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Original Scientific Paper

Preparation of Some Derivatives of *p*-Hydroxybenzenesulphonamides*. III. Some *N*-Alkyl- and *N*-Aryl Derivatives of *p*-(Carboxymethoxy)benzenesulphonamide

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Series of *N*-alkyl- and *N*-aryl derivatives of *p*-(carboxymethoxy)benzenesulphonamide were prepared by condensation of corresponding sulphochlorides with amines. These compounds, which are structuraly related to phenoxyacetic acid[1] and to sulphonamides, are expected to have some phytohormonic properties.

Continuing our work on synthetic compounds with phytohormonic activity[2–5] possesing also some pharmacologic properties, we are describing in the present paper the preparation of some derivatives of *p*-hydroxybenzenesulphonamides.

The esters I—VII (Table I) were prepared by condensation of *p*-(carbomethoxymethoxy)benzenesulphonyl chloride and *p*-(carbethoxymethoxy)benzenesulphonyl chloride[4] respectively, with an appropriate amine in a mixture of acetone and ether. The ester VIII was prepared by condensation of the corresponding phenolate with methyl chloroacetate in absolute methanol.

The acids (IX—XIV) (Table I) were prepared by refluxing the corresponding esters with 10% sodium hydroxide solution.

The esters II, V and VII were characterized as products of hydrolysis X, IX and XI respectively.

EXPERIMENTAL

All melting points are uncorrected

1-(p-Carbomethoxymethoxybenzenesulphonamido)propane (I)

Into a solution of 10 g. (0.038 mole) of *p*-(carbomethoxymethoxy)benzenesulphonyl chloride[4] in 50 ml. of dry acetone, 5.5 g. (0.093 mole) of *n*-propylamine in 50 ml. of absolute ether were added with stirring at a temperature of 25—35°. The reaction

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* Paper II.: B. Stavrić and E. Cerkovnikov. *Croat. Chem. Acta* **32** (1960) 203.

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TABLE I

Number	R	R'	R"
I	$-CH_3$	$-CH_2CH_2CH_3$	—H
II	$-CH_3$	$-CH(CH_3)_2$	—H
III	$-CH_3$	$-C_6H_4-CH_3$ (4—)	—H
IV	$-CH_3$	$-C_6H_4-CH_3$ (2—)	—H
V	$-C_2H_5$	$-CH_2CH_2CH_3$	—H
VI	$-C_2H_5$	$-CH_2CH=CH_2$	—H
VII	$-C_2H_5$	$-(CH_2)_3CH_3$	—H
VIII	$-CH_3$	thiazolyl—2	—H
IX	—H	$-CH_2CH_2CH_3$	—H
X	—H	$-CH(CH_3)_2$	—H
XI	—H	$-(CH_2)_3CH_3$	—H
XII	—H	$-C_6H_4-CH_3$ (4—)	—H
XIII	—H	$-C_6H_4-CH_3$ (2—)	—H
XIV	—H	$-(CH_2)_3CH_3$	$-(CH_2)_3CH_3$

mixture was kept at room temperature for 24 hours. After standing an oily by-product separated on the bottom of the flask. The acetone-ether solution was washed twice with 50 ml. of dilute hydrochloric acid and then with 50 ml. of water. The solvent was removed under reduced pressure. The residue was a crystalline yellow-brown product (8.20 g., 75.5%). This product was recrystallized from 50% ethanol to yield colourless needles melting at 65—66°.

Anal. $C_{12}H_{17}NO_5S$ (287.33) calc'd.: C 50.16; H 5.97; N 4.88%
found: C 49.97; H 5.88; N 4.75%

2-(p-Carbomethoxymethoxybenzenesulphonamido)propane (II)

From 10 g. (0.038 mole) of *p*-(carbomethoxymethoxy)benzenesuphonyl chloride[4] in 50 ml. of absolute acetone and 5.5 g. (0.093 mole) of *iso*-propylamine in 50 ml. of absolute ether using the method as described for I, 9.2 g. (84.5%) of a crude crystalline product was obtained. The product was recrystallized from 50% ethanol as colourless prisms, m.p. 111.5—113°.

Anal. $C_{12}H_{17}NO_5S$ (287.33) calc'd.: N 4.88%
found: N 5.08%

1-(p-Carbomethoxymethoxybenzenesulphonamido)-4-methylbenzene (III)

Into a solution of 5.2 g. (0.021 mole) of *p*-(carbomethoxymethoxy)benzenesulphonyl chloride[4] in 20 ml. of absolute acetone, 3.0 g. (0.028 mole) of *p*-toluidine in 20 ml. of absolute ether was added with stirring. During the addition of the amine the reaction mixture was cooled in an ice bath. The reaction mixture was left at room temperature for two hours, and then added dropwise with stirring into 50 ml. of water acidified with 1 ml. of concentrated hydrochloric acid. A yellow oily product separated and after keeping it in a refrigerator for several days 5.2 g. of a crystalline product was obtained (yield 79%). The product was recrystallized from 96% ethanol as colourless needles, m.p. 154—156°.

