Antituberculous Compounds. I. Synthesis of *p*-Acetamidocinnamaldehyde Thiosemicarbazone

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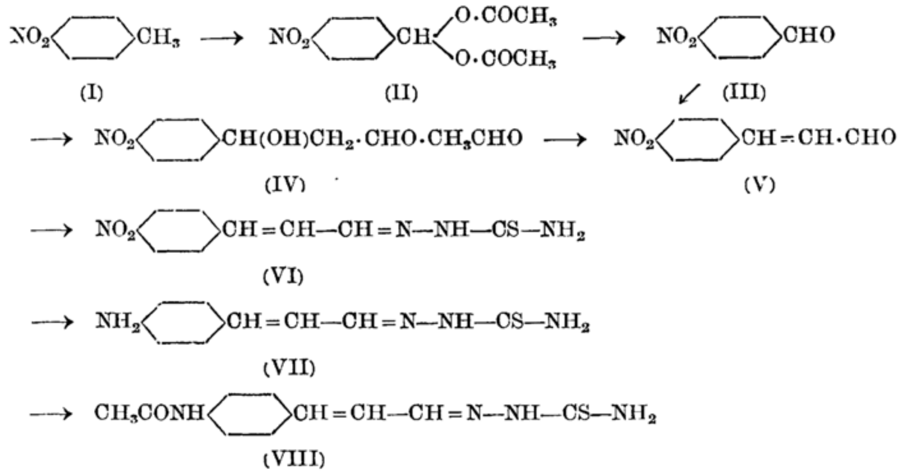
(Received November 2, 1951)

Some thiosemicarbazones of *p*-substituted aromatic aldehydes have been shown to have the antituberculous activity by Domagk and Behnisch.(1) Among the few thiosemicarbazones active in vivo, *p*-acetamidobenzaldehyde thiosemicarbazone has recently gained much interest and many patients have been treated with this chemotherapeutic agent. The author became interested in preparing *p*-acetamidocinnamaldehyde thiosemicarbazone (VIII) in the expectation that this substance could have antituberculous activity.

This synthesis of (VIII) may be illustrated by the following series of reactions.

p-Nitrobenzaldiacetate (II) was prepared from *p*-nitrotoluene (I) by the method of Organic Syntheses(2) with certain modifications. The diacetate was easily converted to *p*-nitrobenzaldehyde (III) by hydrolysis. The aldehyde was condensed with acetaldehyde to form β-(*p* - nitrophenyl) - β - hydroxypropionaldehyde acetaldehyde addition compound (IV).(3) The dehydration of the addition compound to form *p*-nitrocinnamaldehyde (V) was accomplished by heating it with hydrochloric acid in acetic acid or methanol. The preparation of (V) by the method of Fecht(4) was also executed and found to give better yields compared with the



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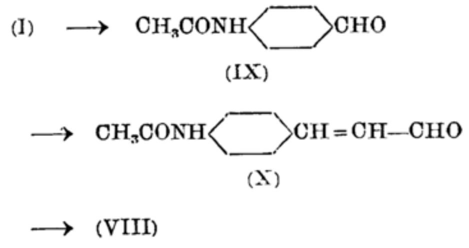
(1) G. Domagk, R. Behnisch, F. Mietzsch and H. Schmidt, *Naturwiss.*, **33**, 315 (1946).

(2) "Organic Syntheses," Vol. 18, 61.

(3) C. F. Göhring, *Ber.*, **18**, 372 (1885).

(4) H. Fecht, *Ber.*, **40**, 3898 (1907).

procedure mentioned above. The condensation of (V) with thiosemicarbazide to give *p*-nitrocinnamaldehyde thiosemicarbazone (VI) was performed by the usual procedure. The attempts to reduce (VI) with sodium sulfide or disulfide were unsuccessful; but when sodium hydrogen sulfide was employed, reasonable yields of *p*-aminocinnamaldehyde thiosemicarbazone (VII) were obtained. The reduction with ferrous sulfate also proceeded in ethanol but with lower yields. (VII) was readily acetylated by acetic anhydride in 50 % aqueous acetic acid or ethanol to yield *p*-acetamidocinnamaldehyde thiosemicarbazone (VIII). Another approach to (VIII) is illustrated in the following scheme.



p-Acetamidobenzaldehyde (IX) was prepared from *p*-nitrotoluene (I) by refluxing with a solution of sulfur and sodium hydroxide in ethanol followed by acetylation of the ether extract, giving the product melting at 153—155° (yield: 24 % of the theoretical.⁽⁵⁾,⁽⁶⁾ For the preparation of *p*-acetamidocinnamaldehyde Beard's method was followed according to the description in Chemical Abstracts **44**, 8862 (1950) with the following modifications; (a) the product was recrystallized from water, omitting the ether extraction; (b) optimum reaction temperature was found to be −5—10°. From 3.3 g. of *p*-acetamidobenzaldehyde was obtained 0.46 g. (12 %) of the desired product melting at 174—175.5°.

Experimental⁽⁷⁾

***p*-Nitrobenzaldiacetate (II).**—To a solution of 50 g. of *p*-nitrotoluene in 400 ml. of acetic anhydride is added 80 ml. of concentrated sulfuric acid.

When the mixture has been cooled to 0°, a solution of 100 g. (1.0 mole) of chromium trioxide in 400 ml. of acetic anhydride⁽⁸⁾ is added slowly, with stirring, at such a rate that the temperature does not exceed 10°, and stirring is continued for two hours at 5°—10° in an ice-water bath after the addition is completed. Further treatment is similar to that described in Organic Syntheses. The product, after drying in a vacuum desiccator, weighs 63—69 g. (68—75% of the theoretical), m. p. 122°—124°.

