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3-Acetyltropolone (**1**) was treated with diethyl oxalate in the presence of sodium ethoxide to afford 3-(2-ethoxalyl-1-oxoethyl)tropolone (**2**) as a minor product and its cyclized 2-ethoxycarbonyl-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (**3**) as the major product. The former was readily converted to the latter. Then, as a stable synthon bearing a 1,3-dicarbonyl group, 2-(2-ethoxalyl-1-oxoethyl)-7-methylaminotropone (**5**) was prepared. The reactions of compound **5** with hydroxylamine, hydrazine, and methylhydrazine were carried out to give troponoids possessing an isoxazole or a pyrazole ring. The parent compounds, 3-(3-pyrazolyl)tropolone (**13**) and 3-(1-methylpyrazol-3-yl)tropolone (**21**), were obtained *via* hydrolysis and decarboxylation. Similarly, 2-ethoxycarbonyl-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (**3**) reacted with hydroxylamine, hydrazine, and methylhydrazine to yield troponoids possessing a heterocyclic ring.

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Introduction.

3-Acetyltropolone (**1**) has a reactive acetyl group at the 3-position and exists partly in the tautomeric β -diketo form. On the basis of this reactive and positional features of the acetyl group, our work has been focused on the synthesis of heterocycle-fused troponoid compounds [1,2]. On the other hand, few troponoids possessing a heterocyclic ring as a side-chain are known as follows: 4-(3- and 5-pyrazolyl)- [3,4], 4-(5-isoxazolyl)- [4], 3-(4-thiazolyl)- [5,6], 3-(2-quinolyl)- [7,8], and 3-(1,6-, 1,7-, and 1,8-naphthyridin-2-yl)tropolones [9]. It is well known that 1,3-dicarbonyl compounds, such as β -diketones and β -keto esters, are very useful materials for construction of heterocyclic ring in synthetic organic chemistry. In spite of great expectations, synthesis and reactions of 4-(2-ethoxalyl-1-oxoethyl)tropolone is known as only an example in troponoid chemistry [4]. Now, in order to extend 3-acetyltropolone chemistry, the present paper deals with conversion of the acetyl group into the 1,3-dicarbonyl group and its application to the synthesis of troponoids having an isoxazole or a pyrazole ring.

Results and Discussion.

Preparation of 2-Ethoxalyl-1-oxoethyl-substituted Troponoids.

According to Takase's method [4], when the reaction of 3-acetyltropolone (**1**) with diethyl oxalate was carried out at room temperature in the presence of sodium ethoxide, the desired 3-(2-ethoxalyl-1-oxoethyl)tropolone (**2**) was isolated in only 25% yield, however, a cyclized product, 2-ethoxycarbonyl-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (**3**), was obtained as the major product in 65% yield. The latter compound **3** might be produced by intramolecular cyclization of the former product **2**. An ethanolic solution of compound **2** was refluxed for 2 hours to cyclize into the product **3** quantitatively.

Instead of compound **2**, 2-(2-ethoxalyl-1-oxoethyl)-7-methylaminotropone (**5**) was readily obtained in a quantitative yield as a stable synthon by the reaction of 2-acetyl-7-methylaminotropone (**4**) with a diethyl oxalate.

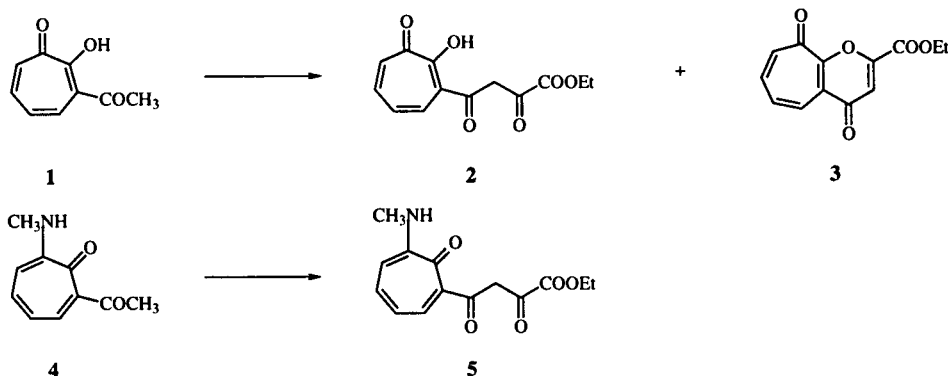
Reaction of 2-(2-Ethoxalyl-1-oxoethyl)-7-methylaminotropone (**5**) with Hydroxylamine.

Previously, it was reported that 4-(2-ethoxalyl-1-oxoethyl)tropolone reacted with hydroxylamine to afford its oxime at the 3'-carbonyl carbon atom in a short time and to produce a cyclized product, 4-(3-ethoxycarbonylisoxazol-5-yl)tropolone, in a prolonged reaction [4]. This suggests that the 3'-carbonyl carbon atom is more reactive than the 1'-carbonyl carbon atom because of existence of the ester group on the 3'-carbonyl carbon atom. A solution of 2-(2-ethoxalyl-1-oxoethyl)-7-methylaminotropone (**5**) and hydroxylamine in methanol was refluxed for 2 hours to afford the desired 2-(3-ethoxycarbonylisoxazol-5-yl)-7-methylaminotropone (**6**). Its structure was established from the results of the reaction of 4-(2-ethoxalyl-1-oxoethyl)tropolone described above, in addition to elemental analysis and spectral data. The alkaline hydrolysis of compound **6** was carried out at room temperature and at reflux temperature to yield quantitatively 2-(3-carboxylisoxazol-5-yl)-7-methylaminotropone (**7**) and 3-(3-carboxylisoxazol-5-yl)tropolone (**8**), respectively. However, decarboxylation of both **7** and **8** was unsuccessful.

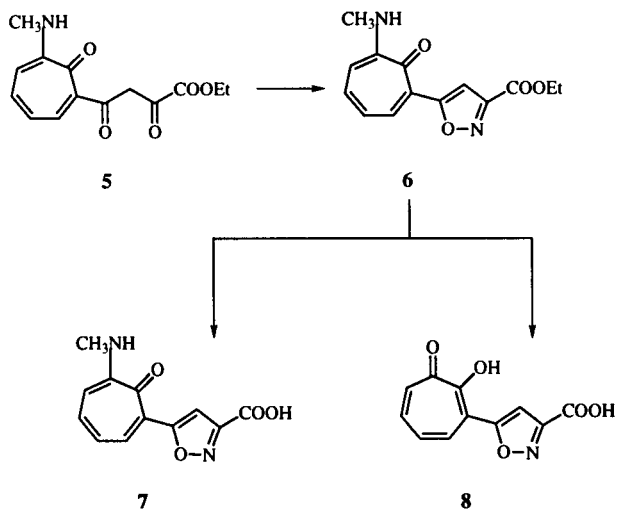
Reaction of Compound **5** with Hydrazine.

