[Chem. Pharm. Bull. 17(10)2065—2070(1969)]

UDC 547.298.507

Syntheses of 3-Sulfonamidopropionamidine Derivatives[1]

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(Received March 19, 1969)

A series of thirty-one sulfonamidopropionamidine derivatives have been synthesized and evaluated for antiviral activity. The synthesis of the sulfonamidopropionamidine series was prepared from the corresponding nitriles *via* ethyl imidates. The compounds synthesized were tested as to their inhibitory effect on polio virus in membrance culture and influenza virus in mice. The results of testing these compounds were found ineffective on the polio virus. However, among the intermediate nitrile derivatives, three compounds, **11**, **12** and **22**, exerted slight effect and final amidine derivatives, five compounds, **7**, **8**, **11**, **18** and **19**, showed marked effects on the influenza virus in mice. Especially, 3-(4-ethylbenzenesulfonamido)propionamidine hydrochloride (**7**) was found comparable to that of Adamantanamine Hydrochloride.

Ueda, *et al.*[3] suggested that antiviral activity of 4-acetamidonaphthalene-1-alkanoylsulfonamide, 4-acetamidobenzene-1-alkanoylsulfonamide and 4-alkylbenzene-1-alkanoylsulfonamide were associated with surfactant activity, particularly protein affinity in host cells, distributability in host cells infected with virus and lipid affinity in virus particles. This suggestion indicates that antiviral agents may be found out by the balancing of surfactant activity of compounds having appropriate antiviral groupings.

On the other hand, Ueda, *et al.*[4] showed that propionamidine was of interest as an appropriate antiviral grouping in the study on 3-acylamidopropionamidine derivatives. These findings led to conceive an idea to make antiviral agents by introducing propionamidino grouping into an arylsulfonamide.

This paper is concerned with the syntheses of 3-alkyl-, 3-benzene- and 3-naphthalenesulfonamidopropionamidine derivatives. Any of 3-sulfonamidopropionamidine derivatives is unknown in literature to date.

The synthetic process of these compounds were considered in reference to the amidine synthetic method of Pinner[5] and Hilgetag,[6] as shown in Chart 1.

At first, 3-sulfonamidopropionitriles were obtained in good yields by refluxing sulfonylchloride with β-aminopropionitrile in pyridine. The product was obtained by the precipitation from the reaction mixture with the addition of water (method 1): This method, however, was

1) This work was presented at the 24th Annual Meeting of the Pharmaceutical Society of Japan, Kyoto, April 1967.
2) Location: *a*) *138, Shirogane-Sankocho, Minato-ku, Tokyo*; *b*) *35, Shinano-machi, Shinjuku-ku, Tokyo.*
3) T. Ueda, T. Itoh and S. Toyoshima, *Chem. Pharm. Bull.* (Tokyo), **1**, 278 (1958); T. Ueda, S. Toyoshima and T. Wachi, *ibid.*, **1**, 379 (1953); T. Wachi and T. Wada, *ibid.*, **2**, 423, 429 (1954); T. Itoh, *Yakugaku Zasshi*, **79**, 1240 (1959); T. Ueda, S. Toyoshima and T. Tsuji, *Keio. J. Med.*, **8**, 57 (1959); I. Nakata, *Yakugaku Zasshi*, **80**, 1063 (1960); T. Tsuji, J. Kawabata, S. Kobayashi and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **12**, 1451 (1964); T. Itoh, S. Toyoshima and T. Ueda, Papers read at the Annual Meeting of the Pharmaceutical Society of Japan, 1954.
4) T. Ueda, Y. Okamoto, T. Tsuji and M. Muraoka, *Chem. Pharm. Bull.* (Tokyo), **16**, 2355 (1968).
5) A. Pinner, "Die Imidoäther und ihre Derivate," Berlin, Germany, 1892; A. Pinner and F. Klein, *Chem. Ber.*, **10**, 1889 (1877).
6) G. Hilgetag, H. Paul, J. Günther and M. Witt, *Chem. Ber.*, **97**, 704 (1964).

