

New Syntheses of Condensed Heterocycles from Isoxazole Derivatives. II. Pyrazolo[4,3-*b*]pyridine.

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The easy cleavage of isoxazole rings by catalytic hydrogenation (1), which has been described in previous papers (2-8), suggested to us the utilization of the chain of atoms produced on hydrogenation of 5-methyl-3-isoxazole derivatives for a new synthesis of substituted pyrazolo[4,3-*b*]pyridine (XI).

For this purpose 1-(5-methyl-3-isoxazolyl)-1,3-butanedione (I) was obtained by the Claisen condensation of 5-methyl-3-acetylisoxazole (9) with ethyl acetate or by the condensation of 5-methyl-3-carbomethoxyisoxazole (10) with acetone. In order to confirm the structure of compound I and also to explain the structure of compound XI, compound I reacted with hydrazine to give compound II.

Raney nickel hydrogenation of compound II caused the cleavage of the isoxazole ring to yield 1-[3(5)-methyl-5(3)-pyrazolyl]-1-imino-1,3-butanedione (III); this latter reacted with hydrazine to yield compound IV, whose ir

and uv spectra were in every detail identical with those of the authentic 3,3'(5,5')dimethyl-5,5'(3,3')dipyrazole (IV) (11) obtained by another synthesis. Moreover, attempts to bring about the cyclization of compound III, *i.e.* to obtain pyrrolopyrazole (VI) were unsuccessful. On the contrary 3(5)methyl-5(3)acetylpyrazole (V) (5) was obtained by forcing cyclization.

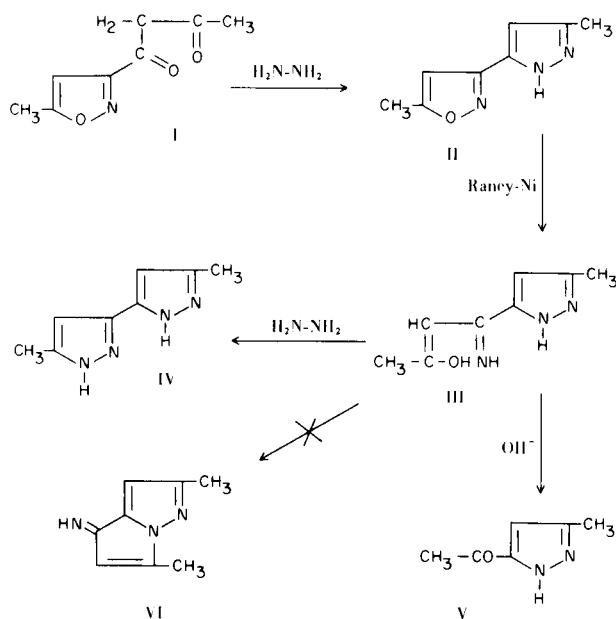
The structure of 1-(5-methyl-3-isoxazolyl)-1,3-butanedione (I) having once been established unequivocally, 1-(5-methyl-3-isoxazolyl)-2-hydroxyimino-1,3-butanedione (VII) was obtained by reaction of compound I with nitrous acid.

Treatment of VII with hydrazine led to 3-[3(5)methyl-4-nitroso-5(3)pyrazolyl]-5-methylisoxazole (VIII). The aim of bringing about a new synthesis of pyrazolo[4,3-*b*]pyridine was achieved by Raney nickel hydrogenation of compound VIII; 3,5-dimethyl-7-aminopyrazolo[4,3-*b*]pyridine (XI) was obtained directly. It was impossible to isolate the probable intermediate compound IX. The alternative structure of 2,6-dimethyl-3-imino-4-aminopyrrolo[1,2-*b*]pyrazole (X) ought also to be taken into consideration.

