Chemistry of Natural Compounds, Vol. 31, No. 5, 1995

SYNTHESIS BASED ON β-PHENYLETHYLAMINES. IX. SYNTHESIS OF SULFIDES OF β-PHENYLETHYLAMINES AND OF N-BENZYLTETRAHYDROISOQUINOLINES

T. I. Golodnyuk and V. I. Vinogradova

UDC 574.554.576.546.221

New bimolecular sulfur-containing β-phenylethylamines and N-benzyltetrahydroisoquinolines have been synthesized from formyl derivatives of diaryl sulfides. The possibility of using metals as catalysts for obtaining diaryl sulfides in the reaction of ortho*-substituted benzaldehydes with SCl_2 has been shown for the first time.*

Among natural sulfur-containing compounds (antibiotics, proteins, etc.) particular interest is presented by alkaloids. Several papers have been published recently on the isolation of sulfur-containing alkaloids from the plant *Biflustra perfrogilis* [1] and of the benzyltetrahydroisoquinoline alkaloid imbricatine from the starfish *Dermasteria imbricata* [2]. The presence in the molecule of an additional center in the form of an S atom and of a C–S bond capable of being cleaved under the action of electrophilic and nucleophilic reagents makes sulfur-containing compounds of interest from the points of view of organic synthesis [3] and of practical application. Expansion of the group of sulfur-containing alkaloids will permit an understanding of the contribution of the sulfur atom to the change in the properties of these substances.

Sulfides of benzyltetrahydroisoquinoline bases can be obtained either from formyl derivatives of diaryl sulfides followed by their condensation with phenylethylamines (route A) or from N-benzyltetrahydroisoquinolines (route B). In our opinion, direction B is more attractive, since it is a direct one-stage route from the N-benzyltetrahydroisoquinolines that we have synthesized previously [4, 5] to the desired sulfides. However, we have found no usable methods of synthesizing analogous sulfides in the literature, and our experiments in this direction have proved unsuccessful. Therefore, following a general principle in the synthesis of complex natural compounds, we placed the key stage — the formation of sulfides — at the beginning of the scheme (route A).

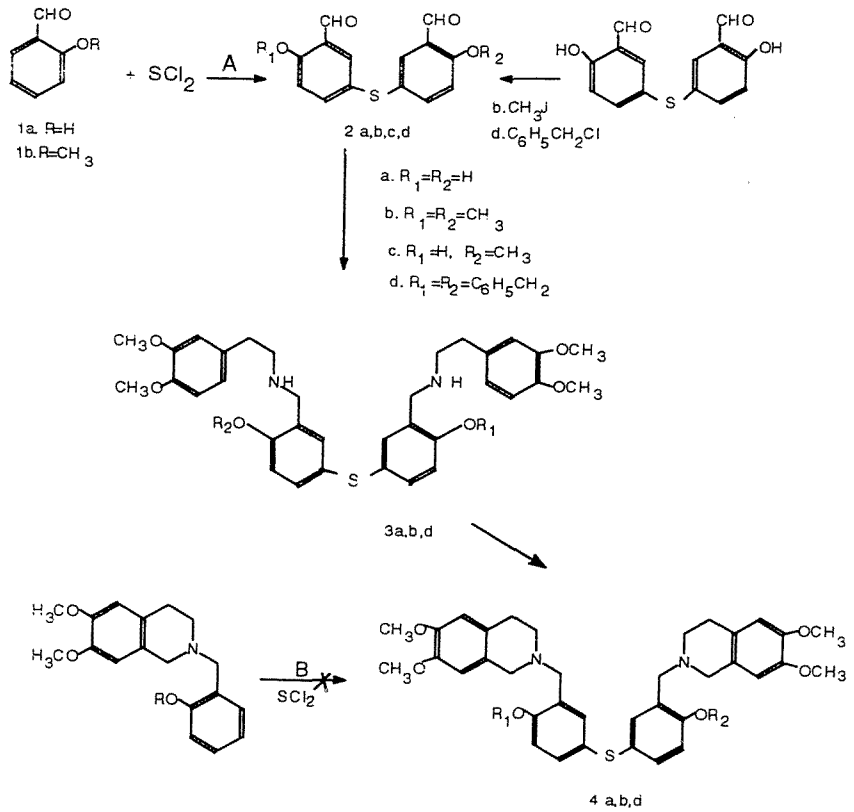
Traditional methods of synthesizing sulfides are reactions using elementary sulfur or inorganic sulfur derivatives (Na_2S,H_2S, SCl_2, S_2Cl_2) and also syntheses based on sulfenyl halides or the nucleophilic substitution of thiols with the participation of aryl halides [6]. The preparation of the required sulfide intermediates (**2**) is not described in the literature; however, there are reports of the successful use of SCl_2 for synthesizing a number of sulfides from cresol at 0°C in CH_2Cl_2 [7].

