Synthesis of Alkyl Esters of 4-Amino-2-sulfamoylbenzoic Acid

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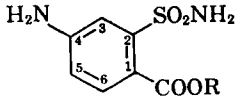
Nine esters of 4-nitro-2-sulfamoylbenzoic acid were prepared by the alcoholysis reaction of passing hydrogen chloride into a refluxing solution of 6-nitrosaccharin in the appropriate alcohol. Reduction of these alkyl 4-nitro-2-sulfamoylbenzoates using hydrogen and palladium-on-carbon catalyst gave the following alkyl 4-amino-2-sulfamoylbenzoates: methyl; ethyl; *n*-propyl; isopropyl; *n*-butyl; *sec*-butyl; *n*-pentyl; 1-ethylpropyl; and *n*-hexyl. Also synthesized was isopropyl 6-amino-2-sulfamoylbenzoate. Many of these compounds possessed marked anticonvulsant activity as indicated by their prevention of the effect of strychnine or maximal electric shock in mice.

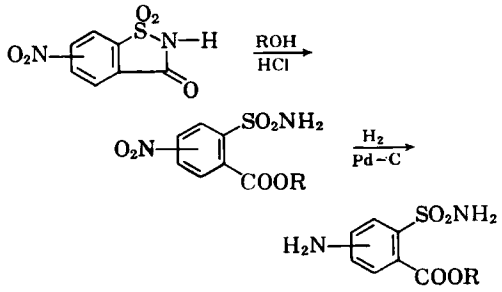
A NUMBER of alkyl esters of 4 (or 6)-amino-2-sulfamoylbenzoic acid were prepared for pharmacological screening. The ten compounds synthesized are listed and their properties given in Table I, and have the following formula



A

R = CH_3, C_2H_5, n-C_3H_7, i-C_3H_7, i-C_3H_7(6-NH_2), n-C_4H_9, s-C_4H_9, n-C_5H_{11}, $CH(C_2H_5)_2$, n-C_6H_{13}

Nine esters of 4-nitro-2-sulfamoylbenzoic acid (Table II) were prepared by the alcoholysis reaction of passing hydrogen chloride into a refluxing solution of 6-nitrosaccharin in the appropriate alcohol (1). The 6-nitrosaccharin was prepared by the permanganate oxidation of 4-nitro-2-sulfamoyltoluene (2). Isopropyl 6-nitro-2-sulfamoylbenzoate was synthesized by refluxing 4-nitrosaccharin in acidified 2-propanol. The 4-nitrosaccharin was prepared by nitration of 2-sulfobenzoic acid, followed by reaction with phosphorus pentachloride to form the diacid chloride, and then treatment with anhydrous ammonia (3). Reduction of these 4 (or 6)-nitro-2-sulfamoylbenzoates using hydrogen and palladium-on-carbon catalyst gave the desired amino esters. The reaction sequence is



Pharmacological testing has shown several of the alkyl 4-amino-2-sulfamoylbenzoates to possess marked anticonvulsant activity.[1] The most potent anticonvulsant compound in this series, as indicated by potency in preventing the effect of strychnine or maximal electric shock in mice, was the isopropyl ester. The methyl and ethyl esters were much less potent.[2]

EXPERIMENTAL

4-Nitro-2-sulfamoylbenzoic Acid Esters.—These esters were prepared by acidic alcoholysis of 6-nitrosaccharin (prepared according to Noyes) (2) in the appropriate alcohol. The compounds are listed and their properties given in Table II. The procedure used will be illustrated by the following account of the synthesis of ethyl 4-nitro-2-sulfamoylbenzoate. Two and one-half grams (0.01 mole) of 6-nitrosaccharin was dissolved in 25 ml. of absolute ethanol and poured into a dry 50-ml. two-neck flask. The solution was heated under reflux for 2 hours, with continuous passage of dry hydrogen chloride gas through the solution. The current of hydrogen chloride gas was discontinued and the reflux condenser removed; the solution was then heated for several minutes to expel hydrogen chloride. At the beginning of the reflux period it was noted that the color of the solution of 6-nitrosaccharin in ethanol was yellow, but as the reaction proceeded, it gradually became lighter, thus showing the progress of the reaction. On cooling and slow evaporation, the hot solution yielded crystals. Recrystallization from absolute ethanol gave 2.7 Gm. (90%) of crystalline solid, m.p. 139–141°.

Isopropyl 6 - Nitro - 2 - sulfamoylbenzoate.—Four and one-half grams (0.02 mole) of 4-nitrosaccharin (prepared according to Hamor) (3) was dissolved in 50 ml. of warm dry 2-propanol in a 100-ml. round-bottom flask fitted with a gas inlet tube and a reflux condenser topped by a calcium chloride drying tube. The solution was refluxed for 2 hours, with hydrogen chloride gas being passed in for 46 minutes of this time. Evaporation of the solvent and recrystallization of the resulting solid from 2-propanol, followed by washing with cold 2-propanol gave 2.8 Gm. (50%) of white crystalline compound, m.p. 130–133°.

4 - Amino - 2 - sulfamoylbenzoic Acid Esters.—These esters were prepared by reduction of the corresponding nitro compounds, using hydrogen and palladium-on-carbon catalyst. The compounds thus synthesized are listed and their properties given in Table I. The procedure used will be shown by the following account of the synthesis of ethyl

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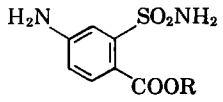
[1] The authors are indebted to Smith Kline and French Laboratories, Philadelphia, Pa., for pharmacological testing.

