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SULFOALKYLATION OF 1,2-DIHYDRO-3,6-PYRIDAZINE- AND 2,3-DIHYDRO-1,4-PHTHALAZINEDIONES AND THEIR N-PHENYL DERIVATIVES BY 1,3-PROPANE-SULTONE AND BROMOALKANESULFONATES

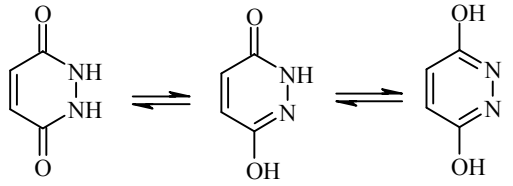
L. Rastyanite, G. K. Kupyatis, A. Matiyeshka, and O. Eicher-Lorka

When 1,2-dihydropyridazine-3,6-, 2,3-dihydrophthalazine-1,4-, 1-phenyl-1,2-dihydropyridazine-3,6-, and 2-phenyl-2,3-dihydrophthalazine-1,4-diones react with 1,3-propanesultone and bromoalkanesulfonates, depending on the nature of the sulfoalkylating agent in the case of 1,2-dihydropyridazine-3,6- and 2,3-dihydrophthalazine-1,4-diones, either N,O- or O,O^1-disulfoalkylated compounds may be formed, while O-monosulfoalkylated reaction products may be formed in the case of the N-phenyl-substituted derivatives of the above-indicated azinediones.

Keywords: bromoalkanesulfonates, 1,2-dihydropyridazine-3,6-dione, 2,3-dihydrophthalazine-1,4-dione, 1,3-propanesultone, 1-phenyl-1,2-dihydropyridazine-3,6-dione, 2-phenyl-2,3-dihydro-phthalazine-1,4-dione, phase-transfer catalysis, sulfoalkylation.

Derivatives of 1,2-dihydro-3,6-pyridazinedione (**1a**) are part of the composition of herbicidal compositions [1]. Compound **1a** is used as a plant growth regulator [2] and also, such as 2,3-dihydro-1,4-phthalazinedione (**1b**), to prepare drugs [3].

For dione **1a** (as for **1b**), the existence of three tautomeric forms **A-C** is possible:



A **B** **C**

We know that alkylation of dione **1a** by alkyl halides can occur both in form **A** [4] and in form **B** [5, 6]. No literature data are available on introduction of sulfoalkyl groups into the azinediones indicated above by substitution reactions. Only synthesis of N-monosulfoethyl derivatives of **1a** and **1b** by addition of their NH group to vinylsulfonate are described [7, 8].

Institute of Chemistry, Vilnius LT-2600, Lithuania; e-mail: algula@takas.lt. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1547-1551, November, 2002. Original article submitted January 8, 2001.

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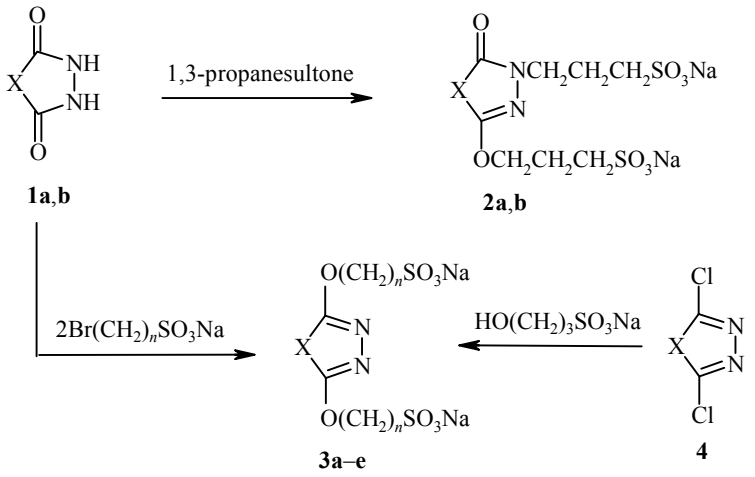
Sulfoalkylation of **1a** by 1,3-propanesultone under phase-transfer catalysis conditions in the presence of triethylbenzylammonium chloride (TEBA) for a reagent ratio of 1:2 led to formation of the N,O-disulfoalkylated product **2a**. Formation of compound **2a** was confirmed by the presence in its ^{1}H NMR spectrum of two doublet signals for protons of the –CH=CH– group at 7.32 ppm and 7.41 ppm, and also a strong stretching vibration band for the CO group in pyridazinedione in its IR spectrum at 1671 cm^{-1} [9]. In the case of sulfoalkylation in an aqueous-alcoholic solution in the presence of base, according to the ^{1}H NMR spectrum, along with formation of product **2a**, hydrolysis of the sultone occurred with formation of 3-hydroxypropanesulfonate. The mixture of sulfonates obtained could not be separated. Under the conditions described above for phase-transfer catalysis of dione **1b** with 1,3-propanesultone for a reagent ratio of 1:2, the N,O-disulfopropylated derivative **2b** is also formed:



1, **2 a** X = CH=CH, **b** X = 1,2-C_6H_4, **3a**, **c**, **e** X = CH=CH, **b**, **d** X = 1,2-C_6H_4, **a**, **b** n = 3, **c**, **d** n = 1, **e** n = 2

Replacing the sultone with sodium 3-bromoalkanesulfonates and carrying out the reaction in a one-phase system in the presence of sodium hydroxide promoted formation of symmetric disulfoalkylated products. When diones **1a,b** were refluxed in aqueous medium in the presence of a sodium hydroxide – sodium 3-bromopropanesulfonate mixture (reagent ratio 1:2:2), we obtained O,O^1-disulfopropylated derivatives **3a,b**. The reaction of azinediones **1a,b** with sodium bromomethanesulfonate proceeded analogously, also with formation of O,O^1-disulfomethyl-substituted products **3c,d**. Under the conditions described above, only dione **1a** easily reacted with sodium 2-bromoethanesulfonate to form disodium 3,6-di(2-sulfonatoethoxy)pyridazine (**3e**). But when dione **1b** was reacted under the same conditions with 2-bromoethanesulfonate, not only was the O,O^1-disulfoethylated derivative formed but also (as a result of dehydrobromination of the starting sulfonate) sodium vinylsulfonate. Its formation was confirmed by the presence in the ^{1}H NMR spectrum of signals at 6.10 ppm and 6.95 ppm, typical for protons in the –CH=CH$_2$ group. The mixture of sulfonates could not be separated.

Formation of O,O^1-disulfoalkylated derivatives is proven by the presence in their ^{1}H NMR spectra of singlets from the –CH=CH– group at 7.26, 7.23, and 7.23 ppm (for **3a,c**, and **e**), two symmetric multiplets in the intervals for protons of the aromatic ring, 7.80-8.22 ppm and 7.88-8.27 ppm (for **3b,d**), and also the fact that the ^{1}H NMR spectra for compound **3a** are identical to the spectrum for the compound obtained from 3,6-dichloropyridazine (**4**) and sodium 3-hydroxypropanesulfonate under phase-transfer catalysis conditions.

Under the described phase-transfer catalysis conditions, 1-phenyl-1,2-dihydropyridazine-3,6-dione (**5a**) and 2-phenyl-2,3-dihydrophthalazine-1,4-dione (**5b**) reacted with 1,3-propanesultone to form the O-sulfoalkylated products **6a,b**. Under noncatalytic conditions in the presence of an aqueous sodium hydroxide

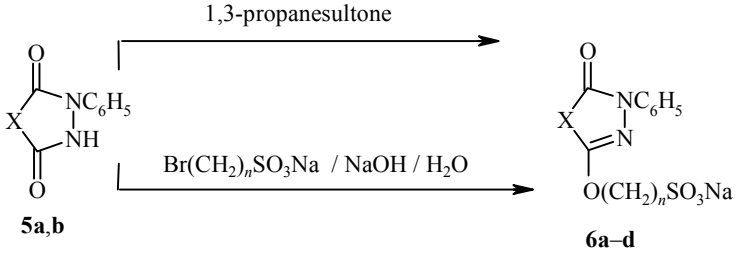
TABLE 1. Physicochemical and Spectral Characteristics of Synthesized Compounds **2, 3, 6**