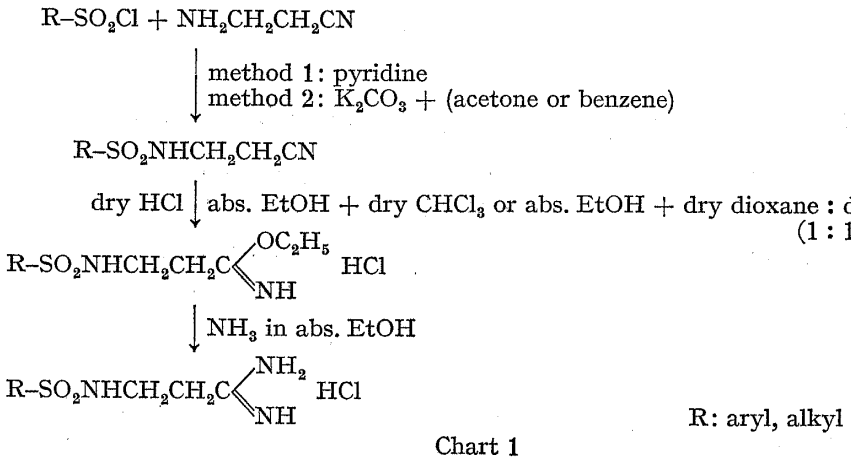


Chart 1

found unpreferable for the preparation of 3-(alkylsulfonamido)propionitrile, because it was very soluble in water. For the preparation, it was found suitable to use acetone or benzene in the presence of potassium carbonate as acid acceptor in lieu of pyridine, therein, the product was obtained by the distillation of the solvent from the reaction mixture after the refluxing (method 2). The nitriles prepared are listed in the Table I.

The identification of these nitriles were conducted by the survey of elementary analysis data and infrared absorption spectra. The nitriles absorbed in the region of 2260—2280 cm^{-1}, 1310—1330 cm^{-1} and 1130—1160 cm^{-1}. The first region was assigned to $\nu_{C\equiv N}$ *i.e.* cyanogen group, and the second and third, assigned to ν_{SO_2} *i.e.* sulfonamido group.[7]

3-Sulfonamidopropionitrile in absolute alcohol was converted to ethyl 3-sulfonamidopropionimidate hydrochloride by the reaction with dried hydrogen gas. The ethyl imidate hydrochloride which had been precipitated in the reaction mixture was dried and reacted with alcoholic ammonia solution to afford 3-sulfonamidopropionamidine hydrochloride.

Thus, 31 compounds of 3-sulfonamidopropionamidine derivatives were synthesized in crystalline state of hydrochlorides. These compounds are listed in Table II.

For the identification of the compounds of 3-sufonamidopropionamidine hydrochloride, infrared absorption spectra were examined as for amidino group $-C(=NH)NH_2$ and sulfonamido grouping $-SO_2NH-$. As shown in Table III, these compounds absorbed commonly in the regions of 1680—1700 cm^{-1}, 1310—1330 cm^{-1} and 1130—1160 cm^{-1}. The first region may

