[CONTRIBUTION FROM SCHENLEY LABORATORIES, INC.]

Antituberculous Compounds 2,4-Disubstituted Benzaldehyde Thiosemicarbazones

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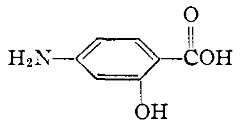
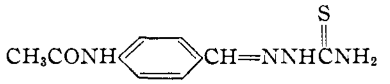
A series of compounds related to *p*-aminosalicylic acid and *p*-acetylaminobenzaldehyde thiosemicarbazone has been prepared for evaluation against *Mycobacterium tuberculosis*. These compounds were prepared from the corresponding 2-alkoxy-4-nitrotoluenes. The most active compound was 4-acetylamino-2-*n*-amyloxybenzaldehyde thiosemicarbazone.

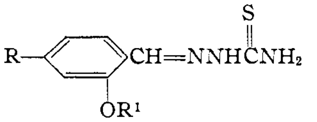
The efficacy of *p*-aminosalicycic acid (PAS) (I) and *p*-acetylaminobenzaldehyde thiosemicarbazone[2] (II) in the treatment of tuberculosis has been the subject of considerable research in recent years. These compounds both contain an amino group para to a doubly bound carbon atom. The incorporation of a 2-hydroxyl group in II would produce a class of compounds III which would be expected to possess antitubercular activity. After the inception of this work, Drain, Goodacre and Seymour[3] published the *in vitro* pharmacological data for 2-hydroxy-4-nitrobenzaldehyde thiosemicarbazone and 2-hydroxy-4-aminobenzaldehyde thiosemicarbazone. The latter compound was thirty times as active as II. At the present time we would like to publish data on a related series of compounds which were synthesized as outlined in the flow sheet.



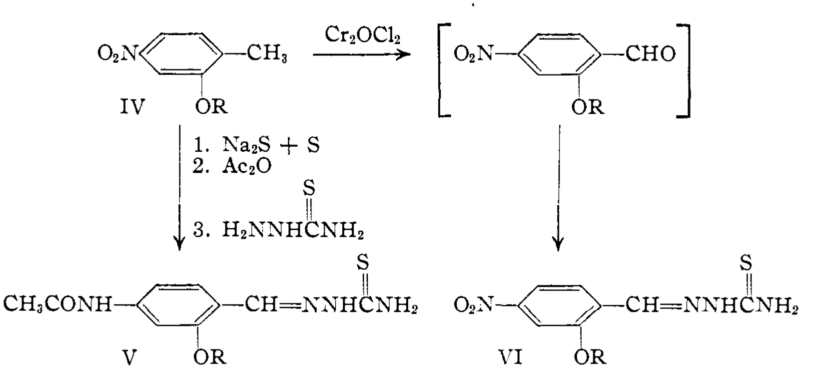
I



II



III



The 2-alkoxy-4-nitrotoluenes (IV) (Table I) were converted to the corresponding 2-alkoxy-4-aminobenzaldehydes using the method of Blanksma.[4] The substituted benzaldehydes were not characterized because of their tendency to oil out or form the polymeric anil. Instead the crude product was acetylated and the acetyl derivative reacted with thiosemicarbazide to give the desired thiosemicarbazones V (Table III).

Attempts to prepare the 2-alkoxy-4-nitrobenzaldehydes by using manganese dioxide and sulfuric acid, selenium dioxide, or chromium trioxide and acetic acid were either unsuccessful or gave very low yields. The reaction using chromyl chloride was satisfactory, and again the substituted benzaldehydes were not isolated but converted directly to the thiosemicarbazones, VI (Table II).

The pharmacology of these compounds will be reported elsewhere.

The authors were indebted to Drs. K. Ladenburg and B. Puetzer for their encouragement throughout this project.

Experimental

2-Hydroxy-4-nitrotoluene.—This material was prepared in 90–95% yield using the method of Ullmann.[5]

2-Alkoxy-4-nitrotoluene.—Into a 1-l. three-necked flask equipped with a sealed stirrer, reflux condenser and Glascol mantle were charged 102 g. (0.66 mole) of 2-hydroxy-4-nitrotoluene, 30 g. (0.75 mole) of sodium hydroxide and 400 ml. of water. The mixture was stirred, heated to 100° and 0.75 mole of the alkyl *p*-toluenesulfonate added. After three to four hours at 100° the reaction mixture was chilled to 5°, the resultant slurry filtered, and the filter cake washed with water until the drippings ran almost colorless. The wet cake was recrystallized by dissolving in 2–2.5 volumes of hot ethanol.