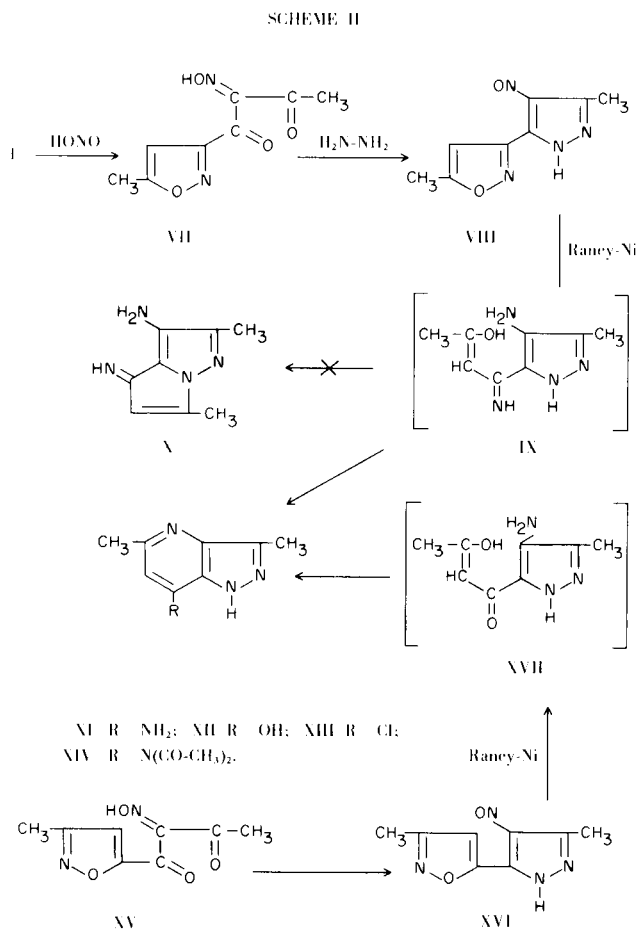
Indeed, on the one hand the ir and mass spectra (see experimental) agree both with structure XI and with structure X; on the other hand the nmr spectra showed a peak at δ 12.05 which is considered as corresponding to an NH pyrazole proton rather than to an NH proton. Moreover, as has already been pointed out, the carbonyl group of compound III failed to exhibit any reactivity with the pyrazole proton, and hence any possibility of cyclization to a pyrrolopyrazole compound VI has been ruled out.

However, unequivocal evidence for the structure of 3,5-dimethyl-7-aminopyrazolo[4,3-*b*]pyridine (XI) was given by the reaction of compound XI with nitrous acid, yielding 3,5-dimethyl-7-hydroxypyrazolo[4,3-*b*]pyridine (XII). The same compound was obtained by independent synthesis through compounds XV \rightarrow XVI \rightarrow XVII \rightarrow XII. Compound XI reacted with acetic anhydride to yield 3,5-dimethyl-7-diacetylamino pyrazolo[4,3-*b*]pyridine

SCHEME 1



(XIV). On reaction with phosphorus oxychloride compound XII yielded the 7-chloro derivative (XIII).



Most of the compounds described were tested for their action upon the central nervous system and the cardiovascular system, and for their analgesic, hypocolesterolemic, antifungal, antiprotozoan and antiviral properties. The only compounds exhibiting any biological properties are 3-[3(5)-methyl-4-nitroso-5(3)pyrazolyl]-5-methylisoxazole (VIII) and 3,5-dimethyl-7-diacetylaminopyrazolo[4,3-*b*]pyridine (XIV). At a concentration of 6.25 mcg./ml. compound VIII inhibited the growth of the fungus *M. canis*. Compound XIV, in a concentration of 20 mcg./ml., exerted an antidepressant effect upon the central nervous system, checked by the reserpine reversal test in mice.

EXPERIMENTAL

All melting points (Kofler) are uncorrected. Ir (nujol mull): Perkin-Elmer infracord 137 spectrophotometer; uv (ethanol): Beckmann DB (with recorder) spectrophotometer; nmr: Jeol C-60H spectrometer (TMS as internal reference). Mass spectra were

registered on an Hitachi Perkin-Elmer spectrometer. Microbiological and pharmacological tests were performed by Bristol Laboratories, Syracuse, New York.

1-(5-Methyl-3-isoxazolyl)-1,3-butanedione (I).

This product was briefly (12) described by Claisen (13). It was obtained using the following method. A mixture of 14 g. (0.1 mole) of 5-methyl-3-carbomethoxyisoxazole, 6 g. (0.1 mole) of acetone and 2.3 g. (0.1 mole) of sodium in 400 ml. of dry ether or 12.5 g. (0.1 mole) of 3-acetyl-5-methylisoxazole, 9 g. (0.1 mole) of ethyl acetate and 2.3 g. (0.1 mole) of sodium in 400 ml. of dry ether was stirred overnight. The sodium salt (19 g.) of I obtained was filtered, washed with ether, and dissolved in water. The filtered aqueous solution was acidified with 2 *N* hydrochloric acid and the solid obtained was collected and dried. Sublimation yielded an analytical sample of white needles, m.p. 82°; copper salt, m.p. 213°; with ferric chloride in ethanol it gave a red colour; ir cm^{-1} , 3125 (CH) and 1645, 1635 (CO).

Anal. Calcd. for $\text{C}_8\text{H}_9\text{NO}_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.20; H, 5.48; N, 8.36.

3-[5(3)-Methyl-3(5)-pyrazolyl]-5-methylisoxazole (II).

