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Synthesis of Pyrazolone Derivatives. XXXIX.[1] Synthesis and Analgesic Activity of Pyrano[2,3-*c*]pyrazoles

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Syntheses of pyrano[2,3-*c*]pyrazoles by means of the reaction of 3-ethoxycarbonyl-5-hydroxy-1-methyl(or phenyl)pyrazole (Ia, b) and acetylenecarboxylates or ethyl acetoacetate were examined. The reactions of Ia, b with acetylenecarboxylates gave 3-ethoxycarbonyl-4-substituted-1-methyl(or phenyl)pyrano[2,3-*c*]pyrazol-6(1*H*)-ones (IIa—c) in 5.9—23.9% yields. The Pechmann–Duisberg reaction of Ia—c with ethyl acetoacetate gave 3-ethoxycarbonyl-4-methyl-1-substitutedpyrano[2,3-*c*]pyrazol-6(1*H*)-ones (VIIa—c) in 33.1—46.2% yields. Similar reactions of 5-hydroxy-3-methylcarbamoyl-1-phenyl(or *m*-chlorophenyl)pyrazoles (IXa, b) with ethyl acetoacetate gave 4-methyl-3-methylcarbamoyl-1-phenyl(or *m*-chlorophenyl)pyrano[2,3-*c*]pyrazol-6(1*H*)-ones (Xa, b) in 17.4—30% yields.

The newly synthesized pyrano[2,3-*c*]pyrazoles (Xa, Xb, XII) showed analgesic activity in mice when tested by two methods.

Keywords——pyrazole; pyrazolone; pyrano[2,3-*c*]pyrazole; acetylenecarboxylate; analgesic activity

Among pyrazoles and pyrazolones a number of chemically and pharmacologically interesting compounds have been found.[2] Studies of a series of pyrazolone derivatives have also been carried out in our laboratory and some biologically interesting compounds and reactions have been reported previously.[3] As a continuation of our work, this paper deals with studies on the syntheses and analgesic actions of pyrano[2,3-*c*]pyrazoles.

Chemistry

Since pyrazolopyridines are promising analgesic and antiinflammatory agents, various synthetic studies on these compounds have been reported.[4] We considered that the introduction of a pyran ring instead of the pyridine ring, that is, syntheses of pyranopyrazoles, might give pharmacologically interesting compounds. Thus, preparations of pyrano[2,3-*c*]pyrazoles were attempted initially by the reactions of 3-ethoxycarbonyl-5-hydroxy-1-methyl(or phenyl)-pyrazole (Ia, b)[5,6] with acetylenecarboxylates. The reaction of Ia with dimethyl acetylenedicarboxylate (DMAD) in refluxing xylene[7] gave 3-ethoxycarbonyl-4-methoxycarbonyl-1-methylpyrano[2,3-*c*]pyrazol-6(1*H*)-one (IIa) (11.5%) and dimethyl (3-ethoxycarbonyl-5-hydroxy-1-methylpyrazol-4-yl)fumarate (III) (33.5%). Similar reaction of Ia with methyl propiolate afforded 3-ethoxycarbonyl-1-methylpyrano[2,3-*c*]-pyrazol-6(1*H*)-one (IIc) (23.9%). The other possible adducts could not be isolated from the reaction mixture. The reaction of Ib with DMAD gave 3-ethoxycarbonyl-4-methoxycarbonyl-1-phenylpyrano[2,3-*c*]pyrazol-6-(1*H*)-one (IIb) (5.9%) and dimethyl (3-ethoxycarbonyl-1-phenylpyrazol-5-yl)oxyfumarate (IV) (9.9%). However, the reaction of Ib with methyl propiolate did not proceed. The ultraviolet (UV) spectra of IIa—c showed absorption maxima at 320 nm due to the lactone ring and their infrared (IR) absorptions at 1740—1770 cm^{-1} indicated the presence of α-pyrone.[8] The possible isomers (II′) were not detected. The IR and nuclear magnetic resonance (NMR) spectra of III and IV were consistent with the above structures. The IR spectrum of III showed the hydroxyl group around 3000 cm^{-1} and its NMR spectrum showed only a vinyl proton at δ 6.96 ppm. On the other hand IR and NMR spectra of IV showed

no hydroxyl group, and two olefinic protons were observed at δ 6.36 and 6.86 ppm.