4-Acetylamino-2-ethoxybenzaldehyde Thiosemicarbazone.—A modification of the procedure described by Blanksma[4] for the preparation of 4-amino-2-methoxybenzaldehyde was used. Into a 1-l. three-necked flask fitted with a reflux condenser were charged 45.3 g. (0.25 mole) of 2-ethoxy-4-nitrotoluene and 400 ml. of 95% ethanol. While the mixture was heated to reflux a solution of 60.0 g. (0.25 mole) of sodium sulfide nonahydrate and 8.0 g. (0.25 mole) of sulfur was prepared by heating the two components in a beaker on a hot-plate. This solution was added to the refluxing ethanol solution and the mixture refluxed vigorously for five hours. The reaction mixture was steam distilled to remove solvent and some 2-ethoxy-*p*-toluidine (usually three hours sufficed). After chilling the mixture in the flask overnight the supernatant liquid was decanted and the semi-solid mass transferred to a 250-ml. beaker. Fifty milliliters of acetic anhydride was added and then 4–5 drops of C.P. sulfuric acid. Acetylation proceeded rapidly and a dark brown solution was obtained which was added to a boiling solution of 300 ml. of ethanol and 50 ml. of water. The mixture was boiled 10–15 minutes to decompose excess acetic anhydride and 15.0 g. (0.155 mole) of thiosemicarbazide in 100 ml. of boiling water added. A heavy yellow precipitate formed quickly. After heating for an additional one-quarter hour, the slurry was chilled for

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(1) The Upjohn Co., Kalamazoo, Mich.

(2) Schenley "Tibione" brand of Amithiozone.

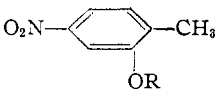
(3) D. J. Drain, *et al.*, *J. Pharm. Pharmacol.*, **1**, 784 (1949).

(4) J. J. Blanksma, *Rec. trav. chim.*, **29**, 408 (1910).

(5) F. Ullmann, *Ber.*, **38**, 3787 (1905).

TABLE I

2-ALKOXY-4-NITROTOLUENES

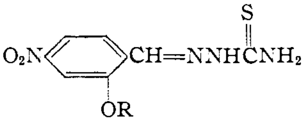


No.	R	Yield, %	M.p., °C.	Empirical formula	Analyses, % Calcd. Carbon	Calcd. Hydrogen	Calcd. Nitrogen	Found Carbon	Found Hydrogen	Found Nitrogen
1	CH_3[a]	60	71	$C_8H_9O_3N$						
2	C_2H_5[b]	52	60–61	$C_9H_{11}O_3N$						
3	n-C_3H_7	71.5	48–49	$C_{10}H_{13}O_3N$	61.53	6.65	7.18	61.55	6.78	7.09
4	n-C_4H_9	70.1	50–52	$C_{11}H_{15}O_3N$	63.15	7.17	6.68	63.08	7.21	6.73
5	n-C_5H_{11}	73	40–41	$C_{12}H_{17}O_3N$	64.57	7.63	6.27	64.60	7.41	6.44

[a] CH_3, lit. F. Ullmann and R. Fitzenkamm, *Ber.*, **38**, 3790 (1905). [b] C_2H_5, lit. L. Spiegel, N. Munblit and H. Kaufmann, *ibid.*, **39**, 3240 (1906).

TABLE II

2-ALKOXY-4-NITROBENZALDEHYDE THIOSEMICARBAZONES

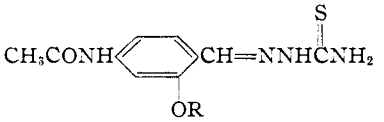


No.	R	Yield, %	M.p., °C.	Empirical formula	Analyses, % Calcd. Nitrogen	Calcd. Sulfur	Found Nitrogen	Found Sulfur
1	CH_3	37.7	250–251[a]	$C_9H_{10}O_3N_4S$	22.04	12.59	21.89	12.85
2	C_2H_5	39.3	238.5[a]	$C_{10}H_{12}O_3N_4S$	20.89	11.94	20.28	11.65
3	n-C_3H_7	38.6	225[b]	$C_{11}H_{14}O_3N_4S$	19.85	11.33	19.95	11.38
4	n-C_4H_9	51.0	214.5[c]	$C_{12}H_{16}O_3N_4S$	18.91	10.81	18.83	10.83

[a] Recrystallized from acetic acid. [b] Recrystallized from methanol. [c] Recrystallized from ethanol.

