Antituberculous Compounds. IV. Thiosemicarbazones and Related Compounds

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α-Bromo-4-nitrocinnamaldehyde thiosemicarbazone has been found to posses *in vitro* action against *Staphylococcus aureus* and *Escherichia coli.*[1] In the present study, semicarbazones and guanylhydrazones of α-bromo-4-nitrocinnamaldehyde (I) and 1-(4-nitrophenyl)-2-bromo-1-buten-3-one were prepared in an attempt to increase the biological effect. Corresponding derivatives of 4-nitrocinnamaldehyde (II) and 4-nitrobenzalacetone were prepared in order to examine the effect of Br-substitution at the α-position of α,β-unsaturated carbonyl compounds. Nitromethane derivatives of I and II were also synthesized.

Furthermore, thiosemicarbazones of 4-nitro, 4-amino, and 4-acetamido-acetophenones were prepared in an attempt to compare their antituberculous activities with those of their vinylogs synthesized previously.[2]

Experimental[3]

α-Bromo-4-nitrocinnamaldehyde.—To a solution of 8.9 g. of 4-nitrocinnamaldehyde[4] in 80 cc. of glacial acetic acid was added 8 g. of bromine. When the red color of the mixture had almost completely disappeared, 6.9 g. of anhydrous potassium carbonate was added. After the evolution of gas had ceased, the mixture was heated in a water bath for ten minutes, giving 11.5 g. of slightly yellow crystals melting at 137–138°. On adding water the filtrate produced a further crop melting at 133–134° which yielded 0.4 g. of the product melting at 136–138° on recrystallization from 10 cc. of ethanol. Both crops were recrystallized from ethanol to give 11 g. (86%) of the desired product melting at 138–139°.[5]

Thiosemicarbazone.—To a suspension of 0.8 g. of α-bromo-4-nitrocinnamaldehyde in 20 cc. of hot ethanol was added 0.3 g. of thiosemicarbazide and the whole stirred in a water bath for ten minutes to give yellow precipitates, yield 1 g. (90%), m.p. 218° (decompn.) Recrystallization from ethanol gave slightly yellow long needles, m.p. about 214° (decompn.). Found: N, 16.88%. Calcd. for $C_{10}H_9N_4O_2SBr$: N, 17.00%.

Semicarbazone.—The crude product obtained by heating a mixture of the aldehyde, semicarbazide, and ethanol was recrystallized three times from ethanol, giving tiny yellow prisms melting at 223° (decompn.) in 32% yield. Found: N, 17.91%. Calcd. for $C_{10}H_9N_4O_3Br$: N, 17.90%).

Guanylhydrazone hydrochloride.—A mixture of 1.3 g. of the aldehyde, 0.7 g. of aminoguanidine bicarbonate[6], and 10 cc. of ethanol was acidified

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[1] Katsuhiko Tago and Tamio Nishimura, Presented before the Kanto regional meeting of Nippon Saikin Gakkai, June 27, 1953; chemotherapy **2**, 157—161 (1954).

[2] Tamio Nishimura, This Bulletin, **26**, 253 (1953).

[3] All temperatures are uncorrected.

[4] Tamio Nishimura, This Bulletin, **25**, 54 (1952).

[5] Reported m.p. 136°; Zincke v. Hagen, *Ber.*, **17**, 1816 (1884). Einhorn and Gehrenbeck, *Ann.*, **253**, 351 (1889).

[6] R. L. Shriner and Fred W. Neumann, "Organic Syntheses" Vol. 26, p. 7.

with concentrated hydrochloric acid⁷⁾ and heated in a water bath for several minutes. Pale yellow long prisms were obtained from ethanol and conc. hydrochloric acid; m.p. 265° (decompn.), yield 1.4 g. (80%). Found: Cl, 10.35%. Calcd. for $C_{10}H_{11}N_5O_2BrCl$: Cl, 10.17%.

