Reaction of Ethyl 3-Ethoxymethylene-2,4-dioxovalerate with Monosubstituted Hydrazines (1)

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Reactions of ethyl 3-ethoxymethylene-2,4-dioxovalerate (**1**) with phenyl- and methylhydrazines are described. While the reaction of **1** with phenylhydrazine gave a mixture of ethyl 4-acetyl-1-phenylpyrazole-5-carboxylate (**4**) and ethyl 5-methyl-1-phenylpyrazole-4-glyoxylate (**5**), **1** reacted with methylhydrazine to give ethyl 4-acetyl-1-methylpyrazole-3-carboxylate (**14**) as the sole product.

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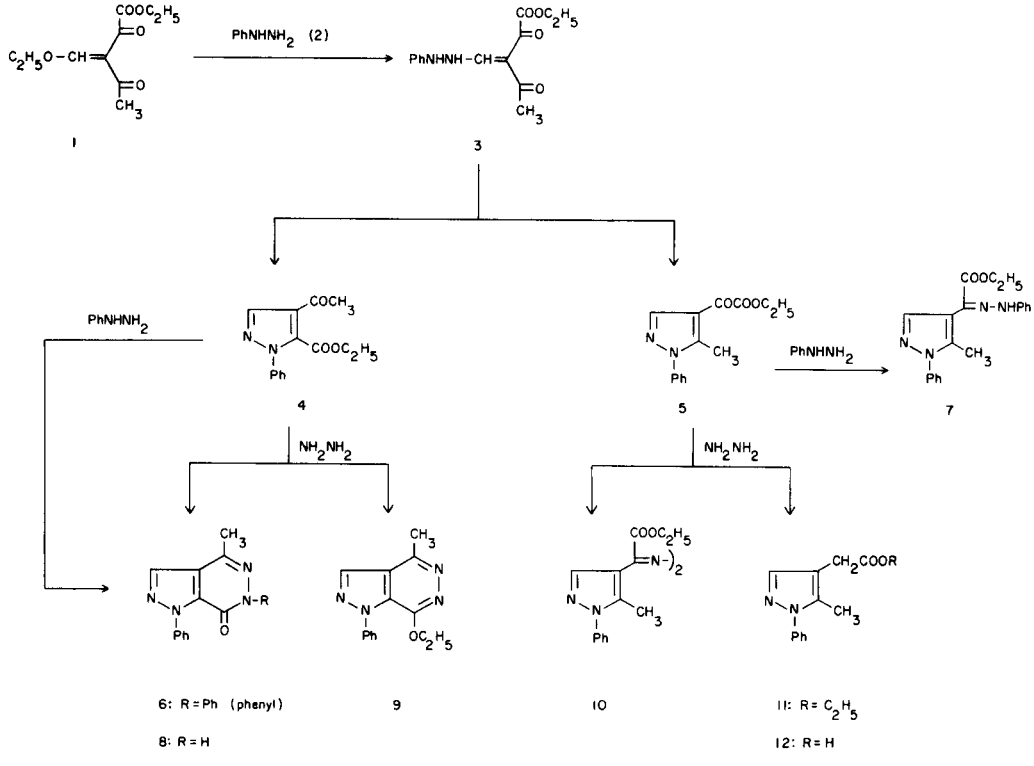
Reaction of 1 with Phenylhydrazine.

Jones has reported the reaction of ethyl ethoxymethyleneoxaloacetate with phenylhydrazine, which yielded only ethyl 1-phenylpyrazole-4,5-dicarboxylate (**2**). In contrast to this result, the reaction of ethyl 3-ethoxymethylene-2,4-dioxovalerate (**1**) with an equimolar amount of phenylhydrazine (**2**) in ether under ice cooling gave ethyl 3-phenylhydrazinomethylene-2,4-dioxovalerate (**3**) which was isolated as a pale yellow powder in good yield. This was very unstable when exposed to air, and analysed without purification by recrystallization. When this compound was then refluxed in ether gently for 5 hours, a mixture of ethyl 4-acetyl-1-phenylpyrazole-5-carboxylate (**4**), m.p. 64-65°, and ethyl 5-methyl-1-phenylpyrazole-4-glyoxylate (**5**), m.p. 48-49°, was obtained in a ratio of 45:55 (3) in 95% yield. These two products were partially separated by fractional recrystallization from ligroin and petroleum ether.

