INVESTIGATIONS IN THE FIELD OF 2,1,3-THIADIAZOLE AND 2,1,3-SELENADIAZOLE

LIX. Carboxy-, Carboxymethyl-, and Carboxyethylbenzo-2,1,3-thiadiazoles*

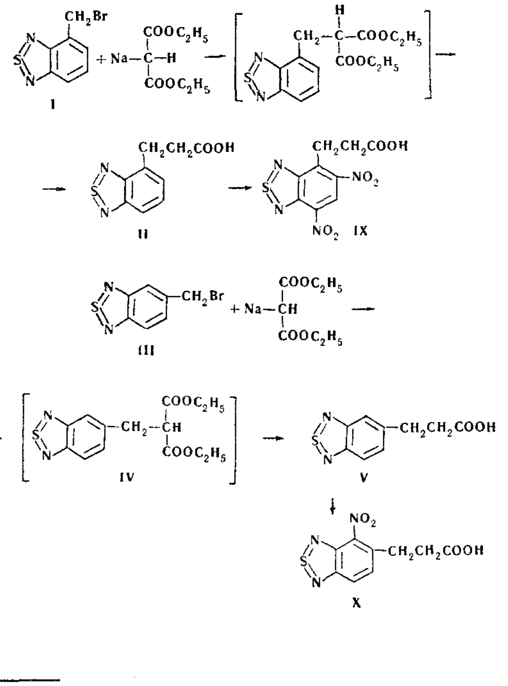
V. G. Pesin, S. A. D'yachenko, and E. V. Golubeva

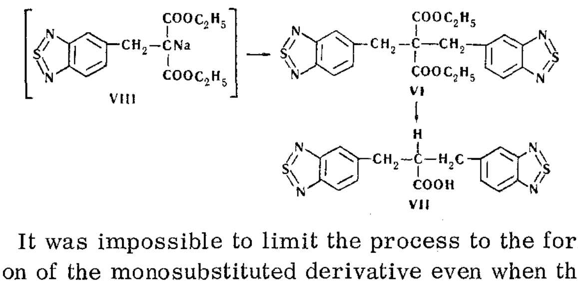
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 4, pp. 619–622, 1969

UDC 547.794.3:541.127:543.422.4

The action of sodiomalonic ester on 4-bromomethylbenzo-2,1,3-thiadiazole forms a malonate which is converted by acid hydrolysis into 4-(β-carboxyethyl)benzo-2,1,3-thiadiazole. When this reaction is carried out with 5-bromomethylbenzo-2,1,3-thiadiazole, mono- and disubstituted malonic esters are formed the acid hydrolysis of which gives the corresponding acids. The nitration of 4-and 5-(β-carboxyethyl)benzo-2,1,3-thiadiazoles forms, respectively, 4-(β-carboxyethyl)-5,7-dinitrobenzo-2,1,3-thiadiazole and 5-(β-carboxyethyl)-4-nitrobenzo-2,1,3-thiadiazole. The reaction of 4-bromomethylbenzo-2,1,3-thiadiazole with potassium cyanide forms two products: 4-cyanomethylbenzo-2,1,3-thiadiazole and 1,2-di(benzo-2,1,3-thiadiazole-4'-yl)-2-cyanoethane.

In the present work we have studied the synthesis of several acid derivatives of benzo-2,1,3-thiadiazole and have compared the pK_a values of these acids with the pK_a values of the corresponding acid derivatives of benzene. The reaction of 4-bromomethylbenzo-2,1,3-thiadiazole (I) with sodiomalonic ester smoothly formed the corresponding malonate, which was converted on acid hydrolysis into 4-(β-carboxyethyl)benzo-2,1,3-thiadiazole (II). When this reaction was carried out with 5-bromomethylbenzo-2,1,3-thiadiazole (III), a 63% yield was obtained of the isomeric malonate IV, forming on acid hydrolysis 5-(β-carboxyethyl)benzo-2,1,3-thiadiazole (V); another reaction product was the disubstituted malonic ester VI, which was converted on acid hydrolysis into the isobutyric acid derivative VII.





It was impossible to limit the process to the formation of the monosubstituted derivative even when the reaction was carried out with a twofold excess of malonic ester. Such a direction of the process has been observed repeatedly in the reaction of benzyl chloride with sodiomalonic ester (the end-products of the reaction consist of approximately 50–60% of benzylmalonic ester and 20–30% of dibenzylmalonic ester) [2,3]. When the reaction is carried out with o- or p-nitrobenzyl chloride, the disubstituted derivative is predominant product and the amount of monosubstituted derivative is very small [4–7]. It has been reported [8] that, 4-methoxy-3-nitrobenzyl chloride gives, with sodiomalonic ester, an 85% yield of the disubstituted malonic ester and that it is impossible to obtain the monosubstituted derivative even when the reaction is carried out with a tenfold excess of malonic ester. These results show that electronegative substituents in the benzene ring favor the formation of the disubstituted and oppose the formation of the monosubstituted derivative.

