Antituberculous Compounds. V. 1-Thiocarbamyl-3-methyl-5-phenyl-2-pyrazoline, 1-thiocarbamyl-3-methyl-5-(4-nitrophenyl)-2-pyrazoline, and Related Compounds

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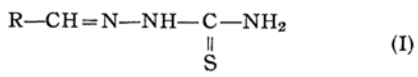
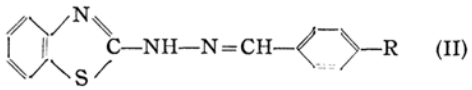
Considerable interest has been aroused by the publication of Domagk, Behnisch, Mietzsch, and Schmidt concerning the antituberculous activity *in vitro* of several thiosemicarbazones of aromatic aldehydes and ketones.[1] An excellent review of the investigation developed by the German workers in correlating structure with activity appeared in 1950.[2] Hoggarth, Martin, Storey, and Young[3] published in 1949 their excellent quantitative *in vivo* evaluation of a considerable number of thiosemicarbazones and compounds of related structure. Furthermore, the extensive synthesis[4] of thiosemicarbazones and related substances, and their *in vitro*[5] and *in vivo*[6] activities were reported by Bernstein et al.

L. Katz[7] prepared a series of the condensation products (II) closely related to the thiosemicarbazone (I), of 2-hydrazinobenzothiazoles with aromatic aldehydes and reported that most active compounds were obtained when the *p*-substituents (R) were carboxymethoxy and dimethylamino radicals.

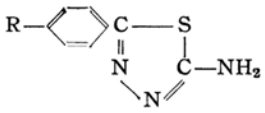


(I)

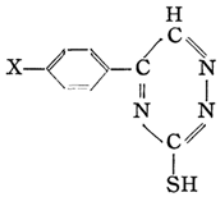


(II)

Bernstein et al.[4] mentioned the preparation of a number of heterocyclic compounds structurally related to I; 5-substituted-2-amino-1,3,4-thiadiazole derivatives (III), and N-(2-benzothiazolyl)-N′-(4-substituted benzal) hydrazone (II). R. Fusco et al.[8,8a] described the synthesis of 5-aryl-3-mercapto-1,2,4-triazines (IV) as new synthetic antitubercular agents.

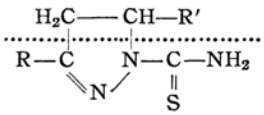


(III)



(IV)

However, the evaluation of 1-thiocarbamyl-2-pyrazolines (V) against *Mycobacterium tuberculosis* has not been reported. A study was therefore inaugurated in this Laboratory with the aim of preparing a number of 1-thiocarbamyl-2-pyrazolines and related substances. It is clear that the structure below the dotted line of (V) coincides with that of the thiosemicarbazone (I). Such a similarity between (V) and (I) was the basis for expecting antitubercular activity in this class of compounds.



(V)

The compounds prepared were 3-methyl-5-phenyl-2-pyrazoline, 3-methyl-5-(4-nitrophenyl)-2-pyrazoline, and their 1-substituted derivatives. The 1-substituents included the $-CS-NH_2$, $-CS-NHC_6H_5$, $-CS-NHCOC_6H_5$, $-CHO$, $-COCH_3$, and $-C_6H_5$ groups. The compounds described herein were prepared as indicated in the flow sheet.

1) G. Domagk, R. Behnish, F. Mietzch and H. Schmidt, *Naturw.*, **33**, 315 (1946); *Chem. Abstr.*, **43**, 3523e (1949).

2) R. Behnisch, F. Miezsch and H. Schmidt, *Am. Rev. Tuberc.*, **61**, 1 (1950).

3) E. Hoggart, A.E. Martin, N.E. Storey, and E.H.P. Young, *Brit. J. Pharm.*, **4**, 248 (1949).

4) J. Bernstein, H.L. Yale, K. Losee, M. Holsing, J. Martins, and W.A. Lott, *J. Am. Chem. Soc.*, **73**, 906 (1951).