When a methanolic solution of compound **5** and hydrazine hydrate was refluxed for 2 hours, 2-(5-ethoxycarbonylpyrazol-3-yl)-7-methylaminotropone (**9**) was obtained in 84% yield. Its structure was confirmed by elemental analysis and spectral data. Compound **9** was stirred in methanol for 2 hours at room temperature in the presence of 10% sodium hydroxide solution to afford 2-(5-carboxypyrazol-3-yl)-7-methylaminotropone (**10**),

Scheme 1



Scheme 2



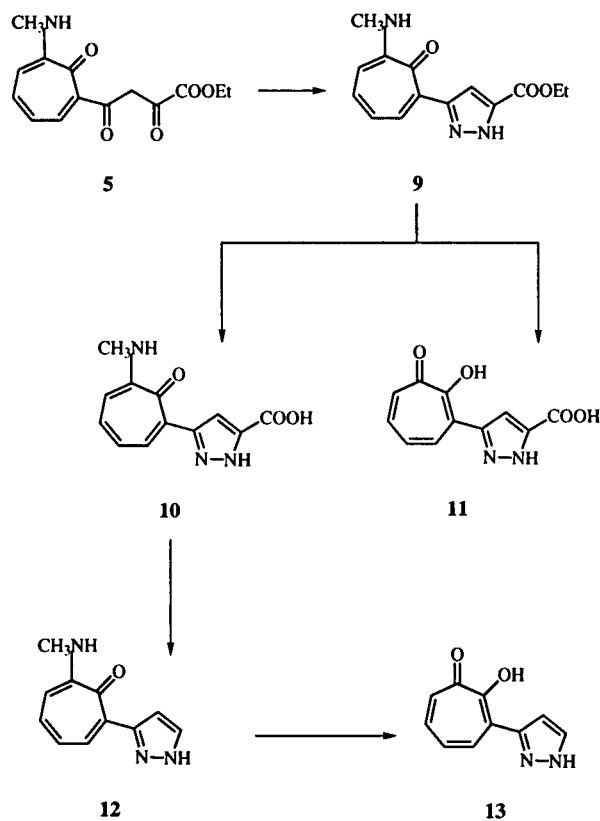
while the hydrolysis under reflux for 12 hours gave quantitatively 3-(5-carboxypyrazol-3-yl)tropolone (11). Compound 10 was heated in quinoline in the presence of copper powder to give 2-(3-pyrazolyl)-7-methylaminotroponone (12), which was hydrolyzed by heating with 10% sodium hydroxide solution to afford 3-(3-pyrazolyl)tropolone (13).

Reaction with Compound 5 with Methylhydrazine.

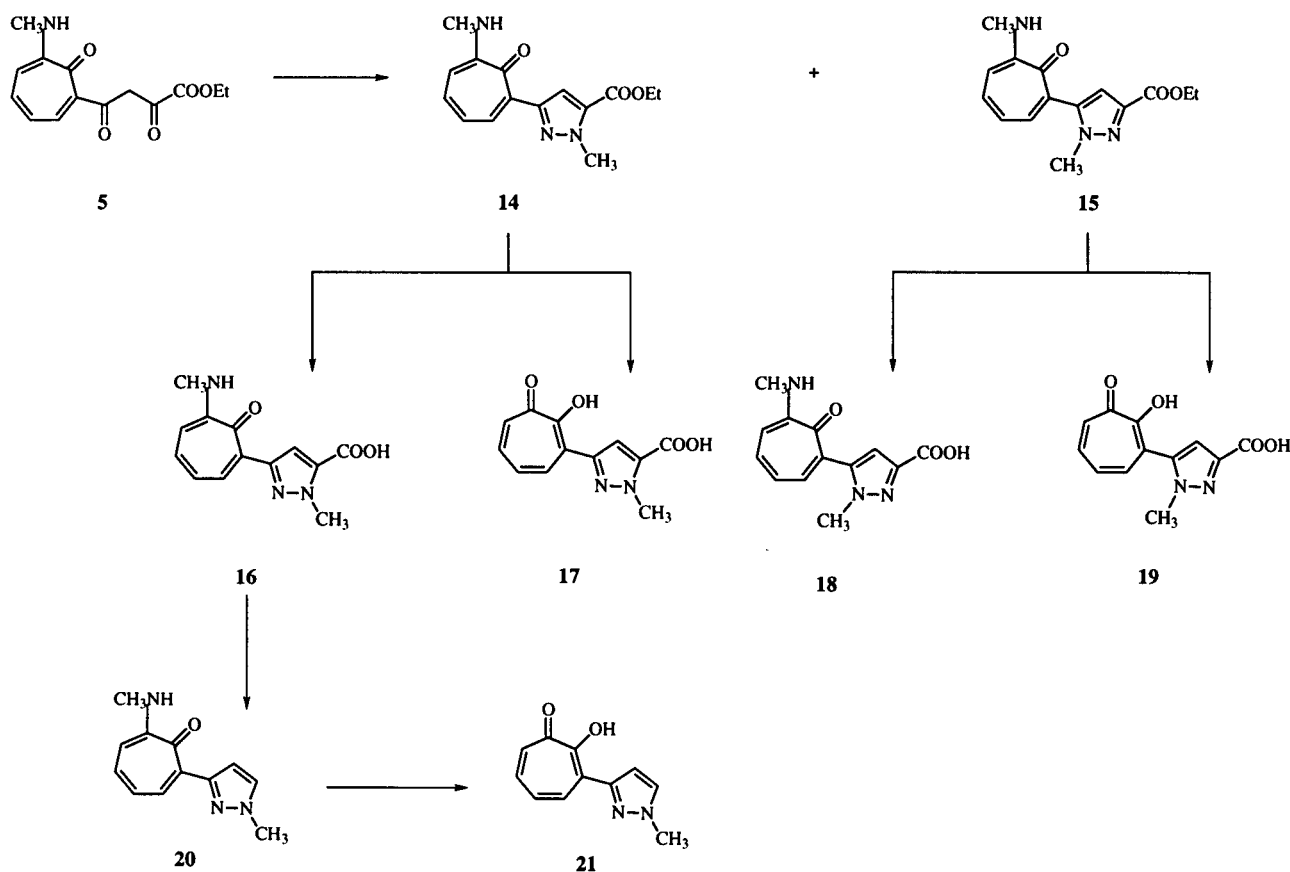
A mixture of compound 5 and methylhydrazine in methanol was heated under refluxing for 2 hours and chromatographed on a silica gel column to give two yellowish products, 2-(5-ethoxycarbonyl-1-methylpyrazol-3-yl)-7-methylaminotroponone (14) and 2-(3-ethoxycarbonyl-1-methylpyrazol-5-yl)-7-methylaminotroponone (15), in 88 and 8% yields, respectively. The structures of both compounds 14 and 15 were suggested from the higher reactivity of the 3'-carbonyl carbon atom, as described

above, and higher nucleophilicity of a nitrogen atom bearing a methyl group in methylhydrazine [10]. Compound 14 in methanol was hydrolyzed in 10% sodium hydroxide solution gave 2-(5-carboxy-1-methylpyrazol-3-yl)-7-methylaminotroponone (16) at room temperature and 3-(5-carboxypyrazol-3-yl)tropolone (17) at reflux temperature in quantitative yields. In a similar manner, alkaline

