CCA-196 547.21.024-547.23:547.544:547.298.1-547.7

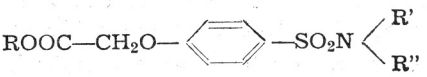
Preparation of Some Derivatives of *p*-Hydroxybenzenesulphonamides. II. Some *N*-Heterocyclic and Other Derivatives of *p*-Carboxymethoxybenzenesulphonamide

B. Stavrić and E. Cerkovnikov***

Institute of Organic Chemistry, Faculty of Pharmacy, University of Zagreb, Croatia, Yugoslavia

Received June 24, 1960; revised February 12, 1960

A series of products with the general formula



where R = —H, —CH_3 or —C_2H_5
R' = —C_6H_5, —CH_2COOH, —C(:NH)NH_2 thyazolyl-2, pyrimidyl-2 or 3,4-dimethylizoxazolyl-5
R" = —H or —C_6H_5

formed by condensation of corresponding sulphonamides with derivatives of halogenoacetic acid or by condensation of corresponding sulphochlorides with some amines is described. These compounds, which are closely related to phenoxyacetic acid and to sulphonamides are expected to have some phytohormonal properties.

In previous papers we described the synthesis[1,2] and reported about the phytohormonic activity[3] of some derivatives of *p*-hydroxybenzenesulphonamides, especially of the compounds having the -$SO_2N(CH_3)_2$ group.

Continuing our work on syntetic compounds with phytohormonic activity, it was of interest to investigate the phytohormonic activity of derivatives of phenoxyacetic acid having in the para position a sulphanylamido group substituted with some heterocyclic or other radicals. For this reason in the present paper we describe the preparation of some derivatives of *p*-hydroxybenzenesulphonamide which contain heterocyclic or other radicals.

As intermediate products we prepared three phenols, *i.e.* 2-(*p*-hydroxybenzenesulphonamido)thiazole (I)[4,5,6,7,8], 2-(*p*-hydroxybenzenesulphonamido)-pyrimidine[8] and *p*-hydroxybenzenesulphoguanidine (VII)[6,7]. Jensen and Christensen[6] described the compound VII with a m.p. 160—162°, but they gave no details for the preparation. Huiltquist *et al.*[8] described this compound as di-(*N*-guanyl-1-phenol-4-sulphonamide) sulphate with m.p. 219.8—220.3°. The

* This paper is part of a thesis required for the degree of doctor (Ph. D) at the University of Zagreb, 1958.

** Present address: E. C. Institute of Chemistry and Biochemistry, Faculty of Medicine, University of Zagreb, Rijeka, Yugoslavia.

starting material for both syntheses was sulphagunanidine. However, the substance which we obtained after diazotization of sulphaguanidine and decomposition of their diazonium salt had m. p. 185.0—185.5°. This compound gave a positive reaction on the free phenolic group with Millon reagent[9].

Above mentioned phenols were prepared from the corresponding amines by diazotization and decomposition of diazonium salts. The decomposition of the diazonium salts and the isolation of phenols was somewhat modified, and the details are given in the experimental part. By keeping the temperature within exactly defined limits only a very small amount of tarry byproducts appeared and the yields were increased.

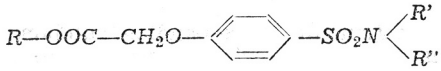
The esters II, VI and VIII were prepared by condensation of the corresponding phenolates with ethyl bromoacetate in absolute ethanol. Compounds IV and V were prepared by condensation of *p*-(carbmethoxymethoxy)benzenesulphonyl chloride respectively *p*-(carbethoxymethoxy)benzenesulphonyl chloride[2] with appropriate amines.

The acids III and IX were prepared by refluxing the corresponding esters (II, VIII) with 10% sodium hydroxide. Compound X was prepared by condensation of the corresponding phenolate with monochloroacetic acid.

Table I shows the substances which were prepared. The phytohormonic activity of some of these compounds was tested, and the preliminary results were published elshere[3].

