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# Syntheses of Pyrazolo[1,2-*a*]pyrazole and Pyrazolo-[5,1-*b*][1,3]oxazine Derivatives[1)]

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As a part of our search for new potent analgesic agents, novel fused pyrazole derivatives were synthesized. The reaction of 3-substituted-5-hydroxypyrazole (I) with ethyl 2-substituted (for example $COCH_3$ or $CO_2C_2H_5$) acylacetates (II) gave mainly pyrazolo[1,2-*a*]pyrazole-1,5(1*H*,5*H*)-diones (III). On the other hand, similar reaction of I with diethyl benzoylmalonate gave mainly pyrazolo[5,1-*b*][1,3]oxazin-5(5*H*)-one (V) but did not give III at all. Thermal and photochemical isomerization of III gave V. Methanolysis of IIIa in the presence of LiOH occurred with retention of the 4-ethoxycarbonyl-5-pyrazolone ring and similar products (VIa and VIf) were obtained by methanolysis of Va and Vf, respectively. Analgesic activities of the present new compounds were all inferior to that of aminopyrine.

**Keywords**——pyrazole; pyrazolo[1,2-*a*]pyrazole; pyrazolo[5,1-*b*][1,3]oxazine;diethyl acetylmalonate; diethyl benzoylmalonate; diethyl phenylacetylmalonate; ethyl 2-acetyl-acetoacetate; analgesic activity

A number of chemically and pharmacologically interesting pyrazole and pyrazolone derivatives have been synthesized during the past seventy years,[2)] and today these compounds are still of interest from a medical view point.[3)] In connection with our search for new antiinflammatory and analgesic agents, we have developed general syntheses of pyrazolo[1,2-*a*]pyrazole (III and IV) and pyrazolo[5,1-*b*][1,3]oxazine (V) derivatives, and the results are reported here.