The structural proof of **4** and **5** was based on the spectral data cited in the experimental and the following chemical reactions. Heating of **4** with **2** in ethanol gave 6,7-dihydro-1,6-diphenyl-4-methylpyrazolo[3,4-*d*]pyridazin-7-one (**6**), but **5** gave ethyl α-phenylhydrazono-5-methyl-1-phenypyrazole-4-glyoxylate (**7**) under the same

Scheme I



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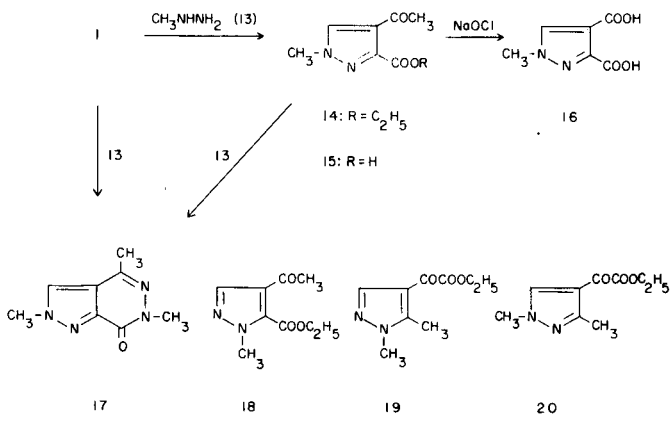
conditions. Moreover, treatment of **4** with hydrazine dihydrochloride in refluxing ethanol afforded 6,7-dihydro-4-methyl-1-phenylpyrazolo[3,4-*d*]pyridazin-7-one (**8**) in 79% yield in addition to 7-ethoxy-4-methyl-1-phenylpyrazolo-[3,4-*d*]pyridazine (**9**) in 7% yield. On the other hand, **5** afforded a mixture of α,α'-azino-*bis*(5-methyl-1-phenylpyrazole-4-glyoxylate) (**10**) in 82% yield and an unexpected product (**11**) in low yield under the same condition. The mass spectrum of **11** showed the molecular ion peak at m/e 244. The proton magnetic resonance (pmr) spectrum exhibited a singlet at δ 3.51 due to a methylene group, and a triplet and a quartet at δ 1.33 and 4.66 due to the ethyl group indicating the presence of the $-CH_2COOC_2H_5$ moiety. Saponification of **11** with ethanolic potassium hydroxide gave the corresponding carboxylic acid (**12**), m.p. 164-165°, which was identical with the data reported (4). Therefore the structure of **11** was established as ethyl 5-methyl-1-phenylpyrazole-4-acetate.

Reaction of **1** with Methylhydrazine.

Bauer (5) has reported the reaction of ethyl ethoxymethyleneoxaloacetate with methylhydrazine to give a mixture of ethyl 1-methylpyrazole-3,4- and 4,5-dicarboxylates. When **1** was, however, treated with methylhydrazine (**13**) in ether under ice cooling, product A, m.p. 69-70°, was isolated as a single product in 63% yield. It is well known that methylhydrazine has two nucleophilic nitrogens. From this point of view and the result of the reaction of **1** with **2**, it was proposed that the structure of product A is one of the following four structures **14**, **18**, **19** and **20**. The structural determination of product A was performed as follows. Product A was refluxed with an equimolar amount

Scheme 2



of **13** in ethanol to give 6,7-dihydro-2,4,6-trimethylpyrazolo[3,4-*d*]pyridazin-7-one (**17**), which was directly obtained by the condensation of **1** with 2 moles of **13** in refluxing ethanol. Compound A was hydrolysed and oxidized with sodium hypochlorite leading to 1-methylpyrazole-3,4-dicarboxylic acid (**16**), which was identical with the sample prepared according to the method of Bauer (5). From these results, Compound A was established as ethyl 4-acetyl-1-methylpyrazole-3-carboxylate (**14**).

EXPERIMENTAL

All melting points were uncorrected. Infrared (ir) and ultraviolet (uv) spectra were taken on a JASCO IRA-1 and Schimadzu UV-200 spectrophotometers. Pmr spectra were determined in a solution of deuteriodimethylsulfoxide with TMS as the internal standard with a Hitachi R-40 spectrometer. Mass spectra were taken with a Hitachi RMU-7L.