Heindel *et al.*[9] examined the chemical shifts of the vinyl protons and methyl esters in isomeric acetylenedicarboxylate adducts and predicted that vinyl protons of fumarate geometry would generally show signals at around δ 6.8 ppm and those of maleate type would show signals at around δ 6.0 ppm; the two methyl esters of the fumarate type would be observed separately in view of the slightly different electronic environments as compared with the maleate type. Compounds (III and IV) displayed vinyl proton resonance at δ 6.86 ppm and δ 6.96 ppm respectively, and the resonances of the two ester methyls were observed separately. Thus, both III and IV appear to have fumarate geometry.

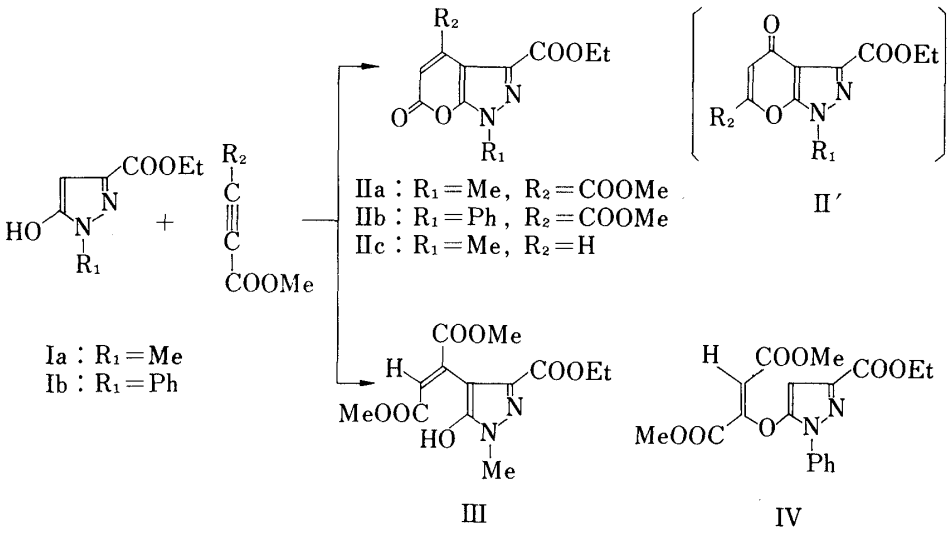


Chart 1

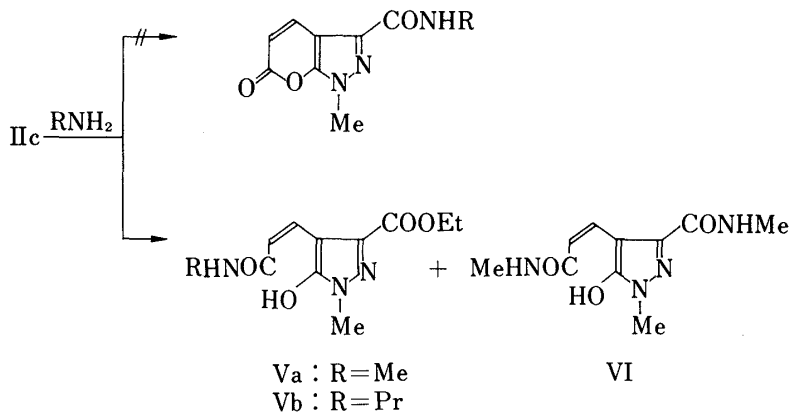


Chart 2

In order to obtain amide derivatives of IIa—c, the reactions of IIa—c with alkylamines were carried out. However, these reactions gave intractable glutinous oils which were probably mixtures of ring-opened compounds. For instance, 3-(3-ethoxycarbonyl-5-hydroxy-1-methylpyrazol-4-yl)-*N*-methylpropenamide (Va) (9.0%) and 3-(5-hydroxy-3-methylcarbamoyl-1-methylpyrazol-4-yl)-*N*-methylpropenamide (VI) (14.0%) were separated from the reaction mixture of IIc with methylamine by column chromatography on silica gel. As for the reaction of IIc with propylamine, only 3-(ethoxycarbonyl-5-hydroxy-1-methylpyrazol-4-yl)-*N*-propylpropenamide (Vb) was isolated.