Compound	Empirical formula	mp, °C*	Found, % / Calculated, %			^{1}H NMR spectrum, δ, ppm, *J* (Hz)	Yield, %
			C	H	S		
2a	$C_{10}H_{14}N_2Na_2O_8S_2$	226 (with dec.)	30.11 / 30.00	3.41 / 3.52	15.90 / 16.02	2.35 (4H, m, CCH_2C); 3.26 (4H, t, *J* = 7.0, CH_2S); 3.98 (4H, t, *J* = 6.5, CH_2N); 4.52 (4H, t, *J* = 6.5, CH_2O); 7.32 and 7.41 (2H, two d, *J* = 9.0, CH=CH)	84.1
2b	$C_{14}H_{14}N_2Na_2O_8S_2$	315 (with dec.)	37.63 / 37.50	3.08 / 3.15	14.38 / 14.30	2.29 (4H, m, CCH_2C); 3.31 (4H, t, *J* = 6.5, CH_2S); 4.23 (4H, t, *J* = 6.5, CH_2N); 4.55 (4H, t, *J* = 6.5, CH_2O); 7.81-8.30 (4H, m, CH arom.)	89.3
3a*[2]	$C_{10}H_{14}N_2Na_2O_8S_2$	256 (with dec.)	30.15 / 30.00	3.51 / 3.52	16.14 / 16.02	2.24 (4H, m, CCH_2C); 3.32 (4H, t, *J* = 6.5, CH_2S); 4.20 (4H, t, *J* = 6.5, CH_2O); 7.26 (2H, s, CH=CH)	78.4
3b	$C_{14}H_{14}N_2Na_2O_8S_2$	>320	37.48 / 37.50	3.24 / 3.15	14.22 / 14.30	2.28 (4H, m, CCH_2C); 3.28 (4H, t, *J* = 6.5, CH_2S); 4.20 (4H, t, *J* = 6.5, CH_2O); 7.80-8.22 (4H, m, CH arom.)	74.7
3c	$C_6H_6N_2Na_2O_8S_2$	242 (with dec.)	20.82 / 20.83	1.87 / 1.75	18.58 / 18.63	4.23 (4H, s, CH_2O); 4.23 (2H, s, CH=CH)	82.3
3d	$C_{10}H_8N_2Na_2O_8S_2$	>300	30.41 / 30.46	1.96 / 2.04	16.68 / 16.72	4.70 (4H, s, CH_2O); 7.88-8.27 (4H, m, CH arom.)	87.4
3e	$C_8H_{10}N_2Na_2O_8S_2$	234 (with dec.)	23.18 / 23.12	2.64 / 2.70	17.14 / 17.22	3.75 (4H, t, *J* = 7.0, CH_2S); 3.85 (4H, t, *J* = 7.0, CH_2O); 7.23 (2H, s, CH=CH)	80.1
6a*[2]	$C_{13}H_{13}N_2NaO_5S$	>300	47.08 / 47.00	4.09 / 3.98	9.58 / 9.65	2.33 (2H, m, CCH_2C); 3.28 (2H, t, *J* = 6.5, CH_2S); 4.02 (2H, t, *J* = 6.5, CH_2O); 7.20 and 7.28 (2H, two d, *J* = 9.0, CH=CH); 7.53-7.88 (5H, m, CH arom.)	88.4
6b	$C_{17}H_{15}N_2NaO_5S$	>300	53.52 / 53.40	4.12 / 3.95	8.23 / 8.38	2.35 (2H, m, CCH_2C); 3.33 (2H, t, *J* = 6.5, CH_2S); 3.99 (2H, t, *J* = 6.5, CH_2O); 6.95-7.72 (4H, m, CH arom.)	66.3
6c	$C_{11}H_9N_2NaO_5S$	224-225	43.37 / 43.42	3.03 / 2.98	10.43 / 10.50	4.25 (2H, s, CH_2); 7.28 and 7.30 (2H, d, CH=CH); 7.35-7.59 (5H, m, CH arom.)	79.2
6d	$C_{15}H_{11}N_2NaO_5S$	>300	50.86 / 50.83	3.16 / 3.12	8.89 / 9.03	4.59 (2H, s, CH_2); 6.92-7.84 (9H, m, CH arom.)	70.4

* Compounds **3b, d** and **6a, b, d** decompose without melting.