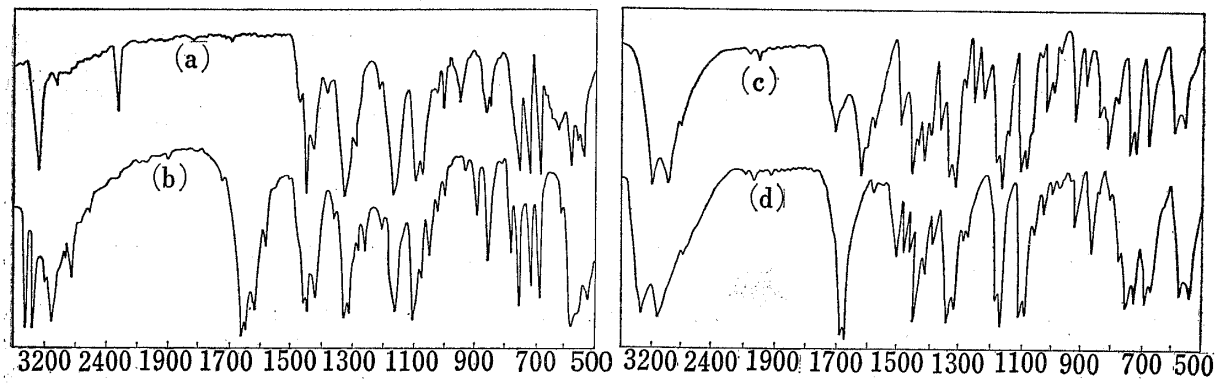
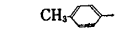
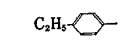
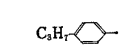
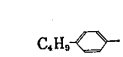
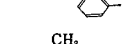
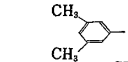
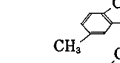
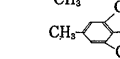
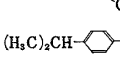
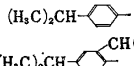
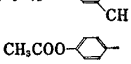
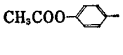
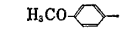
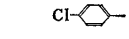
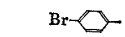
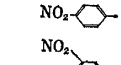
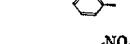
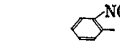


Fig. 1. Infrared Spectra of $C_6H_5SO_2NHCH_2CH_2CN$: (a), $C_6H_5SO_2NHCH_2CH_2C{=}O(NH_2)$: (b), $C_6H_5SO_2NHCH_2CH_2C{-}OC_2H_5(=NH)\cdot HCl$: (c) and $C_6H_5SO_2NHCH_2CH_2C(=NH)\cdot NH_2\cdot HCl$: (d) in KBr Pellet

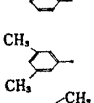
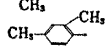
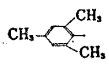
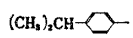
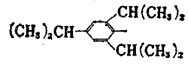
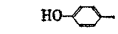
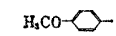
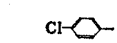
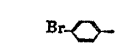
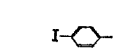
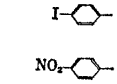
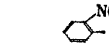
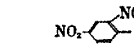
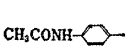
7) K.C. Schreiber, *Anal. Chem.*, **21**, 1168 (1949); L.J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen & Co., Ltd., London, 1964, p. 363.