As the yields of pyrano[2,3-*c*]pyrazoles in the above syntheses (Chart 1) were not favorable, the Pechmann-Duisberg reaction[10] using Ia—c and ethyl acetoacetate was examined. The

reaction of Ia—c with ethyl acetoacetate in refluxing xylene in the presence of sulfuric acid proceeded successfully to give 1-alkyl-3-ethoxycarbonyl-4-methylpyrano[2,3-*c*]pyrazol-6(1*H*)-ones (VIIa—c). The oxidation of VIIb with selenium dioxide gave 3-ethoxycarbonyl-4-formyl-1-phenylpyrano[2,3-*c*]pyrazol-6(1*H*)-one (VIII).

As described above, the reactions of IIa—c with alkylamines did not give the desired amide derivatives. Therefore, the reactions of 5-hydroxy-3-methylcarbamoyl-1-phenyl-(or *m*-chlorophenyl)pyrazoles (IXa, b)[11] with ethyl acetoacetate were carried out to afford the desired amides, 4-methyl-3-methylcarbamoyl-1-phenyl(or *m*-chlorophenyl)pyrano[2,3-*c*]-

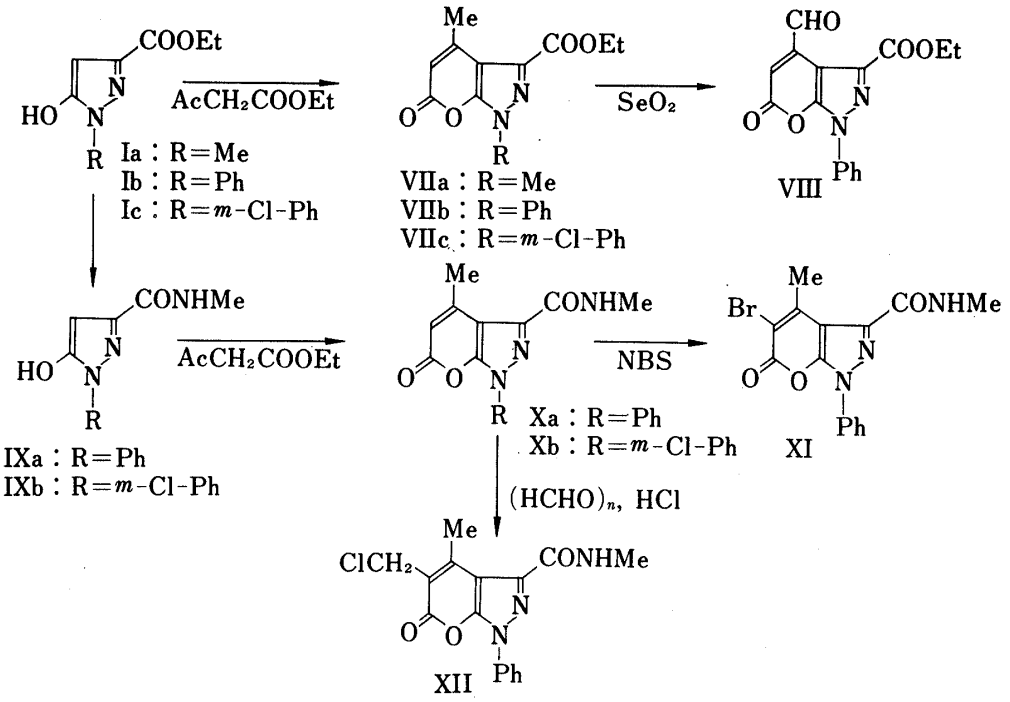


Chart 3

TABLE I. 1,3,4-Trisubstitutedpyrano[2,3-*c*]pyrazol-6(1*H*)ones

Compd. No.	mp (°C)	Yield (%)	UV: λ_{max}^{EtOH} nm (log ε)	Formula	Analysis (%) Calcd (Found) C	H	N
IIa	90— 93	11.5	240(3.62) 322(3.69)	$C_{12}H_{12}N_2O_6$	51.43 (51.26	4.32 4.16	9.99 9.90)
IIb	131—133	5.9	245(4.02) 324(3.67)	$C_{17}H_{14}N_2O_6$	59.65 (59.31	4.12 3.92	8.18 8.05)
IIc	123—126	23.9	252(3.58) 315(3.98)	$C_{10}H_{10}N_2O_4$	54.05 (54.22	4.54 4.51	12.61 12.86)
VIIa	170—171	46.2	253(3.43) 310(3.99)	$C_{11}H_{12}N_2O_4$	55.93 (55.88	5.12 5.07	11.86 11.89)
VIIb	151—153	38.9	241(3.99) 265(3.96) 3.10(3.96)	$C_{16}H_{14}N_2O_4$	64.42 (64.53	4.73 4.68	9.39 9.45)
VIIc	133—134	33.1	244(3.92) 305(3.95)	$C_{16}H_{13}ClN_2O_4$	57.76 (57.22	3.94 4.13	8.42 8.60)
VIII	163—165	28.8		$C_{16}H_{12}N_2O_5$	61.54 (61.39	3.87 3.86	8.97 8.66)
Xa	200—202	30.2	237(3.91) 269(3.91) 308(3.93)	$C_{15}H_{13}N_3O_3$	63.59 (63.40	4.63 4.44	14.83 14.92)
Xc	208—209	17.4	242(3.89) 307(3.92)	$C_{15}H_{12}ClN_3O_3$	56.70 (56.81	3.81 3.76	13.23 13.06)