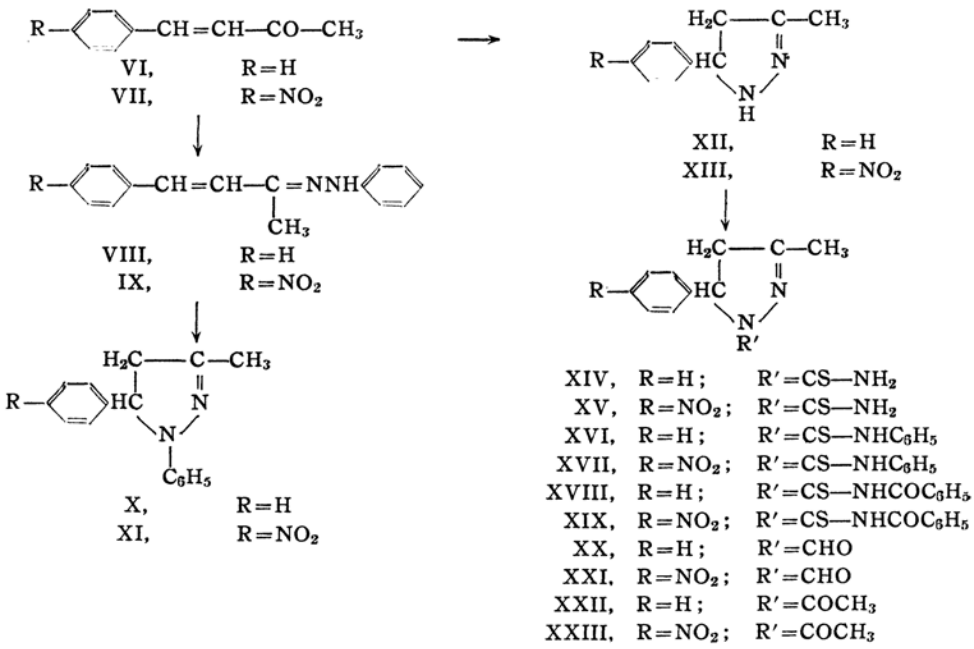
5) R. Donovick, F. Pansy, G. Stryker and J. Bernstein, *J. Bacteriol.*, **59**, 667 (1950).

6) D. Hamre, J. Bernstein and R. Donovick, ibid. 675.

7) Leon Katz, *J. Am, Chem. Soc.* **73**, 4007 (1951).

8) R. Fusco, P. Mantegazza, S. Rossi and R. Tommasini, *Boll. soc. ital. biol. sper.*, **27**, 1730-2 (1951); *Chemi. Abstr.*, **46**, 9199 (1952).

8*a*) R. Fusco, S. Rossi, G. Mantegazza and R. Tommasini, *Ann. chim.* (Rome), **42**, 94-104 (1952); *Chem. Abstr.*, **47**, 4301*c* 1953).



Benzalacetone (VI) was prepared according to the method described in Organic Syntheses,[9] and *p*-nitrobenzalacetone (VII) according to the procedure reported previously.[10] (VI) and (VII) were converted to the phenylhydrazones (VIII, IX) which were then cyclized to the pyrazolines (X, XI) by heating with glacial acetic acid. 3-Methyl-5-phenyl-2-pyrazoline (XII) was obtained in a 67% yield by the action of 80% hydrazine hydrate upon (VI) in ethanol according to the description of Beech et al.[11] (VII) and hydrazine hydrate in ethanol gave smoothly 3-methyl-5-(4-nitrophenyl)-2-pyrazoline (XIII) at room temperature. 1-Thiocarbamyl-3-methyl-5-(4-nitrophenyl)-2-pyrazoline (XV) was obtained in small yields when (XIII) and pottasium thiocyanate in water was acidified with glacial acetic acid and then heated on a water bath, a considerable amount of the 1-acetyl derivative being isolated from the reaction mixture, whereas in good yields when acidified with hydrochloric acid. On the basis of this finding, 1-thiocarbamyl-3-methyl-5-phenyl-2-pyrazoline (XIV) was easily obtained by the same procedure. The 1-(N-phenylthiocarbamyl)-derivatives (XVI, XVII) were prepared by the action of phenylisothiocyanate on (XII) and (XIII) in petroleum ether at room temperature. The 1-(N-benzoylthiocarbamyl)-derivatives (XVIII, XIX) were obtained by the action of ammonium thiocyanate plus benzoyl chloride on (XII) and (XIII). (XII) and (XIII) were easily converted to 1-formyl derivatives (XX, XXI) by heating with formic acid and to 1-acetyl derivatives (XXII, XXIII) by heating with glacial acetic acid.