TABLE III

4-ACETAMINO-2-ALKOXYBENZALDEHYDE THIOSEMICARBAZONES



No.	R	Yield, %	M.p., °C.	Empirical formula	Analyses, % Calcd. Nitrogen	Calcd. Sulfur	Found Nitrogen	Found Sulfur
1	CH_3	28.0	233[a]	$C_{11}H_{14}O_2N_4S$	21.05	12.03	21.03	11.86
2	C_2H_5	45.0	238.5[a]	$C_{12}H_{16}O_2N_4S$	20.00	11.41	19.65	11.28
3	n-C_3H_7	29.5	229.5[a]	$C_{13}H_{18}O_2N_4S$	19.03	10.88	19.27	11.13
4	n-C_4H_9	42.3	216[a]	$C_{14}H_{20}O_2N_4S$	18.18	10.38	18.43	10.45
5	n-C_5H_{11}	40.4	174.5[b]	$C_{15}H_{22}O_2N_4S$	17.38	9.93	17.31	10.01

[a] Recrystallized from aqueous isopropyl alcohol. [b] Recrystallized from methanol.

four to five hours. The solid was collected on a Büchner funnel and dried *in vacuo* at 60°. The weight of yellow material, m.p. 229–232°, was 31.5 g. or 45% of theory based on 2-ethoxy-4-nitrotoluene. The other 2-alkoxy-4-nitrotoluenes were treated similarly to give the corresponding thiosemicarbazones.

2-Ethoxy-4-nitrobenzaldehyde Thiosemicarbazone.—Into a 250-ml. three-necked flask equipped with a sealed stirrer, dropping funnel and ice-water bath were charged 9.1 g. (0.05 mole) of 2-ethoxy-4-nitrotoluene and 30 ml. of chloroform. Into the dropping funnel was placed a solution of 18.7 g. (0.1 mole) of chromyl chloride and 30 ml. of chloroform. The chromyl chloride–chloroform solution was added to the stirred reaction mixture at 10-minute intervals in the course of two hours so that the temperature did not exceed 35–40°. After stirring an additional five hours the reaction mixture was allowed to stand over the weekend. The semi-solid reaction mixture was decomposed by the cautious addition of 100 ml. of water, and then extracted with seven 100-ml. portions of ether. The extracts were dried over magnesium sulfate, treated with 1–2 g. of Darco G-60 and the solvent removed. The residue was taken up in 250 ml. of hot 95% ethanol and 5.0 g. (0.05 mole) of thiosemicarbazide in 50 ml. of boiling water added. As the mixture boiled a yellow precipitate began to separate. After one-quarter hour the slurry was removed from the hot-plate and chilled at 5° for three to four hours. The solid was collected on a Büchner funnel, reslurried in 50 ml. of ethanol, refiltered, and dried at 60° *in vacuo*. The weight of yellow material, m.p. 228–230°, was 5.9 g. or 39.8%.

Isolation of 2-Methoxy-4-nitrobenzaldehyde.—In one experiment after the addition of the chromyl chloride–chloroform mixture to a chloroform solution of 2-methoxy-4-nitrotoluene and subsequent standing the decomposed reaction mixture was steam distilled. Three aqueous distillates of 500 ml. each were obtained. The first and second fractions contained unreacted starting material and aldehyde, whereas the third distillate contained aldehyde principally. A considerable amount of aldehyde remained behind in the distilling flask. The solid from the third fraction was recrystallized from methanol–water from which the 2-methoxy-4-nitrobenzaldehyde separated as fine lemon-colored needles; m.p. 119.5–120.5°.

Anal. Calcd. for $C_8H_7O_4N$; C, 53.04; H, 3.86; N, 7.73. Found: C, 53.13; H, 3.78; N, 7.67.

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