pyrazol-6(1*H*)-ones (Xa, b). 5-Bromo-4-methyl-3-methylcarbamoyl-1-phenylpyrano[2,3-*c*]-pyrazol-6(1*H*)-one (XI) was obtained by the reaction of Xa with *N*-bromosuccinimide (NBS), and 5-chloromethyl-4-methyl-3-methylcarbamoyl-1-phenylpyrano[2,3-*c*]pyrazol-6(1*H*)-one (XII) was prepared from Xa and paraformaldehyde in the presence of hydrochloride in 80% acetic acid.

Analgesic Activity

The analgesic activities of Xa, Xb, XI, and XII were examined in comparison with that of aminopyrine by oral administration to mice, in terms of the number of writhings induced by acetic acid[12] or the pain threshold[13] using a Natsume KN-205B apparatus. These pharmacological results are shown in Fig. 1 and Fig. 2. Compounds Xa, b revealed activities almost equal to that of aminopyrine (70% inhibition) and XII showed 50% inhibition in the acetic acid writhing method (Fig. 1). However, Xa and Xb gave pain thresholds of 40 mmHg, and they were less active than aminopyrine (65 mmHg).

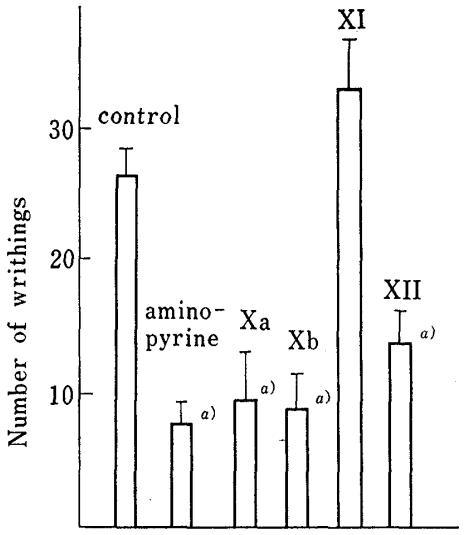


Fig. 1. Analgesic Activity of Pyrano[2,3-*c*]-pyrazoles at a Dose of 100 mg/kg on Acetic Acid–induced Writhing in Mice

The bars are standard errors.
a) $p<0.01$.

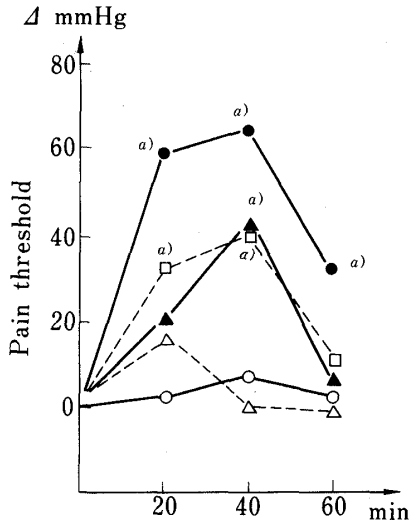


Fig. 2. Pain Threshold Elevating Effects at a Dose of 100 mg/kg

a) $p<0.05$.
—○—: control, —●—: aminopyrine,
---□---: Xa, —▲—: Xb, ---△---: XII.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. UV spectra were recorded with a Hitachi EPS-3T recording spectrophotometer, and IR spectra were measured with an IR-S machine from Nihon Bunko Spectroscopic Co. Ltd. NMR spectra were measured with a Japan Electron Optics Laboratory Co. JNM-100 spectrometer using tetramethylsilane as an internal standard. Mass spectra were obtained on a Hitachi RMU-6E mass spectrometer equipped with a double focusing system.