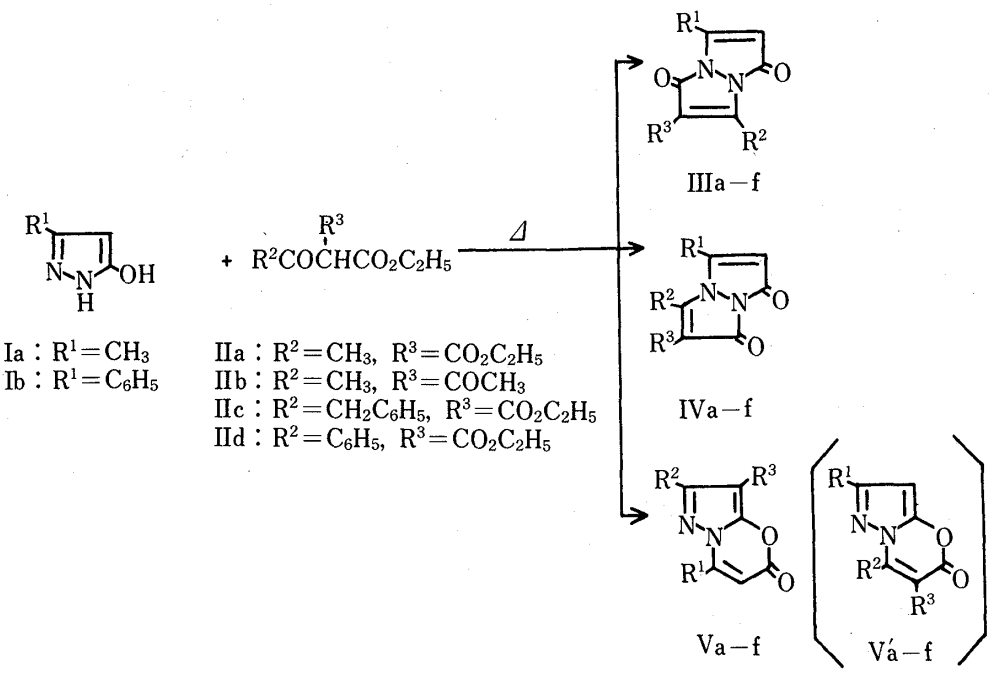



Chart 1

It is well-known that the reaction of 1,3-disubstituted-5-hydroxypyrazoles with acylacetates having an alkyl group at the 2-position gives pyrano[2,3-*c*]pyrazol-6(1*H*)-one[3b] derivatives. During our investigations of the reaction of 5-hydroxypyrazole derivatives with various β-keto esters, we found that the reaction of Ia, b[4] with excess IIa, c, d[5] or IIb[6] having a carbonyl group on the 2-position at 150—160 °C for 15 min gave novel cyclized products, pyrazolo[1,2-*a*]pyrazole-1,5(1*H*,5*H*)-dione (*anti*-pyrazolopyrazolidione[7] III), pyrazolo[1,2-*a*]pyrazole-1,7(1*H*,7*H*)-dione (*syn*-pyrazolopyrazolidione[7] IV) and pyrazolo[5,1-*b*][1,3]-oxazin-5(5*H*)-one (pyrazololactone[7] V). These reaction products could be easily separated by column chromatography over silica gel. In their ultraviolet (UV) spectra, *anti*-pyrazolopyrazolidione (IIIa) showed $\lambda_{max}^{dioxane}$ 334 nm (log ε: 4.23), *syn*-pyrazolopyrazolidione (IVa); $\lambda_{max}^{dioxane}$ 358 nm (log ε: 4.17), and pyrazololactone (Va); $\lambda_{max}^{dioxane}$ 282 nm (log ε: 4.05). The UV spectra of IIIa and IVa were quite similar to those of 3,7-dimethylpyrazolo[1,2-*a*]pyrazole-1,5(1*H*,5*H*)-dione, $\lambda_{max}^{dioxane}$ 325 nm (log ε: 4.16), and 3,5-dimethylpyrazolo[1,2-*a*]pyrazole-1,7(1*H*,7*H*)-dione, $\lambda_{max}^{dioxane}$ 354 nm (log ε: 3.93), respectively, which were obtained from 3-methyl-4-chloro-5-hydroxypyrazole by Kosower and his coworkers.[8] The UV spectrum of Va was also quite similar to that of 2,7-dimethylpyrazolo[5,1-*b*][1,3]oxazin-5(5*H*)-one, $\lambda_{max}^{dioxane}$ 286 nm (log ε: 4.07), which was obtained by photochemical conversion of 3,7-dimethylpyrazolo[1,2-*a*]pyrazole-1,5(1*H*,5*H*)-dione by Kanety and his coworkers.[9] On the basis of the above results, we proposed the structures IIIa, IVa and Va shown in Chart 1. Elemental analyses and mass spectra (MS) [*m/e*: 236 ($M^+$)] of IIIa, IVa and Va established the same formula, $C_{11}H_{12}N_2O_4$ (which indicates that the reaction between Ia and IIa proceeded with eliminations of water and ethanol). In the proton nuclear magnetic resonance ($^1$H-NMR) in $CDCl_3$, *anti*-pyrazolopyrazolidione (IIIa), *syn*-pyrazolopyrazolidione (IVa) and pyrazololactone (Va) did not show the signal of NH proton. On the other hand, the signals of the olefinic proton of IIIa, IVa and Va appeared at δ 5.72, 5.85 and 6.11 ppm, respectively. Infrared (IR) spectra of these compounds showed the presence of ester and carbonyl groups in IIIa (1700, 1740 $cm^{-1}$), IVa (1700, 1758 $cm^{-1}$) and ester and lactone carbonyl groups in Va (1700, 1780 $cm^{-1}$), but did not show an NH absorption band. The above spectral and analytical observations clearly support our initial assignments of the structures of IIIa and IVa, but do not rule out the alternative structure V′a for Va. In order to define the structure of the pyrazololactone (Va or V′a), the following experiments were performed. Treatment of Va with lithium hydroxide in methanol–water and subsequent acidification with hydrochloric acid gave colorless crystals (VIa) of mp 108—110 °C in 80% yield. The IR spectrum of the product showed the presence of a hydroxy group at 3000—2400 $cm^{-1}$ and carbonyl groups at 1680 and 1720 $cm^{-1}$, the MS showed *m/e*: 268 ($M^+$) and the $^1$H-NMR spectrum ($CDCl_3$) showed the signal of an olefinic proton at δ 5.84 ppm and the signal of a methyl ester group at δ 3.66 ppm. We presumed the structure VIa for the product (mp 108—110 °C) from these spectral data. Then treatment of VIa with diazomethane gave colorless crystals (VIIa) of mp 57—58 °C in 71.4% yield. In the $^1$H-NMR spectrum ($CDCl_3$) of VIIa, the methoxy group signal appeared at δ 4.01 ppm, and the MS of VIIa showed *m/e*: 282 ($M^+$). These data clearly indicate formation of VIa and VIIa. Then the methyl ester (VIIa) was hydrogenated in ethanol over 10% palladium charcoal to give methyl 3-(4-ethoxycarbonyl-5-methoxy-3-methyl-1-pyrazolyl)butyrate (VIIIa) in 79.5% yield. The structure of VIIIa was confirmed as follows; the MS showed *m/e*: 284 ($M^+$), the IR spectrum showed the presence of carbonyl groups at 1700 and 1740 $cm^{-1}$ and the $^1$H-NMR spectrum ($CDCl_3$) showed the signal of the methylene protons of butyrate at δ 3.20—2.50 ppm and the signal of the methine proton of the butyrate moiety at δ 5.00—4.60 ppm. If the structure is VIII′a, the methylene proton signal should not be observed in the $^1$H-NMR spectrum, so the structure VIIIa was clearly confirmed. Thus, the structures of Va, VIa and VIIa were also confirmed. Treatment of Vf as described for Va also gave VIf, VIIf and VIIIf without any ambiguity in the $^1$H-NMR

assignments. From the above results, the pyrazololactone structure obtained from the reaction of I with II was clearly assigned as V, not V′.

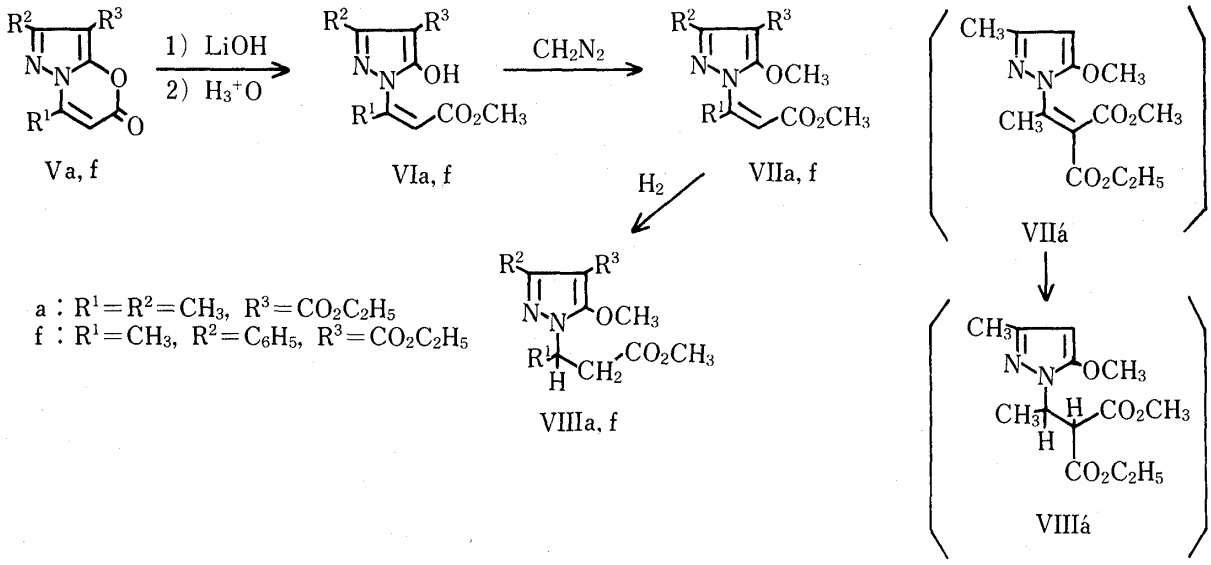



Chart 2

TABLE I. Product Ratio of Pyrazolo[1,2-*a*]pyrazoles (III, IV) and Pyrazolo-[5,1-*b*][1,3]oxazines (V) Obtained from the Reaction of I with II

| Starting materials | $R^1$ | $R^2$ | $R^3$ | Product ratio | Total yield (%) |
|---|---|---|---|---|---|
| Ia+IIa | $CH_3$ | $CH_3$ | $CO_2C_2H_5$ | IIIa : IVa : Va = 10 : 1 : 1 | 83.3 |
| Ia+IIb | $CH_3$ | $CH_3$ | $COCH_3$ | IIIb : IVb : Vb = 18 : 2 : 1 | 76.2 |
| Ia+IIc | $CH_3$ | $CH_2C_6H_5$ | $CO_2C_2H_5$ | IIIc : IVc : Vc = 16 : 1 : 1 | 75.5 |
| Ib+IIa | $C_6H_5$ | $CH_3$ | $CO_2C_2H_5$ | IIId : IVd : Vd = 16 : 1 : 0 | 80.6 |
| Ib+IIb | $C_6H_5$ | $CH_3$ | $COCH_3$ | IIIe : IVe : Ve = 12 : 1 : 0 | 59.7 |
| Ia+IId | $CH_3$ | $C_6H_5$ | $CO_2C_2H_5$ | IIIf : IVf : Vf = 0 : 1 : 20 | 75.5 |

Syntheses of *anti*-pyrazolopyrazolidione (III), *syn*-pyrazolopyrazolidione (IV) and pyrazololactone (V) having a carbonyl group as $R^3$ have not been reported up to the present, and they are probably not available *via* Kosower's procedure[8] because his procedure is only applicable to compounds with symmetrical substitution on the two rings. Thus, the present procedure should be valuable for the syntheses of pyrazole derivatives.

