O- and *N*-Substituted Products from the Treatment of 3,5-Dichloro-2-pyridone with Benzenesulfonyl Chlorides

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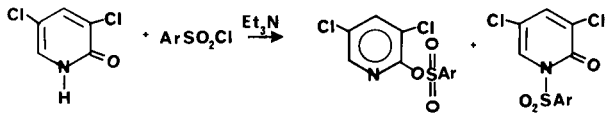
Treatment of 3,5-dichloro-2-pyridone with various benzenesulfonyl chlorides in the presence of triethylamine at 25° yielded both *O*- and *N*-sulfonylated products. These isomers were isolable, relatively stable compounds which were distinguished by their ir and uv spectra.

Our interest in the preparation of 2-pyridyl alkanesulfonates (1) prompts us to report an interesting finding in a related area. We have studied the reaction of 3,5-dichloro-2-pyridone (I) with various arenesulfonyl chlorides in the presence of triethylamine at 25° and have found that both *O*- and *N*-sulfonated products result. Prior to this report, only three publications (1,2,3) have reported preparations of 2-pyridyl sulfonates. Two of these (2,3) described the preparation of an arenesulfonate ester, but did not report the formation of an *N*-substituted product.

Although there are no previous examples of both *O*- and *N*-sulfonylations with 2-pyridone, a few examples of *O*- and *N*-acylations have been reported. Treatment of the sodium salt of 2-pyridone with an *aroyl* chloride yielded both *O*- and *N*-acyl derivatives (4). The first example of both *O*- and *N*-acylation of 2-pyridone by an *alkanoyl* halide was reported in 1968 (5). Spectroscopic evidence was given for both acetyl derivatives (prepared from the thallium salt of 2-pyridone at -40°), however, the *N*-acetyl compound quickly rearranged to the acetate ester at room temperature.

We have treated I with a number of benzenesulfonyl chlorides and obtained both the sulfonate ester III and sulfonamide IV in fair yields (see Table I).

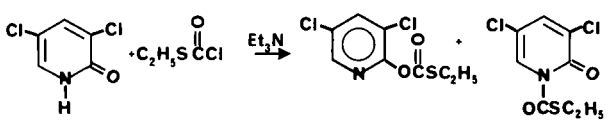


I II III IV

Both isomers III and IV were stable during the few months of this preparative study; however, slow decomposition occurred after longer standing.

The physical and spectroscopic data (Tables I and II) of the *O*- and *N*-substituted products (III and IV, respectively) indicate significantly different properties. Thus, the *O*-substituted isomers have absorptions at 274-279 mμ in the uv and carbon-hydrogen deformations at 12.2-12.5 μ in the ir while the *N*-substituted products exhibit higher melting points (45-90° greater), absorption at longer wavelengths (327-331 mμ) in the uv, carbonyl absorptions (5.9-6.0 μ) and different carbon-hydrogen deformations (11.5-11.9 μ) in the ir. The nmr spectral data of three pairs of aromatic ester-pyridone isomers (III-B and IV-B, III-F and IV-F, VI and VII, in Table II and Experimental) indicated an apparent anomalous effect caused by the proximity of the 2-nitro substituent to the 6-pyridyl hydrogen in IV-F. The difference in chemical shifts between the 4- and 6-hydrogens in amides IV-B and VII was 0.57 δ while in amide IV-F it was 0.25 δ. In the esters, III-B, III-F and VI, this difference was 0.21 to 0.39 δ. This effect can be explained by an anisotropic effect of the nitro group on the 6-hydrogen, or else by some small contribution due to hydrogen bonding between the 6-hydrogen and the oxygen of the nitro group (6).