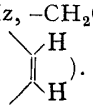
3-Ethoxycarbonyl-4-methoxycarbonyl-1-methylpyrano[2,3-*c*]pyrazol-6(1*H*)-one (IIa) and Dimethyl (3-Ethoxycarbonyl-5-hydroxy-1-methylpyrazol-4-yl)fumarate (III)——A mixture of 1.7 g (10 mmol) of Ia, 20 ml of xylene, and 1.42 g (10 mmol) of DMAD was refluxed for 10 h with stirring. The reaction mixture was cooled and the resulting crystals (III) were separated by filtration. The filtrate was evaporated to dryness to give an oil, which was separated by silica gel column chromatography. The first chloroform eluate was collected and concentrated to give crystals, which were recrystallized from ethanol to give colorless needles (IIa). IR ν_{max}^{KBr} cm^{-1}: 1750 (C=O). NMR ($CDCl_3$) δ: 1.40 (3H, t, $J=7$ Hz, $-CH_2\underline{CH_3}$), 3.95 (6H, s, N–CH_3 and O–CH_3), 4.20 (2H, q, $J=7$ Hz, $-\underline{CH_2}CH_3$), 6.30 (1H, s, ). MS *m/e*: 280 (M^+). mp, UV and elemental analytical data are listed in Table I.

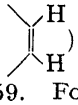
The second chloroform eluate yielded crystals (III) whose IR spectrum was identical with that of the above obtained crystals. Recrystallization of the combined crystals from ethyl acetate gave colorless

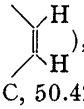
prisms of mp 137—140°C. Yield 1.04 g (33.5%). IR ν_{max}^{KBr} cm^{-1}: 2500—3000 (OH), 1730 (C=O). NMR ($CDCl_3$) δ: 1.36 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 3.78, 3.83, 3.88 (each, 3H, each s, 2×$-COOCH_3$, N–CH_3), 6.96 (1H, s, ), 8.70—9.50 (1H, broad, OH). MS m/e: 312 (M^+). *Anal.* Calcd for $C_{13}H_{16}N_2O_7$: C, 50.00; H, 5.16; N, 8.97. Found: C, 50.00; H, 5.20; N, 9.21.

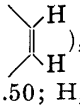
3-Ethoxycarbonyl-4-methoxycarbonyl-1-phenylpyrano[2,3-*c*]pyrazol-6(1*H*)-one (IIb) and Dimethyl (3-Ethoxycarbonyl-1-phenylpyrazol-5-yl)oxyfumarate (IV)——A mixture of 2.32 g (10 mmol) of Ib, 20 ml of xylene, and 1.42 g (10 mmol) of DMAD was refluxed for 10 h with stirring. The solvent was distilled off, and the residue was separated by silica gel column chromatography. The first chloroform–ethyl acetate (9: 1) eluate yielded crystals, which were recrystallized from ethanol to give colorless needles. IR ν_{max}^{KBr} cm^{-1}: 1770, 1730 (C=O). NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 4.00 (3H, s, $-COOCH_3$), 4.50 (2H, q, J=7 Hz, $-C\underline{H}_2CH_3$), 6.44 (1H, s, ), 7.42—8.00 (5H, m, –Ph). MS m/e: 342 (M^+). mp, UV and elemental analytical data are listed on Table I.

From the second eluate, colorless plates (from ether) (IV) were obtained. Yield 370 mg (9.9%), mp 110—113°C. IR ν_{max}^{KBr} cm^{-1}: 1740, 1690 (C=O). NMR ($CDCl_3$) δ: 1.36 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 3.75 and 3.85 (each 3H, each s, $-COOCH_3$×2), 4.34 (2H, q, J=7 Hz, $-C\underline{H}_2CH_3$), 6.36 and 6.86 (each 1H, each s, two olefinic protones), 7.42 (5H, s, –Ph). MS m/e: 374 (M^+). *Anal.* Calcd for $C_{18}H_{18}N_2O_7$: C, 57.75; H, 4.85; N, 7.48. Found: C, 57.76; H, 4.75; N, 7.76.

3-Ethoxycarbonyl-1-methylpyrano[2,3-*c*]pyrazol-6(1*H*)-one (IIc)——A mixture of 1.7 g (10 mmol) of Ia, 0.84 g (10 mmol) of methyl propiolate and 20 ml of xylene was treated in the same manner as for the synthesis of IIa. Colorless needles from ethanol. IR ν_{max}^{KBr} cm^{-1}: 1740 (C=O). NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 3.95 (3H, s, N–CH_3), 4.44 (2H, q, J=7 Hz, $-C\underline{H}_2CH_3$), 6.15 and 8.08 (2H, each d, J=10.8 Hz, ). MS m/e: 222 (M^+). mp, UV and elemental analytical data are listed on Table I.