Ethyl 3-Phenylhydrazinomethylene-2,4-dioxovalerate (**3**).

To a solution of **1** (4.28 g., 0.02 mole) of anhydrous ether (40 ml.), phenylhydrazine (2.16 g., 0.02 mole) dissolved in anhydrous ether (20 ml.) was added under ice cooling and stirring. The precipitate formed was collected by filtration, washed with cold ether and dried to give **3** (5.26 g., 95%), m.p. 55-60°; ir ν max (potassium bromide) cm^{-1}: 1740 (CO).

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.94; H, 5.94; N, 10.12.

Pyrazole Cyclization of **3**.

An ether solution (100 ml.) of **3** (2.76 g., 0.01 mole) was refluxed gently for 5 hours. The mixture was cooled, dried (magnesium sulfate), and evaporated to give a semisolid (2.45 g.) which showed a single spot on thin-layer chromatography (alumina/benzene), but the presence of two components was evident in its pmr spectrum. Repeated recrystallization from ligroin gave ethyl 4-acetyl-1-phenylpyrazole-5-carboxylate (**4**) (0.61 g.) as colorless needles, m.p. 64-65°; ir ν max (potassium bromide) cm^{-1}: 1740, 1680 (CO); pmr δ: 1.23 (3H, t, J = 6 Hz, CH_2CH_3), 2.53 (3H, s, $COCH_3$), 4.38 (2H, q, J = 6 Hz, CH_2CH_3), 7.58 (5H, m, Aromatic-H), 8.12 (1H, s, C_3-H).

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.58. Found: C, 65.18; H, 5.55; N, 10.62.

The filtrate of the recrystallization from ligroin was concentrated, and the residue was recrystallized from petroleum ether repeatedly to give ethyl 5-methyl-1-phenylpyrazole-4-glyoxylate (**5**) (0.49 g.) as colorless needles, m.p. 48-49°; ir ν max (potassium bromide) cm^{-1}: 1740, 1660 (CO); pmr δ: 1.45 (3H, t, J = 6 Hz, CH_2CH_3), 2.64 (3H, s, CH_3), 4.49 (2H, q, J = 6 Hz, CH_2CH_3), 7.58 (5H, m, Aromatic-H), 8.48 (1H, s, C_3-H).

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.28; H, 5.75; N, 11.01.

6,7-Dihydro-1,6-diphenyl-4-methylpyrazolo[3,4-*d*]pyridazin-7-one (**6**).

A mixture of **4** (258 mg., 1 mmole) and phenylhydrazine hydrochloride (145 mg., 1 mmole) in ethanol (20 ml.) was refluxed for 10 hours. After evaporation of the solvent, the residue was recrystallized from ethanol to give **6** (254 mg., 84%), m.p. 174-175°; ir ν max (potassium bromide) cm^{-1}: 1680 (CO); pmr δ: 2.65 (3H, s, CH_3), 7.40-7.70 (10H, m, Aromatic-H), 8.60 (1H, s, C_3-H).

Anal. Calcd. for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.33; H, 4.50; N, 18.70.

Ethyl α-Phenylhydrazono-5-methyl-1-phenylpyrazole-4-glyoxylate (**7**).

A mixture of **5** (258 mg., 1 mmole) and phenylhydrazine hydrochloride (145 mg., 1 mmole) in ethanol (20 ml.) was refluxed for 10 hours. After evaporation of the solvent, the residue was recrystallized from benzene-ligroin to give **7** (229 mg., 74%), m.p. 151-153°; ir ν max (potassium bromide) cm^{-1}: 1735 (CO); pmr δ: 1.45 (3H, t, J = 6 Hz, CH_2CH_3), 2.60 (3H, s, CH_3), 4.40 (2H, q, J = 6 Hz, CH_2CH_3), 7.20-7.60 (10H, m, Aromatic-H), 7.90 (1H, s, C_3-H), 12.50 (1H, bs, NH).

Anal. Calcd. for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.12; H, 5.94; N, 16.35.

Reaction of **4** with Hyrazine Dihydrochloride.