Table I. 3-Sulfonamidopropionitrile R-$SO_2NHCH_2CH_2CN$

No	R	Method	Yield[a] (%)	Appearance (Recryst. solvt.)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
1	CH_3—	2	21.4	plates (H_2O)	58—59	$C_4H_8O_2N_2S$	32.43	5.44	18.91	32.61	5.18	18.98
2	C_2H_5—	2	29.2	plates (H_2O)	49—50	$C_5H_{10}O_2N_2S$	37.03	6.22	17.28	36.88	6.15	17.18
3	C_3H_7—	2	31.4	plates (H_2O)	39—40	$C_6H_{12}O_2N_2S$	40.09	6.87	15.90	39.98	6.53	16.14
4		1	22.0	plates (EtOH)	109—110	$C_{10}H_{12}O_2N_2S$	53.55	5.40	12.49	53.49	5.27	12.41
5		1	76.4	plates (dil. EtOH)	58—59	$C_9H_{10}O_2N_2S$	51.41	4.79	13.33	51.21	4.72	13.56
6		1	78.5	plates (dil. EtOH)	86[b]	$C_{10}H_{12}O_2N_2S$	53.55	5.40	12.49	53.21	5.41	12.41
7		1	97.9	powders (EtOH+ether)	58—60	$C_{11}H_{14}O_2N_2S$	55.44	5.92	11.76	55.21	5.84	11.50
8		1	78.1	needles (dil. EtOH)	78	$C_{12}H_{16}O_2N_2S$	57.13	6.39	11.11	56.99	6.22	11.25
9		1	86.1	powders (dil. EtOH)	55	$C_{13}H_{18}O_2N_2S$	58.65	6.81	10.52	58.46	6.62	10.77
10		1	73.1	oil	—	$C_{10}H_{12}O_2N_2S$	53.55	5.40	12.49	—	—	—
11		1	34.3	prisms (dil. EtOH)	70—71	$C_{11}H_{14}O_2N_2S$	55.44	5.92	11.76	55.46	5.61	11.87
12		1	41.0	prisms (dil. EtOH)	81	$C_{11}H_{14}O_2N_2S$	55.44	5.92	11.76	55.26	5.84	12.01
13		1	83.2	needles (EtOH)	114—115	$C_{12}H_{16}O_2N_2S$	57.13	6.39	11.11	56.79	6.26	10.97
14		1	45.9	plates (dil. EtOH)	101	$C_{12}H_{16}O_2N_2S$	57.13	6.39	11.11	57.23	6.39	11.19
15		1	54.0	needles (dil. EtOH)	134—135	$C_{18}H_{28}O_2N_2S$	64.25	8.39	8.33	64.21	8.32	8.31
16		1	65.0	oil	—	$C_{11}H_{12}O_4N_2S$	49.24	4.51	10.44	—	—	—
17		1	53.9	needles (EtOH)	93—94	$C_{10}H_{12}O_3N_2S$	49.98	5.04	11.66	50.14	5.04	11.41
18		1	69.3	needles (dil. EtOH)	83—84	$C_9H_9O_2N_2SCl$	44.17	3.71	11.45	44.50	3.64	11.58
19		1	81.0	needles (dil. EtOH)	97—98	$C_9H_9O_2N_2SBr$	37.38	3.14	9.69	37.28	3.03	9.83
20		1	74.1	plates (dil. EtOH)	102—104	$C_9H_9O_2N_2SI$	32.15	2.70	8.33	32.16	4.25	8.43
21		1	35.0	plates (EtOH)	149—150	$C_9H_9O_4N_3S$	42.35	3.53	16.47	42.14	3.64	16.66
22		1	76.4	needles (EtOH)	131—132	$C_9H_9O_4N_3S$	42.35	3.53	16.47	42.78	3.58	16.71
23		1	86.5	plates (acetone)	129—130	$C_9H_9O_4N_3S$	42.35	3.53	16.47	42.42	3.53	16.61
24		1	27.0	plates (EtOH)	133—134	$C_9H_8O_6N_4S$	36.01	2.69	18.67	35.92	2.70	18.44
25		1	77.0	needles (EtOH)	179—180	$C_{11}H_{13}O_3N_3S$	49.43	4.90	15.73	49.73	4.83	15.92
26		1	70.3	plates (dil. EtOH)	101—103	$C_9H_{11}O_2N_3S$	48.00	4.92	18.66	47.99	5.00	18.82
27		1	43.5	powders (dil. EtOH)	105—106	$C_{13}H_{12}O_2N_2S$	59.98	4.65	10.76	59.76	4.79	10.90
28		1	97.5	Plates (EtOH)	124—125	$C_{13}H_{12}O_2N_2S$	59.98	4.65	10.76	60.20	4.82	10.94
29		1	72.4	plates (acetone)	157—158	$C_{15}H_{15}O_3N_3S$	56.77	4.76	13.24	56.41	4.91	13.22

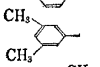
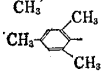
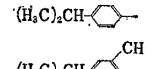
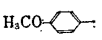
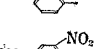
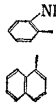
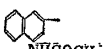
a) from corresponding sulfonyl chloride b) lit. 6) mp 86°

Table II. 3-Sulfonamidopropionamidine Hydrochloride $R\text{-}SO_2NHCH_2CH_2C(=NH)\cdot NH_2\cdot HCl$