3-(3-Ethoxycarbonyl-5-hydroxy-1-methylpyrazol-4-yl)-*N*-methylpropenamide (Va) and 3-(5-Hydroxy-1-methyl-3-methylcarbamoylpyrazol-4-yl)-*N*-methylpropenamide (VI)——A solution of 0.2 g of IIc in 5 ml of 30% methylamine–methanol was allowed to stand for 2 days at room temperature. The solvent was distilled off, and the residue was separated by silica gel column chromatography. From the first chloroform eluate, crystals of mp 143—144°C (from ethanol) were obtained. Yield 20 mg (9%). IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 1710 (ester C=O), 1630 (amide C=O). NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 2.85 (3H, d, J=4 Hz, $NHCH_3$), 3.64 (3H, s, N–CH_3), 4.30 (2H, q, J=7 Hz, $-C\underline{H}_2CH_3$), 5.50 and 7.34 (each 1H, each d, J=13 Hz, ), 6.54 (1H, m, NH). MS m/e: 253 (M^+). *Anal.* Calcd for $C_{11}H_{15}N_3O_4$: C, 52.17; H, 5.97; N, 16.59. Found: C, 52.01; H, 5.72; N, 16.38.

From the second chloroform eluate, colorless needles (VI) were obtained. Yield 30 mg (14%), mp 174—176°C (from ethanol). IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 1620 (C=O). NMR (DMSO-d_6) δ: 2.70 (3H, d, J=4 Hz, 3-position $-CONHCH_3$ or ), 2.76 (3H, d, J=4 Hz, or 3-position $-CONHCH_3$), 3.60 (3H, s, N–CH_3), 5.61 and 7.50 (each 1H, each d, J=13 Hz, ), 8.00 and 9.00 (each 1H, br, $-CONHCH_3$×2). MS m/e: 238 (M^+). *Anal.* Calcd for $C_{10}H_{14}N_4O_3$: C, 50.42; H, 5.92; N, 23.52. Found: C, 50.36; H, 5.97; N, 23.11.

3-(3-Ethoxycarbonyl-5-hydroxy-1-methylpyrazol-4-yl)-*N*-propylpropanamide (Vb)——*n*-Propylamine (0.1 g) was added to a solution of 0.1 g of IIc in absolute methanol and the mixture was treated in the same manner as for the synthesis of Va. Yield 50 mg (40%), mp 121—124°C. IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 1730 (C=O). NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7 Hz, $-CH_2CH_2CH_3$), 1.40 (3H, t, J=7 Hz, $-COOCH_2C\underline{H}_3$), 1.55 (2H, q, J=7 Hz, $-CH_2C\underline{H}_2CH_3$), 3.32 (2H, q, J=7 Hz, $NH-C\underline{H}_2CH_2CH_3$), 3.74 (3H, s, N–$CH_3$), 4.39 (2H, q, J=7 Hz, $-COOC\underline{H}_2CH_3$), 5.60 and 7.04 (each 1H, each d, J=13 Hz, ), 6.61 (1H, br, NH), 14.80 (1H, s, –OH). MS m/e: 281 (M^+). *Anal.* Calcd for $C_{13}H_{19}N_3O_4$: C, 55.50; H, 6.81; N, 14.94. Found: C, 55.60; H, 6.60; N, 15.13.

1,4-Dimethyl-3-ethoxycarbonylpyrano[2,3-*c*]pyrazol-6(1*H*)-one (VIIa)——A mixture of 1.7 g (10 mmol) of Ia, 20 ml of xylene, 2.62 g (20 mmol) of ethyl acetoacetate, and 2 drops of conc. sulfuric acid was refluxed for 2 h, then cooled. The resulting crystals were collected by filtration. Crystals were also obtained from the filtrate. Recrystallization from ethanol gave colorless needles. IR ν_{max}^{KBr} cm^{-1}: 1760, 1730 (C=O). NMR ($CDCl_3$) δ: 1.44 (3H, t, J=7 Hz, $-COOCH_2C\underline{H}_3$), 2.60 (3H, s, ), 3.98 (3H, s, N–CH_3), 4.48 (2H, q, J=7 Hz, $-COOC\underline{H}_2CH_3$), 5.98 (1H, s, ). MS m/e: 236 (M^+). mp, UV and elemental analytical data are listed in Table I.