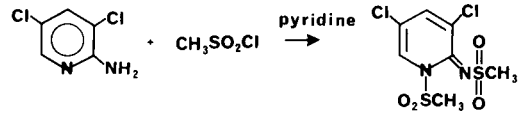
It was of interest to consider whether both III and IV occurred in concurrent, competing reactions, or whether only one isomer was formed and then rearranged partly during the course of the reaction. After III-B and IV-B were treated separately under the preparative conditions with triethylamine, tlc on silica gel revealed that neither compound isomerized.



I V VI VII

An interesting and related finding resulted in the course of our treatment of I with ethyl chlorothioformate (V), under the above reaction conditions. Here again, both *O*- (VI) and *N*-acylated (VII) products resulted.

In view of the striking difference between alkane- and arenesulfonyl chlorides in their reactions with this 2-pyridone, it was of interest to compare their action with the corresponding 2-amino analog, 2-amino-3,5-dichloropyridine (VIII). When equimolar quantities of VIII and methanesulfonyl chloride were allowed to react at 25° in pyridine, a good yield of only the bis-sulfonamide resulted (IX).



VIII IX

This was unexpected inasmuch as equimolar quantities of methanesulfonyl chloride and unsubstituted 2-aminopyridine in pyridine gave only 2-methanesulfonamidopyridine (7), which was found to exist predominately in the imino-form. Similarly, equimolar quantities of 2-aminopyridine and benzenesulfonyl chloride (8) or 4-acetamidobenzenesulfonyl chloride (9) in pyridine afford good yields of only the 2-arenesulfonamidopyridine.

EXPERIMENTAL (10)

Reaction of 4-Chlorobenzenesulfonyl Chloride with 3,5-Dichloro-2-pyridone, General Method for Preparation of III and IV.

A solution of 4-chlorobenzenesulfonyl chloride, (21.1 g., 0.10 mole), in toluene (100 ml.) was added to 3,5-dichloro-2-pyridone (I) (11), 16.4 g. (0.10 mole), in toluene (100 ml.) containing triethylamine, (12.7 g., 0.125 mole), during 10 minutes maintaining at 27-28° with some external cooling. The mixture was stirred for 1 hour at 25°, filtered, and the solids (triethylamine hydrochloride) washed on the filter with fresh toluene, letting the wash combine with the filtrate. The filtrate was evaporated under vacuum and the resultant crude solids taken up in boiling cyclohexene, 200 ml. The solids which crystallized after chilling were removed by filtration and dried, yielding 17.5 g. (52%) of 1-(4-chlorobenzenesulfonyl)-3,5-dichloro-2-pyridone (IV-B), m.p. 144-148.5°. The analytical sample, obtained from additional recrystallization with cyclohexene, had m.p. 148-150°.

Partial evaporation and chilling of the first cyclohexene recrystallization-filtrate yielded 3,5-dichloro-2-pyridyl-4-chlorobenzenesulfonate (III-B), 5.6 g. (17%), m.p. 101-104°. Purification was accomplished by chromatography on a silica gel column, eluting with a cyclohexane-benzene mixture (1:1), which gave a white solid, m.p. 103-104.5° (see Table I for analytical data and Table II for spectroscopic data).