No	R	Yield[a] (%)	Appearance (Recryst. solvt.)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
1	CH_3—	58.0	needles (EtOH)	139—140	$C_4H_{12}O_2N_3SCl$	23.83	6.00	20.84	23.86	5.85	21.04
2	C_2H_5—	71.1	powders (EtOH)	118—119	$C_5H_{14}O_2N_3SCl$	29.20	6.86	20.43	28.85	6.58	20.72
3	C_3H_7—	68.3	powders (EtOH)	103—105	$C_6H_{16}O_2N_3SCl$	31.37	7.02	18.29	31.51	7.31	18.48
4		12.6	plates (EtOH)	152—154	$C_{10}H_{16}O_2N_3SCl$	43.24	5.81	15.13	43.41	5.93	15.45
5		49.7	prisms (EtOH)	168—169	$C_9H_{14}O_2N_3SCl$	40.98	5.35	15.94	41.31	5.18	16.07
6		72.0	prisms (EtOH+ether)	143[b]	$C_{10}H_{16}O_2N_3SCl$	43.24	5.81	15.13	43.20	5.81	15.11
7		60.5	plates (EtOH+ether)	145—146	$C_{11}H_{18}O_2N_3SCl$	45.28	6.22	14.40	45.43	6.11	14.36
8		58.0	powders (EtOH+ether)	152	$C_{12}H_{20}O_2N_3SCl$	47.13	6.59	13.74	46.98	6.54	13.50
9		58.1	needles (EtOH+ether)	154	$C_{13}H_{22}O_2N_3SCl$	48.81	6.93	13.14	48.62	6.58	12.99
10		67.5	plates (EtOH)	182—183	$C_{10}H_{16}O_2N_3SCl$	43.24	5.81	15.13	43.44	5.58	15.33
11		52.1	plates (EtOH+ether)	163	$C_{11}H_{18}O_2N_3SCl$	45.28	6.22	14.40	44.99	6.02	14.61
12		78.2	prisms (EtOH)	170	$C_{11}H_{18}O_2N_3SCl$	45.28	6.22	14.40	45.24	5.90	14.27
13		61.4	plates (EtOH)	197—198	$C_{12}H_{20}O_2N_2SCl$	47.13	6.59	13.74	46.99	6.57	13.56
14		54.8	needles (EtOH+ether)	158	$C_{12}H_{20}O_2N_3SCl$	47.13	6.59	13.74	46.96	6.26	13.51
15		53.9	powders (EtOH)	197—198	$C_{18}H_{32}O_2N_3SCl$	55.43	8.27	11.03	55.15	7.98	10.77
16		44.0	powders (EtOH+ether)	188	$C_9H_{14}O_3N_3SCl$	38.64	5.04	15.02	38.47	4.80	15.17
17		77.5	plates (EtOH+ether)	129—130	$C_{10}H_{16}O_3N_3SCl$	40.88	5.49	14.31	41.00	5.52	14.40
18		67.3	plates (EtOH+ether)	164—165	$C_9H_{13}O_2N_3SCl_2$	44.17	3.71	11.75	44.50	3.46	11.58
19		68.2	plates (EtOH)	168—169	$C_9H_{13}O_2N_3$-SClBr	31.54	3.82	12.26	31.72	3.64	12.46
20		61.2	plates (EtOH)	191—192	$C_9H_{13}O_2N_3SClI$	27.74	3.36	10.78	28.12	3.25	10.85
21		59.0	prisms (dil. EtOH)	143—144	$C_9H_{13}O_4N_4SCl$	35.01	4.24	18.15	34.76	4.07	18.36
22		76.0	prisms (dil. EtOH)	126—127	$C_9H_{13}O_4N_4SCl$	35.01	4.24	18.15	35.28	4.22	18.41
23		68.0	prisms (dil. EtOH)	113—114	$C_9H_{13}O_4N_4SCl$	35.01	4.24	18.15	35.33	4.00	17.87
24		41.1	powders (dil. EtOH)	114	$C_9H_{12}O_6N_5SCl$	30.55	3.42	19.80	30.41	3.52	19.91
25		51.7	needles (EtOH+ether)	72—73	$C_{11}H_{17}O_3N_4SCl$	41.21	5.34	17.78	40.98	5.36	17.50
26		54.9	plates (EtOH+ether)	120	$C_9H_{16}O_2N_4SCl_2$	34.29	5.12	17.77	34.30	5.38	17.75
27		79.1	plates (EtOH+ether)	97—98	$C_9H_{16}O_2N_4SCl_2$	34.29	5.12	17.77	34.33	5.22	17.84
28		47.4	needles (EtOH+ether)	190—191	$C_{13}H_{16}O_2N_3$-SCl·H_2O	50.07	5.82	13.48	50.20	5.62	13.30
29		16.0	prisms (EtOH)	221—222	$C_{13}H_{16}O_2N_3$-SCl·H_2O	50.07	5.82	13.48	49.92	5.52	13.41
30		44.9	plates (EtOH+ether)	85	$C_{15}H_{19}O_3N_4$-SCl·H_2O	46.33	5.44	14.41	46.03	5.61	14.62
31		69.0	plates (dil. EtOH)	222—223	$C_{13}H_{18}O_2N_4$-SCl·H_2O	40.73	5.26	14.62	40.77	5.25	14.62