9) N.L. Drake and P. Allen, Jr., "Organic Syntheses" Coll. Vol. I, p. 77 (1946).
10) Tamio Nishimura, This Bulletin, **26**, 253 (1953).
11) S.G. Beech, J.H. Turnbull and Walter Wilson, *J. Chem. Soc.* 1952, 4689.

Experimental

Benzalacetone phenylhydrazone (VIII).—Heating a mixture of benzalacetone (1.4 g.), phenylhydrazine hydrochloride (1.5 g.), sodium acetate trihydrate (1.6 g.), and methanol (20 cc.) gave 1.8 g. (76%) of the desired product melting at 152–158°. Recrystallization from methanol yielded yellow plates melting at 155–157°.[13]

4-Nitrobenzalacetone phenylhydrazone (IX).—By the foregoing procedure, an almost quantitative yield of the hydrazone was obtained in red microcrystals melting at 194–196°.[14]

1-Phenyl-3-methyl-5-phenyl-2-pyrazoline (X).—A mixture of benzalacetone phenylhydrazone (1 g.) and glacial acetic acid (3 cc.) was heated in an oil bath of 130° for 1 hour. Crystals (0.8 g.) separated on cooling were recrystallized from 13 cc. of methanol to give the desired product, yellow long prisms melting at 112–113°.[15]

1-Phenyl-3-methyl-5-(4-nitrophenyl)-2-pyrazoline (XI).—The crude product obtained similarly from 1 g. of the phenylhydrazone (IX) was three times recrystallized from ethanol, yielding 0.6 g. of apricot yellow needles, m. p. 113–113.5°.[16]

12) All temperatures are uncorrected.
13) Reported m.p. 157°. See E. Fischer, *Ber.*, 17, 576 (1884).
14) Reported m.p. 195-196°. See K. Auwers and H. Voss, *Ber.*, 42, 4425 (1909).
15) K. Auwers and H. Voss (loc. cit.) give m.p. 115-116°.
16) K. Auwers and H. Voss (loc. cit.) give m.p. 112-113°.

3-Methyl-5-phenyl-2-pyrazoline (XII).—Following the procedure of Beech et al.[11], 11 g. (67 %) of the desired pyrazoline, b. p. 140–142°/13 mm.[17] was obtained from benzalacetone (14.6 g.), 80 % hydrazine hydrate (11 g.), and ethanol (40 cc.).

3-Methyl-5-(4-nitrophenyl)-2-pyrazoline (XIII).—A mixture of 9.6 g. of 4-nitrobenzalacetone, 4 g. of 80 % hydrazine hydrate, and 20 cc. of ethanol was stirred at room temperature. As soon as the ketone dissolved, yellow precipitates[18] began to separate, but dissolved again to make a clear red solution, and then the whole slowly solidified on further stirring. The cake was filtered, washed with ethanol, suspended in 100 cc. of water and acidified with 10 % hydrochloric acid. The solution was filtered and neutralized partially with 10 % sodium hydroxide, forming a resinous orange substance which was filtered off. The filtered solution was made slightly alkaline to give cream yellow crystals, m. p. 98–100°. After a recrystallization from 20 cc. of ethanol, 6.6 g. (65 %) of the desired product, m. p. 97–102°, was obtained. Further recrystallization from ethanol gave an elevation of the melting point to 104–107° (Found: N, 20.60 %. Calcd. for $C_{10}H_{10}N_3O_2$: N, 20.58 %.). As this substance is likely to change to red resinous material, it is desirable to store it in sealed brown colored ampules.