Scheme 3



Scheme 4



hydrolysis of compound **15** gave quantitatively 2-(3-carboxy-1-methylpyrazol-5-yl)-7-methylaminotroponone (**18**) and 3-(3-carboxyl-1-methylpyrazol-5-yl)troponone (**19**). Consequently, compound **16** was heated at reflux in quinoline in the presence of copper powder for 2 hours to afford 2-(1-methylpyrazol-3-yl)-7-methylaminotroponone (**20**) in 93% yield. Its structure was confirmed by elemental analysis and spectral data. Furthermore, an NOE experiment was performed. An irradiation on the 1'-methyl signal gave enhancement of 5'-H proton at δ 7.37 but no enhancement of 3-H proton at δ 8.33. Thus, the structures of compound **20** and related compounds **14** and **16** were established. Additionally, the structure of compound **15** also must be 2-(3-ethoxycarbonyl-1-methylpyrazol-5-yl)-7-methylaminotroponone. Then, a parent compound, 3-(1-methylpyrazol-3-yl)troponone (**21**), was obtained by heating compound **20** in quinoline in the presence of copper powder.

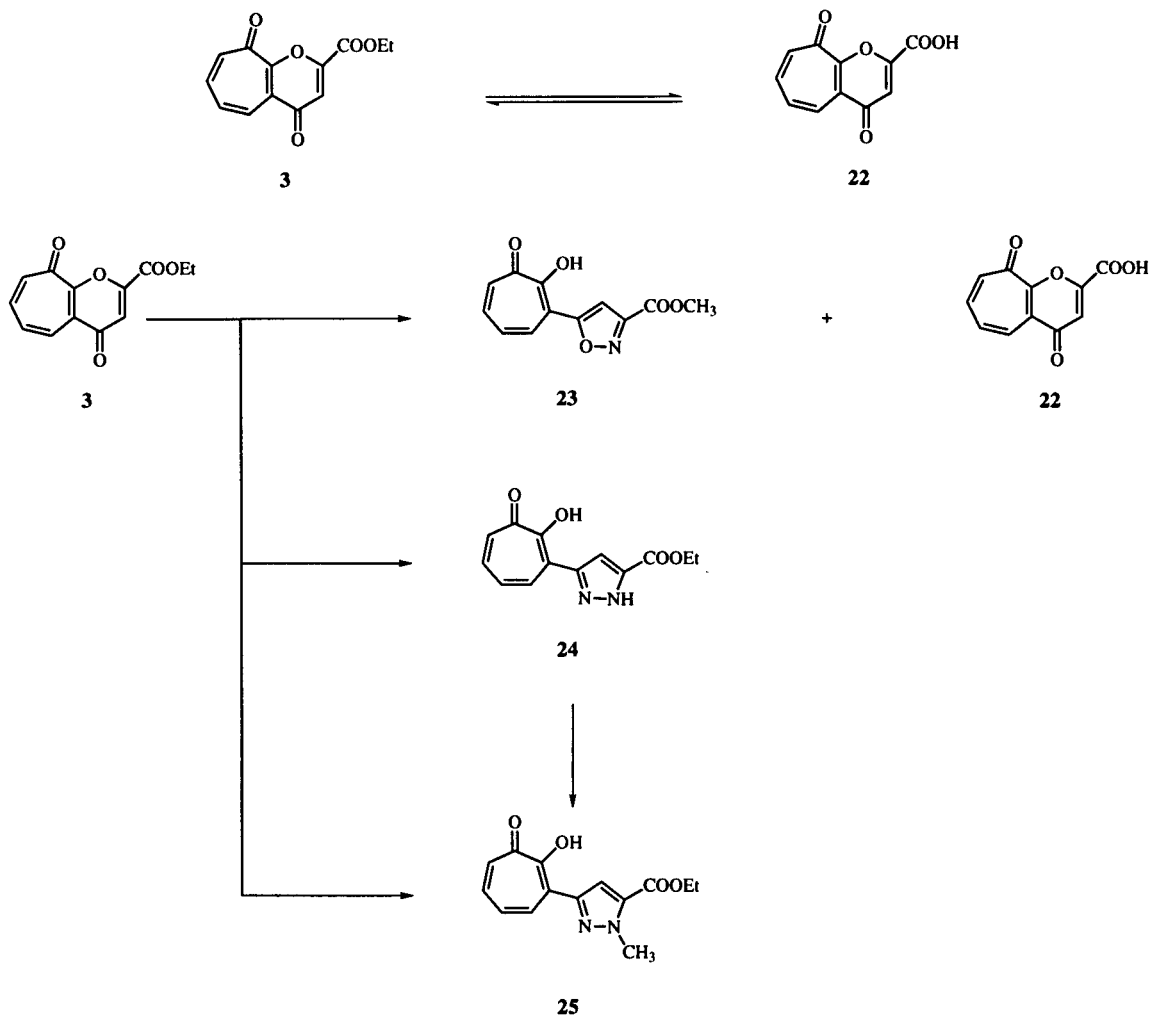
Reactions of 2-Ethoxycarbonyl-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (**3**).

A methanolic solution of compound **3** was refluxed for 4 hours in the presence of 12*M* hydrochloric acid to yield 2-carboxy-4,9-dihydrocyclohepta[*b*]pyran-4,9-dione (**22**). Compound **22** was heated in ethanol containing a few drops of concentrated sulfuric acid to give ester **3**.

Nucleophilic attacks of hydroxylamine [11] and hydrazines [12] on the 4-pyrone system usually proceeds through opening of the ring and recyclization to yield various nitrogen-containing heterocycles. When compound **3** was treated with hydroxylamine to give the hydrolyzed product **22** as a major product and 3-(3-methoxycarbonylisoxazol-5-yl)troponone (**23**) in only 4% yield. By this process, transesterification was observed in addition to isoxazole formation.

A methanolic solution of compound **3** was heated with hydrazine to afford 3-(5-ethoxycarbonylpyrazol-3-yl)tro-

Scheme 5



polone (24). The reaction with methylhydrazine gave 3-(5-ethoxycarbonyl-1-methylpyrazol-3-yl)tropolone (25). In the ^1H nmr spectrum, its methyl signal was observed at δ 4.26 and the value is comparable to that of δ 4.23 for 1'- CH_3 signal of compound 14. The methylation of compound 24 with methyl iodide gave compound 25.

EXPERIMENTAL

Measurements.

All melting points were determined with a Yanagimoto MP S-2 apparatus and are uncorrected. The ir spectra were taken on a JASCO A-102 spectrophotometer. The nmr spectra were recorded with a JEOL JNM-EX 90 spectrometer (90 MHz for ^1H and 22.5 MHz for ^{13}C) and partly with a JEOL JNM-PMX60SI (60 MHz for ^1H) and a JEOL JNM-A500 spectrometer (500 MHz for ^1H and 125 MHz for ^{13}C). The mass spectra were measured on a JEOL JMS-01-SG spectrometer.

Reaction of 3-Acetyltropolone (1) with Diethyl Oxalate.