A mixture of **4** (258 mg., 1 mmole) and hydrazine dihydrochloride (157 mg., 1 mmole) in EtOH (20 ml.) was refluxed for 10 hours. After evaporation of the solvent, the residue was recrystallized from ethanol to give

6,7-dihydro-4-methyl-1-phenylpyrazolo[3,4-*d*]pyridazin-7-one (**8**) (154 mg., 68%), m.p. 217-218°, ir ν max (potassium bromide) cm^{-1}: 1685 (CO); pmr δ: 2.55 (3H, s, CH_3), 8.50 (1H, s, C_3-H), 11.50 (1H, bs, NH).

Anal. Calcd. for $C_{12}H_{10}N_4O$: C, 63.70; H, 4.46; N, 24.77. Found: C, 63.66; H, 4.43; N, 24.59.

The filtrate was concentrated, and the residue was recrystallized from ligroin to give 7-ethoxy-4-methyl-1-phenylpyrazolo[3,4-*d*]pyridazin-7-one (**9**) (18 mg., 7%) as colorless needles, m.p. 121-123°. Uv λ max (ethanol) nm (log ε): 285 (3.74); pmr δ: 1.33 (3H, t, J = 6 Hz, CH_2CH_3), 2.86 (3H, s, CH_3), 4.66 (2H, q, J = 6 Hz, CH_2CH_3), 7.50-7.70 (5H, m, Aromatic-H), 8.30 (1H, s, C_3-H). Mass: m/e 254 (M^+).

Anal. Calcd. for $C_{14}H_{14}N_4O$: C, 66.12; H, 5.55; N, 22.04. Found: C, 66.04; H, 5.48; N, 21.81.

Reaction of **5** with Hydrazine Dihydrochloride.

A mixture of **5** (1.13 g., 0.005 mole) and hydrazine dihydrochloride (0.8 g., 0.006 mole) in ethanol (50 ml.) was refluxed for 10 hours. After evaporation of the solvent, the residue was made alkaline with saturated sodium bicarbonate, extracted with chloroform, and dried (sodium sulfate). Evaporation of the solvent gave a crystalline residue, which was recrystallized from ligroin to give α,α'-azino-*bis*(1-phenyl-5-methylpyrazole-4-glyoxylate) (**10**) (0.88 g., 84%) as pale yellow needles, m.p. 196-197°; ir ν max (potassium bromide) cm^{-1}: 1740 (CO); pmr (deuteriochloroform) δ: 1.40 (6H, t, J = 6 Hz, 2 × CH_2CH_3), 2.60 (6H, s, 2 × CH_3), 4.45 (4H, q, J = 6 Hz, 2 × CH_2CH_3), 7.65 (10H, s, Aromatic-H), 7.85 (2H, s, 2 × C_3-H); ms: m/e 512 (M^+).

Anal. Calcd. for $C_{28}H_{28}N_6O_4$: C, 65.51; H, 5.51; N, 16.40. Found: C, 65.84; H, 5.31; N, 16.40.

After evaporation of the solvent, the residue was submitted to alumina column chromatography and eluted with benzene. The first eluate was evaporated to give a crystalline residue, which was recrystallized from petroleum ether to give ethyl 5-methyl-1-phenylpyrazole-4-acetate (**11**) (42 mg.) as colorless needles, m.p. 44-44.5°; ir ν max (potassium bromide) cm^{-1}: 1740 (CO); pmr (deuteriochloroform) δ: 1.29 (3H, t, J = 6 Hz, CH_2CH_3), 2.31 (3H, s, CH_3), 3.51 (2H, s, CH_2), 4.22 (2H, q, J = 6 Hz, CH_2CH_3), 7.68 (1H, s, C_3-H); ms: m/e 244 (M^+).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.88; H, 6.60; N, 11.47. Found: C, 69.07; H, 6.64; N, 11.22.

5-Methyl-1-phenylpyrazole-4-acetic Acid (**12**).

A mixture of **11** (25 mg., 0.1 mmole) and potassium hydroxide (6 mg.) in 95% ethanol (10 ml.) was warmed at 50° for 1 hour. After evaporation of the solvent, the residue was dissolved in water (5 ml.). The solution was acidified with concentrated hydrochloric acid, and the precipitate formed was collected by filtration and recrystallized from benzene to give **12** (8 mg.) as colorless needles, m.p. 164-165°; ir ν max (potassium bromide): 1720 (CO).