TABLE I

List of prepared substituted derivatives of p-*carboxymethoxybenzenesulphonamide*



Compound	R	R'	R''	m.p.
II	C_2H_5-	thyazolyl-2	-H	241—242°
III	H-	thyazolyl-2	-H	220°
IV	CH_3-	3,4-dimethyl-isoxazolyl-2	-H	155—156°
V	H-	$-C_6H_5$	$-C_6H_5$	75.0—76.5°
VI	C_2H_5-	pyrimidyl-2	-H	222.5—223.8°
VIII	C_2H_5-	$-C(:NH)NH_2$	-H	212.5—213.5°
IX	H-	$-C(:NH)NH_2$	-H	202.5—203.5°
X	H-	$-CH_2-COOH$	-H	171—172°

EXPERIMENTAL

The melting points are uncorrected

2-(p-Carbethoxymethoxybenzenesulphonamido)thiazole (II)

Into a solution of 1.0 g., (0.0435 mole) of sodium in 100 ml. of absolute ethanol, 6.0 g., (0.0234 mole) of 2-(hydroxybenzenesulphonamido)thiazole (I)[4] were added. During the addition the reaction mixture was stirred and refluxed for 15 minutes at 60°. Then 4.0 ml. (6.0 g., 0.0359 mole) of ethyl bromoacetate[10] were added, and the stirring and refluxing contiuned for two hours. Sodium bromide and the product precipitated during the reaction. After cooling, the reaction mixture was filtered, and the crystaline product was recrystallized from 70% ethanol. Colourless needles m. p. 241—242° (yield: 71%). Sodium salt, ($C_{13}H_{13}N_2NaO_5S_2$), m. p. 299—300°.

Anal. 13.91 mg. subst.: 23.35 mg. CO_2, 5.10 mg. H_2O
1.92 mg. subst.: 0.137 ml. N_2 (32°, 754 mm)
$C_{13}H_{14}N_2O_5S_2$ (342.38) calc'd.: C 45.61; H 4.12; N 8.18%
found: C 45.80; H 4.10; N 7.92%

2-(p-Carboxymethoxybenzenesulphonamido)-thiazole (III)

A suspension of 0.40 g., (0.0012 mole) of II was refluxed for 15 minutes on a warm water bath with 4 ml. of 10% sodium hydroxide. The reaction mixture was decolourised with charcoal and the filtrate acidified with hydrochloric acid (1:1) to *p*H 1. After cooling the crude product was isolated (0.27 g., i. e. 71—75%) and recrystallized from water. Colourless needles, m. p. 220°.

Anal. 12.90 mg. subst.: 19.79 mg. CO_2, 3.54 mg. H_2O
1.78 mg. subst.: 0.142 ml. N_2 (30°, 759 mm)
$C_{11}H_{10}N_2O_5S$ (314.32) calc'd.: C 42.03; H 3.20; N 8.91%
found: C 41.86; H 3.07; N 8.97%

3,4-Dimethyl-5-(p-carbmethoxymethoxybenzenesulphonamido)isoxazole (IV)

To a solution of 8.0 g., (0.0317 mole) of *p*-(carbmethoxymethoxy)benzenesulphonyl chloride[2] in 33 ml. of freshly distilled pyridine, 6.0 g., (0.0468 mole) of 3,4-dimethyl-5--aminoisoxazole were added. The reaction mixture was refluxed for half an hour, and after cooling it was poured into 150 ml. of water and acidified with concentrated hydrochloric acid. After cooling in a refrigerator for several days 1.6 g., (15.5%) of crystalline product was obtained. An analytical sample was recrystallized from 96% ethanol. Colourless prisms, m. p. 155—156°.

Anal. 14.03. mg. subst.: 25.43 mg. CO_2, 5.58 mg. H_2O
$C_{14}H_{16}N_2O_6S$ (340.34) calc'd.: C 49.40; H 4.74%
found: C 49.46; H 4.45%

N-(p-carboxymethoxybenzenesulphonyl)-N,N-diphenyl amid (V)

Into a solution of 3.2 g., (0.0189 mole) of diphenylamine in 10 ml. of freshly destilled pyridine 2.4 g., (0.0089 mole) of *p*-(carbethoxymethoxy)benzenesulphonyl chloride[2] were added. The reaction mixture was refluxed for two hours at 50—55° and after that it was extracted with ether. The ethereal solution was washed with water, treated with charcoal, and precipitated with petroleum ether. After cooling a crystalline product was obtained, which was recrystallized from ether — petroleum ether. Yield: 1.0 g., *i. e.* 30%. Colourless prisms, m. p. 75.0—76.5°.