To a solution of 3-acetyltropolone (1) (328 mg, 2.0 mmoles) in absolute ethanol (15 ml) containing sodium ethoxide, prepared from sodium (120 mg, 5.2 mmoles) and absolute ethanol (2 ml), was added diethyl oxalate (800 mg, 5.5 mmoles). After stirring for 17 hours at room temperature, the mixture was diluted with water, acidified with acetic acid, and extracted with chloroform. The evaporation residue was chromatographed on a Kieselgel 60 (30 g) with chloroform-methanol (10:1).

3-(2-Ethoxyoxalyl-1-oxoethyl)tropolone (2) was obtained from the former fraction in a yield of 134 mg (25%) as yellow crystals, mp 103-104°; ir (chloroform): ν max 1690 (C=O), 1614 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.39 (3H, t, J = 7.1 Hz, CH_3), 2.67 (1H, s, CH_2), 4.37 (2H, q, J = 7.1 Hz, CH_2), 7.08-7.80 (4H, m), 8.03 (1H, d, J = 9.3 Hz, 4-H); ms: m/z (%) 264 (M^+ , 1), 191 (40), 163 (73), 149 (100), 121 (27).

Anal. Calcd. for $\text{C}_{13}\text{H}_{12}\text{O}_6$: C, 59.09; H, 4.58; M_r^+ , 264.0634. Found: C, 58.91; H, 4.60; M_r^+ , 264.0621.

2-Ethoxycarbonyl-4,9-dihydrocyclohepta[b]pyrane-4,9-dione (3) was obtained from the later fraction in a yield of 345 mg (65%) as orange crystals (from ethanol), mp 145-147°; ir (chloroform): ν max 1746 (C=O), 1665 (C=O), 1605 cm^{-1} (C=O); ^1H nmr (deuteriodimethyl sulfoxide, 90 MHz): δ 1.36 (3H, t, J = 7.1 Hz, CH_3), 4.42 (2H, q, J = 7.1 Hz, CH_2), 7.14 (1H, s, 3-H), 7.11-7.85 (4H, m); ^{13}C (deuteriodimethyl sulfoxide, 22.5 MHz): δ 13.8 (CH_3), 62.8 (CH_2), 116.2 (-CH=), 127.0 (=C<), 127.4 (-CH=), 131.5 (-CH=), 137.7 (-CH=), 138.2 (-CH=), 153.1 (=C<), 159.2 (=C<), 159.3 (=C<), 178.8 (=C<), 178.9 (=C<); ms: m/z (%) 246 (M^+ , 100), 201 (10).

Anal. Calcd. for $\text{C}_{13}\text{H}_{10}\text{O}_5$: C, 63.41; H, 4.09; M_r^+ , 246.0528. Found: C, 63.09; H, 4.04; M_r^+ , 246.0551.

Cyclization of 2 to 3.

A solution of compound 2 (264 mg, 1.0 mmole) in ethanol (5 ml) was refluxed for 2 hours. After removal of the solvent, the residue was recrystallized from ethanol to give compound 3 in a yield of 241 mg (98%).

Reaction of 2-Acetyl-7-methylaminotropone (4) with Diethyl Oxalate.

A solution of 2-acetyl-7-methylaminotropone (4) (2.12 g, 12 mmoles) in absolute ethanol (90 ml) containing sodium ethoxide, prepared from sodium (690 mg, 30 mmoles) and absolute ethanol (12 ml), was added diethyl oxalate (4.40 g, 60 mmoles). The mixture was stirred for 15 hours at room temperature. The reaction mixture was diluted with water and acidified with 6M hydrochloric acid. A precipitate was collected and recrystallized from benzene-hexane to afford 2-(2-ethoxyoxalyl-1-oxoethyl)-7-methylaminotropone (5) in a yield of 3.11 g (93%) as orange needles, mp 135-136°; ir (chloroform): ν max 3320 (NH), 1738 (C=O), 1571 cm^{-1} (C=O); ^1H nmr (deuteriochloroform, 90 MHz): δ 1.35 (3H, t, J = 7.1 Hz, CH_3), 3.12 (3H, d, J = 5.6 Hz, N- CH_3), 4.34 (2H, q, J = 7.1 Hz, CH_2), 6.49-6.81 (2H, m), 7.23-7.51 (1H, m), 7.34 (2H, s, CH_2), 7.86 (1H, dd, J = 10.0, 1.3 Hz, 3-H), 8.09 (1H, br, NH); ^{13}C (deuteriochloroform, 22.5 MHz): δ 14.1 (CH_3), 30.0 (N- CH_3), 62.2 (CH_2), 104.9 (=C<), 108.7 (=CH-), 120.3 (=CH-), 128.3 (=CH-), 132.7 (=C<), 140.9 (=CH-), 159.6 (=C<), 162.6 (=C<), 163.7 (=C<), 173.5 (=C<), 197.7 (=C<); ms: m/z (%) 277 (M^+ , 5), 204 (29), 176 (37), 162 (100).

Anal. Calcd. for $\text{C}_{14}\text{H}_{15}\text{NO}_5$: C, 60.64; H, 5.45; N, 5.05; M_r^+ , 277.0950. Found: C, 60.51; H, 5.31; N, 5.08; M_r^+ , 277.0945.

Reaction of Compound 5 with Hydroxylamine.

A solution of compound 5 (1.11 g, 4.0 mmoles) and hydroxylamine hydrochloride (360 mg, 5.2 mmoles) in methanol (60 ml) was refluxed for 2 hours. After removal of the solvent, the residue was chromatographed on a Kieselgel 60G (150 g) with chloroform-methanol (10:1) to afford 2-(3-ethoxycarbonylisoxazol-5-yl)-7-methylaminotropone (6) in a yield of 972 mg (89%) as light orange crystals, mp 161-162°; ir (chloroform): ν max 3312 (NH), 1737 (C=O), 1603 cm^{-1} (C=O); ^1H nmr (deuteriochloroform, 90 MHz): δ 1.44 (3H, t, J = 7.1 Hz, CH_3), 3.13 (3H, d, J = 5.4 Hz, N- CH_3), 4.47 (2H, q, J = 7.1 Hz, CH_2), 6.53-6.90 (2H, m), 7.27-7.50 (1H, m), 7.76 (1H, s, 4'-H), 8.04 (1H, br, NH), 8.29 (1H, dd, J = 10.1, 1.2 Hz, 3-H); ^{13}C nmr (deuteriochloroform, 22.5 MHz): δ 14.2 (CH_3), 30.0 (N- CH_3), 62.0 (CH_2), 105.9 (-CH=), 109.0 (-CH=), 120.6 (-CH=), 122.5 (=C<), 136.1 (-CH=), 139.1 (-CH=), 157.2 (=C<), 158.2 (=C<), 160.4 (=C<), 170.0 (=C<), 171.5 (=C<); ms: m/z (%) 274 (M^+ , 44), 201 (67), 175 (100), 160 (49).

Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_4$: C, 61.30; H, 5.14; N, 10.22; M_r^+ , 274.0954. Found: C, 61.21; H, 5.06; N, 10.32; M_r^+ , 274.0937.