1-Thiocarbamyl-3-methyl-5-phenyl-2-pyrazoline (XIV).—A mixture of 1.5 g. of benzalacetone, 1 g. of 80 % hydrazine hydrate, and 10 cc. of ethanol was refluxed gently on a water bath for 1 hour. After removing the ethanol under reduced pressure, the residue was mixed with ammonium thiocyanate (1.1 g.) and water (20 cc.). The whole was acidified with 10 % hydrochloric acid and the undissolved red oil was removed by filtration. The solution was then heated on a water bath for 5 hours to give yellow plates, m. p. 228–229° (decomp.), yield 0.5 g. (23 %). Recrystallization from ethanol changed the melting point to 230–231° (decomp.) (Found: N, 19.12 %. Calcd. for $C_{11}H_{13}N_3S$: N, 19.12 %).

1-Thiocarbamyl-3-methyl-5-(4-nitrophenyl)-2-pyrazoline (XV).—A mixture of 3-methyl-5-(4-nitrophenyl)-2-pyrazoline (2.1 g.), ammonium thiocyanate (1.1 g.), and water (40 cc.) was acidified with 10 % hydrochloric acid to pH 2.2 and an undissolved red tarry substance was removed by decantation. The solution was then heated on a water bath for 3 hours to form the desired product melting at 268–269° (decomp.), slightly orange yellow prisms (Found: N, 21.68 %. Calcd. for $C_{11}H_{12}N_4O_2S$: N, 21.20 %). Several recrystallizations from ethanol yielded faintly yellow prisms, m. p. 271° (decomp.).

1-(N-Phenylthiocarbamyl)-3-methyl-5-phenyl-2-pyrazoline (XVI).—Phenyl isothiocyanate[19] (1.4 g.) and 3-methyl-5-phenyl-2-pyrazoline (1.6 g.) were mixed and stirred at room temperature. The whole solidified immediately. The white solid was triturated with petroleum ether, filtered and washed with petroleum ether, to obtain the product, m. p. 166–167°, yield 2.8 g. On recrystallization from 200 cc. of methanol, there was obtained 2.1 g. (70 %) of colorless prisms, m. p. 160–161°. Further recrystallization from methanol did not change the melting point. (Found: N, 13.82 %. Calcd. for $C_{17}H_{17}N_3S$: N, 14.23 %).

1-(N-Phenylthiocarbamyl)-3-methyl-5-(4-nitrophenyl)-2-pyrazoline (XVII).—A solution of 3-methyl-5-(4-nitrophenyl)-2-pyrazoline (0.51 g.), and phenyl isothiocyanate (0.34 g.) in benzene (4 cc.) was allowed to stand at room temperature for several days. After removing benzene, reddish brown syrup was extracted with 25 cc. of ether and the ether extract was dried over anhydrous sodium sulfate. The ether was evaporated to form a red oil which changed to a glass-like solid after several days. The solid was extracted with 15 cc. of hot methanol and the methanol was removed to give crystalline residue. Recrystallization from methanol gave tiny slightly greenish-yellow needles melting at 141–142°, yield 0.33 g. (38 %). Further recrystallization elevated the melting point to 143–144° (Found: N, 16.41 %. Calcd. for $C_{17}H_{16}N_4O_2S$: N, 16.46 %).

1-(N-Benzoylthiocarbamyl)-3-methyl-5-phenyl-2-pyrazoline (XVIII).—Benzoyl chloride (4.2 g.) was added dropwise to a suspension of ammonium thiocyanate (2.4 g.) in acetone (24 cc.) and the whole refluxed gently for several minutes. To this reaction mixture was added dropwise a solution of 3-methyl-5-phenyl-2-pyrazoline (prepared from 1.5 g. of benzalacetone and 0.9 g. of 80 % hydrazine hydrate) in acetone. The content was refluxed for several minutes after the addition was completed and then poured into 200 cc. of water. Yellow crystals were collected, washed with water and recrystallized from ethanol. The yield was 2.2 g. (69 % based on benzalacetone), m.p. 185–185.5° (decomp.), greenish yellow plates (Found: N, 13.07 %. Calcd. for $C_{18}H_{17}N_3OS$: N, 13.00 %).

1-(N-Benzoylthiocarbamyl)-3-methyl-5-(4-nitrophenyl)-2-pyrazoline (XIX).—This compound was similarly prepared, yellow prisms (from acetone), yield 2.7 g. (73 %) from 2.2 g. of 3-methyl-5-(4-nitrophenyl)-2-pyrazoline, m. p. 199–200° (decomp.) Found: N, 15.41 %. Calcd. for $C_{18}H_{16}N_4O_3S$: N, 15.21 %).