The formation of the monosubstituted malonate IV in 60% yield by the reaction of III with sodiomalonic ester shows that the electron-accepting nature of the thiadiazole ring as a substituent in a benzene ring is scarcely exhibited under the conditions of this reaction. The bromide III behaves similarly to benzyl chloride. A possible explanation of the formation of the disubstituted product is that the monosubstituted compound obtained initially, because of the high reactivity of the hydrogen of the CH group, reacts with sodiomalonic ester to form the sodio derivatives VIII which then reacts with a second molecule of the bromide. It was mentioned above that in the reaction of I with sodiomalonic ester the monosubstituted derivative is the main product. This is apparently due to steric hindrance.

The structure of compound VI was shown by determining its molecular weight, its conversion into the acid VII, and by IR spectroscopy.

When the acids II and V were nitrated with fuming nitric acid at 0° C, good yields of 4-(β-carboxyethyl)-5,7-dinitrobenzo-2,1,3-thiadiazole (IX) and 5-(β-carboxyethyl)-4-nitrobenzo-2,1,3-thiadiazole (X), respectively, were obtained.

---

*For part LVIII, see [1].

Results of Potentiometric Titrations

No.	Benzo-2,1,3-thiadiazole derivatives	pK_a	Benzene derivatives	pK_a
1	4-Carboxybenzo–2,1,3-thiadiazole [13]	5.00±0.02	Benzoic acid*	5.74±0.05
2	4-Carboxymethylbenzo-2,1,3-thiadiazole [9]	5.60±0.04	Phenylacetic acid**	5.88±0.05
3	5-Carboxymethylbenzo-2,1,3-thiadiazole [9]	5.46±0.04		
4	5-Carboxymethyl-4-nitrobenzo-2,1,3-thiadiazole	4.99±0.05	o-Nitrophenylacetic acid [15]***	5.63±0.05
5	4-Carboxymethyl-5-chlorobenzo-2,1,3-thiadiazole [1]	5.40±0.1		
6	7-Carboxymethyl-4-chlorobenzo-2,1,3-thiadiazole [1]	5.44±0.04	p-Nitrophenylacetic acid [16]****	5.32±0,04
7	4-(β-Carboxyethyl)benzo-2,1,3-thiadiazole	5.99±0.02	Phenylpropionic acid	6.12±0,05
8	5-(β-Carboxyethyl)benzo-2,1,3-thiadiazole	6.12±0.04		
9	5-(β-Carboxyethyl)-4-nitrobenzo-2,1,3-thiadiazole	5.86±0.06	p-Nitrophenylpropionic acid	5.82±0.04
10	4-(β-Carboxyethyl)-5,7-dinitrobenzo-2,1,3-thiadiazole	5.35±0.06	2,4-Dinitrophenylpropionic acid [17]	5.75±0:05

---

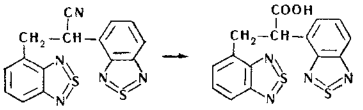
*The pK_a value of benzoic acid was determined earlier [20]under different conditions.

**The pK_a value of phenylacetic acid was determined earlier [14]under different conditions.

***The pK_a value of o-nitrophenylacetic acid was determined earlier [18] under different conditions.

****The pK_a value of p-nitrophenylacetic acid was determined earlier [19] under different conditions.

4- and 5-Carboxymethylbenzo-2,1,3-thiadiazoles (**XI** and **XII**) were obtained [9] by the hydrolysis of 4- and 5-cyanomethylbenzo-2,1,3-thiadiazoles (**XIII**) and (**XIV**). The latter were obtained by the reaction of the thiadiazoles I and III with potassium cyanide. In agreement with the statement of the previous authors [9], the reaction of the bromide I with potassium cyanide forms, in addition to the cyanide **XIII**, a substance with mp 192–193° C. We have established that the latter is 1,2-di-(benzo-2,1,3-thiadiazol-4'-yl)-2-cyanoethane (**XV**) and is apparently formed by the reaction of the cyanide **XIII** and the bromide I [10, 11]. The structure of the cyanide **XV** was shown by its conversion into the acid **XVI** and by IR spectroscopy.



XV XVI

The pK_a values of some of the acids isolated were determined (see table). Titration was carried out on an LPU-01 potentiometer using a pair of glass and calomel electrodes. A carbonate-free 0.1 N solution of caustic potash was used as the alkaline titrant. The concentration of the substances was 0.01 mole in 50 ml of 50% acetone at 25° C. The pK_a values were calculated as described by Albert and Serjeant [12].