***p*-Nitrocinnamaldehyde (V).**—(a) A mixture of 2.3 grams of β-(*p*-nitrophenyl)-β-hydroxypropionaldehyde acetaldehyde addition compound,⁽³⁾ 7 ml. of glacial acetic acid and 7 ml. of concentrated hydrochloric acid was heated on a steam-bath. When the aldehyde had dissolved (about one minute), 14 ml. of water were added to the mixture. After cooling, seperated crystals were filtered and washed with water; yield: 17 g. (94 %), m. p. 137—140°. (b) Fecht's method with the following modification.—In a 500 ml. three-necked flask fitted with a mechanical stirrer, a thermometer and a burette were placed 50 g. of *p*-nitrobenzaldhyde and 100 ml. of freshly distilled acetaldehyde. The mixture was stirred and cooled in an ice salt mixture. A solution (20 %) of potassium hydroxide in methanol was added dropwise to the mixture from the burette until the alkaline reaction was obtained and during the reaction period it was maintained to be alkaline by the additional dropping of the potassium hydroxide solution, amounting 4.8 ml.; the internal temperature was maintained at 0°—5° throughout the procedure, and for 40 minutes thereafter. At the end of this period, the mixture solidified. One hundred and sixty ml. of acetic anhydride were added and heated for 30 minutes on a steam-bath. The solution was poured into 1.2 l. of hot water and heated on a steam-bath for 20 minutes after the addition of 160 ml. of concentrated hydrochloric acid, where the yellow needles separated. The mixture was allowed to stand overnight and crystals were filtered by suction and washed with water. One crystallization from 1.6 l. of 30 % acetic acid gave 37.5 g. (64.4 %) of the desired product, melting at 140~142°.

***p*-Nitrocinnamaldehyde Thiosemicarbazone (VI).**—To a solution of 18.2 g. of thiosemicarbazide in 700 ml. of hot ethanol was added 35.4 g. of *p*-nitrocinnamaldehyde and the mixture was heated on a steam-bath for 30 minutes. After cooling, yellow precipitates were filtered by suction, washed with ethanol and dried, giving 47 g. (94%) of the desired product, melting at 224° (decomp.). A small sample was recrystallized from ethanol to give the material with the same m. p. (Anal. Calcd. for $C_{10}H_{10}O_2SN_4$: N, 22.38 %. Found: N, 22.24 %).

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(5) Friedl. **4**, 136.

(6) Gabriel and Herzog, *Ber.*, **16**, 2003 (1883).

(7) All temperatures are uncorrected.

(8) Recently, we encountered an explosion on dissolving chromium trioxide in acetic anhydride, the cause of which seems to be local heating of the mixture. Without any hazard, the cooling by tap water has been executed after the total acetic anhydride had been poured in one portion, into the flask containing chromium trioxide but the explosion which we experienced occurred before the cooling was started. Therefore, it is preferable to cool acetic anhydride before being mixed with chromium trioxide.

p-Aminocinnamaldehyde Thiosemicarbazone (VII).—After saturation of a mixture of 200 ml. of ethanol and 64 ml. of 2 N aqueous sodium hydroxide solution with hydrogen sulfide, 20 g. of p-nitrocinnamaldehyde thiosemicarbazone was added to the mixture in one portion. The mixture was heated on a steam-bath without stirring. When the mixture began to boil, the bath was removed. After the boiling has subsided, the mixture was heated for 10 minutes with stirring and allowed to stand overnight at room temperature. Separated crystals were collected on a filter, washed with ethanol, water and finally ethanol giving 15.5 g. (70 %) of pure product, m. p. 207° (decomp.) (Anal. Calcd. for $C_{10}H_{12}SN_4$: C, 54.53; H, 5.50%. Found: C, 54.29; H, 5.27%).

p-Acetamidocinnamldehyde Thiosemicarbazone (VIII).—(a) To 11 g. of p-aminocinnamaldehyde thiosemicarbazone suspended in 110 ml. of ethanol was added 11 ml. of acetic anhydride and the mixture was stirred for ten minutes. After standing overnight, precipitated solid was filtered and washed with water to give 10.4 g. (80 %) of the desired product, m. p. 223—225° (decomp.). Recrystalization from 500 ml. of ethanol yielded 8.4 g. (66 %) of p-acetamidocinnamaldehyde thiosemicarbazone, m. p. 224—225° (decomp.). Faint yellow plate was obtained by recrystallization of a small sample from ethanol, m. p. 225° (decomp.) (Anal. Calcd. for $C_{12}H_{14}OSN_4$: C, 54.95; H, 5.38 %. Found: C, 54.89; H, 5.48 %).

(b) Eight-tenths g. of p-acetamidocinnamaldehyde was dissolved in 30 ml. ethanol and to the solution 0.4 g. of thiosemicarbazide was added. The mixture was heated on a steam-bath and stirred for 30 minutes while yellow solid precipitated. After cooling, the solid was filtered and washed with ethanol. It weighed 1.1 g. (100 %), m. p. 224° (decomp.). After one recrystallization from ethanol, there was obtained pure material melting at 225° (decomp.).

The author wishes to acknowledge his indebtedness to Miss T. Harada (Agricultural Department, the University of Tokyo) for the microanalytical data.

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