1-Formyl-3-methyl-5-phenyl-2-pyrazoline (XX).—A solution of 1.7 g. of 3-methyl-5-phenyl-2-pyrazoline in 8 cc. of formic acid was heated for 1 hour on a water bath. Methanol was added to the reaction mixture and removed under reduced pressure. This procedure was repeated twice more to give a yellow oil. The oil was dissolved in 2 cc. of 25 % methanol and the methanol solution poured into 10 cc. of water. By rubbing the wall of the beaker a white precipitate was formed, which was filtered, and washed with water, m. p. 66–69°, colorless needles. This was recrystallized from 25 % methanol to yield 1.1 g. (55 %) of the desired product, m. p. 65–78° before drying, m. p. 88.5–89° after drying in a desiccator (Found: N, 14.75 %. Calcd. for $C_{11}H_{12}N_2O$: N, 14.89 %).

1-Formyl-3-methyl-5-(4-nitrophenyl)-2-pyrazoline (XXI).—3-Methyl-5-(4-nitrophenyl)-2-pyrazo-

17) S.G. Beech, et al. (loc. cit.) give b.p. 166°/35mm.

18) Intermediate formation of the precipitates was not observed when the reaction temperature was higher.

19) F. B. Dains, R. Q. Brewster and C. P. Olander, "Organic Syntheses", Col. Vol. I. p. 447 (1946).

line (1.1 g.) was dissolved in 5 cc. of formic acid and heated on a water bath for 1 hour. After removing the formic acid, methanol was added and removed under reduced pressure. This procedure was repeated once more to give dull orange yellow crystals. Recrystallizations from 25 % methanol gave a sample melting at 121–122°, yield 0.7 g. (60 %), pale yellow plates (Found: N, 18.05 %. Calcd. for $C_{11}H_{11}N_3O_3$: N, 18.02 %).

1-Acetyl-3-methyl-5-phenyl-2-pyrazoline (XXII).—A mixture of 1.7 g of 3-methyl-5-phenyl-2-pyrazoline, 2 cc. of acetic anhydride, and 10 cc. of water was stirred at room temperature. Colorless oil separated was extracted with ether (20 cc.) and the ether washed with water containing sodium hydroxide, with water containing hydrochloric acid and then with distilled water and dried over anhydrous sodium sulfate. Evaporation of ether at room temperature gave 1.1 g. of colorless crystals. On recrystallization from ether, there was obtained a sample melting at 77.5-78°.[20]

1-Acetyl-3-methyl-5-(4-nitrophenyl)-2-pyrazoline (XXIII).—

(a) A mixture of 0.5 g. of 3-methyl-5-(4-nitrophenyl)-2-pyrazoline and 2.5 cc. of glacial acetic acid was heated on a water bath. Duration of heating and yield were as follows: 1 hour, 0.17 g. (28 %); 3 hours, 0.21 g. (34 %); 5 hours, 0.28 g. (45 %); 8 hours, 0.25 g. (40 %). The crude product of m. p. 136–137° was dissolved in hot water and the filtered solution was allowed to stand for 1–2 weeks at room temperature, giving large yellow crystals melting at 138° (Found: C, 58.57; H, 5.67; N, 16.90 %. Calcd. for $C_{12}H_{13}N_3O_3$: C, 58.27; H, 5.30; N, 16.99 %).

(b) To a suspension of 3-methyl-5-(4-nitrophenyl)-2-pyrazoline (0.8 g.) in 5 cc. of water 0.8 cc. of acetic anhydride was added dropwise and with stirring. The precipitate was washed with water and with cold ether to remove the red gummy substance, giving yellow powder melting at 137–138°. Recrystallizations from ether gave the desired product of m. p. 137–139°.

20) Beech et al. (loc. cit.) give m.p. 77-79°.

Summary

The preparation is described of 3-methyl-5-phenyl-2-pyrazoline, 3-methyl-5-(4-nitrophenyl)-2-pyrazoline and their 1-phenyl, thiocarbamyl, N-phenylthiocarbamyl, N-benzoylthiocarbamyl, formyl, and acetyl derivatives which were to be tested for antituberculous activity.

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