It is interesting that the ratio of III and V was greatly affected by variation of $R^2$ of the acylacetate (II); for example, as shown in Table I, in the case of $R^2$ = alkyl group, *anti*-pyrazolopyrazolidione (III) was a major product, while in the case of $R^2$ = phenyl, pyrazololactone (V) was a major product. Namely the treatment of 3-methyl-5-hydroxypyrazole (Ia) with diethyl benzoylmalonate (IId) afforded Vf in good yield together with a small amount of IVf, but did not afford *anti*-pyrazolopyrazolidione (IIIf, $R^1$ = methyl, $R^2$ = phenyl). Similar reactions of Ia with IIb, Ia with IIc, Ib with IIa and Ib with IIb gave IIIb, IIIc, IIId and IIIe, respectively, together with IVb and Vb, IVc, and Vc, IVd, and IVe, respectively, as minor products. The structures of IIIb—e, IVb—f and Vb—f were also confirmed in the same manner as in the cases of IIIa, IVa and Va. It is interesting that the minor products, *syn*-pyrazolopyrazolidiones (IVa—f), show strong fluorescence under UV irradiation (254 nm).

*anti*-Pyrazolopyrazolidione (III), *syn*-pyrazolopyrazolidione (IV) and pyrazololactone

TABLE II. 2,3,7-Trisubstituted Pyrazolo[1,2-*a*]pyrazole-1,5(1*H*, 5*H*)-dione Derivatives (III)

| Compd. No. | mp (°C) | UV $\lambda_{max}^{EtOH}$ nm (log ε) | IR $\nu_{max}^{KBr}$ cm$^{-1}$ (CO) | Formula | Analysis (%) Calcd (Found) | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| IIIa | 116—118 | 331 (4.20) | 1740, 1700 | $C_{11}H_{12}N_2O_4$ | 55.95 | 5.12 | 11.86 |
| | | | | | (55.91 | 5.15 | 11.80) |
| IIIb | 121—122 | 336 (4.15), 224 (4.08) | 1750, 1705, 1670 | $C_{10}H_{10}N_2O_3$ | 58.25 | 4.89 | 13.59 |
| | | | | | (58.18 | 4.91 | 13.63) |
| IIIc | 155—156 | 331 (4.16) | 1710, 1690 | $C_{17}H_{16}N_2O_4$ | 65.38 | 5.16 | 8.97 |
| | | | | | (65.69 | 5.30 | 8.85) |
| IIId | 129—130 | 341 (4.18), 249 (4.08), 231 (4.07) | 1750 (sh), 1730, 1690 | $C_{16}H_{14}N_2O_4$ | 64.42 | 4.73 | 9.39 |
| | | | | | (64.42 | 4.77 | 9.41) |
| IIIe | 166—167 | 338 (4.13), 251 (4.10) | 1700, 1675 | $C_{15}H_{12}N_2O_3$ | 67.16 | 4.51 | 10.44 |
| | | | | | (66.96 | 4.46 | 10.39) |

Abbreviation: sh (shoulder).

TABLE III. 2,3,5-Trisubstituted Pyrazolo[1,2-*a*]pyrazole-1,7(1*H*, 7*H*)-dione Derivatives (IV)

| Compd.[a] No. | mp (°C) | UV $\lambda_{max}^{EtOH}$ nm (log ε) | IR $\nu_{max}^{KBr}$ cm$^{-1}$ (CO) | Formula | Analysis (%) Calcd (Found) | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| IVa | 240—242 | 362 (4.11) | 1758, 1700 | $C_{11}H_{12}N_2O_4$ | 55.95 | 5.12 | 11.86 |
| | | | | | (56.04 | 5.15 | 11.86) |
| IVb | 216—217 | 370 (4.16), 245 (4.10) | 1755, 1670 | $C_{10}H_{10}N_2O_3$ | 58.25 | 4.89 | 13.59 |
| | | | | | (58.13 | 4.80 | 13.70) |
| IVc | 163—164 | 364 (4.11), 235 (4.10) | 1780 (sh), 1755, 1690 | $C_{17}H_{16}N_2O_4$ | 65.38 | 5.16 | 8.97 |
| | | | | | (65.25 | 4.94 | 8.97) |
| IVd | 212—214 | 362 (3.90), 285 (3.89), 244 (4.04) | 1770, 1700, 1680 | $C_{16}H_{14}N_2O_4$ | [b] | | |
| IVe | 153—154 | 370 (3.90), 255 (4.09) | 1765, 1670 | $C_{15}H_{12}N_2O_3$ | 67.16 | 4.51 | 10.44 |
| | | | | | (66.85 | 4.43 | 10.16) |
| IVf | 180—181 | 364 (4.09), 265 (3.88) | 1780, 1715, 1680 | $C_{16}H_{14}N_2O_4$ | 64.42 | 4.73 | 9.39 |
| | | | | | (64.88 | 4.64 | 9.30) |

Abbreviation: sh (shoulder).

*a*) These derivatives have strong fluorescence.

*b*) This compound was determined by mass spectrometry [*m/e*: 298 ($M^+$)] because of the very small quantity of pure sample obtained.

(V) were also obtained in similar ratios to those given above by using a high-boiling aprotic solvent such as xylene or toluene as the reaction solvent. We could not find any catalyst able to increase the formation of IV and V, while in the presence of a catalytic amount of toluenesulfonic acid, the total yield of the reaction was greatly decreased, probably because of decomposition of acylacetate (II). The reaction of Ia with ethyl 2-cyanoacetoacetate gave colorless crystals of mp 231—232 °C in 37.9% yield, but this product was not *anti*-pyrazolopyrazolidione (III), *syn*-pyrazolopyrazolidione (IV) or pyrazololactone (V) on the bases of MS [*m/e*: 207 ($M^+$)] and UV, IR and $^1$H-NMR spectra, and the product has not been identified.

