[CONTRIBUTION FROM THE FULMER CHEMICAL LABORATORY, THE STATE COLLEGE OF WASHINGTON]

The Addition of the Thiol Group to Schiff Base Systems. I. Benzalanthranilic Acid¹

By Gardner W. Stacy and Richard J. Morath²

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The addition of a variety of thiols to benzalanthranilic acid is described. Most of the thiols studied have given excellent yields of the corresponding addition products. In the case of several primary and secondary mercaptans somewhat lower yields have been obtained.

As the formation of benzylpenicillin from benzylpenicillenic acid in minute yield³ would seem to involve the addition of a thiol group to a tautomeric Schiff base system, it has appeared of interest to investigate various factors related to such reactions. Initial experiments in this direction are to deal with Schiff base structures which cannot exist in tautomeric forms.

Although the addition of the thiol group to Schiff bases where subsequent cyclization is possible, as in the case of thiazolidone formation, has been well established in several investigations,4 comparatively few instances have been reported wherein a simple addition product has been obtained. For example, the possible addition of p-thiocresol to benzalaniline has been investigated,5 and in this case, no addition product could be isolated, but instead N-benzylaniline and bis-(ptolyl) disulfide were obtained as products. In a similar experiment in this Laboratory, the addition of thio- β -naphthol to benzalaniline was attempted, but without success. Here, no reaction occurred, and a major part of the thio- β -naphthol was recovered.

In connection with the preparation of thiazolidones, Surrey⁶ observed that the expected thiazolidone (III), which was the usual type of product in the case of other Schiff bases investigated, was not



obtained by the interaction of mercaptoacetic acid and benzalanthranilic acid. Rather, a substance resulted having the composition of the supposed

(1) Presented in part before the Division of Medicinal Chemistry at the 12th International Congress of Pure and Applied Chemistry, New York, N. Y., September 10, 1951.

(2) Abstracted in part from a thesis submitted by Richard J. Morath in partial fulfillment of the requirements for the Degree of Master of Science, The State College of Washington, June, 1951.

(3) V. du Vigneaud, F. H. Carpenter, R. W. Holley, A. H. Livermore and J. R. Rachele in "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson and R. Robinson, ed's., Princeton University Press, Princeton, N. J., 1949, p. 1018.

(4) (a) A. R. Surrey, THIS JOURNAL, **71**, 3354 (1949); (b) H. D. Troutman and L. M. Long, *ibid.*, **70**, 3436 (1948).

(5) H. Gilman and J. B. Dickey, ibid., 52, 4573 (1930).

(6) A. R. Surrey, ibid., 69, 2911 (1947).

intermediate (II), which corresponded to a simple addition product of a thiol and Schiff base. The structure (II) for this addition product, although not rigorously confirmed, seems quite reasonable, particularly in the light of other reactions involving Schiff bases.⁷

Since confirmation of Surrey's observation was readily obtained, it appeared that benzalanthranilic acid might serve as a convenient model for initial studies of addition of thiols to Schiff base systems. This has proved to be the case, for it has been found that a number of different thiols readily add to benzalanthranilic acid to give simple addition products of the type I (Table I). The general procedure used involved stirring the thiol and benzalanthranilic acid in benzene at room temperature. The benzalanthranilic acid dissolved fairly rapidly, and then as the reaction ensued, an addition product began to precipitate from solution. In several instances a catalytic amount of piperidine⁸ was added to the reaction mixture. It is questionable, however, as to whether the piperidine had any significant effect in respect to the yield of addition product obtained, since yields in the absence of piperidine generally seemed to be of the same order as those obtained with piperidine added to the reaction mixture.

The yields in most cases were excellent, the

behavior of all thiols investigated being quite similar to that previously reported for mercaptoacetic acid.⁶ Several primary and secondary mercaptans reacted to form addition products in somewhat lower yield. In comparison with the addition of thiols to substituted acrylonitriles,⁹ it was thought possible that tertiary thiols might not react as readily, and that this would be reflected in a lower yield of addition product obtained. With *t*-butyl mer-

captan this did not hold true, however, for the yield was comparable with those of a majority of the other thiols investigated. It should also be noted that p-thiocresol, which had been found not to add to benzalaniline,⁵ readily added to benzalanthranilic acid.

The addition products were colorless after recrystallization, but in some instances, on standing in air or *in vacuo*, developed a yellow coloration. As this did not occur, however, when the substances were stored in the absence of light, color develop-

(8) R. M. Ross, This Journal, 71, 3458 (1949).

(9) R. M. Ross, H. L. Bushey and R. J. Rolih, ibid., 73, 540 (1951).

 ^{(7) (}a) J. C. Sheehan and J. J. Ryan, *ibid.*, 73, 1204 (1951); (b)
 M. Busch, Ber., 37, 2691 (1904); M. Busch and A. Rinck, *ibid.*, 38, 1761 (1905).