Hydrolysis of Compound 6.

a) To a suspension of compound 6 (274 mg, 1.0 mmole) in methanol (50 ml) was added 10% sodium hydroxide solution (10 ml). The mixed solution was stirred for 2 hours at room temperature, acidified with 6M hydrochloric acid, and extracted with chloroform. Evaporation of the solvent gave 2-(3-carboxyisoxazol-5-yl)-7-methylaminotropone (7) in a yield of 246 mg (quantitative) as yellow crystals (from methanol), mp 196-197°; ir (potassium bromide): ν max 3330 (NH), 2925 (OH), 1720 (C=O), 1605 cm^{-1} (C=O); ^1H nmr (deuteriodimethyl sulfoxide, 400 MHz): δ 3.08 (3H, d, J = 5.1 Hz, N- CH_3), 6.80 (1H, d, J = 10.6 Hz, 6-H), 6.85 (1H, dd, J = 10.3, 9.9 Hz, 4-H), 7.52 (1H, dd, J = 10.3, 9.9 Hz, 5-H), 7.59 (1H, s, 4'-H), 8.20 (1H, d, J = 10.3 Hz, 3-H), 8.77 (1H, d, J = 5.1 Hz, NH); ^{13}C nmr (deuteriodimethyl sulfoxide, 100 MHz): δ 29.9 (N- CH_3), 104.9 (-CH=), 109.5 (-CH=), 119.7 (-CH=), 120.5 (=C<), 135.1 (-CH=), 139.7 (-CH=), 157.6 (=C<), 158.4 (=C<), 161.2 (=C<), 170.0 (=C<), 170.7 (=C<).

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_4$: C, 58.53; H, 4.09; N, 11.38. Found: C, 58.77; H, 4.22; N, 11.47.

b) A suspended solution of compound 6 (1.10 g, 4.0 mmoles) in methanol (80 ml) was refluxed for 12 hours in the presence of 10% sodium hydroxide solution (40 ml). After cooling, the mixture was acidified with 6M hydrochloric acid to afford 3-(3-carboxyisoxazol-5-yl)troponone (8) in a yield of 894 mg (96%) as yellow crystals, mp >300°; ir (potassium bromide): ν max 3150 (OH), 1725 (C=O), 1600 cm^{-1} (C=O); ^1H nmr (deuteriodimethyl sulfoxide, 400 MHz): δ 7.28 (1H, dd, J = 10.2, 9.9 Hz, 5-H), 7.41 (1H, d, J = 10.3 Hz, 7-H), 7.61 (1H, dd, J = 10.3, 10.2 Hz, 6-H), 7.65 (1H, s, 4'-H), 8.40 (1H, d, J = 9.9 Hz, 4-H); ^{13}C nmr (deuteriodimethyl sulfoxide, 100 MHz): δ 106.8 (-CH=), 118.7 (=C<), 125.4 (=C<), 126.9 (-CH=), 136.8 (-CH=), 139.5 (-CH=), 157.9 (=C<), 160.9 (=C<), 167.9 (=C<), 168.4 (=C<), 172.3 (=C<).

Anal. Calcd. for $\text{C}_{11}\text{H}_7\text{NO}_3$: C, 56.66; H, 3.03; N, 6.01. Found: C, 56.45; H, 3.15; N, 5.93.

Reaction of Compound 5 with Hydrazine Hydrate.

A solution of compound 5 (277 mg, 1.0 mmole) and hydrazine hydrate (61 mg, 1.2 mmoles) in methanol (20 ml) was refluxed for 2 hours to yield 2-(5-ethoxycarbonylpyrazol-3-yl)-7-methylaminotropone (9) in a yield of 229 mg (84%) as yellow crystals, mp 282-283°; ir (potassium bromide): ν max 3300 (NH), 1717 (C=O), 1612 cm^{-1} (C=O); ms: m/z (%) 273 (M^+ , 100).

Anal. Calcd. for $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_3$: C, 61.53; H, 5.53; N, 15.38; M_r^+ , 273.1113. Found: C, 61.55; H, 5.63; N, 15.34; M_r^+ , 273.1112.

Hydrolysis of Compound 9.

a) To a suspension of compound 9 (1.36 g, 5.0 mmoles) in methanol (100 ml) was added 10% sodium hydroxide solution (50 ml). The mixture was stirred for 2 hours at room temperature and then acidified with 6M hydrochloric acid to give 2-(5-carboxypyrazol-3-yl)-7-methylaminotropone (10) in a yield of 227 mg (83%) as pale yellow crystals, mp 276-277°; ir (potassium bromide): ν max 3284 (NH), 2900 (OH), 1690 (C=O),

1603 cm^{-1} (C=O); ms: m/z (%) 273 (M^+ , 100), 228 (17), 201 (30).

Anal. Calcd. for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 59.01; H, 4.46; N, 17.15.

b) A suspended solution of compound **9** (1.36 g, 5.0 mmoles) in methanol (100 ml) was refluxed for 12 hours in the presence of 10% sodium hydroxide solution (50 ml). After cooling, the mixture was acidified with 6*M* hydrochloric acid to give 3-(5-carboxypyrazol-3-yl)tropolone (**11**) in a yield of 1.16 g (quantitative) as pale yellow crystals, mp $>300^\circ$; ir (potassium bromide): ν max 3330 (NH), 3200 (OH), 1690 (C=O), 1605 cm^{-1} (C=O); ^1H nmr (deuteriodimethyl sulfoxide, 400 MHz): δ 7.21-7.26 (1H, m, 5-H), 7.39-7.41 (1H, m, 7-H), 7.45-7.55 (1H, m, 6-H), 7.61 (1H, s, 4'-H), 8.44 (1H, d, $J = 9.9$ Hz, 4-H).

Anal. Calcd. for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.47; N, 12.07. Found: C, 55.30; H, 3.49; N, 12.28.

Decarboxylation of Compound **10**.

A solution of compound **10** (1.22 g, 5.0 mmoles) in quinoline (3.5 ml) was refluxed for 2 hours in the presence of copper powder (113 mg). The copper powder was filtered and rinsed with chloroform. After removal of chloroform, the residue was chromatographed on a Kieselgel 60G (200 g) with ethyl acetate. The desired fraction was rechromatographed on a Kieselgel 60G (100 g) with chloroform-methanol (10:1) to give 7-methylamino-2-(3-pyrazolyl)tropolone (**12**) in a yield of 485 mg (48%) as red needles (from ethanol), mp 188-189 $^\circ$; ir (chloroform): ν max 3305 (NH), 3225 (NH), 1602 cm^{-1} (C=O); ^1H nmr (deuteriochloroform, 60 MHz): δ 3.15 (3H, d, $J = 5.6$ Hz, CH_3), 6.5-7.5 (3H, m), 6.73 (1H, d, $J = 2.2$ Hz, -CH=), 7.68 (1H, d, $J = 2.2$ Hz, -CH=), 8.10 (1H, d, $J = 10.0$ Hz, 3-H), 8.61 (1H, br, NH).

Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.65; H, 5.51; N, 20.88. Found: C, 65.89; H, 5.53; N, 20.92.

3-(3-Pyrazolyl)tropolone (**13**).