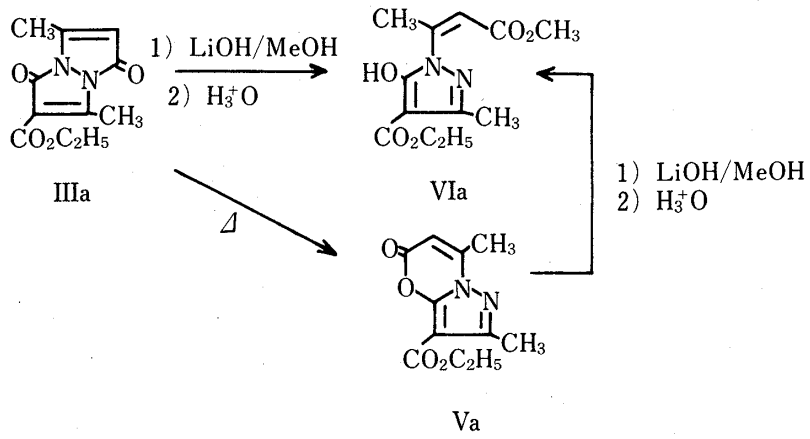



Chart 3

In order to examine the chemical properties of IIIa, the following experiments were performed. Treatment of IIIa with lithium hydroxide in methanol–water and subsequent acidification with hydrochloric acid gave colorless crystals of mp 108—110 °C in 70% yield; this product was identical with VIa prepared from Va. When *anti*-pyrazolopyrazolidione (IIIa) was heated for 3 h in dimethylformamide (DMF), pyrazololactone (Va) was obtained in 30% yield with recovery of 60% of IIIa. We considered that the formation of VIa by the treatment of IIIa with lithium hydroxide may be due to activation of the carbonyl groups by the pyrazole ring.

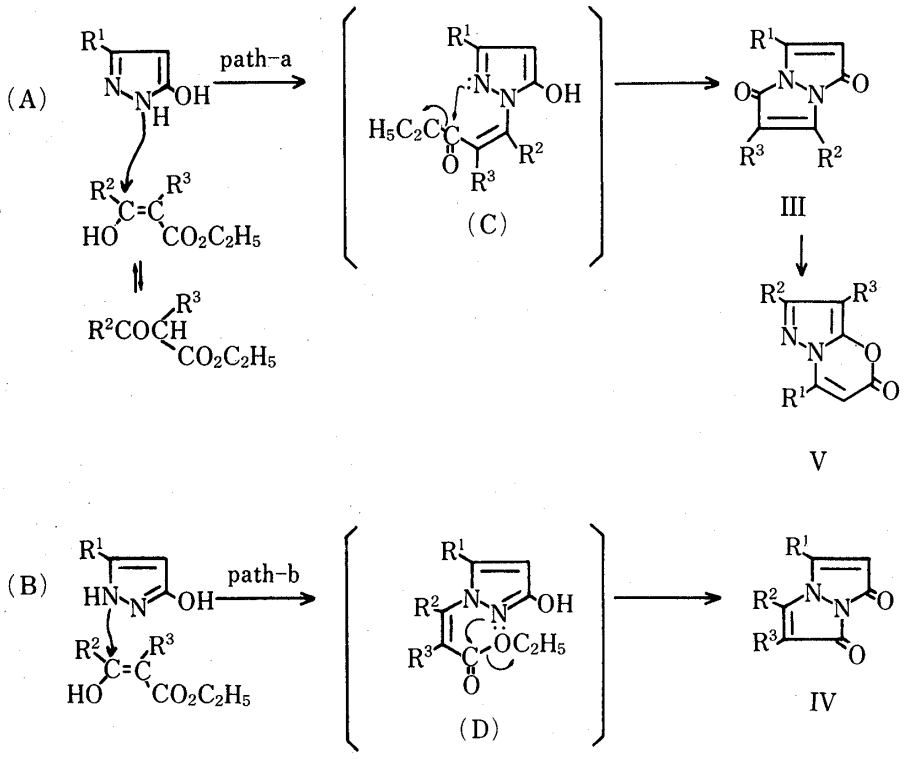
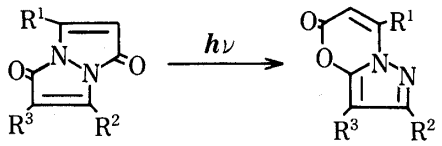



Chart 4. Possible Pathways for the Formation of Compounds III, IV and V

A possible pathway of the present thermal reaction can be suggested as follows on the basis of the above experiments; tautomer (A) or (B) of I adds initially to the enol form[10] of II to give the intermediate (C) or (D), which then cyclizes to III or IV (path-a and path-b).

Under the reaction conditions used, thermal rearrangement of III to V is possible. Thus, we considered that IIIf ($R^1$ = methyl, $R^2$ = phenyl) may rearrange to the stable form Vf, because IIIf is unstable.




III V

Chart 5

TABLE IV. Photochemical Isomerization of Pyrazolo[1,2-*a*]pyrazole-1,5(1*H*, 5*H*)-dione Derivatives (III)

| Starting material | Reaction solvent | Reaction time (h) | Mercury lamp (100 W) | Product | Yield (%) | Recryst. solv. |
|---|---|---|---|---|---|---|
| IIIa | $CH_3CN$ | 2 | High pressure | Va | 60.1 | Isopropanol |
| IIIb | $CH_3CN$ | 2 | High pressure | Vb | 67.2 | Isopropanol–petroleum ether |
| IIIc | $CH_3CN$ | 2 | High pressure | Vc | 75.0 | Isopropanol |
| IIId | $CH_3CN$ | 2 | High pressure | NR | — | — |
| IIId | $CH_3COCH_3$ | 2 | High pressure | Vd | 5.0 | Ethanol |
| IIId | $CH_3COCH_3$ | 4 | Low pressure | Vd | 54.5 | Ethanol |
| IIIe | $CH_3COCH_3$ | 4 | High pressure | DC | — | — |
| IIIe | $CH_3COCH_3$ | 6 | Low pressure | DC | — | — |
| IIIe[a)] | $CH_3CN$ | 6 | High pressure | Ve | 4.0 | Ethanol |

Abbreviations: NR (no reaction), DC (decomposition).
*a*) Benzophenone was added as a photosensitizer.