4-Nitrocinnamaldehyde.—This compound was prepared as reported before.⁴⁾

Semicabazone.—A solution of 0.9 g. of the aldehyde, and 0.6 g of acetone semicarbazone in 50 cc. of ethanol was adjusted to pH 3.0 with 10% hydrochloric acid and heated in a water bath for thirty minutes. Crystals were filtered, washed well with ethanol, suspended in 20 cc. of hot ethanol, filtered hot, and washed again with ethanol to give 1 g. (84%) of the desired product, m.p. 232° (decompn.), yellow plates. Found: N, 23.82%. Calcd. for $C_{10}H_{10}N_4O_3$: N, 23.95%).

Guanylhydrazone hydrochloride.—Tiny yellow prisms (from ethanol and concentrated hydrochloric acid), easily soluble in hot ethanol and hot water and insoluble in hot benzene, yield 64%, m.p. 238° (decompn.). Found: Cl, 13.50%. Calcd. for $C_{10}H_{12}N_5O_2Cl$: Cl, 13.15%.

4-Nitrobenzalacetone.—This compound was synthesized as reported previously.²⁾

Semicarbazone.—From 0.96 g. of the ketone and semicarbazide in ethanol was obtained 1.1 g. (89%) of the desired product, m.p. 234° (decompn.), canary yellow crystals. The crude material (0.2 g.) dissolved in 25 cc. of hot pyridine gave tiny needles melting at 235° (decompn.) on adding 40 cc. of water. Found: N, 22.21%. Calcd. for $C_{11}H_{12}N_4O_3$: N, 22.57%.

Guanylhydrazone hydrochloride.—Tiny yellow needles melting at 270° (decompn.) obtained from 0.96 g. of the ketone were recrystallized form 150 cc. of ethanol containing a small amount of concentrated hydrochloric acid, giving 1.2 g. (85%) of the pure hydrochloride melting at 270° (decompn.). Found: Cl, 12.59%. Calcd. for $C_{11}H_{14}N_5O_2Cl$: Cl, 12.50%.

1-(4-Nitrophenly)-2-bromo-1-buten-3-one. — This compound was prepared according to the method reported before.²⁾

Semicarbazone.—Long pale yellow prisms (from ethanol) melting at 229° (decompn.) from the ketone and semicarbazide, yield 82%, halogen test positive, Found: N, 17.10%. Calcd. for $C_{11}H_{11}N_4O_3Br$: N, 17.13%.

Guanylhydrazone hydrochloride.—Yellow prisms (from ethanol and concentrated hydrochloric acid), m.p. 249–250° (decompn.), yield 87%. Found: Cl, 9.74%. Calcd. for $C_{11}H_{13}N_5O_2BrCl$: Cl, 9.78%.

ω-Nitro-4-nitrostyrene.—The same procedure as mentioned by David E. Worral⁸⁾ in their description of the synthesis of nitrostyrene, was used to prepare this compound.

From 1.5 g. of 4-nitrobenzaldehyde and 0.6 cc. of nitromethane⁹⁾ was obtained 0.5 g. (26%) of the desired product melting at 203–204° (decompn.)¹⁰⁾, consisting of yellow prisms (from ethanol).

1-(4-Nitrophenyl)-4-nitro-1,3-butadiene. — The crude material obtained similarly as above from 1.8 g. of 4-nitrocinnamaldehyde and 0.7 g. of nitromethane was recrystallized from ethanol, giving 0.4 g. (18%) of yellow needles, m.p. 200–201° (decompn.). Found: N, 12.69%. Calcd. for $C_{10}H_8N_2O_4$: N, 12.73%.

1-(4-Nitrophenyl)-2-bromo-4-nitro-1,-3butadiene.—α-Bromo-4-nitrocinnamaldehyde (1.3g.) and nitromethane (0.4 cc.) were condensed at 5–12°. On recrystallization from ethanol of the crude product, 0.32 g. (15%) of tiny yellow prisms, m.p. 182–182.5°, were obtained. Found: N, 9.49%. Calcd. for $C_{10}H_7N_2O_4Br$: N, 9.37%.