*[2] Obtained by method A.

solution, diones **5a,b** reacted with sodium 3-bromopropanesulfonate to also form compounds **6a,b**, and when reacted with sodium bromomethanesulfonate they formed the O-sulfomethyl derivatives **6c,d**. Upon reaction of diones **5a,b** with 2-bromoethanesulfonate, judging from the ^{1}H NMR spectra, as in the case mentioned above, along with the O-sulfoethyl derivative we saw formation of sodium vinylsulfonate as a result of dehydrobromination.



5,**b** **6a–d**

5, **6 a** X = CH=CH, n = 3, **b** X = 1,2-C_6H_4, n = 3; **6 c** X = CH=CH, n = 1, **d** X = 1,2-C_6H_4, n = 1

EXPERIMENTAL

The IR spectra were taken on a Specord IR-75 in KBr tablets. The ^{1}H NMR spectra were recorded on a Hitachi R22 (90 MHz), D_2O as the solvent, DSS as the internal standard. Sodium 3-bromo-1-propanesulfonate was obtained by the procedure in [10], sodium 3-hydroxy-1-propanesulfonate was obtained as in [11], sodium bromomethanesulfonate as in [12], 1-phenyl-1,2-dihydropyridazine-3,6-dione [13], and 2-phenyl-2,3-dihydrophthalazine-1,4-dione as in [14]. The physicochemical and spectral characteristics of compounds **2, 3**, and **6** are shown in Table 1.

Disodium 3-[6-Oxo-3-(3-sulfonatopropoxy)-1,6-dihydro-1-pyridazinyl]propanesulfonate (2a). A solution of NaOH (1.6 g, 40 mmol) in H_2O (30 ml) was added to 1,2-dihydropyridazine-3,6-dione (2.24 g, 20 mmol), then a solution of 1,3-propanesultone (4.88 g, 40 mmol) in benzene (20 ml) and TEBA (0.2 g) were added. The reaction mixture was refluxed for 1 h with vigorous stirring, this was cooled down to room temperature, the layers separated, the aqueous layer was evaporated down until the first crystals appeared, the residue was allowed to stand in a refrigerator. The precipitated crystals were filtered out, washed with *i*-PrOH and Et_2O. They were recrystallized from an EtOH–H_2O mixture, 1:1.

Disodium 3-[1-Oxo-4-(3-sulfonatopropoxy)-1,2-dihydro-2-phthalazinyl]propanesulfonate (2b) was obtained similarly to compound **2a** from 2,3-dihydrophthalazine-1,4-dione (3.24 g, 20 mmol), NaOH (1.6 g, 40 mmol) in H_2O (30 ml), 1,3-propanesultone (4.88 g, 40 mmol) in benzene (20 ml) and TEBA (0.2 g).

Disodium 3,6-Di(3-sulfonatopropoxy)pyridazine (3a). A. Dione **1** (2.24 g, 20 mmol) and NaOH (1.2 g, 40 mmol) were dissolved in H_2O (30 ml). Sodium 3-bromo-1-propanesulfonate (9.0 g, 40 mmol) were added to the solution and refluxed for 4 h. The solution was filtered, the water was distilled off under vacuum until crystals appeared. EtOH and Et_2O (30 ml of each) were added to the residue, the precipitated crystals were filtered out and recrystallized from H_2O.