On comparing the pK_a values of the acid derivatives of benzo-2,1,3-thiadiazole and the pK_a values of the corresponding benzene derivatives it can be seen that the pK_a values are substantially lower only for the acid 1 (see table) as compared with benzoic acid and for the acid 4 as compared with o-nitrophenylacetic acid. The similar pK_a values of the acid 2 and o-phenylacetic acid deserve attention.

EXPERIMENTAL

4-(β-Carboxyethyl)benzo-2,1,3-thiadiazole (II). To a solution of 0.23 g (0.01 mole) of metallic sodium in 15 ml of absolute ethanol was added 1.6 g (0.01 mole) of malonic ester. The mixture was stirred for an hour, and then a solution of 2.29 g (0.01 mole) of compound I in 25 ml of dry benzene was added rapidly. The resulting mixture was left at 20° C for 10 hr, and then 100 ml of water was added. The benzene layer was separated off, the aqueous layer was extracted again with benzene, and the benzene extracts were dried with sodium sulfate. After the distillation of the benzene, the residue (a light yellow oil) was boiled for 10 hr with 60 ml of 20% hydrochloric acid and cooled, and the precipitate that deposited was filtered off, giving 1.6 g (81%) of white needles with mp 103–104° C (from water). The product is readily soluble in alkalies, benzene, ethanol, and carbon tetrachloride, and sparingly soluble in ether, petroleum ether, and water. Found, %: N 13.41, 13.30; S 15.12, 15.01. Calculated for $C_9H_8N_2O_2S$, %: N 13.46; S 15.38.

5-(β-Carboxyethyl)benzo-2,1,3-thiadiazole (V) and 1,3-di(benzo-2,1,3-thiadiazol-5'-yl)-2,2-diethoxycarbonylpropane (VI). To a solution of 0.92 g (0.04 mole) of metallic sodium in 40 ml of absolute ethanol was added 6.4 g (0.04 mole) of malonic ester. After the mixture had been stirred for 1 hr, a solution of 9.2 g (0.04 mole) of compound III in 80 ml of absolute ethanol was added. The precipitate that deposited after some hours was filtered off and was washed successively with ethanol and water, giving 5.1 g (29%) of compound VI in the form of white needles with mp 105–106° C (from ethanol). Found, %: N 12.31, 12.53; S 13.89, 13.79. Calculated for $C_{21}H_{20}N_4O_4S_2$, %: N 12.28; S 14.04. IR spectrum, KBr, ν, cm^{-1}: 1725 (C=O) 1180, 1250 (C–O–C).

The ethanolic filtrate was evaporated in vacuum in the cold, the oily residue was washed with water and extracted with benzene, and the benzene layer was dried with sodium sulfate. After the benzene had been distilled off, the oily residue (7.8 g) was boiled with 120 ml of 20% hydrochloric acid for 8–10 hr, the mixture was cooled, and the precipitate of V that deposited (4.8 g) was crystallized from water, mp 117–118° C. Found, %: N 13.90, 13.96; S 15.23, 15.10. Calculated for $C_9H_8N_2O_2S$, %: N 13.46; S 15.38.

1,3-Di(benzo-2,1,3-thiadiazol-5'-yl)-2-carboxypropane (VII). A mixture of 2 g of the malonate VI and 40 ml of 10% ethanol in caustic potash was boiled for 3 hr, poured into 200 ml of water, and acidified with hydrochloric acid to pH 5. This gave 1.35 g (90%) of a substance with mp 141–142° C (from ethanol), soluble in dilute alkalies. Found, %: N 15.74, 16.25; S 17.37, 17.42. Calculated for $C_{16}H_{12}N_4O_2S_2$, %: N 15.70; S 17.90.

5-Carboxymethyl-4-nitrobenzo-2,1,3-thiadiazole. With stirring and cooling 1 g of the thiadiazole XII was slowly added to 10 ml of nitric acid (d 1.5). The reaction mixture was kept at 20° C for 30 min and was then poured onto ice. The precipitate that deposited was filtered off and washed with water, giving 0.9 g (73%) of a substance with mp 180–182° C (from ethanol). Found, %: N 17.96; S 13.45, 13.33. Calculated for $C_8H_5N_3O_4S$, %: N 17.60; S 13.40.

4-Cyanomethylbenzo-2,1,3-thiadiazole (XIII) and the cyanide (XV).