Anal. 11.66 mg. subst.: 26.75 mg. CO_2, 4.52 mg. H_2O
3.25 mg. subst.: 0.113 ml. N_2 (30°, 758 mm)
$C_{20}H_{17}NO_5S$ (383.40) calc'd.: C 62.65; H 4.47; N 3.65%
found: C 62.59; H 4.33; N 3.89%

2-(p-Carbethoxymethoxybenzenesulphonamido)pyrimidine (VI)

Into a solution of 0.5 g., (0.0217 mole) of sodium in 50 ml. of absolute ethanol, 3.0 g., (0.0119 mole) of 2-(*p*-hydroxybenzenesulphonamido)pyrimidine[8] were added and the reaction mixture was refluxed for 15 minutes. To the warm mixture 2.0 ml. (3.0 g., 0.0179 mole) of ethyl monobromoacetate[10] were added and refluxed for four hours. The reaction mixture was treated with charcoal, and the filtrate was diluted with water. An oily product was obtained, which after standing and cooling solidified. Pale-yellow crystals were obtained (2.7 g., *i. e.* 67%), and recrystallized from 50% ethanol. Colourless plates, m. p. 222.5—223.8°.

Anal. 8.935 mg. subst.: 16.490 mg. CO_2, 3.390 mg. H_2O
$C_{14}H_{15}N_3O_5S$ (337.34) calc'd.: C 49.84; H 4.48%
found: C 50.36; H 4.25%

p-*Hydroxybenzenesulphoguanidine* (VII)[6]

Into a stirred solution of 500 ml. of a 5% solution of sulphuric acid and 20.0 g., (0.0933 mole) of *p*-aminobenzenesulphoguanidine, a solution of 10.0 g., (0.1449 mole) of sodium nitrite in 50 ml. water were added. The temperature was kept at 8—10°. The resulting yellow solution was added dorpwise to 100 ml. of water warmed up to 85—90° under vigorous stirring. After the addition of the diazonium salt was completed the reaction mixture was stirred at 85—90° for further 30 minutes, and decolourised with charcoal. The filtrate was neutralised with hot 20% solution of barium hydroxide. After cooling the barium sulphate was removed, and the filtrate evaporated to about 400 ml. On standing overnight 8.5 g. of crude crystallized product were obtained which was purified by recrystallization from water. Yield: 28—30%. Colourless needles, m. p. 185.0—185.5° (recorded m. p. 160—162° [6]).

Anal. 1.98 mg. subst.: 0.343 ml. N_2 (28°, 757 mm)
$C_7H_9N_3O_3S$ (215.23) calc'd.: N 19.52%
found: N 19.56%

p-*(Carbethoxymethoxy)benzenesulphoguanidine* (VIII)

To a solution of 0.51 g., (0.0222 mole) of sodium in 38 ml. of absolute methanol, 2.8 g., (0.0130 mole) of VII were added. The mixture was stirred and refluxed for 20 minutes. Into the warm reaction mixture 1.9 ml., (2.85 g., 0.0170 mole) of ethyl monobromoacetate were added, and the mixture was stirred and refluxed for two hours. After cooling, the crude crystalline product was collected and recrystallized from 60% ethanol. Yield: 50—56%. Colourless needles, m. p. 212.5—213.5°.

Anal. 10.27 mg. subst.: 16.45 mg. CO_2, 4.58 mg. H_2O
$C_{11}H_{15}N_3O_5S$ (301.31) calc'd.: C 43.84; H 5.02%
found: C 43.71; H 4.99%

p-*(Carboxymethoxy)benzenesulphoguanidine* (IX)

2.0 g., (0.0066 mole) of VIII was hydrolysed with 30 ml. of 10% solution of sodium hydroxide, as described for III.

The crude product was recrystallized from water. Colourless needles melting at 202.5—203.5°. Yield: 66—70%.