To a solution of compound **12** (302 mg, 1.5 mmoles) in methanol (15 ml) was added 10% sodium hydroxide solution (15 ml). After refluxing for 7 hours, the mixture was acidified with 6*M* hydrochloric acid and extracted with chloroform to 3-(3-pyrazolyl)tropolone (**13**) in a yield of 273 mg (97%) as red needles, mp 177-178 $^\circ$; ir (potassium bromide): ν max 3344 (NH), 3175 (OH), 1595 cm^{-1} (C=O); ^1H nmr (deuteriodimethyl sulfoxide, 400 MHz): δ 3.51 (1H, br, OH), 7.17 (1H, d, $J = 2.2$ Hz, -CH=), 7.20 (1H, dd, $J = 10.3, 9.5$ Hz, 5-H), 7.37 (1H, d, $J = 9.5$ Hz, 7-H), 7.47 (1H, dd, $J = 9.5, 9.5$ Hz, 6-H), 7.82 (1H, d, $J = 2.2$ Hz, -CH=), 8.49 (1H, d, $J = 10.3$ Hz, 4-H).

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.52; H, 4.10; N, 14.67.

Reaction of Compound **5** with Methylhydrazine.

A solution of compound **5** (1.39 g, 5.0 mmoles) and methylhydrazine (300 mg, 6.5 mmoles) in methanol (80 ml) was refluxed for 2 hours. After removal of the solvent, the residue was chromatographed on a Kieselgel 60G (200 g) with ethyl acetate.

2-(5-Ethoxycarbonyl-1-methylpyrazol-3-yl)-7-methylaminotropolone (**14**) was obtained from the former fraction in a yield of 1.27 g (88%) as yellow crystals (from benzene-hexane), mp 139-140 $^\circ$; ir (chloroform): ν max 3315 (NH), 1718 (C=O), 1598 cm^{-1} (C=O); ^1H nmr (deuteriochloroform, 90 MHz): δ 1.37 (3H, t, $J = 7.2$ Hz, CH_3), 3.06 (3H, d, $J = 5.4$ Hz, NH-CH_3), 4.23 (3H,

s, $>\text{N-CH}_3$), 4.34 (2H, q, $J = 7.2$ Hz, CH_2), 6.47-6.86 (2H, m), 7.16-7.37 (1H, m), 7.79 (1H, br, NH), 7.80 (1H, s, 4'-H), 8.35 (1H, dd, $J = 10.0, 1.2$ Hz, 3-H); ^{13}C nmr (deuteriochloroform, 22.5 MHz): δ 14.3 (CH_3), 29.8 (NH-CH_3), 39.5 ($>\text{N-CH}_3$), 60.8 (CH_2), 108.6 (-CH=), 113.8 (-CH=), 121.2 (-CH=), 129.3 (=C<), 132.7 (=C<), 136.4 (-CH=), 137.0 (-CH=), 149.5 (=C<), 157.4 (=C<), 160.3 (=C<), 173.5 (=C<); ms: m/z (%) 287 (M^+ , 100), 259 (15).

Anal. Calcd. for $C_{15}H_{17}N_3O_3$: C, 62.70; H, 5.97; N, 14.63; M_r^+ , 287.1269. Found: C, 62.90; H, 5.76; N, 14.64; M_r^+ , 287.1252.

2-(3-Ethoxycarbonyl-1-methylpyrazol-5-yl)-7-methylaminotropolone (**15**) was obtained from the later fraction in a yield of 112 mg (8%) as yellow crystals (from benzene-hexane), mp 137-138 $^\circ$; ir (chloroform): ν max 3328 (NH), 1715 (C=O), 1600 cm^{-1} (C=O); ^1H nmr (deuteriochloroform, 90 MHz): δ 1.37 (3H, t, $J = 7.1$ Hz, CH_3), 3.09 (3H, d, $J = 5.4$ Hz, NH-CH_3), 3.72 (3H, s, $>\text{N-CH}_3$), 4.36 (2H, q, $J = 7.1$ Hz, CH_2), 6.60-6.80 (2H, m), 6.70 (1H, s, 4'-H), 7.29-7.48 (2H, m), 8.00 (1H, br, NH); ^{13}C nmr (deuteriochloroform, 22.5 MHz): δ 14.0 (CH_3), 29.3 (NH-CH_3), 37.7 ($>\text{N-CH}_3$), 59.9 (CH_2), 108.4 (-CH=), 108.9 (-CH=), 119.6 (-CH=), 125.8 (=C<), 137.4 (-CH=), 139.3 (-CH=), 141.2 (=C<), 145.6 (=C<), 157.0 (=C<), 161.7 (=C<), 172.5 (=C<); ms: m/z (%) 287 (M^+ , 100), 242 (38), 214 (56).

Anal. Calcd. for $C_{15}H_{17}N_3O_3$: C, 62.70; H, 5.97; N, 14.63; M_r^+ , 287.1270. Found: C, 62.85; H, 5.89; N, 14.50; M_r^+ , 287.1258.

Hydrolysis of Compound **14**.

a) To a suspension of compound **14** (287 mg, 1.0 mmole) in methanol (20 ml) was added 10% sodium hydroxide solution (10 ml). The mixed solution was stirred for 2 hours at room temperature, acidified with 6*M* hydrochloric acid, and extracted with chloroform. The evaporation of the solvent gave 2-(5-carboxy-1-methylpyrazol-3-yl)-7-methylaminotropolone (**16**) in a yield of 259 mg (quantitative) as pale yellow crystals, mp 239-240 $^\circ$; ir (potassium bromide): ν max 3290 (NH), 1712 (C=O), 1603 cm^{-1} (C=O); ^1H nmr (deuteriodimethyl sulfoxide, 90 MHz): δ 3.03 (3H, d, $J = 5.3$ Hz, NH-CH_3), 4.17 (3H, s, $>\text{N-CH}_3$), 6.60 (1H, d, $J = 10.1$ Hz, 6-H), 6.73 (1H, dd, $J = 10.0, 9.8$ Hz, 4-H), 7.32 (1H, dd, $J = 10.1, 9.8$ Hz, 5-H), 7.74 (1H, s, 4'-H), 8.18 (1H, br, NH), 8.35 (1H, d, $J = 10.0$ Hz, 3-H); ^{13}C nmr (deuteriodimethyl sulfoxide, 22.5 MHz): δ 29.6 (NH-CH_3), 39.3 ($>\text{N-CH}_3$), 108.4 (-CH=), 113.5 (-CH=), 119.9 (-CH=), 127.8 (=C<), 133.0 (=C<), 135.8 (-CH=), 136.5 (-CH=), 148.7 (=C<), 157.4 (=C<), 161.0 (=C<), 172.8 (=C<).