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59. Found: C, 66.45; H, 5.73.

Ethyl 4-Acetyl-1-methylpyrazole-3-carboxylate (**14**).

To a solution of **1** (8.65 g., 0.04 mole) in anhydrous ether (800 ml.), anhydrous ether solution (100 ml.) of methylhydrazine (1.84 g., 0.04 mole) was added under ice cooling and stirring. The solution was dried (sodium sulfate) and the solvent was evaporated to dryness. The residue was recrystallized from ligroin to give **14** (4.92 g., 63%) as colorless needles, m.p. 69-70°; ir ν max (potassium bromide) cm^{-1}: 1730, 1660 (CO); pmr δ: 1.43 (3H, t, J = 6 Hz, CH_2CH_3), 2.56 (3H, s, CH_3), 3.97 (3H, s, N-CH_3), 4.45 (2H, q, J = 6 Hz, CH_2CH_3), 7.86 (1H, s, C_5-H); ms: m/e 196 (M^+).

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.39; H, 6.20; N, 14.16.

4-Acetyl-1-methylpyrazole-3-carboxylic Acid (**15**).

To a solution of **14** (196 mg., 1 mmole) in ethanol (10 ml.), a solution of potassium hydroxide (56 mg., 1 mmole) in water (1 ml.) was added, and the mixture was warmed at 40° for 2 hours. After evaporation of the solvent *in vacuo*, the residue dissolved in water (10 ml.) was acidified with concentrated hydrochloric acid with ice cooling. The precipitate was collected and recrystallized from methanol to give **15** (147 mg., 88%) as colorless needles, m.p. 230-231°; ir ν max (potassium bromide) cm^{-1}: 1720 (CO); pmr δ: 2.50 (3H, s, $COCH_3$), 3.95 (3H, s, N-CH_3), 8.60 (1H, s, C_5-H).

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 50.09; H, 4.84; N, 16.72.

1-Methylpyrazole-3,4-dicarboxylic Acid (**16**).

To a mixture of 5% sodium hypochloride solution (15 ml.) and sodium hydroxide (0.24 g.), **15** (0.5 g.) was added, and the mixture was heated at 70° for 5 hours. After decomposition of excess sodium hypochlorite with sodium bisulfite, the mixture was acidified with concentrated hydrochloric acid with ice cooling. The precipitate was collected and recrystallized from water to give **16** (215 mg.), 229-231°; pmr δ: 3.90 (3H, s, N-CH_3), 8.35 (1H, s, C_5-H).

Anal. Calcd. for $C_6H_6N_2O_4$: C, 42.36; H, 3.56; N, 16.47. Found: C, 42.52; H, 3.66; N, 16.49.

6,7-Dihydro-2,4,6-trimethylpyrazolo[3,4-*d*]pyridazin-7-one (**17**).

(i) To a solution of **1** (2.14 g., 0.01 mole) in anhydrous ether (200 ml.), a solution of methylhydrazine (0.92 g., 0.02 mole) in anhydrous ether (50 ml.) was added at room temperature with stirring. The reaction mixture was refluxed for 2 hours and chilled. The precipitate formed was collected and recrystallized from ethanol to give **17** (1.02 g., 57%) as colorless needles, m.p. 210-215°; ir ν max (potassium bromide) cm^{-1}: 1650 (CO); pmr δ: 2.38 (3H, s, CH_3), 3.62 (3H, s, N-CH_3), 4.14 (3H, s, N-CH_3), 8.54 (1H, s, C_3-H).

Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.45. Found: C, 53.65; H, 5.51; N, 31.65.

(ii) A mixture of **14** (1.96 g., 0.01 mole) and methylhydrazine (0.46 g., 0.01 mole) in ethanol (20 ml.) was refluxed for 2 hours. After evaporation of the solvent, the residue was recrystallized from ethanol to give **17** (1.42 g., 80%), which was identical with the sample prepared as in (i) in all respects.

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REFERENCES AND NOTES

(1) A part of thia work was presented at the 27th Kinki Local Meeting of the Pharmaceutical Society of Japan, Kobe, 1977.

(2) R. G. Jones and C. W. Whitehead, *J. Org. Chem.*, **20**, 1342 (1955).

(3) Determined from its pmr spectral examination.

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