To find the optimum conditions of synthesis, we performed the analogous reactions with salicylaldehyde (**1a**) and SCl_2. The results of the reaction with salicylaldehyde, which has an electron-accepting formyl group, depended substantially on the temperature: at 0°C and at room temperature no reaction took place, while raising the temperature led to the formation of a difficultly separable mixture of polysulfides $(OHC_6H_3CHO)_2S_n$, where n = 1-8. The use of a solvent and the addition of pyridine or triethylamine did not increase the yield.

The ineffectiveness of the conditions employed for (**1a**) impelled us to use catalysts, which expanded the limits of this reaction. We succeeded in obtaining the sulfide (**2a**) in satisfactory yield (30-40%) by using metal chlorides ($AlCl_3$, $CuCl_2$, $SnCl_2$, $ZnCl_2$) as catalysts. The replacement of anhydrous metal chlorides by metals simplified the process and made it considerably more effective. The preparation of sulfides under the action of SCl_2 in the presence of catalytic amounts of metals has not been performed previously. We compared the activities of the catalysts in the reaction of salicyl aldehyde and SCl_2 and obtained the following series (the yields of sulfides are given in parentheses):

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent, fax (3712) 89 14 75. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 731-735, September-October, 1995. Original article submitted November 11, 1994.

 0009-3130/95/3105-0612$12.50



Zn(76%) > Sn(36%)-Cu-Al > Fe(25%) > Pb(10%).

It can be seen from these results that under our conditions the most active catalyst was metallic zinc, which gives a fairly reactive complex that readily breaks down subsequently.

Under the same conditions (Zn catalyst, yield 24%), *ortho*-methoxybenzaldehyde showed a lower reactivity than salicylaldehyde, which is apparently due to the participation of the hydroxy group of the latter not only in stabilizing the transitional δ-complex but also in converting it into a stable intermediate quinolide compound, which is impossible for a methoxy or benzyloxy group.

An independent synthesis of (**2**b) was carried out by the methylation of the sulfide of salicylaldehyde. The monomethyl ether (**2**c) was formed as a by-product in ratio of 2:1.

The method employed proved to be ineffective in the case of *ortho*-benzyloxybenzaldehyde, which reacted differently, giving a series of sulfide products. Compound (**2**d) was therefore obtained by the benzylation of (**2**a).

In spite of its pronounced selectivity, the method of obtaining the key sulfides (**2**) that we had developed permitted us to solve successfully the problem of synthesizing the desired sulfides (**3**a, b, d) and (**4**a, b, d). For this purpose, the sulfides of salicylaldehdye, of *ortho*-methoxybenzaldehyde, and of *ortho*-benzyloxybenzaldehyde that we had obtained (**2**a, b, and d, respectively) were condensed with homoveratrylamine in benzene with the elimination of water by azeotropic distillation. The reaction products — imines —, after reduction with sodium tetrahydroborate, gave the corresponding phenylethylamines (**3**a, b, d), the subsequent cyclization of which by the Pictet–Spengler reaction led to the substituted di[3-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)phenyl] sulfides (**4**a, b, d) [8].

EXPERIMENTAL

***ortho*-Methoxybenzaldehyde [9].** To a solution of 2.4 g of KOH in 45 ml of methanol were added 5.02 g of salicylaldehyde and then 6.4 g of freshly redistilled methyl iodide. The reaction mixture was boiled under reflux for 7 h, after

which the solvent was distilled off, and the residue was dissolved in water and extracted with ether. The ethereal extract was washed three times with water. After the solvent had been distilled off, 3.35 g (60%) of *ortho*-methoxybenzaldehdye was obtained.