3-Ethoxycarbonyl-4-methyl-1-phenylpyrano[2,3-*c*]pyrazol-6(1*H*)-one (VIIb)——A mixture of 1.16 g (5 mmol) of Ib, 20 ml of xylene, 1.30 g (10 mmol) of ethyl acetoacetate, and 2 drops of conc. sulfuric acid was refluxed for 2 h. The solvent was distilled off, and the residue was separated by silica gel chromatography. From the chloroform eluate, colorless needles (from ethanol) were obtained. IR ν_{max}^{KBr} cm^{-1}: 1750, 1730 (C=O). NMR ($CDCl_3$) δ: 1.46 (3H, t, $J=7$ Hz, $-CH_2C\underline{H}_3$), 2.64 (3H, s, $\diagdown\!\!\diagup CH_3$), 4.48 (2H, q, $J=7$ Hz, $-C\underline{H}_2CH_3$), 6.00 (1H, s, $H\diagdown\!\!\diagup$), 7.40—7.90 (5H, m, –Ph). MS *m/e*: 298 (M^+). mp, UV and elemental analytical data are listed in Table I.

1-(*m*-Chlorophenyl)-3-ethoxycarbonyl-4-methylpyrano[2,3-*c*]pyrazol-6(1*H*)-one (VIIc)——A mixture of 0.5 g (1.88 mmol) of Ic, 3 ml of acetic acid and 0.38 g of ethyl acetoacetate was refluxed for 4 h. The reaction mixture was treated in the same manner as for the synthesis of VIIb to give colorless needles (from ethanol). IR ν_{max}^{KBr} cm^{-1}: 1740 (C=O). NMR ($CDCl_3$) δ: 1.46 (3H, t, $J=7$ Hz, $-CH_2C\underline{H}_3$), 2.63 (3H, s, $\diagdown\!\!\diagup CH_3$), 4.48 (2H, q, $J=7$ Hz, $-C\underline{H}_2CH_3$), 6.03 (1H, s, $H\diagdown\!\!\diagup$), 7.40—8.00 (4H, m, aromatic protons). MS *m/e*: 332 (M^+), 334 (M+2). mp, UV and elemental analytical data are listed in Table I.

3-Ethoxycarbonyl-4-formyl-1-phenylpyrano[2,3-*c*]pyrazol-6(1*H*)-one (VIII)——A mixture of 0.3 g of VIIb, 0.2 g of selenium dioxide and 20 ml of xylene was refluxed for 8 h, then cooled. Selenium dioxide was removed by filtration, and the filtrate was evaporated to dryness. The residue was separated by silica gel chromatography. From the first chloroform eluate, the starting material (VIIb, 80 mg) was recovered. From the second eluate, colorless prisms (from ethanol) were obtained. IR ν_{max}^{KBr} cm^{-1}: 1700—1760 (C=O). NMR ($CDCl_3$) δ: 1.46 (3H, t, $J=7$ Hz, $-CH_2C\underline{H}_3$), 4.52 (2H, q, $J=7$ Hz, $-C\underline{H}_2CH_3$), 6.62 (1H, s, $H\diagdown\!\!\diagup$), 7.40—8.00 (5H, m, –Ph), 10.75 (1H, s, –CHO). MS *m/e*: 312 (M^+). mp and elemental analytical data are listed on Table I.

4-Methyl-3-methylcarbamoyl-1-phenylpyrano[2,3-*c*]pyrazol-6(1*H*)-one (Xa)——A mixture of 2.32 g of IXa,[11] 20 ml of xylene, 2.6 g of ethyl acetoacetate and 2 drops of conc. sulfuric acid was refluxed for 2 h, and the reaction mixture was treated in the same manner as for the synthesis of VIIb to give colorless needles (from ethanol). IR ν_{max}^{KBr} cm^{-1}: 3350 (NH), 1720 (lactone C=O), 1660 (amide C=O). NMR ($CDCl_3$) δ: 2.72 (3H, s, $\diagdown\!\!\diagup CH_3$), 3.03 (3H, d, $J=4$ Hz, $NHCH_3$), 6.00 (1H, m, NH), 7.38—7.92 (5H, m, –Ph). MS *m/e*: 283 (M^+). mp, UV and elemental analytical data are listed in Table I.