[2] Loev and Kormendy describe the synthesis of several of these compounds by a different method and give the preliminary pharmacological results in a recent paper (4).

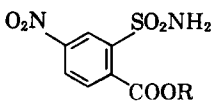
TABLE I.—ALKYL 4-AMINO-2-SULFAMOYLBENZOATES[a]



No.	R	Formula	M.p.,[b] °C.	Recrystallizing Solvent	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	CH_3	$C_8H_{10}N_2O_4S$	183[c]	Absol. ethanol	76	41.73	42.00	4.37	4.54
2	C_2H_5	$C_9H_{12}N_2O_4S$	152–153	Absol. ethanol	66	44.25	44.48	4.95	4.82
3	n-C_3H_7	$C_{10}H_{14}N_2O_4S$	148–149	Absol. ethanol	70	46.49	46.70	5.46	5.51
4	i-C_3H_7	$C_{10}H_{14}N_2O_4S$	120	Absol. ethanol	61	46.49	46.78	5.46	5.68
5	n-C_4H_9	$C_{11}H_{16}N_2O_4S$	108	Absol. ethanol	65	48.51	48.47	5.92	5.79
6	s-C_4H_9	$C_{11}H_{16}N_2O_4S$	102–104	Ethanol-H_2O	47	48.51	48.70	5.92	5.97
7	n-C_5H_{11}	$C_{12}H_{18}N_2O_4S$	93–94	Absol. ethanol	78	50.33	50.42	6.33	6.30
8	$CH(C_2H_5)_2$	$C_{12}H_{18}N_2O_4S$	121–123	Ethanol-H_2O	43	...	...	...	...
9	n-C_6H_{13}	$C_{13}H_{20}N_2O_4S$	103–104	Ethanol-H_2O	66	51.98	51.95	6.71	6.65
10	i-C_3H_7 (isopropyl 6-amino-2-sulfamoylbenzoate)	$C_{10}H_{14}N_2O_4S$	120.5–121.5	Ethanol-H_2O	58	46.49	46.70	5.46	5.58

[a] Analyses were performed by Elek Micro Analytical Laboratories, Los Angeles, Calif. [b] Melting points were taken either with a Fisher-Johns melting point apparatus or by the capillary tube method, and are uncorrected. [c] Reported m.p. 180° (5).

TABLE II.—ALKYL 4-NITRO-2-SULFAMOYLBENZOATES[a]



No.	R	Formula	M.p.,[b] °C.	Recrystallizing Solvent	Yield, %	Reaction Medium	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
11	CH_3	$C_8H_8N_2O_6S$	193[c]	Methanol	70	Methanol	36.92	37.01	3.09	3.08
12	C_2H_5	$C_9H_{10}N_2O_6S$	139–141	Absol. ethanol	90	Absol. ethanol	39.41	39.64	3.67	3.73
13	n-C_3H_7	$C_{10}H_{12}N_2O_6S$	102–103	1-Propanol	76	1-Propanol	41.66	41.81	4.19	4.19
14	i-C_3H_7	$C_{10}H_{12}N_2O_6S$	128	2-Propanol	52	2-Propanol	41.66	41.82	4.19	4.26
15	n-C_4H_9	$C_{11}H_{14}N_2O_6S$	87–88	1-Butanol	66	1-Butanol	43.70	43.91	4.66	4.69
16	s-C_4H_9	$C_{11}H_{14}N_2O_6S$	140–143	Ethanol-H_2O	60	2-Butanol	...	...	...	...
17	n-C_5H_{11}	$C_{12}H_{16}N_2O_6S$	77–79	Ethanol	50	1-Pentanol	45.56	45.45	5.09	4.98
18	$CH(C_2H_5)_2$	$C_{12}H_{16}N_2O_6S$	70–95	Ethanol-H_2O	33	3-Pentanol	...	...	...	...
19	n-C_6H_{13}	$C_{13}H_{18}N_2O_6S$	70–72	Ethanol	71	1-Hexanol	...	...	...	...
20	i-C_3H_7 (isopropyl 6-nitro-2-sulfamoylbenzoate)	$C_{10}H_{12}N_2O_6S$	130–133	...	49	2-Propanol	...	...	...	...

[a] Analyses were performed by Elek Micro Analytical Laboratories, Los Angeles, Calif. [b] Melting points were taken either with a Fisher-Johns melting point apparatus or by the capillary tube method, and are uncorrected. [c] Reported m.p. 191° (5).

4-amino-2-sulfamoylbenzoate. Ethyl 4-nitro-2-sulfamoylbenzaote (3.4 Gm., 0.012 mole) in 75 ml. of ethyl acetate was reduced with hydrogen at about 3 Atm. pressure with 1.5 Gm. of 5% palladium-on-carbon catalyst. Filtration of the mixture, using a small amount of a filter aid, and evaporation of the filtrate followed by recrystallization of the resultant solid from absolute ethanol gave 2.0 Gm. (66%) of ethyl 4-amino-2-sulfamoylbenzoate, m.p. 152–153°.

Isopropyl 6 - Amino - 2 - sulfamoylbenzoate.—This compound was synthesized by reduction of isopropyl 6-nitro-2-sulfamoylbenzoate in a manner similar to that used for preparation of the 4-amino-2-sulfamoylbenzoic acid esters. Its properties are listed in Table I.

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(4) Loev, B., and Kormendy, M., *J. Org. Chem.*, **27**, 2177 (1962).
(5) Szabo, L., *Bull. Soc. Chim. France*, **20**, 771(1953).