TABLE I

Products from 3,5-Dichloro-2-pyridone and Benzenesulfonyl Chlorides

	Substituted Benzenesulfonyl Chloride (II)	Product Molecular Formula	*O*-Substituted (III)					*N*-Substituted (IV)					Calculated		
			M.p., °C	Yield %	Analyses C	H	N	M.p., °C	Yield %	Analyses C	H	N	C	H	N
A		$C_{11}H_7Cl_2NO_3S$	75-77 (a)	13	43.31	2.31	4.47	137-140 (a)	23	43.14	2.36	4.47	43.44	2.31	4.60
B	4-Cl	$C_{11}H_6Cl_3NO_3S$	103-104.5	17	39.03	1.92	3.95	148-150 (b)	52	39.02	1.74	4.02	39.02	1.79	4.14
C	3,4-Cl_2	$C_{11}H_5Cl_4NO_3S$	102-104 (c)	10	35.78	1.23	3.70	158-160 (d)	35	35.13	1.45	3.57	35.42	1.35	3.75
D	3-NO_2	$C_{11}H_6Cl_2N_2O_5S$	82-84 (e)	4	37.84	1.92	7.91	169-171 (e)	34	37.40	1.81	7.93	37.84	1.73	8.02
E	4-NO_2	$C_{11}H_6Cl_2N_2O_5S$	109-111 (c)	28	37.51	1.84	7.78	184-186 (f)	31	37.51	1.70	7.81	37.84	1.73	8.02
F	2-NO_2-4-Cl	$C_{11}H_5Cl_3N_2O_5S$	114-115 (g)	35	34.16	1.45	7.14	158-159 (g)	14	34.12	1.34	7.09	34.44	1.31	7.30
G	3-NO_2-4-Cl	$C_{11}H_5Cl_3N_2O_5S$	105.5-107 (e)	43	34.15	1.40	7.20	165.5-167 (e)	14	34.17	1.38	7.20	34.44	1.31	7.30

Recrystallization solvents: (a) methanol, (b) cyclohexene, (c) cyclohexane, (d) benzene, (e) trichloroethylene, (f) dichloromethane, (g) butanone.

TABLE II

Spectroscopic Data

Compound (c)	Ultraviolet (a) λ max, mμ (ε x 10^{-3})		λ mμ (ε x 10^{-3})		Infrared (Nujol) λ (C=O)	μ (C=C)	(O=S=O)		(d)	(e)	Nmr (b) δ, ppm H4	H6
I	240	(6.09)	320	(5.48)	5.9	6.3	--	--	11.9	--	7.63 (f)	7.92 (f)
IIIA	221	(18.5)	274	(4.36)	--	--	7.3	8.4	--	12.4		
IVA	229 (g)	(17.8)	327	(5.17)	5.9	6.2	7.3	8.4	11.5	--		
IIIB	230	(18.9)	278	(3.86)	--	--	7.3	8.4	--	12.4	7.84	8.12
IVB	239	(19.8)	327	(4.84)	5.9	6.2	7.3	8.4	11.5	--	7.49	8.06
IIIC					--	--	7.3	8.4	--	12.5		
IVC					5.9	6.3	7.3	8.5	11.6	--		
IIID					--	--	7.3	8.5	--	12.4		
IVD					6.0	6.3	7.3	8.4	11.6	--		
IIIE					--	--	7.3	8.5	--	12.4		
IVE					5.9	6.3	7.4	8.4	11.6	--		
IIIF	220	(24.9)	279	(5.18)	--	--	7.3	8.5	--	12.2	7.86	8.07
IVF	<218	(-)	331	(4.51)	6.0	6.3	7.3	8.5	11.6	--	7.56	7.81
IIIG					--	--	7.3	8.5	--	12.3		
IVG					6.0	6.3	7.3	8.4	11.6	--		

(a) In methanol. (b) In deuteriochloroform. (c) Refer to text and Table I; III = ester, IV = sulfonamide. (d) Diene C-H out of plane deformation. (e) Aromatic C-H out of plane deformation. (f) In deuteriochloroform plus deuteriotrifluoroacetic acid. (g) Shoulder.

Samples of III-B and IV-B were tested separately for possible isomerization under preparation conditions by dissolving 0.34 g. (1.0 mmole) in toluene, (2 ml.) with and without triethylamine, (0.17 ml., 1.25 mmoles), and allowed to stand in closed vials at 25° for 1 hour. The solutions were then examined by tlc on silica gel sheets, developed with a cyclohexane-benzene mixture (4:1). Each solution gave only one spot, indicating that no isomerization had occurred; III-B, R_f 0.72; IV-B, R_f 0.46.

Reaction of Ethyl Chlorothioformate with 3,5-Dichloro-2-pyridone (VI) (VII).

