Antituberculous Compounds. III. N-Acyl Derivatives of *p*-Aminocinnamaldehyde and *p*-Aminobenzaldehyde thiosemicarbazones[1]

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Several N-acyl derivatives of *p*-aminocinnamaldehyde thiosemicarbazone were prepared in order to study the effects of a variety of acyl groups on its antituberculous activity. In the course of this study, it was found that *p*-dimethylacrylylaminocinnamaldehyde thiosemicarbazone, when tested by subcutaneous injection of its oily suspension,[2] had markedly reduced toxicity compared with other thiosemicarbazones prepared in this laboratory. As it was considered that this effect would be due to the presence of α,β-double bond in dimethylacrylyl radical, the experiment was extended to combine α,β-unsaturated acids having fewer carbon atoms with *p*-aminocinnamaldehyde and *p*-aminobenzaldehyde thiosemicarbazones. The preparation of the higher analogs was not undertaken since the higher acyl groupings seemed to decrease the activity.[3]

Dimethylacrylic acid was prepared by the usual method.[4][5][6] Dimethylacrylyl chloride was first prepared by the action of thionyl chloride on dimethylacrylic acid[7] in unsatisfactory yields, but later phosphorus trichloride was found to give a better yield and pure material. Phenylacetyl chloride and cinnamyl chloride were employed in the experiments, in the form of etheral solutions without isolation of the substances.[8] Methacrylic acid was prepared by hydrolysis of methyl methacrylate[9] and the corresponding chloride was obtained according to the method described by Rehberg et al.[10] *p*-Aminocinna-

(1) Most part of this study has been presented before the annual meeting of the Chemical Society of Japan in Tokyo on April 5, 1952.

(2) Toraichi Takebe, Unpublished data.

(3) Katsuhiko Tago, Unpublished data; Robert Behnish, Fritz Mietsch and Hans Schmidt, *Am. Rev. of Tuberc.*, **61**, 1 (1950).

(4) J. B. Conant and Neal Tuttle, *Org. Syn.* Col, Vol. 1, p. 193.

(5) J. B. Conant and Neal Tuttle, ibid., p. 338.

(6) Barbier and Léser, *Bl.* (3) 33, 815.

(7) H. Staudinger and E. Ott. *Ber.*, **44**, 1636 (1911).

(8) G. A. Schmidt and David A. Shirley, *J. Am. Chem. Soc.* **71**, 3804 (1948).

(9) Ryozo Inoue, *J. Soc. Chem. Ind., Japan*, **45**, 385 (1942).

(10) C. E. Rehberg, Marion B. Dixon and C. H. Fisher, *J. Am. Chem. Soc.* **67**, 208 (1945).

Table 1

Thiosemicarbazones

Aldehydes	Yield %	Solvent for recrystallization	M. P. °C	Empirical formula	Nitrogen %	
					Calcd.	Found
p-Benzoylamino-cinnamaldehyde[a]	43	pyridine and water	233—4 (decomp.)	$C_{17}H_{16}ON_4S$	17.23	17.37
p-Phenylacetylamino-cinnamaldehyde[b]	39	pyridine and water	223 (decomp.)	$C_{18}H_{18}ON_4S$	16.56	16.65
p-Dimethylacrylyl-aminocinnamaldehyde[a]	53	pyridine and water	234—5 (decomp.)	$C_{15}H_{18}ON_4S$	18.55	18.27
p-Dimethylacrylyl-aminobenzaldehyde[a]	39	glacial acetic acid	224 (decomp.)	$C_{13}H_{16}ON_4S$	20.27	20.17
p-(*p*-Tolylsulfonyl)-aminocinnamaldehyde[a]	73	pyridine and water	241—2 (decomp.)	$C_{17}H_{18}O_2N_4S_2$	14.94	15.06
p-*n*-Caproylamino-cinnamaldehyde[a]	46	ethanol	197	$C_{16}H_{22}ON_4S$	17.60	17.44
p-*n*-Caproylamino-benzaldehyde[a]	53	ethanol	201 (decomp.)	$C_{14}H_{20}ON_4S$	19.16	18.84

(a) Pure chloride was used. The reaction was carried out in pyridine.

(b) This substance was prepared as with *p*-cinnamylaminocinnamaldehyde thiosemicarbazone.

maldehyde and *p*-aminobenzaldehyde thiosemicarbazones could be prepared smoothly by the reduction of the corresponding nitrothiosemicarbazones with sodium hydrogen sulfide.[11]

All the N-acyl derivatives of *p*-aminocinnamaldehyde and *p*-aminobenzaldehyde thiosemicarbazones except for succinoyl and crotonyl derivatives were obtained by the action of acid chloride or its etheral solution on the amino thiosemicarbazones in pyridine. An attempted preparation of the crotonyl derivatives in pyridine did not succeed, but Schotten-Baumann's reaction in methyl acetate gave the desired products in reasonable yields. The compounds not described in the experimental part are listed in Table 1.

Biological evaluations of these thiosemicarbazones will be published elswhere. This paper is concerned only with their synthesis and characterization.