a) from corresponding 3-sulfonamidopropionitrile b) lit. 6) mp 144°

TABLE III. Infrared Spectra Data[a] of 3-Sulfonamidopropionamidine Hydrochlorides
$R\text{-}SO_2NHCH_2CH_2C(=NH)NH_2 \cdot HCl$

No	Compounds	$\nu_{C=N^+}$	$\nu_{AS\ SO_2}$	$\nu_{S\ SO_2}$
1	CH_3-	1700	1310	1145
2	C_2H_5-	1690	1310	1135
3	C_3H_7-	1690	1310	1135
4		1660, 1625sh	1330, 1310	1175, 1160, 1140
5		1690, 1680	1340, 1310	1180, 1165
6		1680	1330	1160
7		1690	1330	1155
8		1690	1330	1155
9		1685	1330	1155
10		1685	1330, 1310	1165, 1130
11		1700	1320	1170, 1160, 1135
12		1680	1315	1155
13		1685	1320	1150
14		1690	1335, 1315	1160
15		1695	1360, 1325	1160, 1150
16		1705	1310	1160
17		1690sh, 1685	1325, 1315, 1305	1160, 1115
18		1690	1325	1150
19		1695	1325	1150
20		1685, 1645sh	1310	1160
21		1690	1350, 1320	1160, 1135, 1115
22		1705	1350, 1310	1155, 1110
23		1695	1365, 1345	1160, 1130
24		1690	1345	1160
25		1695	1330, 1310	1160
26		1685	1320, 1305	1150
27		1700	1335	1160, 1135
28		1705	1350, 1300	1160, 1130
29		1680	1350, 1320	1150, 1135
30		1690	1365, 1325	1150, 1125
31		1690sh, 1700	1370, 1350	1160, 1130

a) IR spectra were determined on a Shimadzu IR-27G Infrared Spectrophotometer in KBr pellets.

be assigned to $\nu C=N^+$ *i.e.* amidino group.[8] Though the acid amide[9] which was derived from ethyl 3-benzenesulfonamidopropionimidate hydrochloride[10] by the thermal decomposition, absorbed in the region of about 1650 cm^{-1}, as shown in Fig. 1.

They were distinguished cleary from 3-sulfonamidopropionamidine hydrochloride in viewpoint of elementary analysis. The second and third regions may be assigned to νSO_2 streching *i.e.* sulfonamido grouping,[7] since there was not any interfering absorption near these regions.

Thus, the structures of the objective compounds were elucidated by the elementary analysis data and the infrared absorption spectra.

Next, the compounds synthesized were tested as to their inhibitory effect on polio virus in membrane culture and influenza virus in mice.