Anal. $C_{16}H_{17}NO_5S$ (335.37) calc'd.: C 57.30; H 5.11; N 4.18%
found: C 57.33; H 4.92; N 4.29%

1-(p-Carbomethoxymethoxybenzenesulphonamido)-2-methylbenzene (IV)

From 5.2 g. (0.021 mole) of *p*-(carbomethoxymethoxy)benzenesulphonyl chloride[4] in 20 ml. of absolute acetone and 3.0 g. (0.028 mole) of *o*-toluidine in 20 ml. of absolute ether, as described for III, 4.1 g. (62.3%) of a crystalline product was obtained.

The product was recrystallized from 96% ethanol: m.p. 139—141°.

Anal. $C_{16}H_{17}NO_5S$ (335.37) calc'd.: C 57.30; H 5.11; N 4.18%
found: C 57.60; H 5.08; N 4.10%

1-(p-Carbethoxymethoxybenzenesulphonamido)propane (V)

Into a solution of 10 g. (0.036 mole) of *p*-(carbethoxymethoxy)benzenesulphonyl chloride[4] in 50 ml. of absolute acetone, 5.3 g. (0.089 mole) of *n*-propylamine in 50 ml. of absolute ether were added as described for I. 6.5 g (60%) of the crystalline product was obtained. Crystallization from 60% ethanol gave the analytical sample as colourless needles, m.p. 84—85.5°.

Anal. $C_{13}H_{19}NO_5S$ (301.35) calc'd.: N 4.64%
found: N 4.65%

1-(p-Carbethoxymethoxybenzenesulphonamido)-2-propene (VI)

Into a solution of 20 g. (0.072 mole) of *p*-(carbethoxymethoxy)benzenesulphonyl chloride[4] in 80 ml. of absolute acetone, 10.2 g. (0.178 mole) of allylamine in 80 ml. of absolute ether were added and the preparation was carried out as described for I. The solvents were evaporated to yield and oil. After keeping it in a refrigerator for several days a crystalline product (8.3 g., 38%) was obtained, which was recrystallized from 60% ethanol as colourless plates, m.p. 78—79°.

Anal. $C_{13}H_{17}NO_5S$ (299.34) calc'd.: C 52.16; H 5.73; N 4.68%
found: C 51.90; H 5.78; N 4.76%

1-(p-Carbethoxymethoxybenzenesulphonamido)butane (VII)

From 20 g. (0.072 mole) of *p*-(carbethoxymethoxy)benzenesulphonyl chloride[4] in 80 ml. of absolute acetone and 13.1 g. (0.178 mole) of *n*-butylamine in 80 ml. of absolute ether an oily product was obtained as described for I. After keeping it in refrigerator for two days a crystalline product was obtained. The crude product was recrystallized from diluted ethanol to yield 11.0 g. (48.5%) of colourless crystals. An analytical sample was recrystallized from 50% ethanol; m.p. 60—61.5°.

Anal. $C_{14}H_{21}NO_5S$ (315.38) calc'd.: N 4.44%
found: N 4.66%

2-(p-Carbomethoxymethoxybenzenesulphonamido)thiazole (VIII)

Into a solution of 1.54 g. (0.067 mole) of sodium in 154 ml. of absolute methanol, 10 g. (0.039 mole) of 2-(*p*-hydroxybenzenesulphonamido)thiazole[6] were added. The reaction mixture was stirred during the addition and refluxed for 1 hour. Then, 9.23 ml. (11.33 g., 0.104 mole) of methyl chloroacetate[7] were aded and the stirring and refluxing continued for two hours. Sodium chloride precipitated during the reaction. After cooling the reaction mixture was filtered, the filtrate decolourized with charcoal, and again filtered. The filtrate was evaporated until crystallization occured. It was recrystallized from 50% ethanol as colourless needles. Yield: 4,3 g., 33.9%, m.p. 218.0—220.5°.

Anal. $C_{12}H_{12}N_2O_5S_2$ (328.37) calc'd.: C 43.89; H 3.68; N 8.52%
found: C 43.87; H 3.72; N 8.75%

VIII was hydrolyzed as described for IX to yield 2-(*p*-carboxymethoxybenzenesulphonamido)thiazole[4] with m.p. 220°.

1-(p-Carboxymethoxybenzenesulphonamido)propane (IX)

A suspension of 0.35 g. (0.001 mole) of I was refluxed for 20 minutes on a boiling water bath with 10 ml. of 10% sodium hydroxide solution. The reaction mixture was decolourised with charcoal and the filtrate adjusted with hydrochloric acid (1:1) to *pH* 1. The crude product (0.28 g., 84.8%) was isolated and recrystallized from water as colourless plates, m.p. 124.5—125.5°.