Di(3-formyl-4-hydroxyphenyl) Sulfide (2a). A solution of 1.18 g of salicylaldehyde in 7 ml of absolute methylene chloride was treated with 0.015 g of Zn powder and then, with stirring, 0.59 g of SCl_2 in 2 ml of methylene chloride was added in drops. The mixture was left for 24 h, the solvent was distilled off, and the residue was triturated with benzene. This led to the separation of 1.01 g (76%) of the sulfide, with mp 155-157°C. Found: M 273.9608, $C_{14}H_{10}SO_4$. Calculated: M 273.9595. Mass spectrum, *m/z* (I_{rel}, %) 274 (M^+, 100), 246(10), 228, 217, 204, 185, 171, 153(10), 121(10), 97, 78(30). PMR spectrum (100 MHz, pyridine, ppm, J, Hz): 6.96 (2H, d, J = 8.5, H-5), 7.48 (2H, dd, J = 2, J = 8.5), 7.92 (2H, d, J = 2, H-2), 10.34 (s, CHO), 10.7-11.2 (br.s, OH, H_2O).

Di(3-formyl-4-methoxyphenyl) Sulfide (2b). 1. A solution of 0.48 g of *ortho*-methoxybenzaldehyde in 4 ml of absolute methylene chloride was treated with 0.007 g of Zn, and then, with stirring, 0.22 g of sulfur dichloride in 1 ml of methylene chloride was added in drops. The reaction mixture was left for a day, and the solvent was distilled off. The residual oil was boiled with hexane. The hexane layer was decanted off and concentrated. This gave 0.25 g (24%) of sulfide (**2b**), mp 88-90°C. Found: M 302.0591, $C_{16}H_{14}O_4S$. Calculated: M 302.0599. Mass spectrum, *m/z* (I_{rel}, %), 302 (M^+, 100), 287(10), 273(3), 259(13), 256, 242(6), 231(3), 216(5), 200(8), 187(7), 171(15), 167(25), 152(15), 149(7), 139(12), 123(15), 108(12), 95(18), 92(17), 75(20). PMR spectrum (100 MHz, pyridine, J, Hz) 3.89($2OCH_3$), 6.77 (2H, d, J = 8, H-5), 7.48 (2H, dd, J = 2, J = 8, H-6), 7.76 (2H, d, J = 2, H-2), 10.35 (s, CHO).

2. A solution of 3 g of sulfide (**2a**) in 60 ml of methanol was treated with 3.9 g of freshly redistilled methyl iodide, and the mixture was boiled for 9 h. After elimination of the solvent, the residue was extracted with ether from aqueous solution. The ethereal extract was dried with sodium sulfate and was then concentrated. The resulting oil was dissolved in benzene and the solution was washed with 4% caustic potash. The residue after the solvent had been distilled off was crystallized from methanol to give 0.77 g (24%) of sulfide (**2b**), mp 86-88°C. After acidification, the alkaline solution yielded the sulfide (**2c**) (12%). Mass spectrum, *m/z* (I_{rel}, %): 288 (M^+, 100).

Di(3-formyl-4-benzyloxyphenyl) Sulfide (2d). A solution of 3 g of sulfide (**2a**) in 60 ml of ethyl alcohol was treated with 3.2 g of freshly calcined potash and 3.2 g of benzyl chloride. The reaction mixture was boiled for 6 h. After the end of the reaction the solid matter was filtered off, and the mother liquor was concentrated and extracted with chloroform from aqueous solution. The chloroform extract was dried with sodium sulfate, and, after the solvent had been distilled off, 2.95 g (60%) of sulfide (**2d**) was obtained. Found: M 454.1231, $C_{28}H_{22}O_4$. Calculated: M 454.1239. Mass spectrum, *m/z* (I_{rel}, %): 454(M^+, 100).

Preparation of Sulfides (3a, b, d). To a solution of 2.81 g of homovertrylamine in 80 ml of benzene was added 2.14 g of sulfide (**2a**) and the mixture was boiled for 10 h with elimination of water by azeotropic distillation. The solvent was distilled off, and the residue was reduced with 5 g of sodium tetrahydroborate in a 10:1 mixture of methanol and chloroform at 0°C. After evaporation, the residue was treated with water and extracted with ether, and then with chloroform. The extracts were dried with Na_2SO_4 and concentrated. A solution of the residue in acetone was acidified with concentrated HCl. The crystals of the hydrochloride of the amine (**3**) that deposited were separated off.