Ethyl chlorothioformate, 27.9 g. (0.24 mole), was added dropwise with stirring in 25 minutes at 25-30° to a solution of 3,5-dichloro-2-pyridone, (40.0 g., 0.25 mole) and triethylamine (29.6 g., 0.29 mole), in toluene, 300 ml. The reaction mixture was allowed to stir for 1 hour at 25°, filtered, and the solids washed on the funnel with fresh toluene, letting the washings combine with the filtrate. The composite toluene solution was washed twice with 50 ml. portions of 4% sodium hydroxide, then once with 1% acetic acid, and finally with water until neutral. The toluene was removed under vacuum, leaving an oil which partly crystallized. The oil, which was separated by filtration, crystallized on chilling and was purified by recrystallization from petroleum ether (30-60°), giving 8.9 g. (14%) of 3,5-dichloro-2-pyridyl *S*-ethyl thiocarbonate (VI), m.p. 51-52.5°; ir (Nujol), λ (μ): 5.8 (ester C=O), 9.3 (C-O); uv (methanol), λ (mμ):277 (ε 3.95 x 10^3); nmr (deuteriochloroform), δ (ppm):1.38 (t, $3CH_3$, J 7 cps), 2.94 (q, CH_2, J 7 cps), 7.81 (d, pyridine H4, J 2.5 cps), 8.20 (d, pyridine H6, J 2.5 cps).

The solids from which VI was separated as an oil by filtration were purified by recrystallization from 2-propanol, giving 9.0 g. (15%) of 3,5-dichloro-1-(ethylthiocarbonyl)-2-pyridine (VII), m.p. 82-83.5°; ir (Nujol), λ (μ): 5.9, 6.0, 6.1, 6.3, 8.9, 11.6; uv (methanol), λ (mμ): 242 (ε 5.38 x 10^3), 335 (ε 5.14 x 10^3); nmr (deuteriochloroform), δ (ppm): 1.35 (t, CH_3, J 7 cps), 2.93 (q, CH_2, J 7 cps), 7.52 (d, pyridone H4, J 2.5 cps), 8.09 (d, pyridone H6, J 2.5 cps).

Anal. Calcd. for $C_{11}H_6Cl_2N_2O_5S$: C, 37.84; H, 1.73; N, 8.02. VI, Found: C, 37.51; H, 1.70; N, 7.81. VII, Found: C, 37.51; H, 1.84; N, 7.78.

N,N'-Bis(methanesulfono)-3,5-dichloro-1,2-dihydro-2-iminopyridine (X).

Methanesulfonyl chloride, 21.1 g. (0.18 mole), was added slowly with stirring and cooling at 0° to a solution of 2-amino-3,5-dichloropyridine, (30.0 g., 0.18 mole) dissolved in dry pyridine (23.2 g., 0.29 mole). After allowing to stand at room temperature overnight, the reaction mixture was poured into ice water with stirring. The yellow solids were removed by filtration, dried, slurried with absolute ethanol (200 ml.) at 25° and the slurry filtered. The dried yellow solid, 22.0 g. (97% based on methanesulfonyl chloride), m.p. 187-189°, was further purified by recrystallization from benzene to m.p. 188.5-189.5°; ir (Nujol), λ (μ): 6.5, 6.9, 7.0, 7.4, 7.6, 8.6, 11.0, 12.0, 13.2 (all v.s., except 6.5); uv (methanol), λ (mμ): 227 (ε 10.4 x 10^3), 279 (ε 3.94 x 10^3), 287 shoulder (ε 3.19 x 10^3); nmr (deuteriochloroform), δ (ppm): 3.60 (s $6CH_3$), 7.88 (d, pyridone H6; J 2.5 cps), 8.40 (d, pyridone H4; J 2.5 cps).

Anal. Calcd. for $C_7H_8Cl_2N_2O_4S_2$: C, 26.34; H, 2.53; N, 8.78. Found: C, 25.99; H, 2.65; N, 8.60.

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