Anal. Calcd. for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 59.21; H, 5.11; N, 15.83.

b) A suspension of compound **14** (287 mg, 1.0 mmole) in methanol (20 ml) was refluxed for 12 hours in the presence of 10% sodium hydroxide solution (10 ml). After cooling, the mixture was acidified with 6*M* hydrochloric acid and extracted with chloroform. The evaporation of the solvent gave 3-(5-carboxy-1-methylpyrazol-3-yl)tropolone (**17**) in a yield of 246 mg (quantitative) as pale yellow crystals, mp 237-238 $^\circ$; ir (potassium bromide): ν max 2875 (OH), 1712 (C=O), 1618 cm^{-1} (C=O); ^1H nmr (deuteriodimethyl sulfoxide, 90 MHz): δ 4.28 (3H, s, $>\text{N-CH}_3$), 7.18-7.57 (3H, m), 7.80 (1H, s, 4'-H), 8.58 (1H, d, $J = 9.5$ Hz, 4-H); ^{13}C nmr (deuteriodimethyl sulfoxide, 22.5 MHz): δ 39.5 ($>\text{N-CH}_3$), 113.6 (-CH=), 120.5 (-CH=), 126.9 (-CH=), 129.3 (=C<), 133.7 (=C<), 136.5 (-CH=), 137.1 (-CH=), 146.3 (=C<),

160.6 (=C<), 169.2 (=C<), 171.1 (=C<); ms: m/z (%) 246 (M^+ , 100).

Anal. Calcd. for $C_{12}H_{10}N_2O_4$: C, 58.53; H, 4.09; N, 11.38; M_r^+ , 246.0640. Found: C, 58.58; H, 4.30; N, 11.13; M_r^+ , 246.0659.

Hydrolysis of Compound 15.

a) To a suspension of compound **15** (144 mg, 0.5 mmole) in methanol (10 ml) was added 10% sodium hydroxide solution (5 ml). The mixed solution was stirred for 2 hours at room temperature, acidified with 6*M* hydrochloric acid, and extracted with chloroform. Evaporation of the solvent from the extract gave 2-(3-carboxy-1-methylpyrazol-5-yl)-7-methylaminotroponone (**18**) in a yield of 130 mg (quantitative) as pale yellow crystals, mp 214-215°; ir (potassium bromide): ν max 3244 (NH), 3050 (OH), 1688 (C=O), 1598 cm^{-1} (C=O); 1H nmr (deuteriodimethyl sulfoxide, 400 MHz): δ 3.02 (3H, d, $J = 5.1$ Hz, NH-CH₃), 3.21 (1H, br, OH), 3.62 (3H, s, >N-CH₃), 6.66 (1H, s, 4'-H), 6.70 (1H, dd, $J = 10.3, 9.5$ Hz, 4-H), 6.73 (1H, d, $J = 10.3$ Hz, 6-H), 7.43 (1H, dd, $J = 10.3, 10.3$ Hz, 5-H), 7.46 (1H, d, $J = 9.5$ Hz, 3-H), 8.32 (1H, d, $J = 5.1$ Hz, NH); ^{13}C nmr (deuteriodimethyl sulfoxide, 100 MHz): δ 29.7 (NH-CH₃), 37.9 (>N-CH₃), 108.9 (-CH=), 109.2 (-CH=), 119.7 (-CH=), 125.8 (=C<), 138.2 (-CH=), 139.7 (-CH=), 141.8 (=C<), 145.9 (=C<), 157.4 (=C<), 163.2 (=C<), 172.6 (=C<).

Anal. Calcd. for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 59.85; H, 5.23; N, 15.99

b) A suspension of compound **15** (144 mg, 0.5 mmole) in methanol (10 ml) was refluxed for 12 hours in the presence of 10% sodium hydroxide solution (5 ml). After cooling, the mixture was acidified with 6*M* hydrochloric acid and extracted with chloroform. Evaporation of the solvent gave 3-(3-carboxy-1-methylpyrazol-5-yl)troponone (**19**) in a yield of 98 mg (80%) as pale yellow crystals, mp 221-222°; ir (potassium bromide): ν max 2950 (OH), 1688 (C=O), 1600 cm^{-1} (C=O); 1H nmr (deuteriochloroform, 60 MHz): δ 4.00 (3H, s, >N-CH₃), 6.9-7.6 (4H, m), 7.48 (1H, s, 4'-H), 8.13 (1H, br, OH), 8.59 (1H, d, $J = 10.0$ Hz, 4-H).

Anal. Calcd. for $C_{12}H_{10}N_2O_4$: C, 58.53; H, 4.09; N, 11.38. Found: C, 58.82; H, 4.36; N, 11.61.

Decarboxylation of Compound 16.

A solution of compound **16** (1.04 g, 4.0 mmoles) in quinoline (2 ml) was refluxed for 2 hours in the presence of copper powder (90 mg). The copper powder was filtered and rinsed with ethyl acetate. After removal of ethyl acetate, the residue was chromatographed on a Kieselgel 60G (120 g) with ethyl acetate to give 2-(1-methylpyrazol-3-yl)-7-methylaminotroponone (**20**) in a yield of 800 mg (93%) as brownish crystals (from ethanol), mp 156-157°; ir (chloroform): ν max 3330 (NH), 1600 cm^{-1} (C=O); 1H nmr (deuteriochloroform, 90 MHz): δ 2.99 (3H, d, $J = 5.4$ Hz, NH-CH₃), 3.90 (3H, s, >N-CH₃), 6.42-6.83 (2H, m), 7.16 (1H, d, $J = 2.2$ Hz, 4'-H), 7.16 (1H, dd, $J = 8.6, 1.3$ Hz, 5-H), 7.37 (1H, d, $J = 2.2$ Hz, 5'-H), 8.33 (1H, dd, $J = 10.0, 1.3$ Hz, 3-H); ^{13}C nmr (deuteriochloroform, 22.5 MHz): δ 29.8 (NH-CH₃), 39.0 (>N-CH₃), 108.4, 108.5 (-CH=), 121.1 (-CH=), 130.2 (-CH=), 130.5 (=C<), 135.8 (-CH=), 137.1 (-CH=), 151.4 (=C<), 157.2 (=C<), 173.7 (=C<).

Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 67.24; H, 6.19; N, 19.28.

3-(1-Methylpyrazol-3-yl)troponone (**21**).

To a solution of compound **20** (215 mg, 1.0 mmole) in methanol (20 ml) was added 10% sodium hydroxide solution (10 ml). After refluxing for 7 hours, the mixture was acidified with 6*M* hydrochloric acid and extracted with chloroform to 3-(1-methylpyrazol-3-yl)troponone (**21**) in a yield of 200 mg (98%) as brownish crystals, mp 122-123°; ir (chloroform): ν max 3300 (OH), 1620 cm^{-1} (C=O); 1H nmr (deuteriochloroform, 400 MHz): δ 3.97 (3H, s, N-CH₃), 7.07-7.12 (1H, m), 7.23 (1H, d, $J = 2.2$ Hz, -CH=), 7.29-7.39 (2H, m), 7.44 (1H, d, $J = 2.2$ Hz, -CH=), 8.52 (1H, d, $J = 10.6$ Hz, 4-H); ^{13}C nmr (deuteriochloroform, 100 MHz): δ 39.2 (>N-CH₃), 109.3 (-CH=), 122.2 (-CH=), 127.2 (-CH=), 129.5 (=C<), 130.9 (-CH=), 137.1 (-CH=), 138.0 (-CH=), 148.7 (=C<), 169.7 (=C<), 171.0 (=C<).