Di[4-hydroxy-3-(3,4-dimethoxyphenethylaminomethyl)phenyl] Sulfide (3a). Melting point of the hydrochloride 137-139°C. Yield 93%. Mass spectrum, *m/z* (I_{rel}, %): M^+ (absent), 600 (M^+-4, 0.2), 193 (2.3), 181(15), 152(100), 151(52), 137(20), 107(11).

Di[4-methoxy-3-(3,4-dimethoxyphenethylaminomethyl)phenyl] Sulfide (3b). Melting point of the hydrochloride 180-182°C. Yield 60%. Mass spectrum, *m/z* (I_{rel}, %): (632^+, 0.2), 481(7.8), 152(100), 151(78), 121(30).

Di[4-benzyloxy-3-(3,4-dimethoxyphenethylaminomethyl)phenyl] Sulfide (3d). Melting point of the hydrochloride 115-117°C. Yield 60%. Mass spectrum, *m/z* (I_{rel}, %): 784(M^+, 0.2), 633(40), 181(11), 152(68), 151(46), 137(16), 107(9.2), 91(100).

Preparation of (4a, b, d). A solution of 2.4 g of the hydrochloride of a compound (**3**) in 7 ml of methanol was treated with 3 drops of HCl and 12 ml of 30% formalin, and the mixture was boiled for 4 h. Then the solvent and the formalin were distilled off under water-pump vacuum. The residue was converted into the base and was extracted with ether. The etheral extract was dried with Na_2SO_4. After concentration, the hydrochloride of a compound (**4**) was obtained from a 20:1 mixture of acetone and methanol.

Di[4-hydroxy-3-(6,7-dimethoxyisoquinolin-2-ylmethyl)phenyl] Sulfide (4a). Melting point of the hydrochloride 185-187°C, yield 70%. Mass spectrum, *m/z* (I_{rel}, %): M^+ (absent), 207(14), 206(18), 193(39), 192(49), 191(26), 189(36), 178(9), 176(29), 164(100), 152(11), 121(25).

Di[4-methoxy-3-(6,7-dimethoxyisoquinolin-2-ylmethyl)phenyl] Sulfide (4b). Melting point of the hydrochloride 150-152°C, yield 45%. Mass spectrum, *m/z* (I_{rel}, %): 656 (M^+, 0.8), 207(51), 206(62) 192(18), 190(10), 164(100), 121(13).

Di[4-benzyloxy-3-(6,7-dimethoxyisoquinolin-2-ylmethyl)phenyl] Sulfide (4d). Melting point of the hydrochloride 137-139°C, yield 50%. Mass spectrum, *m/z* (I_{rel}, %): 808 (M^+, 1), 618(10), 207(14), 206(20), 193(41), 192(59), 189(65), 176(36), 164(97), 146(35), 121(24), 91(100).

REFERENCES

1. A. J. Blackman, C. E. Ralph, and B. W. Skelton, Austr. J. Chem., **46**, 213 (1993).
2. O. Masashi, M. Takafumi, and F. Tozo, Heterocycles, **33**, 21 (1992).
3. I. V. Koval', Usp. Khim., **63**, 338 (1994).
4. V. I. Vinogradova, T. I. Golodnyuk, N. Tulyaganov, M. S. Yunusov, and N. U. Baratov, Khim. Prir. Soedin., 404 (1993).
5. V. I. Vinogradova, T. I. Golodnyuk, M. S. Yunusov, G. A. Suleimanova, and N. Tulyaganov, Khim. Prir. Soedin., 736 (1993).
6. Comprehensive Organic Chemistry, D. Barton and W. D. Ollis (eds.), Pergamon, Oxford, Vol. 5 (1979) [Russian translation, Khimiya, Moscow (1982)].
7. O. Yoshihiro, M. Kazuhiko, and S. Tyo, Bull. Chem. Soc. Jpn., **64**, 576 (1991).
8. N. U. Baratov, E. G. Mil'grom, V. I. Vinogradova, Ya. V. Rashkes, and M. S. Yunusov, Khim. Prir. Soedin., 854 (1993).
9. T. I. Golodnyuk, V. I. Vinogradova, and M. S. Yunusov, Khim. Prir. Soedin., 981 (1990).