A mixture of 3.35 g. (0.02 mole) of I in 30 ml. of ethanol, 2.10 g. (0.02 mole) of hydrazine hydrochloride and 5.45 g. (0.04 mole) of sodium acetate in 20 ml. of water was refluxed for 2 hours, evaporated to approximately half its volume and poured into ice-water. The solid (2.8 g.) was filtered and crystallized from ethanol-water, m.p. 136°; ir cm^{-1} , 3205 (NH); nmr (deuteriochloroform) δ 2.32 (s, 3H, CH₃), 2.45 (s, 3H, CH₃), 6.34 (s, 1H, CH), 6.45 (s, 1H, CH), 10.73 (s, 1H, NH).

Anal. Calcd. for $\text{C}_8\text{H}_9\text{N}_3\text{O}$: C, 58.88; H, 5.56; N, 25.75. Found: C, 59.03; H, 5.35; N, 25.71.

1-[3(5)-Methyl-5(3)-pyrazolyl]-1-imino-1,3-butanedione (III).

Compound II (2 g.) in 150 ml. of ethanol was hydrogenated for 8 hours with 2 g. of W-2 Raney nickel (15) in a Parr apparatus at 45-50 psi and at room temperature. The catalyst was separated and the solution evaporated under reduced pressure to dryness. Crystallization from benzene gave white crystals (1.7 g.) m.p. 147°; ir cm^{-1} , 3360, 3190 (NH) and 1642 (CO).

Anal. Calcd. for $\text{C}_8\text{H}_{11}\text{N}_3\text{O}$: C, 58.16; H, 6.71; N, 25.44. Found: C, 58.35; H, 6.59; N, 25.26.

3,3'(5,5')Dimethyl-5,5'(3,3')dipyrazole (IV).

Compound III (0.5 g.) (0.003 mole) in 10 ml. of ethanol and 0.32 g. (0.003 mole) of hydrazine hydrochloride in 5 ml. of water were heated to reflux. After 15 minutes the mixture was evaporated to one-third of its volume, water was added to turbidity, and crystallization was induced by cooling and stirring and 0.18 g., m.p. 286° was obtained from aqueous ethanol. This compound was identical with an authentic sample obtained by another method (11).

3(5)-Methyl-5(3)-acetylpyrazole (V).

Compound III (2.0 g.) (0.012 mole) in 25 ml. of 4 *N* sodium hydroxide was warmed at 90° in a water bath; after a few minutes (evolution of ammonia ensued) the mixture was poured into water and extracted with ether; the extract was washed with water, dried and evaporated. Recrystallization of the residue from hexane gave V (0.6 g.), m.p. 99-100°. This compound was identical with an authentic sample of 3(5)-methyl-5(3)-acetylpyrazole (5).

1-(5-Methyl-3-isoxazolyl)-2-hydroxyimino-1,3-butanedione (VII).

A solution of 1.67 g. (0.01 mole) of I in 100 ml. of water containing 2 pellets of sodium hydroxide was stirred at room temperature while a solution of 0.7 g. (0.01 mole) of sodium nitrite in 10 ml. of water was slowly added; acidification with 2 N hydrochloric acid gave a white suspension which was extracted with ether. On evaporation of the dried (sodium sulfate) ether layer, compound VII (1.5 g.) was obtained and recrystallized from water, m.p. 143°; ir cm^{-1} , 3150 (NOH), 1680 and 1720 (CO).

Anal. Calcd. for $\text{C}_8\text{H}_8\text{N}_2\text{O}_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 49.14; H, 4.28; N, 14.36.

3-[3(5)-Methyl-4-nitroso-5(3)-pyrazolyl]-5-methylisoxazole (VIII).

Hydrazine hydrochloride (1 g.) (0.01 mole) in 10 ml. of water was added dropwise to a stirred solution of 1.95 g. (0.01 mole) of VII in 100 ml. of water containing 3 pellets of sodium hydroxide. A green precipitate was instantly obtained; the suspension was stirred 10 minutes, the precipitate (1.3 g.) filtered by suction, dried and recrystallized from benzene, pistachio green scales, m.p. 188°; ir cm^{-1} , 3180 (NH), 1610 (NO); nmr (DMSO) δ , 2.38 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 6.75 (s, 1H, CH), 14.1 (broad, 1H, NH).

Anal. Calcd. for $\text{C}_8\text{H}_8\text{N}_4\text{O}_2$: C, 49.99; H, 4.16; N, 29.16. Found: C, 50.15; H, 4.20; N, 29.03.

3,5-Dimethyl-7-aminopyrazolo[4,3-b]pyridine (XI).