TABLE V. 2,3,7-Trisubstituted Pyrazolo[5,1-*b*][1,3]oxazin-5(5*H*)-one Derivatives (V)

| Compd. No. | mp (°C) | UV $\lambda_{max}^{EtOH}$ nm (log ε) | IR $\nu_{max}^{KBr}$ cm$^{-1}$ (CO) | Formula | Analysis (%) Calcd (Found) | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| Va | 129—130 | 283 (4.04), 224 (1.73) | 1780, 1700 | $C_{11}H_{12}N_2O_4$ | 55.95 (56.10 | 5.12 5.18 | 11.86 11.89) |
| Vb | 198—199 | 286 (4.10), 238 (4.27) | 1780, 1670 | $C_{10}H_{10}N_2O_3$ | 58.25 (58.10 | 4.89 4.75 | 13.59 13.65) |
| Vc | 147—148 | 282 (4.09), 224 (4.25) | 1770, 1700 | $C_{17}H_{16}N_2O_4$ | 65.38 (65.29 | 5.16 5.24 | 8.97 9.00) |
| Vd | 154—155 | 295 (4.04), 256 (4.15) 226 (4.29) | 1760, 1700 | $C_{16}H_{14}N_2O_4$ | 64.42 (64.33 | 4.73 4.69 | 9.39 9.21) |
| Ve | 200—201 | 298 (4.02), 247 (4.35) | 1770, 1670 | $C_{15}H_{12}N_2O_3$ | 67.16 (67.10 | 4.51 4.46 | 10.44 10.53) |
| Vf | 186—187 | 291 (4.19), 230 (sh) | 1780, 1720 | $C_{16}H_{14}N_2O_4$ | 64.42 (64.45 | 4.73 4.68 | 9.39 9.41) |

Abbreviation: sh (shoulder).

The formation of a lactone-ring system by photochemical isomerization of pyrazolo[1,2-*a*]pyrazole analogues has already been reported by Michaelis,[11)] Viebel[12)] and Kanety.[9)]

We also carried out photochemical isomerization of IIIa—e by irradiation with a high

pressure mercury lamp. Irradiation of the *anti*-pyrazolopyrazolidiones (IIIa, IIIb and IIIc) in acetonitrile successfuly formed the pyrazololactones Va, Vb and Vc, respectively. The *anti*-pyrazolopyrazolidiones (IIId and IIIe) with the phenyl group as $R^1$ did not afford the pyrazololactones (Vd and Ve) under the reaction conditions used, while irradiation of IIId and IIIe in acetone gave low conversion (5.0% yield of Vd) only in the former case. When a low-pressure mercury lamp was used, suprisingly, pyrazololactone (Vd) was obtained in 54.5% yield, but similar irradiation of IIIe again resulted in no formation of Ve. The photochemical isomerization of IIIe by irradiation in acetonitrile with a high-pressure mercury lamp in the presence of benzophenone as a photosensitizer provided Ve in only 4.0% yield.

The analgesic activities of IIIa, b, d, IVa, f and Va, f were examined in comparison with that of aminopyrine by oral administration to mice, in terms of the number of writhings induced by acetic acid.[13] The analgesic activities of these compounds were all inferior to that of aminopyrine.

## Experimental

All melting points were recorded with a Yanagimoto micromelting point apparatus and are uncorrected. Spectral data were obtained as follows: IR with a Hitachi 260-50 spectrophotometer; UV with a Shimadzu UV-240 spectrophotometer; MS with a JEOL JMS-01G-2 spectrometer; $^1$H-NMR with a JEOL JMN-FX 100 spectrometer (using tetramethylsilane as an internal standard). Chemical shifts are given in $\delta$ values (ppm) and the abbreviations of signal patterns are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Elemental analyses were carried out with a Yanagimoto C H N Corder MT-2 analyzer.

**2-Ethoxycarbonyl-3,7-dimethylpyrazolo[1,2-*a*]pyrazole-1,5(1*H*,5*H*)-dione (IIIa), 2-Ethoxycarbonyl-3,5-dimethylpyrazolo[1,2-*a*]pyrazole-1,7(1*H*,7*H*)-dione (IVa) and 3-Ethoxycarbonyl-2,7-dimethylpyrazolo[5,1-*b*][1,3]oxazin-5(5*H*)-one (Va)**——Typical Procedure: A mixture of Ia (1.0 g) and IIa (2.0 ml) was heated for 15 min at 150—160 °C. Petroleum ether (10 ml) was added to the cooled reaction mixture to give crude crystals, which were collected by filtration, washed with cold ethanol and purified by silica gel column chromatography [$CHCl_3$–EtOH (3 : 1, vol)].

From the first eluate, colorless crystals of Va were obtained. Yield 0.17 g. mp 129—130 °C (isopropanol). MS *m/e*: 236 ($M^+$). NMR (DMSO-$d_6$) $\delta$: 1.29 (3H, t, $J$=7.1 Hz, $CH_2C\underline{H}_3$), 2.41 (3H, s, $CH_3$ at 2-position), 2.47 (3H, d, $J$=1.2 Hz, $CH_3$ at 7-position), 4.25 (2H, q, $J$=7.1 Hz, $C\underline{H}_2CH_3$), 6.11 (1H, d, $J$=1.2 Hz, CH= at 6-position). Other data are listed in Table V. From the second eluate, colorless crystals of IIIa were obtained. Yield 1.67 g. mp 116—118 °C (ethanol). MS *m/e*: 236 ($M^+$). NMR (DMSO-$d_6$) $\delta$: 1.25 (3H, t, $J$=7.1 Hz, $CH_2C\underline{H}_3$), 2.42 (3H, d, $J$=1.2 Hz, $CH_3$ at 7-position), 2.72 (3H, s, $CH_3$ at 3-position), 4.20 (2H, q, $J$=7.1 Hz, $C\underline{H}_2CH_3$), 5.72 (1H, d, $J$=1.2 Hz, CH= at 6-position). Other data are listed in Table II. From the third eluate, colorless crystals of IVa were obtained. Yield 0.16 g. mp 240—242 °C (ethanol). MS *m/e*: 236 ($M^+$). NMR (DMSO-$d_6$) $\delta$: 1.25 (3H, t, $J$=7.1 Hz, $CH_2C\underline{H}_3$), 2.46 (3H, d, $J$=1.2 Hz, $CH_3$ at 5-position), 2.72 (3H, s, $CH_3$ at 3-position), 4.21 (2H, q, $J$=7.1 Hz, $C\underline{H}_2CH_3$), 5.85 (1H, d, $J$=1.2 Hz, CH= at 6-position). Other data are listed in Table III.

Similar procedures were used for syntheses of IIIb—e, IVb—f and Vb, c, f.