All of the compounds were found ineffective on the polio virus. Among 3-sulfonamidopropionitrile derivatives, however, 3-(3-nitrobenzenesufonamido)propionitrile, 3-(3,5-dimethylbenzenesulfonamido)propionitrile and 3-(2,5-dimethylbenzenesulfonamido)propionitrile exerted slight effects on the influenza virus in mice. Among 3-sulfonamidopropionamidine derivatives, 3-(4-ethylbenzenesulfonamido)propionamidine hydrochloride, 3-(4-propylbenzenesulfonamido)propionamidine hydrochloride, 3-(3,5-dimethylbenzenesulfonamido)propionamidine hydrochloride, 3-(4-chlorobenzenesulfonamido)propionamidine hydrochloride and 3-(4-bromobenzenesulfonamido)propionamidine hydrochloride showed marked effects on the influenza virus in mice.

Especially, the effect of the first compound *i.e.* 3-(4-ethylbenzenesulfonamido)propionamidine hydrochloride was found comparable to that of adamantanamine hydrochloride. The evaluation of this agent as an antiinfluenzal drug will be reported in the near future.

Experimental

Synthesis of 3-(Arylsulfonamido)propionitrile (Method 1)——To a solution of 0.1 mole of β-aminopropionitrile in 50 ml of pyridine was added portion-wise, and with stirring, 0.1 mole of arylsulfonyl chloride. Then, the mixture was refluxed on a water bath for 1 hr. After removal of pyridine, the residue was poured onto ice–water, which began to solidify immidiately. The nitrile thus obtained was purified by recrystallization from suitable solvent. Yield 54—98%.

Synthesis of 3-(Alkylsulfonamido)propionitrile (Method 2)——A mixture of 0.1 mole of β-aminopropionitrile, 0.1 mole of alkylsulfonyl chloride and 0.05 mole of K_2CO_3 in acetone (or benzene) was refluxed on a water bath for 4—5 hr. After precipitates had been filtered off, the filtrate was concentrated under reduced pressure to dryness. The residue was recrystallized from suitable solvent, and chilled for several days, whereupon it set to crystallized. Yield 21—29%.

Ethyl 3-Sulfonamidopropionimidate Hydrochloride——A mixture of 0.05 mole of the 3-sulfonamidopropionitrile obtained above and 0.053 mole of absolute EtOH was diluted with dry $CHCl_3$ (when necessary, dry dioxane in addition to the $CHCl_3$ was employed) until solution was complete. The solution of the nitrile, cooled to 0°, was almost saturated with dry hydrogen chloride, and then allowed to stand in a refrigerator for 2—3 days. The precipitated salt was collected, washed throughly with petroleum ether and dried in a desiccator. Another crop of crystals was obtained by addition of ether to the filtrate. The salt was submitted to the following ammonolysis without further purification.

3-Sulfonamidopropionamidine Hydrochloride——The salt obtained above was treated with 8—12% ethanolic ammonia solution to convert the amidine hydrochloride. After 2—3 days the crude amidine hydrochloride was filtered off, the filtrate diluted with ether and the additional amount of the amidine hydrochloride was collected. The hydrochlorides were readily recrystallized from a suitable solvent. Yield 45—72%.

Acknowledgement The authors are indebted to Miss. H. Yoda of Pharmaceutical Institute of this University for elemental analyses.

8) J.C. Grivas and A. Taurins, *Can. J. Chem.*, 37, 1260 (1959).

9) $C_6H_5SO_2NHCH_2CH_2C{=}O(NH_2)$. *Anal.* Calcd. for $C_9H_{12}O_3N_2S$: C, 47.35; H, 5.30; N, 12.27. Found: C, 47.35; H, 5.20; N, 12.23. mp 117—118°, as colorless needles (recrystallized from EtOH).

10) $C_6H_5SO_2NHCH_2CH_2C{-}OC_2H_5(=NH)\cdot HCl$, mp 138—139°. *Anal.* Calcd. for $C_{11}H_{17}O_3N_2SCl$: C, 45.12; H, 5.85; N, 9.57. Found: C, 44.98; H, 5.53; N, 9.96.