Compound VIII (2 g.) in 100 ml. of ethanol was hydrogenated with 1 g. of W-2 Raney nickel (15) in a Parr apparatus, at 45-50 psi and at room temperature. After 20 hours the catalyst was removed, the solution evaporated under reduced pressure, the residue (1.7 g.) crystallized from ethanol-water; white crystals, m.p. 336° dec.; $\text{uv } m\mu$, λ max, 305, 296 and 278; ir cm^{-1} , 3410, 3340 (NH_2) and 3220 (NH); nmr (DMSO) δ , 2.38 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 6.05 (s, 2H, NH_2), 6.23 (s, 1H, CH), 12.05 (s, 1H, NH); Mass: 162 (M^+), 147, 133, 120, 108, 93 m/e.

Anal. Calcd. for $\text{C}_8\text{H}_{10}\text{N}_4$: C, 59.24; H, 6.21; N, 34.55. Found: C, 59.33; H, 6.14; N, 34.70.

3,5-Dimethyl-7-hydroxypyrazolo[4,3-b]pyridine (XII).

Sodium nitrite (0.5 g.) (0.0072 mole) was added to a solution of 0.6 g. (0.0037 mole) of compound XI in 20 ml. of acetic acid; the mixture was heated in a water bath for 20 minutes, evaporated under reduced pressure to dryness and washed with water; the residue (0.34 g.) was recrystallized from ethanol, yielding white crystals, m.p. 346°; uv and ir spectra were identical with those of the sample obtained by hydrogenation of XVI.

3,5-Dimethyl-7-chloropyrazolo[4,3-b]pyridine (XIII).

Compound XII (2 g.) (0.012 mole) was refluxed with 2 g. (0.01 mole) of phosphorus pentachloride and 20 ml. (0.22 mole) of phosphorus oxychloride for 6 hours; the mixture was evaporated under reduced pressure, ice and ammonia were added, and the brown solution was allowed to stand for 6 hours. The crystals (1.2 g.) were separated, dried and recrystallized from benzene, m.p. 178°; $\text{uv } m\mu$, λ max, 308, 302 and 272; ir cm^{-1} , 3190 (NH).

Anal. Calcd. for $\text{C}_8\text{H}_8\text{N}_3\text{Cl}$: C, 52.89; H, 4.40; N, 23.14. Found: C, 52.55; H, 4.48; N, 22.88.

3,5-Dimethyl-7-diacetylaminopyrazolo[4,3-b]pyridine (XIV).

Compound XI (2 g.) (0.012 mole) was refluxed for 5 minutes with 10 ml. of acetic anhydride; after removal of solvent under reduced pressure, the diacetyl derivative (1.8 g.) was obtained, recrystallized from ethanol, m.p. 223°; hydrochloride, m.p. 302°; ir cm^{-1} , 3180 (NH) 1720 and 1730 (CO); nmr (deuteriochloroform) δ , 4 singlets at 2.28, 2.62, 2.67 and 2.82, 4x (3H, CH_3), 8.54 (s, 1H, CH); 11.80 (s, 1H, NH pyrazolic).

Anal. Calcd. for $\text{C}_{12}\text{H}_{14}\text{N}_4\text{O}_2$: C, 58.52; H, 5.73; N, 22.75. Found: C, 58.66; H, 5.60; N, 22.90.

1-(3-Methyl-5-isoxazolyl)-2-hydroxyimino-1,3-butanedione (XV).

This compound was prepared from 1-(3-methyl-5-isoxazolyl)-1,3-butanedione (14) using the same method reported for VII, m.p. 152° (water).

Anal. Calcd. for $\text{C}_8\text{H}_8\text{N}_2\text{O}_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 48.79; H, 4.16; N, 13.99.

5-[3(5)-Methyl-4-nitroso-5(3)pyrazolyl]-3-methylisoxazole (XVI).

This compound was obtained from XV according to the procedure described for VIII, m.p. 193° (ethanol).

Anal. Calcd. for $\text{C}_8\text{H}_8\text{N}_4\text{O}_2$: C, 49.99; H, 4.16; N, 29.16. Found: C, 49.93; H, 4.28; N, 28.99.

The Hydrogenation of XVI: 3,5-Dimethyl-7-hydroxypyrazolo[4,3-b]pyridine (XII).

This compound was obtained by hydrogenation of XVI according to the procedure described for XI, m.p. 346° (ethanol); $\text{uv } m\mu$, λ max, 306, 296 and 259 sh; ir cm^{-1} , ca. 3400, 1652 (OH) and 3200 (NH); nmr (DMSO) δ , 2.28 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 5.63 (s, 1H, CH), ca. 11.38 (broad, 1H, OH), 13.00 (s, 1H, NH).

Anal. Calcd. for $\text{C}_8\text{H}_9\text{N}_3\text{O}$: C, 58.88; H, 5.56; N, 25.77. Found: C, 58.68; H, 5.44; N, 25.62.

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