Antituberculous Compounds. II. Thiosemicarbazones from Benzalacetones[1]

By Tamio NISHIMURA

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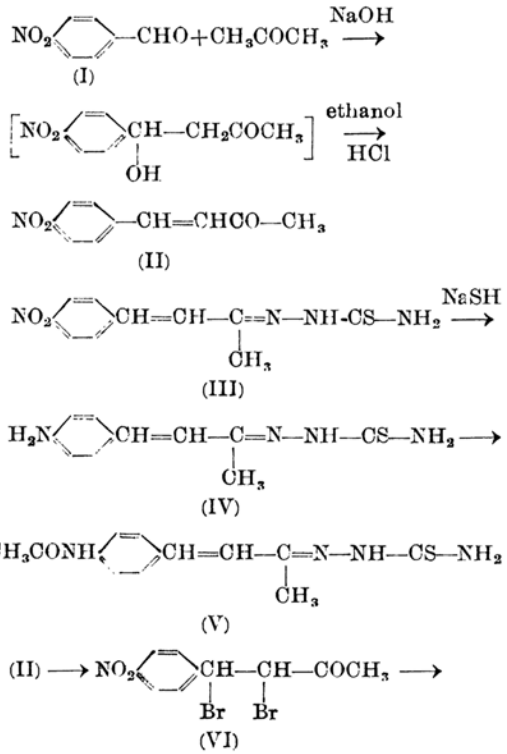
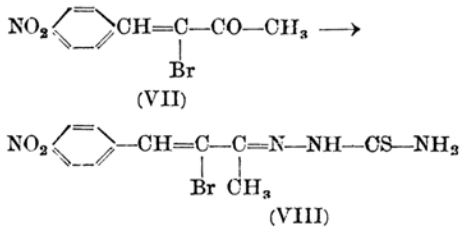
In a previous communication the author has reported the synthesis of *p*-acetamidocinnamaldehyde thiosemicarbazone as a vinylog of Tibion.[2] In our laboratory this thiosemicarbazone has been shown not to have antituberculous activity over that of Tibion in an *in vivo* test.[3] But in connection with this study, it would be interesting to compare the antituberculous activity of the thiosemicarbazones previously reported with that of other vinylogous thiosemicarbazones having similar structure. For this purpose the author synthesized *p*-acetylaminobenzalacetone thiosemicarbazone (V) and 1-(*p*-nitrophenyl)-2-bromo-1-butene-3-one thiosemicarbazone (VIII), according to the following scheme.



(1) A part of this study was presented at the annual meeting of the Chemical Society of Japan in Tokyo on April 5, 1952.

(2) T. Nishimura, This Bulletin, **25**, 54 (1952).

(3) K. Mizunoe, Unpublished data.



p-Nitrobenzaldehyde (I) was prepared from *p*-nitrotoluene as described before.[2] According to the method of Baeyer and Becker,[4] (I) was condensed with acetone and dehydrated to produce *p*-nitrobenzalacetone (II), without giving good results. However, it was found that the condensation reaction proceeded smoothly at room temperature when a mixture of acetone and water (1:1) was used. On condensation and dehydration, Baeyer and Becker's so called "*p*-nitrodicinnamyl methyl ketone"[4] was obtained in a considerable amount. The condensation product, 4-hydroxy-4-(*p*-nitrophenyl)-2-butanone was extracted with ether and dehydrated with hydrochloric acid without isolating it in a crystalline state. (II) was condensed with thiosemicarbazide in ethanol to give *p*-nitrobenzalacetone thiosemicarbazone (III) which was reduced to *p*-aminobenzalacetone thiosemicarbazone (IV) with sodium hydrogen sulfide. *p*-Acetamidobenzalacetone thiosemicarbazone (V) was obtained by acetylation of (IV) with acetic anhydride in ethanol.

1-(*p*-Nitrophenyl)-1, 2-dibromobutan-3-one (VI) was obtained by the action of bromine on (II) in glacial acetic acid, which was converted to 1-(*p*-nitrophenyl)-2-bromo-1-buten-3-one (VII) by dehydrobromination with potassium carbonate or pyridine.

Experimental[5]

***p*-Nitrobenzalacetone** (II).—A mixture of 30.2g. (0.2 mole) of *p*-nitrobenzaldehyde, 60 ml. of acetone and 60 ml. of water in a 300 ml. Erlenmeyer flask was made slightly alkaline by adding

(4) A. Baeyer and P. Becker, Ber. **16**, 1968 (1883).

(5) All temperatures are uncorrected.

4 drops of 10% sodium hydroxide solution. The mixture was shaken for 25 minutes at room temperature while *p*-nitrobenzaldehyde disappeared, yielding a small amount of undissolved "*p*-nitrodicinnamyl methy ketone." The reaction mixture was neutralized with 10% hydrochloric acid and extracted with 120 cc. and then 60 cc. of ether. The ether extracts were combined, filtered and concentrated on a water bath. The concentrated solution was mixed with 60 cc. of ethanol and 40 cc. of 10% hydrochloric acid, heated for 4 hours on a steam bath and allowed to stand overnight at room temperature. Precipitated yellow crystals were collected on a filter, recrystallized from 120 cc. of ethanol and dried in a desiccator, yielding 20.1 g. (53%) of the desired product, m. p. 107—108°. "*p*-Nitrodicinnamyl methyl ketone" (m.p. 244°) which did not dissolve in ethanol on recrystallization amounted to 6.7 g.