	Thiol Addition Products of Benzalanthranilic Acid									
I, R ==	Vield, %ª	Recryst. solvent ^b	M.p., °C.¢	Formula	Carbon Calcd. Found		Analyses, % Hydrogen Caled, Found		Sulfur Caled. Found	
HOOCCH ₂	92	EA-P	$90-91^{d}$	$C_{16}H_{15}NO_4S$	60.55	60.66	4.76	4.79	10.10	9.91
HOOCCH ₂ CH ₂	99*	EA	115-116	$C_{17}H_{17}NO_4S$	61.61	61.69	5.17	5.14	9.6 8	10.17
C ₆ H ₅	91	EA-P	95-98	$C_{20}H_{17}NO_2S$	71.63	71.31	5.11	5.12	9.56	9.30
p-CH ₃ C ₆ H ₄	86	$\mathbf{E}\mathbf{A}$	118-120	$C_{21}H_{19}NO_2S$	72.18	72.25	5.48	5.05	9.18	8,83
C ₆ H ₅ CH ₂	70	Е	109-110	$C_{21}H_{19}NO_2S$	72.18	72.13	5.48	5.46	9.18	9.34
CH ₃ CO	70	I	121 - 123	$C_{16}H_{15}NO_3S$	63.77	64.02	5.02	5.05	10.64	10.71
$(CH_3)_2CH$	57	1	95-99	$C_{17}H_{19}NO_2S$	67.74	68.08	6.34	6.48	10.64	10.48
(CH ₃) ₂ CHCH ₂	62	EA	95-96	$C_{18}H_{21}NO_2S$	68.54	68.91	6.71	7.28	10.16	9.77
CH ₃ CH ₂ CH ₂ CH ₂	49	Е	90 - 92	$C_{18}H_{21}NO_2S$	68.54	68.14	6.71	6.72	10.16	10.02
$(CH_3)_3C^f$	88*	Е	98-100	$C_{18}H_{21}NO_2S$	68.54	68.62	6.71	6.74	10.16	10.22

 TABLE I

 Thiol. Addition Products of Benzalanthranilic Acid

^a Yields indicated were based on the crude product obtained. ^b Analytical samples were recrystallized three to five times. Solvents employed: EA, ethyl acetate; P, petroleum ether (b.p. 30-50°); E, ethanol; I, isopropyl alcohol; combinations denote recrystallizations from mixed solvents. ^c Melting point of analytical sample. ^d Surrey (ref. 6) reported this substance to melt at 101-102°. Irregularities of several degrees were also noted in the melting points of some of the other addition products. ^c Ten drops of piperidine added. ^f Reaction mixture in this case heated under reflux.

ment appeared to be a photochemical phenomenon. The addition products reacted with 2,4-dinitrophenylhydrazine in acid solution to give benzaldehyde 2,4-dinitrophenylhydrazone. The adducts also gave a positive nitroprusside test in 5%sodium hydroxide, even after repeated recrystallization. This demonstrated the probable instability of these substances under such conditions. It is of further interest to note that such behavior was in contrast to that of thiazolidones which are reported to undergo no reaction with hydroxylamine hydrochloride or nitroprusside.¹⁰

Experimental¹¹

Benzalanthranilic Acid.—As the method of Ekeley and Dean¹² did not prove to be completely satisfactory in our hands, the following procedure was employed. To a flask equipped with a water separator and a reflux condenser was added 500 ml. of benzene. After the benzene had been heated under reflux to remove any water that might be present, 69 g. (0.50 mole) of anthranilic acid was added to the flask. Heating was resuned, and 53 g. (0.50 mole) of redistilled benzaldehyde was added. The mixture was heated for about 30 hours, and after 8.4 ml. of water (93% of the theoretical amount) had been obtained, the contents of the flask were allowed to cool. The solid, which readily crystallized from solution, was removed by filtration and air dried. The yield of crude material, m.p. $125-126^{\circ}$, was 104 g. (93%). Three recrystallizations from benzene afforded a colorless, crystalline product, m.p. $125-127^{\circ}$.

Anal. Calcd. for C₁₄H₁₁NO₂: C, 74.65; H, 4.92; neut.

equiv., 225. Found: C, 74.71; H, 4.85; neut. equiv., 223.

Thiol Addition Products of Benzalanthranilic Acid.— Benzalanthranilic acid (0.05 mole) and the appropriate thiol (0.06 mole) were added to 75 ml. of benzene, and the mixtures were stirred over periods of time varying from onehalf hour to 12 hours. Within a short time the benzalanthranilic acid had completely dissolved. Then after several hours the addition product began to precipitate from solution. The product was removed by filtration, and in some instances the mother liquor could be concentrated to obtain additional amounts of material.

The addition product obtained from *n*-butyl mercaptan was sufficiently soluble in benzene so that it could not be crystallized from the reaction mixture at room temperature. However, by allowing the mixture to stand in the refrigerator the product precipitated from solution. Additional amounts of product could be obtained by further cooling the mother liquor.

All addition products formed with accompanying information are presented in Table I.

Attempted Addition of Thio- β -naphthol to Benzalaniline. --To a solution of 8.0 g. (0.044 mole) of benzalaniline in 50 ml. of dry benzene was added a solution of 7.4 g. (0.046 mole) of thio- β -naphthol in 50 ml. of dry benzene. The reaction mixture was stirred for four hours, but during this period no material crystallized from solution. The mixture was then extracted with 5% sodium hydroxide, and the combined alkali extracts were washed with benzene. On acidification of the sodium hydroxide solution with dilute hydrochloric acid, a precipitate separated which proved to be thio- β -naphthol, m.p. 75-77°, 6.4 g. (86% recovery of starting material). The benzene extract was concentrated under reduced pressure, and benzalaniline was obtained.

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⁽¹⁰⁾ H. Erlenmeyer and V. Oberlin, *Helv. Chim. Acta*, **30**, 1329 (1947).

⁽¹¹⁾ All melting points are corrected. The microanalyses were performed by the Clark Microanalytical Laboratory, Urbana, Illinois, and the Galbraith Laboratories, Knoxville, Tennessee.

⁽¹²⁾ J. B. Ekeley and P. M. Dean, THIS JOURNAL, 34, 161 (1912).