A) Two grams of I was added in portions to a solution of 1.5 g of potassium cyanide in 75 ml of ethanol and 5 ml of water. The mixture was boiled with stirring for 3 hr and was then cooled, and the precipitate was filtered off and washed with water, giving 0.6 g of compound XV with mp 192–193° C (from acetic acid). Found, %: C 55.39, 55.44; H 3.54, 3.22; S 19.45, 19.45. Calculated for $C_{15}H_9N_5S_2$, %: C 55.70; H 2.80; S 19.80. IR spectrum, KBr, ν, cm^{-1}: 2240 (–C≡N). The ethanolic filtrate was evaporated to dryness, giving 1 g of a resinous substance XIII with mp 92–93° C (from ethanol). Found, %: S 18.14, 17.96. Calculated for $C_8H_5N_3S$, %: S 18.30.

B) A mixture of 0.5 g of I, 10 ml of dimethyl sulfoxide and 0.25 g of potassium cyanide was left at 20° C for 20 hr. The solution became dark red. The precipitate that deposited on standing was filtered off, giving 0.21 g of substance XV with mp 192–193° C (from acetic acid). On the addition of water, the filtrate yielded 0.1 g of the cyanide **XIII**.

1,2-Di(benzo-2,1,3-thiadiazol-4'-yl)-2-carboxyethane (XVI). A mixture of 1 g of the nitrile XV, 25 ml of 50% sulfuric acid, and 25 ml of acetic acid was boiled for 3 hr. The solution was poured into water. The precipitate that separated out was filtered off and washed with water, giving 1 g (95%) of a substance with mp 179–180° C (from ethanol). Found, %: N 16.04, 16.01; S 18.81, 18.43. Calculated for $C_{15}H_{10}N_4O_2S_2$, %: N 16.37; S 18.70.

5-(β-Carboxyethyl)-4-nitrobenzo-2,1,3-thiadiazole (X). One gram of compound V was added in portions over 30 min to 12 ml of nitric acid (d 1.5) at 0° C, and the mixture was stirred for 30 min at 20° C and was poured onto ice (100 g). The precipitate that deposited was filtered off and washed with water, giving 1 g (85%) of a substance with mp 153–154° C (from aqueous ethanol). Found, %: N 16.96; S 12.35, 12.44. Calculated for $C_9H_7N_3O_4S$, %: N 16.60; S 12.62.

4-(β-Carboxyethyl)-5,7-dinitrobenzo-2,1,3-thiadiazole (IX). In small portions with stirring, 1.5 g of compound II was added to 15 ml of nitric acid (d 1.5) at 0° C. The mixture was kept for 30 min at 20° C and was poured onto ice. The precipitate was filtered off, giving 1.6 g (75%) of a substance with mp 137–138° C (from ethanol). Found, %: N 18.27, 18.14. Calculated for $C_9H_6N_4O_6S$, %: N 18.70.

REFERENCES

1. V. G. Pesin and S. A. D'yachenko, KhGS [Chemistry of Heterocyclic Compounds], 5, 613, 1969.
2. C. A. Bischoff and H. Siebert, Ann., **239**, 92, 1887.
3. R. Fittig and P. Roders, Ann., **256**, 91, 1889.

4. E. Lellmann and G. Schleich, Ber., **20**, 438, 1887.
5. A. Reissert, Ber., **29**, 633, 1896.
6. A. Reissert, Ber., **27**, 2251, 1894.
7. J. L. Everett, J. J. Robers, and W. C. J. Ross, J. Chem. Soc., 2386, 1953.
8. I. I. Straukas and Yu. A. Degutis, Trudy AN Lit. SSR, B4, 43, 47, 1965.
9. V. G. Pesin, I. G. Vitenberg, and A. M. Khaletskii, ZhOKh, **34**, 1272, 1964.
10. S. Gabriel and R. Eschenbach, Ber., **30**, 3018, 1897.
11. H. Janssen, Ann., **250**, 129, 1888.
12. A. Albert and E. Serjeant, Ionization Constants of Acids and Bases [Russian translation], Moscow-Leningrad, p. 123, 1964.
13. V. G. Pesin and E. K. D'yachenko, KhGS [Chemistry of Heterocyclic Compounds], **3**, 1048, 1967.
14. J. F. J. Dippy and F. R. Williams, J. Chem. Soc., 161, 1934.
15. B. Radziszewski, Ber., 648, 1870.
16. S. Gabriel and O. Borgmann, Ber., **16**, 2064, 1883.
17. S. Gabriel and J. Zimmermann, Ber., **12**, 600, 1879.
18. J. F. Dippy, Chem. Rev., **25**, 15, 1939.
19. J. F. Dippy and J. E. Page, J. Chem. Soc., 357, 1938.
20. J. M. Kolthoff and W. Bosch, J. Phys. Chem., **36**, 1695, 1932.

5 January 1967

Leningrad Chemical and
Pharmaceutical Institute