1-(*m*-Chlorophenyl)-4-methyl-3-methylcarbamoylpyrano[2,3-*c*]pyrazol-6(1*H*)-one (Xb)——A mixture of 0.3 g of IXb,[11] 3 ml of acetic acid and 0.15 g of ethyl acetoacetate was refluxed for 4 h. The reaction mixture was treated in the same manner as for the synthesis of VIIb. IR ν_{max}^{KBr} cm^{-1}: 3350 (NH), 1760 (lactone C=O), 1680 (amide C=O). NMR ($CDCl_3$) δ: 2.76 (3H, s, $\diagdown\!\!\diagup CH_3$), 3.08 (3H, d, $J=4$ Hz, $NHCH_3$), 6.08 (1H, s, $H\diagdown\!\!\diagup$), 7.20 (1H, m, NH), 7.30—8.05 (4H, m, aromatic protons). MS *m/e*: 317 (M^+), 319 (M+2). mp, UV and elemental analytical data are listed in Table I.

5-Bromo-4-methyl-3-methylcarbamoyl-1-phenylpyrano[2,3-*c*]pyrazol-6(1*H*)-one (XI)——A stirred solution of 0.2 g of Xa in 30 ml of chloroform was treated with 0.2 g of NBS. The mixture was refluxed for 20 h with stirring. The solvent was distilled off, and the residue was separated by silica gel chromatography using chloroform. The first eluate afforded a white solid, which was crystallized from ethanol, mp 229—232°C, yield 120 mg (47%). IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 1770 (lactone C=O), 1650 (amide C=O). NMR ($CDCl_3$) δ: 2.96 (3H, s, $\overset{CH_3}{|}\!\!\diagup$), 3.02 (3H, d, $J=4$ Hz, $NHC\underline{H}_3$), 7.12 (1H, br, m, NH), 7.40—7.90 (5H, m, –Ph). MS *m/e*: 361 (M^+), 363 (M+2). *Anal.* Calcd for $C_{15}H_{12}BrN_3O_3$: C, 49.74; H, 3.34; N, 11.60. Found: C, 49.50; H, 3.21; N, 11.32.

From the second eluate, the starting material (Xa) (50 mg) was recovered.

5-Chloromethyl-4-methyl-3-methylcarbamoyl-1-phenylpyrano[2,3-*c*]pyrazol-6(1*H*)-one (XII)——Hydrogen chloride gas was passed through a warmed (60°C) and stirred mixture of 0.2 g of Xa, 15 ml of 80% acetic acid and 70 mg of paraformaldehyde for 1 h, and the mixture was allowed to stand for one day at room temperature. The solvent was distilled off and the residue was separated by silica gel chromatography. From the chloroform eluate, colorless prisms of mp 181—183°C (from methanol) were obtained, yield 110 mg (51%). IR ν_{max}^{KBr} cm^{-1}: 3350 (NH), 1710, 1660 (C=O). NMR ($CDCl_3$) δ: 2.92 (3H, s, $\overset{CH_3}{|}\!\!\diagup$), 3.04 (3H, d, $J=4$ Hz, $NHC\underline{H}_3$), 4.65 (2H, s, $-CH_2Cl$), 7.10 (1H, br, m, NH), 7.40—7.90 (5H, m, –Ph). MS *m/e*: 331 (M^+), 333 (M+2). *Anal.* Calcd for $C_{16}H_{14}ClN_3O_3$: C, 57.93; H, 4.25; N, 12.67. Found: C, 58.42; H, 4.16; N, 12.81.

Analgesic Activity Testing——(a) Acetic Acid Writhing Method: Compounds Xa, Xb, XI, XII, each as a suspension in 0.5% CMC, were administered orally to ddy male mice (*ca.* 20 g) at a dose of 100 mg/kg.

Six animals were used to test each dose. Half an hour later, writhing was induced in mice by an intraperitoneal injection of 0.6% acetic acid (10 ml/kg). Ten min later, writhing was observed for a period of 10 min. Numbers of writhings are shown in Fig. 1, together with the results for aminopyrine, for comparison.

(b) Pressure Method: Pain thresholds of ddy male mice (*ca.* 20 g) were measured using a Natsume KN-205B apparatus. Compounds Xa, Xb, XII, each as a suspension in 0.5% CMC, were administered orally at a dose of 100 mg/kg. Five animals were used to test each dose. After administration, pain thresholds were measured at 20 min, 40 min and 60 min later, and are shown in Fig. 2 together with the results for aminopyrine, for comparison.

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