***p*-Nitrobenzalacetone thiosemicarbazone** (III).—Into a hot solution of 4.7 g. of thiosemicarbazide in 200 cc. of ethanol was added 9.6 g. of *p*-nitrobenzalacetone and the mixture was heated on a steam bath, giving 12.2 g. (92%) of the thiosemicarbazone, m. p. 240° (decomp.) (Found: N, 21.10% Calcd. for $C_{11}H_{12}O_2N_4S$: N, 21.21%).

***p*-Aminobenzalacetone thiosemicarbazone** (IV).—A mixture of 4 cc. of 2*N*-sodium hydroxide and 20 cc. of ethanol was saturated with hydrogen sulfide. To this solution was added 1.2 g. of *p*-nitrobenzalacetone thiosemicarbazone in one portion, and the mixture was refluxed for one hour. After cooling, the precipitated crystals were collected, washed with ethanol and water, yielding 0.9 g. (75%) of the desired product melting at 191° (decomp.). This material was dissolved in 7 cc. of pyridine and the solution was filtered. 7 cc. of water was added to the solution and it was allowed to stand overnight in an ice-box. Separated crystals were filtered and washed with ethanol and water, giving 0.8 g. of the same m. p. (Found: N, 23.93%, Calcd. for $C_{11}H_{14}N_4S$: N, 23.92%).

***p*-Acetylaminobenzalacetone thiosemicarbazone** (V).—A mixture of 0.6 g. of *p*-aminobenzalacetone thiosemicarbazone, 10 cc. of ethanol and 0.4 cc. of acetic anhydride was heated on a steam bath until complete dissolution took place. The solution was allowed to stand overnight at room temperature. Crystals were filtered and washed with ethanol and water, giving 0.5 g. (70%) of the desired product melting at 220—221°(decomp.). After recrystallization from 40 cc. of ethanol, there was obtained yellow plate melting at 223° (decomp.). Further recrystallization did not change the m. p. (Found: N, 20.12%. Calcd. for $C_{13}H_{16}ON_4S$: N, 20.28%).

1-(*p*-Nitrophenyl)-1,2-dibromobutane-3-one (VI).—3.2 g. of bromine was added with stirring to a solution of 3.8 g. of *p*-nitrobenzalacetone in 20 cc. of glacial acetic acid. The mixture was allowed to stand for two hours at room temperature and then overnight in an ice-box. Separated crystals were filtered and washed with ethanol and water to give 4.4 g. (63%) of the desired product melting at 118° (decomp.). The m. p. of a small sample recrystallized from glacial acetic acid (or ethanol) was 128° (decomp.) (Found: C, 34.69; H, 2.96; Br, 45.33%. Calcd. for $C_{10}H_9O_3NBr_2$: C, 34.21; H, 2.58; Br, 45.54%).

1-(*p*Nitrophenyl)-2-bromo-1-buten-3-one (VII).—(a) A solution of 1.8 g. of 1-(4-nitrophenyl)-1,2-dibromobutane-3-one in 5 cc. of pyridine was heated for five minutes on a steam bath, followed by addition of 5 cc. of water. After cooling, 1.2 g. (89%) of the desired product melting at 119—120° was obtained. Recrystallization from ethanol gave the pure material melting at 120—121° (Found: C, 44.68; H, 3.28; N, 5.28% Calcd. for $C_{10}H_8O_3NBr$: C, 44.46; H, 2.99; N, 5.19%).

(b) 0.8 g. of bromine was added to a solution of 0.9 g. of 4-nitrobenzalacetone in 5 cc. of glacial acetic acid and the mixture was allowed to stand for 15 minutes. This was followed by the addition of 0.4 g. of anhydrous potassium carbonate. When the evolution of gas had ceased, the mixture was heated on a steam bath for 30 minutes and then 2 ml. of water added. On cooling, resulting crystals were collected and washed with water. The yield of the product melting at 118—119° was 1.0 g. (77%).

1-(*p*-Nitrophenyl)-2-bromo-1-buten-3-one thiosemicarbazone (VIII).—To a hot solution of 0.5 g. of thiosemicarbazide in 25 cc. of ethanol was added 1.4 g. of 1-(*p*-nitrophenyl)-2-bromo-1-buten-3-one and the mixture was refluxed for 20 minutes on a steam bath to give 1.3 g. (75%) of the desired product melting at 182° (decomp.). The crude material was dissolved in 7 cc. of pyridine and reprecipitated by adding 5 cc. of water to the solution to yield the pure substance melting at 191° (decomp.) (Found: Br, 23.05; N, 16.59% Calcd. for $C_{11}H_{11}O_2N_4BrS$: Br, 23.29; N, 16.32%).

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Chemical Laboratory,
The Kitasato Institute, Tokyo, Japan