Anal. $C_{11}H_{15}NO_5S$ (273.30) calc'd.: C 48.34; H 5.52; N 5.13%
found: C 48.40; H 5.69; N 5.42%

By an analogous hydrolysis of V an identical product with m.p. 124.5—125.5° was obtained. There was no depression of m.p. on admixture with sample of IX.

2-(p-Carboxymethoxybenzenesulphonamido)propane (X)

2.4 g. (0.008 mole) of II were hydrolysed with 60 ml. of a 10% solution of sodium hydroxide, as described for IX.

The product was recrystallized for analysis from water as colourless needles, m.p. 145—146°. Yield: 1.8 g., 79%.

Anal. $C_{11}H_{15}NO_5S$ (273.30) calc'd.: C 48.34; H 5.52; N 5.13%
found: C 48.10; H 5.62; N 5.06%

1-(p-Carboxymethoxybenzenesulphonamido)butane (XI)

1.55 g. (0.005 mole) of VII was hydrolysed with 15 ml. of a 10% solution of sodium hydroxide, as described for IX.

The product (1.10 g., 78%) was recrystallized from water as colourless needles, m.p. 129—130.5°.

Anal. $C_{12}H_{17}NO_5S$ (287.33) calc'd.: C 50.16; H 5.97%
found: C 50.20; H 5.82%

1-(p-Carboxymethoxybenzenesulphonamido)-4-methylbenzene (XII)

1.65 g. (0.005 mole) of III was hydrolysed with 10 ml. of a 10% solution of sodium hydroxide, as described for IX.

The product was recrystallized from water as colourless prisms, m.p. 169—170°. Yield 1.39 g., 88%.

Anal. $C_{15}H_{15}NO_5S$ (321.34) calc'd.: C 56.06; H 4.70; N 4.36%
found: C 56.17; H 4.81; N 4.45%

1-(p-Carboxymethoxybenzenesulphonamido)-2-methylbenzene (XIII)

0.85 g. (0.0025 mole) of IV was hydrolysed with 10 ml. of a 10% solution of sodium hydroxide, as described for IX.

The product was recrystallized from 30% ethanol; m.p. 166—166.5°. Yield: 0.77 g., 95%.

Anal. $C_{15}H_{15}NO_5S$ (321.34) calc'd.: C 56.06; H 4.70; N 4.36%
found: C 56.40; H 4.89; N 4.59%

N-(p-Carboxymethoxybenzenesulphonyl)-N,N-dibutyl amide (XIV)

Into a solution of 12.2 g. (0.046 mole) of *p*-(carbomethoxymethoxy)benzenesulphonyl chloride[4] in 30 ml. absolute acetone, 13.5 g. (0.104 mole) of dibutyl amine in 30 ml. of absolute ether were added with stirring at room temperature. The reaction mixture was left at room temperature for 24 hours. The mixture was then evaporated, and the residue washed twice with 50 ml. of diluted hydrochloric acid and then with water. The oily product was hydrolysed with 50 ml. of a 10% solution of sodium hydroxide, as described for IX.

An analitical sample was recrystallized from 30% ethanol as colourless prisms, m.p. 105—106.5°. Yield: 8.4 g., 53.5%.

Anal. $C_{16}H_{25}NO_5S$ (343.37) calc'd.: C 55.96; H 7.33; N 4.08%
found: C 56.04; H 7.39; N 4.21%

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IZVOD

Priprava nekih derivata *p*-hidroksibenzensulfonamida. III. O nekim *N*-alkil i *N*-aril derivatima *p*-(karboksimetoksi)benzensulfonamida

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U nastavku prijašnjih radova[4,5] pripravljena je serija supstancija općenite formule: (*p*-)ROOC—CH_2O—C_6H_4—$SO_2NR'R''$, gdje su R = —CH_3; R' = —$(CH_2)_2CH_3$; —$CH(CH_3)_2$; —C_6H_4—CH_3 (4-); —C_6H_4—CH_3 (2-) ili tiazolil-2 a R'' = —H. R = = —C_2H_5; R' = —$(CH_2)_2CH_3$, —$CH_2CH = CH_2$ ili —$(CH_2)_3CH_3$, a R'' = H, R = —H, R' = —$(CH_2)_2CH_3$, —$CH(CH_3)_2$, — $(CH_2)_3CH_3$, — $C_6H_4CH_3$ (4-) ili —C_6H_4— CH_3 (2-), a R'' = H . R = —H; R' = R'' = — $(CH_2)_3$ CH_3.

Priređeni spojevi su po svojoj kemijskoj konstituciji u uskoj vezi s fenoksioctenom kiselinom[1-3], te se od njih očekuje da posjeduju stanovito fitohormonsko djelovanje.

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