Experimental[12]

β, β-Dimethylacrylyl Chloride.—A mixture of 10 g. of dimethylacrylic acid and 7.5 g. of phosphorus trichloride was warmed at 60—75° for 3.5 hours. The crude chloride obtained by distillation under reduced pressure was further subjected to distillation under ordinary pressure and a portion boiling at 145—150° and amounting to 7.7 g. (65%) was collected.

***p*-Aminobenzaldehyde Thiosemicarbazone.**—200 cc. of ethanol and 80 cc. of 2 N-sodium hydroxide solution were mixed, saturated with hydrogen sulfide and 22.4 g. of *p*-nitrobenzaldehyde thiosemicarbazone was added in one portion. The whole mixture was then refluxed on a steam bath for 30 minutes, while the crystals of the nitro thiosemicarbazone completely disappeared. A resulting dark red colored solution was allowed to stand at room temperature overnight and the separated crystals were collected on a filter, and were washed thoroughly with ethanol and water. Dried material, m. p. 197—198° (decomp.) weighed 14.5 g. (75%).

***p*-Succinoylaminocinnamaldehyde Thiosemicarbazone.**—A mixture of 2.2 g. of *p*-aminocinnamaldehyde thiosemicarbazone, 1.0 g. of succinic anhydride and 20 cc. of ethylacetate was refluxed for 30 minutes. The precipitate was collected, dissolved in sodium hydroxide solution, and the filtered solution was acidified with 10% hydrochloric acid to give 2.2 g. (70%) of the desired product melting at 189° (decomp.). A small sample was recrystallized from ethanol to yield a pure product, m. p. 207—208° (decomp.) (Found: N, 17.47%. Calcd. for $C_{14}H_{16}O_3N_4S$; N, 17.50%).

***p*-Crotonylaminobenzaldehyde Thiosemicarbazone.**[13]—To a mixture of 3.9 g. of *p*-aminobenzaldehyde thiosemicarbazone, 10 cc. of 2N-sopium hydroxide solution and 60 cc. of methylacetate were added dropwise. And then a solution of 2.1 g. of crotonyl chloride in 10 cc. of methylacetate at 5—10° was added with stirring. Yellow crystals were collected, washed with methylacetate and dried, yielding 2.4 g. (46%) of the desired product melting at about 240° (decomp.). On dissolving it in 86 cc. of pyridine and adding 110 cc. of water to the solution, long needles (2.0 g.) of the same m. p. separated. For microanalysis a portion was further recrystallized from ethanol (Found: N, 21.04. Calcd. for $C_{12}H_{14}ON_4S$: N, 21.36%).

(11) Tamio Nishimura, This Bulletin, **25**, 54 (1952).

(12) All temperatures are uncorrected.

(13) Crotonyl chloride was prepared by the action of phosphorus trichloride on α-crotonic acid.

p-Crotonylaminocinnamaldehyde Thiosemicarbazone.[13]—From 2.2 g. of p-aminocinnamaldehyde thiosemicarbazone, 2.4 g. (83%) of the acylated product melting at 222° (decomp.) was obtained in a manner similar to that described above. It was dissolved in 16 cc. of pyridine and 30 cc. of water was added to the solution. Yellow crystals (1.1 g.) of m. p. 227° (decomp.) were collected, redissolved in 20 cc. of pyridine and 40 cc. of water was added to the solution, giving 1 g. (35%) of the pure material melting at 234° (decomp.). An additional recrystallization was without effect on the m. p. (Found: N, 19.40%. Calcd. for $C_{14}H_{16}ON_4S$: N, 19.43%).

p-Cinnamoylaminocinnamaldehyde Thiosemicarbazone.—A mixture of 0.74 g. of cinnamic acid and 0.60 g. of thionyl chloride was heated at 70—90° for an hour and the unreacted thionyl chloride removed by distillation. The residual acid chloride dissolved in ether was added dropwise and with stirring to a cold solution of 1.1g. of p-aminocinnamaldehyde-thiosemicarbazone in pyridine and the reaction mixture was poured into 150 cc. of ice water. The solid was recrystallized by means of pyridine and water; yield 0.6 g. (33%) m. p. 243° (decomp.) (Found: N. 15.60%. Calcd. for $C_{19}H_{18}ON_4S$: N, 15.96%).

p-Methacrylylaminobenzaldehyde Thiosemicarbazone.—A mixture of 1.3 g. of methacrylic acid and 0.7 g. of phosphorous trichloride was kept at 60—70° for fifteen minutes and then at room temperature for two hours. The upper layer was added dropwise to a cold solution of 2 g. of p-aminobenzaldehyde thiosemicarbazone in 10cc. of pyridine. After standing at room temperature for an hour, 15 cc. of water was added to the reaction mixture and allowed to stand in an ice box over-night. The separated solid, after recrystallizations from pyridine and water, gave 0.4g. of colorless plate melting at about 216° (decomp.) (Found: N, 20.93%, Calcd. for $C_{12}H_{14}ON_4S$: N, 21.36%).

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