4-Acetamidoacetophenone.—A suspension of 2.7 g. of 4-aminoacetophenone in 27 cc. of water was treated with 2.7 cc. of acetic anhydride to give 3 g. (85%) of the desired product, consisting of colorless prisms, m.p. 169–170°.¹¹⁾

4-Nitroacetophenone.—The procedure described by Sugasawa¹²⁾ was used with some modification. 4-Aminoacetophenone (6.75 g.) was dissolved in 65 cc. of water and 8 cc. of nitric acid (sp. gr. 1.42) and diazotized with a solution of 9.6 g. of sodium nitrite in 20 cc. of water. The diazo solution was run slowly into a mixture of water (55 cc.), cuprocupric sulfite (prepared from cupric sulfate (12.5 g.) in water (50 cc.) and sodium hydroxide (4 g.) in water (20 cc.)), and sodium nitrite (13.8 g.). After stirring for two hours at room temperature the reaction mixture was extracted six times with 50 cc. portions of ether, the ether removed, and the residue recrystallized from methanol to give 5.07 g. (63%) of the desired product, m.p. 80–81°. A recrystallized sample showed m.p. 82–82.5°.

4-Aminoacetophenone thiosemicarbazone. — A mixture of 0.68 g. of 4-aminoacetophenone, 0.46 g. of thiosemicarbazide and 25 cc. of water was heated in a water bath for nine houres, but the reaction did not take place. Then the mixture was adjusted to pH 3.2¹⁴⁾ with glacial acetic acid and heated for thirty minutes to give 0.84 g. (81%) of the desired product, slightly yellow plates, m.p. 182–183° (decompn.). Recrystallization from ethanol gave a sample melting at 185° (decompn.). Found: N, 26.55%. Calcd. for $C_9H_{12}N_4S$: N, 26.90%.

4-Acetamidoacetophenone thiosemicarbazone.—A solution of 0.46 g. of thiosemicarbazide in 10 cc. of water was added to a solution of 0.89 g. of 4-acetamidoacetophenone in 10 cc. of ethanol.

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7) J. Thiele and R. Bihan. *Ann.*, **302**, 311 (1898).

8) David E. Worrall, "Organic Syntheses" Col. Vol. I. p. 405.

9) F. C. Whitmore and Marion G. Whitmore, Ibid., Col. Vol. I. p. 393.

10) Reported mp. 196—199°. See Johannes Thiele, *Ber.*, 1294 (1899).

11) Klingel (*Ber.*, **18**, 2691 (1885)) and Kunckell (*Ber.* 33, 2641 (1900) reported m.p. 166—167°.

12) S. Sugasawa, N. Sugimoto, J. Iwao and Y. Nakamura, *J. Pharm. Soc. Japan.*, **71**, 225 (1951).

13) H. H. Hodgson, A. P. Mahadevan, and E. R. Ward, "Organic Syntheses" Vol. 28, p. 52.

14) A maximum value of condensation velocity of furfural and semicarbazide was found to be at pH 3.13 by J. B. connant and P. D. Bartlett, *J. Am. Chem. Soc.*, **54**, 2881 (1932).

The whole was adjusted to pH 3.2 with glacial acetic acid, heated in a water bath for one hour, and cooled to yield 1.14 g. (91%) of the desired product, slightly yellow plates, m.p. 223.5° (decompn.) (from ethanol). Found: N, 22.27%. Calcd. for $C_{11}H_{14}N_4OS$: N, 22.39%.

4-Nitroacetophenone thiosemicarbazone.— Similarly was obtained the desired product, yellow needles melting at 240° (decompn.), yield 82%, Found: N, 23.38%. Calcd. for $C_9H_{10}N_4O_2S$: N, 23.38%.

Summary

1) Semicarbazones and guanylhydrazones of 4-nitrocinnamaldehyde, 4-nitrobenzalacetone, α-bromo-4-nitrocinnamaldehyde, and 1-(4-nitrophenyl)-2-bromo-1-buten-3-one, nitromethane derivatives of 4-nitrobenzaldehyde, 4-nitrocinnamaldehyde, and α-bromo-4-nitrocinnamaldehyde, and thiosemicarbazones of 4-amino, 4-acetamido-, and 4-nitroacetophenones were prepared for evaluation of their antibacterial activity.

2) Condensation of the acetophenones with thiosemicarbazide was found to proceed smoothly at pH 3.2 but not at pH 7.

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