SYNTHESIS AND DIURETIC ACTIVITY OF 4-CHLOROSALICYLIC ACID DERIVATIVES

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Substances that manifest diuretic activity [4-6] have been found among 4-chlorosalicyclic acid derivatives. Thus, for example, 4-chloro-5-sulfamoylsalicyl-2,6-dimethylanalide – Xipamide (USA) – exhibits a moderate but prolonged diuretic action [13]. It has been shown that approximately one-third of Xipamide is excreted from the body in the form of O-glucuronide [12]. In that connection, we felt it would be useful to study the diuretic action of 4-chlorosalicylic acid derivatives that have been alkylated by a phenol hydroxyl. In view of the fact that the addition of a butyl radical to the amino group of 3-amino-4-phenoxy-5-sulfamoylbenzoic acid markedly increases diuretic activity and, on the other hand there placement of the furfuryl group in 2-furfurylamino-4-chlor-5-sulfamoylbenzoic acid by a butyl group decreases diuretic activity [16], we felt it would be of interest to synthesize 2-butoxy-4-chloro-5-substituted benzoic acids and study their diuretic action.

The starting 4-chlorosalicylic acid (I) was obtained by method [5]. The alkylation of I by butyl iodide in NaOH aqueous solution under interphase catalysis conditions did not yield positive resutls. We did succeed in alkylating I in acetone in the presence of potassium carbonate by the method in [11]. However, this resulted in the formation of alkylation products both for the phenol hydroxyl and the carboxyl group. Complete alkylation of the phenol group required an excess of butyl iodide of not less than 3 moles per mole of I. This resulted in a good yield of the butyl ester of 2-butoxy-4-chlorobenzoic acid (II). Alkylation of the ethyl ester of 4-chlorosalicylic acid (III), obtained by the method in [15] with butyl iodide under similar conditions produces a good yield of the ethyl ester of 2-butoxy-4-chlorobenzoic acid (IV) and makes it possible to halve the consumption of butyl iodide and potassium carbonate. Alkaline hydrolysis of the esters of II and IV yielded 2-butoxy-4-chlorobenzoic acid (V). The structure of II, IV, and V was confirmed by IR-spectroscopy and element analysis. Compounds II, IV, and V had the following absorption bands in the IR-spectra (at cm^{-1}): II – 1730, 1130 (COOR), 1230, 1072 (Ar–O–C); IV – 1730, 1290, 1132 (COOR), 1235, 1072 (Ar–O–C); V – 3090, 1668, 1440, 1290 (COOH), 1240, 1080 (Ar–O–C). The structure of V was also confirmed by its titration with 0.1 N NaOH in ethanol with phenolphthalein as the indicator.

Sulfochlorination of compound V by chlorosulfonic acid either in chloroform or without a solvent at 65 ± 5°C is accompanied by the splitting of the simple ester bond and the substitution of the carboxyl gorup. This is confirmed by the formation of butyl alcohol and CO_2. We were not able to extract individual sulfochlorides from the resultant oily product which contained no less than three compounds, according to TLC data. When the mixture was treated with ammonia sulfochlorides, the result was a mixture of sulfamides from which we obtained low yields of 4-chloro-5-sulfamoylsalicylic acid (VI) and 2-butoxy-4-chlor-5-sulfamoylbenzoic acid (VII). We also observed the cleavage of the simple ester bond and the subsequent formation of sulfochloride mixtures when esters II and IV were sulfochlorinated under similar conditions. This difficulty could not be overcome by lowering the reaction temperature. Therefore, the sulfochlorination of compound V or its esters by chlorosulfonic acid in order to obtain compound VII is of no preparative significance.

On the other hand, the sulfochlorination of compound I by chlorosulfonic acid at 80°C results in a good yield of 4-chloro-5-chlorosulfonylsalicylic acid (VIII) [6]. One should note that when less than five moles of chlorosulfonic acid per mole of I are used, the yield of compound VIII is markedly reduced. When compound VIII is treated with ammonia by the method in [6], compound VI is produced. A trial mixture of compound VI specimens obtained by both methods did not reduce the compound's mp.