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.45; H, 5.12; N, 13.89.

Hydrolysis of 2-Ethoxycarbonyl-4,9-dihydrocyclohepta[b]pyran-4,9-dione (**3**).

A solution of compound **3** (246 mg, 1.0 mmole) in methanol (10 ml) containing 12*M* hydrochloric acid (3 drops) was refluxed for 4 hours. Evaporation of the solvent gave 2-carboxy-4,9-dihydrocyclohepta[b]pyran-4,9-dione (**22**) in a yield of 148 mg (68%) as pale yellow crystals (from methanol), mp 179-180°; ir (chloroform): ν max 1750 (C=O), 1665 (C=O), 1605 cm^{-1} (C=O); 1H nmr (deuteriochloroform, 60 MHz): δ 6.95-8.1 (5H, m).

Anal. Calcd. for $C_{11}H_8O_5$: C, 60.56; H, 2.77. Found: C, 60.51; H, 2.93.

Esterification of Compound 22.

A solution of compound **22** (130 mg, 0.6 mmole) in ethanol (10 ml) was refluxed for 6 hours in the presence of concentrated sulfuric acid (3 drops). After removal of the solvent, the residue was dissolved in chloroform and washed with water. The organic phase was concentrated to give compound **3** in a yield of 140 mg (95%).

Reaction of 2-Ethoxycarbonyl-4,9-dihydrocyclohepta[b]pyran-4,9-dione (**3**) with Hydroxylamine.

A solution of compound **3** (738 mg, 3.0 mmoles) and hydroxylamine hydrochloride (270 mg, 3.9 mmoles) in methanol (45 ml) was refluxed for 6 hours in the presence of potassium carbonate (270 mg, 2.0 mmoles). After removal of the solvent, the residue was triturated with water and extracted with chloroform. The evaporation residue was chromatographed on a Wakogel B-10 plate (30 x 30 cm). 3-(3-Methoxycarbonylisoxazol-5-yl)troponone (**23**) was obtained from the lower fraction in a yield of 27 mg (4%) as pale yellow crystals (from methanol), mp 183°; ir (potassium bromide): ν max 1620 cm^{-1} (C=O); 1H nmr (deuteriochloroform, 60 MHz): δ 3.65 (3H, s, CH₃), 7.1-8.0 (4H, m), 7.75 (1H, s, 4'-H).

Anal. Calcd. for $C_{12}H_9NO_5$: C, 58.30; H, 3.67; N, 5.67. Found: C, 58.42; H, 4.01; N, 5.51.

Compound **22** was also obtained from the upper fraction in a yield of 780 mg (62%).

Reaction of Compound 3 with Hydrazine.

A solution of compound **3** (738 mg, 3.0 mmoles) and hydrazine hydrate (195 mg, 3.9 mmoles) in methanol (60 ml) was refluxed for 24 hours. Evaporation of the solvent afforded

3-(5-ethoxycarbonylpyrazol-3-yl)tropolone (**24**) in a yield of 239 mg (31%) as yellow crystals (from chloroform), mp 203°; ir (potassium bromide): ν max 3450 (NH), 3175 (OH), 1710 (C=O), 1605 cm^{-1} (C=O); ^1H nmr (deuteriochloroform, 60 MHz): δ 1.35 (3H, t, $J = 7.0$ Hz, CH_3), 4.36 (2H, q, $J = 7.0$ Hz, CH_2), 7.1-7.5 (3H, m), 7.74 (1H, s, 4'-H), 8.59 (1H, d, $J = 9.0$ Hz, 4-H).

Anal. Calcd. for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_4$: C, 59.99; H, 4.65; N, 10.77. Found: C, 60.02; H, 4.66; N, 10.71.

Reaction of Compound **3** with Methylhydrazine.

A solution of compound **3** (738 mg, 3.0 mmoles) and methylhydrazine (180 mg, 3.9 mmoles) in methanol (45 ml) was refluxed for 2 hours. After removal of the solvent, the residue was chromatographed on a Wakogel B-10 plate (30 x 30 cm) with ethyl acetate to give 3-(5-ethoxycarbonyl-1-methylpyrazol-3-yl)tropolone (**25**) in a yield of 467 mg (57%) as yellow crystals (from methanol), mp 169-170°; ir (chloroform): ν max 3100 (OH), 1722 (C=O), 1615 cm^{-1} (C=O); ^1H nmr (deuteriochloroform, 60 MHz): δ 1.39 (3H, t, $J = 7.2$ Hz, CH_3), 4.26 (3H, s, N- CH_3), 4.39 (2H, q, $J = 7.2$ Hz, CH_2), 7.86 (1H, s, 4'-H), 7.0-7.6 (3H, m), 8.65 (1H, d, $J = 9.0$ Hz, 4-H).

Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_4$: C, 61.30; H, 5.14; N, 10.22. Found: C, 61.52; H, 5.17; N, 10.46.

Methylation of Compound **24**.

A mixture of compound **24** (130 mg, 0.5 mmole) and methyl iodide (1 ml) in acetone (10 ml) was heated under refluxing for 8 hours. The evaporation residue was recrystallized from methanol to afford compound **25** in a yield of 115 mg (84%).

REFERENCES AND NOTES

- [1] K. Imafuku, *Kumamoto Daigaku, Kyoyobu Kiyo, Shizen Kagaku Hen*, **25**, 47 (1990).
- [2] K. Imafuku, *Trends in Heterocyclic Chemistry*, Vol 1, A. Kumar, ed, Trivandrum, India, 1990, pp 137-153.
- [3] T. Nozoe, K. Takase and Y. Mochizuki, *Bull. Chem. Soc. Japan*, **37**, 1641 (1964).
- [4] K. Takase, T. Kusunose and T. Nozoe, *Sci. Repts. Tohoku Univ.*, **1**, 72, 33 (1989).
- [5] C.-Y. Qian, Z.-T. Jin, B.-Z. Yin and K. Imafuku, *J. Heterocyclic Chem.*, **26**, 601 (1989).
- [6] Y. Maeda and K. Imafuku, *J. Heterocyclic Chem.*, **32**, 349 (1995).
- [7a] M.-Z. Piao, Y.-Z. Jin and Z.-T. Jin, *Chinese Chem. Letters*, **2**, 101 (1990); [b] M.-Z. Piao, Y.-Z. Jin and Z.-T. Jin, *Youji Huaxue*, **13**, 85 (1993).
- [8] M.-Z. Piao and K. Imafuku, *J. Heterocyclic Chem.*, **32**, 1373 (1995).
- [9] M.-Z. Piao and K. Imafuku, *J. Heterocyclic Chem.*, **33**, 389 (1996).
- [10] A. F. Hegarty, *The Chemistry of the Hydrazo, Azo and Azoxy Groups*, S. Patai, ed, John Wiley & Sons, London, 1975, pp 643-723.
- [11] W. Baker, J. B. Harborne and W. D. Ollis, *J. Chem. Soc.*, 1303 (1952).
- [12] P. Netchitailo, B. Deroi and J. Morel, *J. Heterocyclic Chem.*, **19**, 327 (1982).