**2-Acetyl-3,7-dimethylpyrazolo[1,2-*a*]pyrazole-1,5(1*H*,5*H*)-dione (IIIb), 2-Acetyl-3,5-dimethylpyrazolo[1,2-*a*]pyrazole-1,7(1*H*,7*H*)-dione (IVb) and 3-Acetyl-2,7-dimethylpyrazolo[5,1-*b*][1,3]oxazin-5(5*H*)-one (Vb)**——Treatment of Ia (0.5 g) with IIb (2.0 ml) as described above gave IIIb, IVb and Vb. Vb (first eluate); Yield 0.035 g. mp 198—199 °C (isopropanol). MS *m/e*: 206 ($M^+$). NMR (DMSO-$d_6$) $\delta$: 2.41, 2.42 (each 3H, s, $CH_3$ at 2-position and $COCH_3$), 2.48 (3H, d, $J$=1.2 Hz, $CH_3$ at 7-position), 6.13 (1H, d, $J$=1.2 Hz, CH= at 6-position). Other data are listed in Table V. IIIb (second eluate); Yield 0.69 g. mp 121—122 °C (ethanol). MS *m/e*: 206 ($M^+$). NMR ($CDCl_3$) $\delta$: 2.52, 2.56 (each 3H, s, $CH_3$ at 7-position and $COCH_3$), 2.89 (3H, s, $CH_3$ at 3-position), 5.46 (1H, s, CH= at 6-position). Other data are listed in Table II. IVb (third eluate); Yield 0.076 g. mp 216—217 °C (ethanol). MS *m/e*: 206 ($M^+$). NMR (DMSO-$d_6$) $\delta$: 2.40 (3H, s, $COCH_3$), 2.47 (3H, d, $J$=1.2 Hz, $CH_3$ at 5-position), 2.74 (3H, s, $CH_3$ at 3-position), 5.90 (1H, d, $J$=1.2 Hz, CH= at 6-position). Other data are listed in Table III.

**3-Benzyl-2-ethoxycarbonyl-7-methylpyrazolo[1,2-*a*]pyrazole-1,5(1*H*,5*H*)-dione (IIIc), 3-Benzyl-2-ethoxycarbonyl-5-methylpyrazolo[1,2-*a*]pyrazole-1,7(1*H*,7*H*)-dione (IVc) and 2-Benzyl-3-ethoxycarbonyl-7-methylpyrazolo[5,1-*b*][1,3]oxazin-5(5*H*)-one (Vc)**——Treatment of Ia (0.5 g) with IIc (2.0 ml) as described above gave IIIc, IVc and Vc. Vc (first eluate); Yield 0.067 g. mp 147—148 °C (ethanol). MS *m/e*: 312 ($M^+$). NMR (DMSO-$d_6$) $\delta$: 1.20 (3H, t, $J$=7.1 Hz, $CH_2C\underline{H}_3$), 2.49 (3H, d, $J$=1.0 Hz, $CH_3$ at 7-position), 4.20 (2H, q, $J$=7.1 Hz, $C\underline{H}_2CH_3$), 4.22 (2H, s, $CH_2Ph$), 6.41 (1H, d, $J$=1.0 Hz, CH= at 6-position), 7.40—7.00 (5H, m). Other data are listed in Table V. IIIc

(second eluate); Yield 1.06 g. mp 155—156 °C (isopropanol). MS *m/e*: 312 ($M^+$). NMR (DMSO-$d_6$) $\delta$: 1.23 (3H, t, $J$=7.1 Hz, $CH_2C\underline{H}_3$), 2.43 (3H, d, $J$=1.2 Hz, $CH_3$ at 7-position), 4.23 (2H, q, $J$=7.1 Hz, $C\underline{H}_2CH_3$), 4.53 (2H, s, $CH_2Ph$), 5.74 (1H, d, $J$=1.2 Hz, CH= at 6-position), 7.50—7.15 (5H, m). Other data are listed in Table II. IVc (third eluate); Yield 0.073 g. mp 163—164 °C (ethanol). MS *m/e*: 312 ($M^+$). NMR (DMSO-$d_6$) $\delta$: 1.17 (3H, t, $J$= 7.1 Hz, $CH_2C\underline{H}_3$), 2.22 (3H, d, $J$=1.2 Hz, $CH_3$ at 5-position), 4.17 (2H, q, $J$=7.1 Hz, $C\underline{H}_2CH_3$), 4.59 (2H, s, $CH_2Ph$), 5.86 (1H, d, $J$=1.2 Hz, CH= at 6-position), 7.50—7.00 (5H, m). Other data are listed in Table III.

**2-Ethoxycarbonyl-3-methyl-7-phenylpyrazolo[1,2-*a*]pyrazole-1,5(1*H*,5*H*)-dione (IIId) and 2-Ethoxycarbonyl-3-methyl-5-phenylpyrazolo[1,2-*a*]pyrazole-1,7(1*H*,7*H*)-dione (IVd)**——Treatment of Ib (0.3 g) with IIa (1.0 ml) as described above gave IIId and IVd. IIId (first eluate); Yield 0.42 g. mp 129—130 °C (isopropanol). MS *m/e*: 298 ($M^+$). NMR (DMSO-$d_6$) $\delta$: 1.24 (3H, t, $J$=7.1 Hz, $CH_2C\underline{H}_3$), 2.78 (3H, s, $CH_3$ at 3-position), 4.20 (2H, q, $J$=7.1 Hz, $C\underline{H}_2CH_3$), 6.32 (1H, s, CH= at 6-position), 7.70—7.35 and 8.10—7.85 (5H, m). Other data are listed in Table II. IVd (second eluate); Yield 0.026 g. mp 212—214 °C. MS *m/e*: 298 ($M^+$). Other data are listed in Table III.

**2-Acetyl-3-methyl-7-phenylpyrazolo[1,2-*a*]pyrazole-1,5(1*H*,5*H*)-dione (IIIe) and 2-Acetyl-3-methyl-5-phenylpyrazolo[1,2-*a*]pyrazole-1,7(1*H*,7*H*)-dione (IVe)**——Treatment of Ib (2.0 g) with IIb (5.0 ml) as described above gave IIIe and IVe. IIIe (first eluate); Yield 1.85 g. mp 166—167 °C (ethanol). MS *m/e*: 268 ($M^+$). NMR (DMSO-$d_6$) $\delta$: 2.38 (3H, s, $COCH_3$), 2.78 (3H, s, $CH_3$ at 3-position), 6.35 (1H, s, CH= at 6-position), 7.75—7.35 and 8.10—7.85 (5H, m). Other data are listed in Table II. IVe (second eluate); Yield 0.15 g. mp 153—154 °C (acetonitrile–isopropanol). MS *m/e*: 268 ($M^+$). NMR (DMSO-$d_6$) $\delta$: 2.20 (3H, s, $CH_3$ at 3-position), 2.42 (3H, s, $COCH_3$), 6.26 (1H, s, CH= at 6-position). Other data are listed in Table III.