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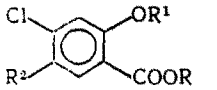
In connection with the fact that we were not able to obtain an acceptable yield of VII by employing the aforementioned method, we designed methods for obtaining VII and other 5-substituted V compounds by starting out with V.



I—IX, XI, XIII—XVI

R=H (I, V—VIII, XI, XV, XVI), Bu (II), Et (III, IV, XIII, XIV), Na (IX); R^1 = H (I, III, VI, VIII), Bu (II, IV, V, VII, IX, XI, XIII—XVI); R^2 = H (I—V), SO_2NH_2 (VI, VII, IX), SO_2Cl (VIII), NO_2 (XI, XIII), NH_2 (XIV, XV), Cl (XVI).

When compound V is nitrated by a nitrating mixture the resultant nitrogen product, according to TLC data, consists of two compounds which are easily separated inasmuch as one of them is soluble in a NaOH solution and the other is not. Element analysis and IR-spectroscopy indicate that the compound which is insoluble in NaOH is 2-butoxy-4-chloronitrobenzene (X). The IR spectrum of compound X lacks a carboxyl group absorption band and has the following absorption bands (in cm^{-1}): 1600, 1345 (NO_2), 1245, 1060 (Ar—O—C), 860, 830 (non-planar vibration of C—H in 1,2,4-substituted benzenes). According to IR spectroscopic and element analysis data the compound that is soluble in an alkaline solution is apparently 2-butoxy-4-chloro-5-nitrobenzoic acid (XI). Further confirmation of the nitro group's position in compound XI was obtained after we established the structure of compound VII. As one might have expected, the degree to which the carboxyl group is replaced by a nitro group is diminished as the reaction temperature is lowered. At 0 ± 5°C compound X accounts for only 2% of the nitro product.

In connection with what has been stated above we studied the nitration of compound IV. The nitration of compound IV with a nitrating mixture of 20 ± 5°C resulted in a good yield of a nitro compound whose structure was confirmed by backstep synthesis from compound XI as well as by IR spectroscopic and element analysis data. The reaction between thionyl chloride and compound XI resulted in the formation of 2-butoxy-4-chloro-5-nitrobenzoic chloroanhydride (XII) which, when treated with ethanol, formed ethyl 2-butoxy-4-chloro-5-nitrobenzoate which was identical to the compound IV nitration product.

The reduction of compounds XI and XIII by stannous dichloride in a mixture of ethanol and conc. HCl resulted in the formation of 2-butoxy-4-chloro-5-aminobenzoic acid (XV) and ethyl 2-butoxy-4-chloro-5-aminobenzoate (XIV). The separation of compound XV from the reaction mixture was quite difficult inasmuch as XV is soluble in both acids and bases. The best yeilds of XV were obtained when XI was reduced by ferrous hydroxide in aqueous ammonia and when XI was hydrated in a NaOH solution at 20°C and at a 1.1 atm hydrogen pressure in the presence of 10% Pd/C.

The diazotization of XV and treatment of the diazonium salt with saturated SO_2 in glacial AcOH by a similar method [8] resulted in the corresponding sulfochloride which was converted without separation into VII. Also obtained from XV by the Sandmeyer reaction was 2-butoxy-4,5-dichlorobenzoic acid (XVI). PMR and IR spectroscopy confirmed the position of the sulfamoyl group in compound VII, the position of the chlorine atom in compound XVI, and subsequently, the amino and nitrogroups in compounds XI-XV. The PMR spectra of compounds VII and XVI exhibited butyl group proton signals at 0.88-4.13, 0.90-4.12 ppm and benzene ring proton signals at 7.38, 7.32 ppm (1H, s; 6-H) and 7.57, 7.77 ppm (1H, s., 3-H), respectively. The absence of any spin-spin interaction between the benzene ring protons indicated their para-position with respect to each other [2]. Any other reciprocal positioning of the substituents in the compounds under consideration would have shown a marked splitting of the benzene ring proton signals, particularly the coherent spin-spin interaction between the protons in the ortho- and meta-positions equivalent to 7-10 and 2-3 Hz respectively [2]. The IR spectra of compounds VII, XI-XVI have absorption bands in the following regions (at cm^{-1}): 1685-1740 (COOH or COOR), 1225-1260, 1015-1060 (Ar—O—C), 830-860 (non-planar vibration of C—H in 1,2,4,5-substituted benzene [1, 10], as well as VII – 1343, 1175 (SO_2NH_2), XI – 1605, 1340 (NO_2), XIII – 1610, 1340 (NO_2), XV – 3400, 3510, (NH_2), XIV – 3395, 3500 (NH_2).