Anal. 12.10 mg. subst.: 17.49 mg. CO_2, 4.22 mg. H_2O
1.08 mg. subst.: 0.147 ml. N_2 (25°, 761 mm)
$C_9H_{11}N_3O_5S$ (237.26) calc'd.: C 39.56; H 4.05; N 15.38%
found: C 39.44; H 3.90; N 15.61%

N-*Acetic acid*-p-*(carboxymethoxy)benzenesulphonamide* (X)

Into a solution of 6.6 g., (0.037 mole) of *p*-hydroxybenzenesulphonamide[11] and 33% sodium hydroxide (about 10 ml.) a solution of 13.8 g., (0.1460 mole) of monochloroacetic acid in 15 ml. water was added dropwise under stirring keeping the pH permanently at 7—8 by addition of 33% solution of sodium hydroxide (about 18 ml.). After the addition was completed, the temperature was raised to the boiling point for a few minutes. After cooling to 70—80°, the reaction mixture was neutralised with hydrochloric acid (1:2), charcoal added and the mixture filtered while still warm. The warm filtrate was acidified with hydrochloric acid (1:2) to Congo Red and evaporated at 100° to dryness. The crystalline product was extracted with absolute ether. Ether was evaporated and the obtained crystals were recrystallized from water. Yield: 30—38%. Colourless needles, m. p. 171—172°.

Anal. 14.21 mg. subst.: 21.62 mg. CO_2, 4.70 mg. H_2O
$C_{10}H_{11}NO_7S$ (289.26) calc'd.: C 41.52; H 3.83%
found: C 41.52; H 3.70%

Acknowledgment. We are indebted to Mrs. E. Jaeger-Stevčevski for the microanalyses.

REFERENCES

1. E. Cerkovnikov and B. Stavrić, *Acta Pharm. Jugoslav.* **6** (1956) 89.
2. B. Stavrić and E. Cerkovnikov, *Croat. Chem. Acta* **31** (1959) 107.
3. B. Stavrić and E. Cerkovnikov, *Acta Pharm. Jugoslav.* **10** (1960) 3.
4. K. Takatori, T. Okuda, and Sh. Hara, *J. Pharm. Soc. Japan* **71** (1951) 1371; *C. A.* **46** (1952) 9535 c.
5. I. Michimasa ann A. Murao, *Pat. Japan* 1112 (1951) *cf. C. A.* **47** (1953) 3883 d.
6. K. A. Jensen and S. A. K. Christensen, *Acta Chem. Scand.* **3** (1949) 207.
7. T. Matsukawa, K. Shirakawa, and H. Kawasaki, *Japan J. Pharm. and Chem.* **21** (1949) 102; *cf. C. A.* **45** (1951) 5649 c.
8. M. E. Huiltquist, R. P. Germann, I. S. Webb, W. B. Wridht, Jr., B. Roth, I. M. Smith, and Subba Row, *J. Am. Chem. Soc.* **73** (1951) 2558.
9. F. Feigl: *Spot Test, Vol.* **II** *Organic Applications,* fourth Engl. Ed., Amsterdam 1954; 134.
10. Auwers and Bernhardi, *Ber.* **24** (1891); *cf. Beilstein H* **2** 214.
11. W. Kermack, W. Spragg, and W. Terbich, *J. Chem. Soc., I* (1939) 608.

IZVOD

Priprava nekih derivata *p*-hidroksibenzensulfonamida. II. O nekim *N*-heterocikličkim i drugim derivatima *p*-(karboksimetoksi) benzensulfonamida

B. Stavrić i E. Cerkovnikov

U nastavku prijašnjih radova[1,2,3] pripravljena je serija supstancija općenite formule ROOC-CH_2O-C_6H_4-$SO_2NR'R''$, gdje su R = vodik, metil ili etil; R' = C_6H_5, -CH_2COOH, tiazolil-2, pirimidil-2, 3,4-dimetilizoksazolil-5 ili -C(:NH)NH_2; R'' = vodik ili -C_6H_5. Opisana je sinteza osam spojeva iz toga reda (II, III, IV, V, VI, VIII, IX, X) (vidi tabelu I), i priprava jednog fenola (VII) kao međuprodukta.

Priređeni spojevi su po svojoj kemijskoj konstituciji u uskoj vezi s fenoksioctenom kiselinom, te se od njih očekuje da posjeduju neko fitohormonsko djelovanje. Neki rezultati fitohormonskih ispitivanja objavljeni su posebno[1,3], dok su daljnja ispitivanja u toku.

ZAVOD ZA ORGANSKU KEMIJU
FARMACEUTSKI FAKULTET
ZAGREB

Primljeno 24. lipnja 1960,
u prerađenom obliku 12. veljače 1961.