B. Obtained similarly to compound **2a** from sodium 3-hydroxy-1-propanesulfonate (3.24 g, 20 mmol), 50% NaOH solution (35 ml), 1,6-dichloropyridazine (1.49 g, 10 mmol), dissolved in *o*-xylene (10 ml), and TEBA (0.2 g) with vigorous stirring for 8 h at 60-70°C. The product was recrystallized from *i*-PrOH–H_2O, 1:2. Yield of **3a** 3.64 g (90.5%); mp 255-256°C (with decomposition). ^{1}H NMR spectrum, δ, ppm, J (Hz): 2.23 (4H, m, CCH_2C); 3.34 (4H, t, J = 6.5, CH_2S); 4.20 (4H, t, J = 6.5, CH_2O); 7.27 (2H, s, CH=CH). Found, %: C 29.91; H 3.64; S 15.73. $C_{10}H_{14}N_2Na_2O_8S_2$. Calculated, %: C 30.00; H 3.52; S 16.02.

Compounds 3b-e were obtained by method A.

Sodium 3-(6-Oxo-1-phenyl-1,6-dihydro-3-pyridazinyloxy)-1-propanesulfonate (6a). A. Obtained similarly to compound **2a** from 1-phenyl-1,2-dihydropyridazine-3,6-dione (3.76 g, 20 mmol), NaOH (0.8 g, 20 mmol), H_2O (30 ml), 1,3-propanesultone (2.44 g, 20 mmol), benzene (30 ml), TEBA (0.2 g) with refluxing for 2 h.

B. Obtained similarly to compound **3a** by method A from 1-phenyl-1,2-dihydropyridazine-3,6-dione (3.76 g, 20 mmol), NaOH (0.8 g, 20 mmol), H_2O (40 ml) and 3-bromo-1-propanesulfonate (4.50 g, 20 mmol). Yield of compound **6a** 4.86 g (72.3%); decomposes at >300°C without melting. ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.35 (2H, m, CCH_2C); 3.27 (2H, t, *J* = 6.5, CH_2S); 4.02 (2H, t, *J* = 6.5, CH_2O); 7.21 and 7.28 (2H, two d, *J* = 9.0, CH=CH); 7.53-7.89 (5H, m, CH arom.). Found, %: C 46.96; H 4.16; S 9.58. $C_{13}H_{13}N_2NaO_3S$. Calculated, %: C 47.00; H 3.98; S 9.65.

Compounds 6b-d were obtained by method A.

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REFERENCES

1. S. Shimano, S. Kobayashi, M. Yanagi, O. Yamada, A. Shida, and F. Futotsuya, US Patent 4561880; *Ref. Zh. Khim.*, 14O437P (1986).
2. Yu. V. Rakitin (editor), *Maleic Acid Hydrazide as a Plant Growth Regulator* [in Russian], Nauka, Moscow (1973), p. 343.
3. B. V. Passet and V. Ya. Vorob'eva, *Technology of Pharmaceutical Chemical Preparations and Antibiotics* [in Russian], Meditsina, Moscow (1977), p. 265.
4. R. L. Hinman and R. J. Landberg, *J. Org. Chem.*, **24**, 724 (1959).
5. J. Druey, K. Meier, and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).
6. K. Eichenberger, A. Stachelin, and J. Druey, *Helv. Chim. Acta*, **37**, 837 (1954).
7. A. LeBerre and B. Dumaitre, *Compt. Rend. Acad. Sci., Ser. C.*, **265**, 642 (1967).
8. A. LeBerre, B. Dumaitre, and J. Petit, *Bull. Soc. Chim. France*, 4376 (1970).
9. A. P. Katritskii (editor), *Physical Methods in Heterocyclic Chemistry*, Khimiya, Moscow (1966), p. 568.
10. J. H. Helberger and J. F. Sproviero, *Liebigs Ann. Chem.*, **666**, 67 (1963).
11. J. H. Helberger, G. Manecke, and R. Heyden, *Liebigs Ann. Chem.*, **562**, 22 (1949).
12. W. M. Lauer and C. M. Langkammerrer, *J. Am. Chem. Soc.*, **57**, 2360 (1935).
13. J. Druey, A. Huni, K. Meier, B. H. Ringier, and A. Stachelin, *Helv. Chim. Acta*, **37**, 510 (1954).
14. J. Dran and D. E. Seymour, *J. Chem. Soc.*, 852 (1955).