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IR spectra were read on Spektromom-2000 (Hungary) and IKS-29 instruments in KBr pellets. PMR spectra were recorded on a RYa-2310 (USSR) instrument with a working frequency of 60 MHz in DMSO-d_4. Internal standard was HMDS. Reaction progress and purity of the resultant compounds were controlled by TLC on Silufol UV-254 plates (Czechoslovakia).

Butyl 2-Butoxy-4-chlorobenzoate (II). A 138.2-g (1-mole) portion of K_2CO_3 was added to a solution of 86.3 g (0.5 mole) of compound I in 800 ml of acetone. The mixture was stirred until CO_2 evolution stopped. Then 276 g (1.5 mole) of butyl iodide was added and the mixture was boiled for 12 h, cooled, filtered, and the residue was then washed with 200 ml of acetone. The acetone was distilled off the combined filtrate and the residue was vacuum redistilled. The collected fraction had a bp of 207-208°C (20 m). The yield of II was 109.6 g (77%) in the form of an odorless, colorless oil, n_D^{20} 1.5122; d_4^{20} 1.1232; MR_D 76.12 (calculated 75.94). Found %: Cl 12.02. $C_{16}H_{21}ClO_3$. Calculated %: Cl 12.45.

In the same way, compound IV was obtained from III by using 1.5 mole of butyl iodide and 1.2 mole of K_2CO_3 per mole of compound III. The yield was 81%; bp 186-188°C (25 mm); n_D^{20} 1.5187; d_4^{20} 1.1162; MR_D 67.02 (calculated 66.70). Found %: Cl 13.35. $C_{13}H_{17}ClO_3$. Calculated %: Cl 13.81.

2-Butoxy-4-chlorobenzoic Acid (V). A mixture of 0.25 mole of II or IV and 360 ml of a 30% KOH solution was boiled for 1 h after which 540 ml of water and activated charcoal were added to the mixture. Then 200 ml of the distillate was distilled off and filtered. The filtrate was cooled and acidified with diluted H_2SO_4 to pH 3.0 and extracted with ether. The extract was dried over Na_2SO_4 and the ether was distilled off, leaving a compound V yield of 54.2 g (95%). mp 50-52°C (hexane), neutralization equivalent — 230.1 (calculated 228.7). Found %: Cl 15.58. $C_{11}H_{13}ClO_3$. Calculated %: Cl 15.50.

4-Chloro-5-chlorosulfonylsalicylic acid (VIII) was obtained by the method described in [6], mp 181-183°C (toluene), which corresponds to the literature data.

4-Chloro-5-sulfamoylsalicylic Acid (VI) was obtained by the method described in [6], mp 258-260°C (water), which corresponds to the literature data.

2-Butoxy-4-chloro-5-sulfamoylbenzoic Acid (VII). A solution of 24.4 g (0.1 mole) of compound XV and 6.9 g (0.1 mole) of $NaNO_2$ in 100 ml of 1 N KOH was added dropwise to 250 ml of conc. HCl at 0 ± 5°C. The resultant solution was added in portions to a mixture of 250 ml of a saturated SO_2 solution in glacial AcOH and 2.5 g of $CuCl_2 \cdot 2H_2O$ at 20 ± 5°C. The reaction mixture was then kept for 4 h at this temperature. The residue was then filtered off, washed with cold water, and added in small portions to 250 ml of 25% NH_3, kept for 1 h at 20 ± 5°C and the ammonia was distilled off up to the vapor temperature of the distillate which was 100°C. The residue was cooled and acidified to pH 2.0 with conc. HCl. The precipitate was filtered off, washed with water, and dried. The yield of compound VII was 16 g (52%), mp 178-180°C (water). Found %: Cl 11.67; N 4.42; S 10.35. $C_{11}H_{14}ClNO_5S$. Calculated %: Cl 11.52; N 4.55; S 10.42.

