**6**) and *N*-Phenylthiomethyl-4-chlorobenzamide (**12**).

A mixture of compounds **6** (1.36 g, 5 mmoles) and **12** (1.39 g, 5 mmoles) was refluxed in phosphorus chloride (6 ml) for 2 hours. The solution was poured into ice-water, neutralized with sodium carbonate and extracted with chloroform. The extract was dried over sodium sulfate and the solvent was evaporated off. The residue was extracted with hot ethanol (50 ml) and the picrates (0.95 g) of the bases were precipitated with picric acid. The bases were liberated and separated by chromatography on a plate of silica gel (developing solvent:benzene). The products **7** (0.3 g) and **10** (0.1 g) were identical in all respects with authentic samples.

2-(4-Chlorophenyl)-6-methyl-4*H*-1,3-benzothiazine (**15**).

Compound **16** (5.8 g, 20 mmoles) was refluxed in phosphorus oxychloride (10 ml) for 2 hours. The mixture was poured into ice-water, neutralized with sodium carbonate and extracted with benzene. The extract was dried over sodium sulfate. The solvent was evaporated off and the residue was extracted with hot ethanol (80 ml), the picrate precipitated from this solution. The base liberated from the picrate was recrystallized from ethanol to give colorless plates, mp 131-133° (12%); pmr (deuteriochloroform): δ 2.36 (3H, s, Me), 4.73 (2H, s, 4-H), 7.10 (1H, dd, J = 8.1, 2.1 Hz, 7-H), 7.14 (1H, d, J = 2.1 Hz, 5-H), 7.24 (1H, d, J = 8.1 Hz, 8-H), 7.38 (2H, d, J = 6.8 Hz, 2',6'-H), 7.92 (2H, d, J = 6.8 Hz, 3',5'-H); cmr (deuteriochloroform): δ 21.03 (Me), 56.77 (4-C), 126.39, 127.60, 128.43, 128.70, 128.98 (Ar methine), 127.18, 131.11, 135.59, 137.23, 137.68 (Ar quaternary), 160.72 (C-2).

Anal. Calcd. for $C_{15}H_{12}ClNS$: C, 65.80; H, 4.42; N, 5.12; Cl, 12.95. Found: C, 65.96; H, 4.32; N, 4.96; Cl, 13.01.

N-(4-Methylphenylthiomethyl)-4-chlorobenzamide (**16**).

p-Thiocresol (12.4 g, 0.1 mole) and *N*-hydroxymethyl-4-chlorobenzamide (15.2 g, 0.1 mole) were dissolved in ethanol (30 ml). A saturated solution of hydrogen chloride in ethanol (20 ml) was added, and the mixture was gently warmed to achieve complete dissolution; it was then allowed to stand overnight at room temperature. The separated colorless crystals were filtered off (yield: 90%). After recrystallization from ethanol: mp 102-104°; pmr (deuteriochloroform): δ 2.32 (3H, s, Me), 4.78 (2H, d, J = 6.1 Hz, 7-H), 6.63 (1H, b, NH), 7.3 (4H, m, 2,3,5,6-H), 7.11 (2H, d, J = 6.9 Hz, 3',5'-H), 7.60 (2H, d, J = 6.9 Hz, 2',6'-H); cmr (deuteriochloroform): δ 21.08 (Me), 45.03 (7-C), 128.41, 128.88, 130.08, 132.21 (Ar methine), 129.91, 132.39, 137.96, 138.07 (Ar quaternary), 166.00 (CO).

Anal. Calcd. for $C_{15}H_{14}ClNOS$: C, 61.74; H, 4.84; N, 4.80. Found: C, 61.62; H, 4.65; N, 5.03.

Mixed Ring-closure Reaction of *N*-Methylphenylthiomethylbenzamide (**13**) and *N*-Phenylthiomethyl-4-chlorobenzamide (**12**).

A mixture of compounds **13** (2.57 g, 10 mmoles) and **12** (2.77 g, 10 mmoles) was refluxed in phosphorus chloride (10 ml) for 2 hours. After decomposition with ice-water and neutralization with sodium carbonate, the reaction mixture was extracted with chloroform. The extract was dried over sodium sulfate and the solvent was evaporated off. The residue was extracted with hot ethanol (50 ml). To the resulting solution picric acid was added to precipitate a mixture of the picrates (0.44 g) of **14** and **15**. The chlorine content of the mixture of the bases liberated from the picrates was 10.60%, corresponding to a content of 81.85% of compound **15**. According to hplc analysis, the ratio of compounds **14**:**15** was 1:5, which is consistent with the value calculated from the elementary analysis for chlorine.

Compounds **14** and **15**, separated by preparative thin-layer chromatography, were identical in every respect with authentic samples.

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