**2-Ethoxycarbonyl-5-methyl-3-phenylpyrazolo[1,2-*a*]pyrazole-1,7(1*H*,7*H*)-dione (IVf) and 3-Ethoxycarbonyl-7-methyl-2-phenylpyrazolo[5,1-*b*][1,3]oxazin-5(5*H*)-one (Vf)**——Treatment of Ia (1.0 g) with IId (5.0 ml) as described above gave IVf and Vf. Vf (first eluate); Yield 2.17 g. mp 186—187 °C (ethanol). MS *m/e*: 298 ($M^+$). NMR (DMSO-$d_6$) $\delta$: 1.20 (3H, t, $J$=7.1 Hz, $CH_2C\underline{H}_3$), 2.53 (3H, d, $J$=1.2 Hz, $CH_3$ at 7-position), 4.21 (2H, d, $J$=7.1 Hz, $C\underline{H}_2CH_3$), 6.22 (1H, d, $J$=1.2 Hz, CH= at 6-position), 7.80—7.35 (5H, m). Other data are listed in Table V. IVf (second eluate); Yield 0.11 g. mp 180—181 °C (ethanol). MS *m/e*: 298 ($M^+$). NMR (DMSO-$d_6$) $\delta$: 1.20 (3H, t, $J$=7.1 Hz, $CH_2C\underline{H}_3$), 1.63 (3H, d, $J$=1.0 Hz, $CH_3$ at 5-position), 3.96 (2H, q, $J$=1.0 Hz, $C\underline{H}_2CH_3$), 5.89 (1H, d, $J$=1.0 Hz, CH= at 6-position), 7.80—7.30 (5H, m). Other data are listed in Table III.

**Conversion of IIIa into Va**——A solution of IIIa (0.5 g) in DMF (10 ml) was heated under reflux for 4 h, then cooled. The mixture was evaporated to dryness under reduced pressure and the residue was chromatographed on silica gel [$CHCl_3$–EtOH (3 : 1, vol)]. From the first eluate, colorless crystals of Va were obtained. Yield 0.15 g (30%). mp 129—130 °C (isopropanol). The physical and spectral data were consistent with those of Va prepared from the reaction of Ia with IIa as described above. From the second eluate, the starting material (IIIa) was recovered. Yield 0.35 g (60%). mp 116—118 °C (ethanol).

**Reaction of Ethyl 2-Cyanoacetoacetate with Ia**——A mixture of Ia (1.0 g) and ethyl 2-cyanoacetoacetate (3.5 ml) was heated for 3.5 h at 150—160 °C. Petroleum ether (10 ml) was added to the cooled reaction mixture to give crude crystals, which were recrystallized from ethanol to give colorless crystals. Yield 0.8 g (37.9%). mp 231—232 °C. MS *m/e*: 207 ($M^+$). IR $\nu_{max}^{KBr}$: 3310 $cm^{-1}$ (NH), 3180 $cm^{-1}$ (OH), 1700 and 1660 $cm^{-1}$ (CO). NMR (DMSO-$d_6$) $\delta$: 2.28 (3H, s), 2.43 (3H, d, $J$=1.2 Hz), 5.61 (1H, d, $J$=1.2 Hz), 9.00—8.60 (2H, br).

**Methyl 3-(4-Ethoxycarbonyl-5-hydroxy-3-methyl-1-pyrazolyl)crotonate (VIa)**——i) From IIIa: LiOH (0.2 g) was added to a solution of IIIa (0.5 g) in 40 ml of MeOH–$H_2O$ (3 : 1, vol) at 0—10 °C and the mixture was stirred for 0.5 h at the same temperature. The reaction mixture was acidified with 2 N HCl and the whole was concentrated under reduced pressure. The precipitates were collected, washed with water and recrystallized from ethanol to give colorless crystals (VIa). Yield 0.35 g (70.0%). mp 108—110 °C. MS *m/e*: 268 ($M^+$). IR $\nu_{max}^{KBr}$: 3000—2400 $cm^{-1}$ (OH), 1720 and 1680 $cm^{-1}$ (CO). NMR ($CDCl_3$) $\delta$: 1.37 (3H, t, $J$=7.1 Hz, $CH_2C\underline{H}_3$), 2.27 (3H, d, $J$=1.2 Hz, $CH_3$), 2.35 (3H, s, $CH_3$ at pyrazole-ring), 3.66 (3H, s, $CH_3$ of ester), 4.35 (2H, q, $J$=7.1 Hz, $C\underline{H}_2CH_3$), 5.84 (1H, d, $J$=1.2 Hz, CH=). *Anal.* Calcd for $C_{12}H_{16}N_2O_5$: C, 53.75; H, 6.01; N, 10.44 Found: C, 53.79; H, 6.12; N, 10.62.

ii) From Va: LiOH (0.04 g) was added to a solution of Va (0.1 g) in 20 ml of MeOH–$H_2O$ (2 : 1, vol) under ice-cooling and the mixture was stirred for 0.5 h. Work-up as described in i) gave VIa. Yield 0.08 g (80.0%). mp 108—110 °C. The physical and spectral data were consistent with those of VIa obtained in i).

**Methyl 3-(4-Ethoxycarbonyl-5-hydroxy-3-phenyl-1-pyrazolyl)crotonate (VIf)**——LiOH (0.2 g) was added to a solution of Vf (1.0 g) in 100 ml of MeOH–THF–$H_2O$ (3 : 1 : 1, vol) at room temperature and the mixture was stirred for 2 h. The reaction mixture was worked up according to the procedure for VIa to give colorless crystals of VIf. Yield 0.9 g (81.3%). mp 85—86 °C (isopropanol). MS *m/e*: 330 ($M^+$). IR $\nu_{max}^{KBr}$: 3600—3350 $cm^{-1}$ (OH), 1735 and 1685 $cm^{-1}$ (CO). NMR ($CDCl_3$) $\delta$: 1.28 (3H, t, $J$=7.1 Hz, $CH_2C\underline{H}_3$), 2.34 (3H, d, $J$=1.4 Hz, $CH_3$), 3.68 (3H, s, $CH_3$ of ester), 4.31 (2H, q, $J$=7.1 Hz, $C\underline{H}_2CH_3$), 5.91 (1H, d, $J$=1.4 Hz, CH=), 7.82—7.20 (5H, m). *Anal.* Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48 Found: C, 62.03; H, 5.68; N, 8.59.

**Methyl 3-(4-Ethoxycarbonyl-5-methoxy-3-methyl-1-pyrazolyl)crotonate (VIIa)**——VIa (0.6 g) was added to an ethereal solution (15 ml) of diazomethane (prepared from *N*-nitrosomethylurea, 1.0 g) at room temperature. After the evolution of nitrogen had ceased, the reaction mixture was evaporated to dryness under reduced pressure. The residue was recrystallized from ethanol–petroleum ether to give colorless crystals of VIIa. Yield 0.45 g (71.4%). mp

57—58 °C. MS *m/e*: 282 ($M^+$). IR $\nu_{max}^{KBr}$: 1725 and 1700 $cm^{-1}$ (CO). NMR ($CDCl_3$) $\delta$: 1.36 (3H, t, $J$=7.1 Hz, $CH_2C\underline{H}_3$), 2.24 (3H, d, $J$=1.1 Hz, $CH_3$), 2.41 (3H, s, $CH_3$ at pyrazole-ring), 3.63 (3H, s, $CH_3$ of ester), 4.01 (3H, s, $OCH_3$), 4.30 (2H, q, $J$=7.1 Hz, $C\underline{H}_2CH_3$), 5.90 (1H, d, $J$=1.1 Hz, CH=). *Anal.* Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.28; H, 6.38; N, 9.97.