Sodium 2-Butoxy-4-chloro-5-sulfamoylbenzoate (IX). A solution of 1.54 g (5 mmole) of compound VII in 10 ml of ethanol was mixed with an equivalent amount of a titrated NaOH solution in ethanol. The solvent was removed in a vacuum water jet pump. The yield of compound IX was 1.83 g (100%), mp >260°C (with decomposition). The neutralization equivalent upon titrating an aqueous-alcohol solution of IX with 0.1 N HCl and a methyl orange indicator was 318.5 (calculated 329.7).

Nitration of Compound V. A nitrating mixture composed of 24 g (0.217 mole) of 57% HNO_3 and 36 g of conc. H_2SO_4 at 0 ± 5°C was added dropwise to a solution of 45.7 g (0.2 mole) of compound V in 200 ml of conc. H_2SO_4. The mixture was stirred for 2 h and decanted on crushed ice. The precipitate was filtered off, washed with water, and dissolved in 300 ml of 1 N NaOH. The solution was filtered and the residue on the filter was washed with water and dried. The yield of compound X was 0.9 g, mp 53-55° (50% ethanol). Found %: Cl 15.18. Calculated, %: Cl 15.44. Filtrate was acidified with conc. HCl to pH 2.0, the precipitate was filtered off, washed with water, and dried. The resultant yield of compound XI was 45.3 g (83%), mp 146-147°C (70% AcOH). Found, %: Cl 13.21. $C_{11}H_{12}ClNO_5$. Calculated %: Cl 12.95.

2-Butyoxy-4-chloro-5-nitrobenzoic Chloroanhydride (XII). A mixture of 8.2 g (0.03 mole) of compound XI, 4.5 ml of $SOCl_2$, and 15 ml of chloroform was boiled for 1 h. The solvent was distilled off and the residue was crystallized from heptane. The yield of XII was 7.6 g (87%), mp 51-54°C. Found %: Cl 24.51. $C_{11}H_{11}Cl_2NO_4$. Calculated %: Cl 24.27.

Ethyl 2-Butoxy-4-chloro-5-nitrobenzoate (XIII). A. A mixture of 5.84 g of XII and 20 ml of ethanol was boiled for 1 h. The solvent was distilled off and the residue was crystallized from heptane. The yield of XIII was 5.72 g (95%), mp 50-52°C. Found %: Cl 11.57. $C_{13}H_{16}ClNO_5$. Calculated %: Cl 11.75.

TABLE 1. Diuresis and Sodium Elimination in White Rats as Affected by Derivatives of 4-Chlorosalicylic Acid at a Dose of 24 mg/kg

Compound	4 h diuresis, ml		4 h sodium elimination, μ equivalents	
	experimental	control	experimental	control
VI	8,8±0,8	3,2±0,4 $P<0,001$	175,0±18,2	71,2±6,0 $P<0,001$
VII	5,8±0,5	3,2±0,4 $P<0,01$	138,0±14,4	74,2±6,0 $P<0,01$
IX	5,7±0,3	3,2±0,2 $P<0,01$	176,0±18,1	73,6±25,6 $P<0,05$
XI	2,4±0,2	3,0±0,2 $P>0,05$	87,4±13,8	80,2±12,0 $P>0,05$
XV	2,2±0,2	2,1±0,2 $P>0,05$	77,0±16,4	80,2±12,0 $P>0,05$
XVI	5,5±0,4	3,2±0,2 $P<0,01$	169,3±16,2	73,6±25,6 $P<0,05$

B. A nitrating mixture composed of 15 g (0.22 mole) of 93% HNO_3 and 20 g of conc. H_2SO_4 at 20 ± 5°C was added dropwise to a solution of 51.3 g (0.3 mole) of IV in 200 ml of conc. H_2SO_4. The mixture was stirred for 2 h and the mxiture was decanted onto crushed ice. This was followed by two 150 ml ether extractions. The ether extract was dried over Na_2SO_4 and the ether was distilled off. The residue was crystallized from heptane, yielding 54.9 g (91%) of compound XIII. No mp temperature depression occurred when a sample of this compound was mixed with a sample of the compound obtained by method A.

Ethyl 2-Butoxy-4-chloro-5-aminobenzoate (XIV). Solution 30, 2 g (0.1 mole) of XIII in 150 ml of ethanol, at 50 ± 5°C was added dropwise to a mixture of 90.3 g (0.4 mole) of $SnCl_2 \cdot 2H_2O$ and 70 ml of conc. HCl and stirred until the oily droplets disappeared (15-20 min). The mixture was then cooled and brought up to pH 10.0 with a 40% NaOH soluton at 20 ± 5°C. This was followed by two 150 ml ether extractions. The ether extract was washed with water and dried over Na_2SO_4. The ether was then distilled off and the residue was crystallized from heptane. The yield of XIV was 25 g (92%), mp 70-72°C. Found %: Cl 13.22; N 4.97. $C_{13}H_{18}ClNO_3$. Calculated %: Cl 13.05; N 5.15.

2-Butoxy-4-chloro-5-amino-benzoic Acid (XV). A. A 5.47-g (0.02-mole) portion of compound XI in 20 ml of 1 N NaOH was hydrated at 20°C and 1.1 atm of hydrogen pressure in the presence of 0.5 g of 10% Pd/C, prepared by method [9]. The catalyst was filtered off and the filtrate was acidified with conc. HCl to pH 1.0, treated with activated charcoal, and filtered. The filtrate was brought to pH 3.0 with an ammonia solution, and the precipitate was filtered off, washed with water, and dried. The yield of compound XV was 4.36 g (90%), mp 142-144°C (chloroform—haptane, 1:1). Found %: Cl 14.62; N 5.43. $C_{11}H_{14}ClNO_3$. Calculated %: Cl 14.55; N 5.75.

B. A solution of 13.7 g (0.05 mole) of XI in 75 ml of a 25% ammonia solution was added with vigorous stirring to a solution of 100 g (0.036 mole) of $FeSO_4 \cdot 7H_2O$ in 150 ml of water at 70°C. The mixture was stirred at 95 ± 3°C for 30 min and then filtered. The precipitate was washed with 200 ml of hot water. The filtrate was cooled and compound XV was separated as described above. The yield of XV was 7.3 g (60%).

C. A mixture of 13.6 g (0.05 mole) of XIV and 80 ml of a 30% KOH solution was boiled for 1 h, then treated with activated charcoal and filtered. The filtrate was cooled and acidified to pH 3.0 with 20% HCl. The precipitate was filtered off, washed with water, and dried. The yield of XV was 11.3 g (93%).

2-Butoxy-4,5-dichlorobenzoic Acid (XVI). A solution of 2.44 g (0.01 mole) of XV and 0.69 g (0.01 mole) of $NaNO_2$ in 10 ml of 1 N KOH was added dropwise to 25 ml of conc. HCl at 0 ± 5°C. The resultant solution was added dropwise to a solution of 1 g (0.01 mole) of CuCl in 10 ml of conc. HCl at 35 ± 5°C. The mixture was stirred for 15 min, the precipitate was filtered off, washed with water, and dried. The yield of XVI was 2.21 g (84%), mp 89-90°C (heptane). Found %: Cl 27.12. $C_{11}H_{12}Cl_2O_3$. Calculated %: Cl 26.95.

EXPERIMENTAL PHARMACOLOGICAL

A study was made of the effect that compounds VI, VII, IX, XV, and XVI have on diuresis and sodium ion excretion in white rats employing the method described in [14]. The experiments were performed on white intact rats weighing 200-250 g, as described earlier [3]. Urine sodium concentration was assayed by flame photometry on a PAZh-1 instrument. The study results are presented in Table 1.

As can be seen from the Table, compounds VI, VII, IX, and XVI increase diuresis by 1.8 to 2.8 times and sodium excretion by 1.7 to 2.2 times in the white rats. Diuretic activity was diminished when a hydroxyl group was replaced by a butoxyl group. Substitution of the sulfamoyl group on the chlorine atom did not induce any significant changes in the diuretic activity of compound V derivatives. On the other hand, compounds XI and XV did not have any significant effect on white rat diuresis and sodium excretion.

Thus, the experiments we conducted indicate that the derivatives of 3-sulfamoyl-4-chlorobenzoic acid represent a promising group of compounds for further research on diuretics.

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