**Methyl 3-(4-Ethoxycarbonyl-5-methoxy-3-phenyl-1-pyrazolyl)crotonate (VIIf)**——VIf (0.5 g) was added to an ethereal solution (20 ml) of diazomethane (prepared from *N*-nitrosomethylurea, 1.0 g) at room temperature. The reaction mixture was worked up according to the procedure for VIIa. Colorless crystals of VIIf were obtained. Yield 0.5 g (96.0%). mp 38—39 °C (ethanol–petroleum ether). MS *m/e*: 344 ($M^+$). IR $\nu_{max}^{KBr}$: 1735 and 1710 $cm^{-1}$ (CO). NMR ($CDCl_3$) $\delta$: 1.18 (3H, t, $J$=7.1 Hz, $CH_2C\underline{H}_3$), 2.31 (3H, d, $J$=1.2 Hz, $CH_3$), 3.66 (3H, s, $CH_3$ of ester), 4.07 (3H, s, $OCH_3$), 4.20 (2H, q, $J$=7.1 Hz, $C\underline{H}_2CH_3$), 5.96 (1H, d, $J$=1.2 Hz, CH=), 7.70—7.20 (5H, m). *Anal.* Calcd for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.13. Found: C, 62.63; H, 5.93; N, 8.14.

**Methyl 3-(4-Ethoxycarbonyl-5-methoxy-3-methyl-1-pyrazolyl)butyrate (VIIIa)**——A solution of VIIa (0.15 g) in 30 ml of ethanol was shaken with 10% Pd-C (0.1 g) under a hydrogen atmosphere for 2 h at room temperature. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel [$CHCl_3$–EtOH (20 : 1, vol)] and the oily product, VIIIa, was obtained from the eluate. Yield 0.12 g (79.5%). MS *m/e*: 284 ($M^+$). IR $\nu_{max}^{CHCl_3}$: 1740 and 1700 $cm^{-1}$ (CO). NMR ($CDCl_3$) $\delta$: 1.36 (3H, t, $J$=7.1 Hz, $CH_2C\underline{H}_3$), 1.41 (3H, d, $J$=6.6 Hz, $CH_3$), 2.37 (3H, s, $CH_3$ at pyrazole-ring), 3.20—2.50 (2H, m, $CH_2$), 3.63 (3H, s, $CH_3$ of ester), 4.11 (3H, s, $OCH_3$), 4.29 (2H, q, $J$=7.1H, $C\underline{H}_2CH_3$), 5.00—4.60 (1H, m, CH).

**Methyl 3-(4-Ethoxycarbonyl-5-methoxy-3-phenyl-1-pyrazolyl)butyrate (VIIIf)**——A solution of VIIf (0.3 g) in 50 ml of ethanol was shaken with 10% Pd-C (0.15 g) under a hydrogen atmosphere for 2 h at room temperature. The reaction mixture was worked up according to the procedure for VIIIa. The oily product, VIIIf, was obtained from the eluate. Yield 0.23 g (76.2%). MS *m/e*: 346 ($M^+$). IR $\nu_{max}^{CHCl_3}$: 1740 and 1700 $cm^{-1}$ (CO). NMR ($CDCl_3$) $\delta$: 1.19 (3H, t, $J$=7.1 Hz, $CH_2C\underline{H}_3$), 1.47 (3H, d, $J$=6.8 Hz, $CH_3$), 3.30—2.50 (2H, m, $CH_2$), 3.64 (3H, s, $CH_3$ of ester), 4.17 (3H, s, $OCH_3$), 4.20 (2H, q, $J$=7.1 Hz, $C\underline{H}_2CH_3$), 5.10—4.70 (1H, m, CH), 7.70—7.10 (5H, m).

**Photochemical Isomerization of IIIa—e**——A solution of IIIa (0.3 g) in acetonitrile (100 ml) purged with $N_2$ was irradiated with a high-pressure mercury lamp for 2 h. The reaction mixture was evaporated to dryness under reduced pressure. The residue was recrystallized from isopropanol to give colorless crystals of (Va). Yield 0.3 g (60.0%). mp 129—130 °C. The physical and spectral data were consistent with those of Va obtained by thermal reaction as described above.

The results of photochemical isomerization of IIIb—e are shown in Table IV.

**3-Ethoxycarbonyl-2-methyl-7-phenylpyrazolo[5,1-*b*][1,3]oxazin-5(5*H*)-one (Vd)**——i) Method-a: A solution of IIId (0.33 g) in acetone (100 ml) purged with $N_2$ was irradiated with a low-pressure mercury lamp for 4 h. The reaction mixture was evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel [$CHCl_3$–EtOH (3 : 1, vol)]. Colorless crystals of Vd were obtained from the eluate. Yield 0.18 g (54.5%). mp 154—155 °C (ethanol). MS *m/e*: 298 ($M^+$). NMR (DMSO-$d_6$) $\delta$: 1.30 (3H, t, $J$=7.1 Hz, $CH_2C\underline{H}_3$), 2.40 (3H, s, $CH_3$), 4.28 (2H, q, $J$=7.1 Hz, $C\underline{H}_2CH_3$), 6.34 (1H, s, CH=), 7.95—7.30 (5H, m). Other data are listed in Table V.

ii) Method-b: A solution of IIId (0.2 g) in acetone (100 ml) purged with $N_2$ was irradiated with a high-pressure mercury lamp for 3 h. The reaction mixture was worked up as described under method-a. Colorless crystals of Vd were obtained from the eluate. Yield 0.01 g (5.0%). mp 154—155 °C. The physical and spectral data were consistent with those of Vd prepared by method-a.

**3-Acetyl-2-methyl-7-phenylpyrazolo[5,1-*b*][1,3]oxazin-5(5*H*)-one (Ve)**——A solution of IIIe (0.4 g) and a catalytic amount of benzophenone (6 mg) in acetonitrile (200 ml) purged with $N_2$ was irradiated with a high-pressure mercury lamp for 6 h. The reaction mixture was worked up as described under method-a for Vd. Colorless crystals of Ve were obtained from the eluate. Yield 0.016 g (4.0%). mp 200—201 °C. MS *m/e*: 268 ($M^+$). IR $\nu_{max}^{KBr}$: 1770 and 1670 $cm^{-1}$ (CO). Other data are listed in Table V.

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