The Synthesis and Reactions of 4-(5-Phenyl-3-pyrazolyl)tropolones

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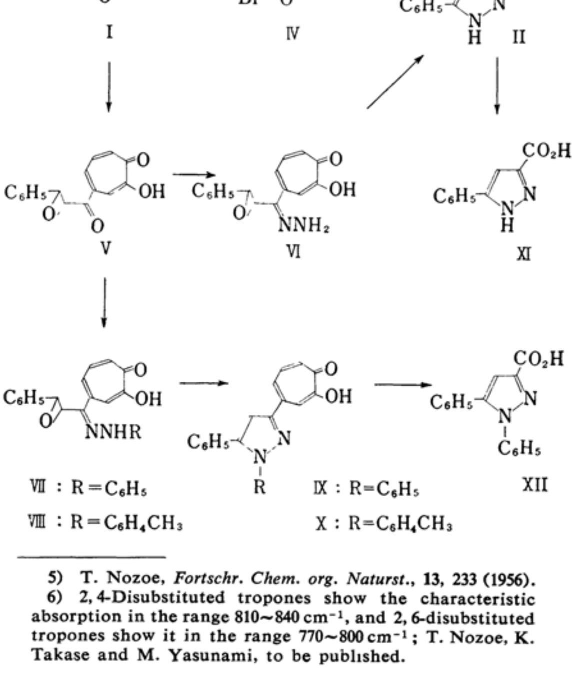
Troponoid compounds containing a non-condensed heteroaromatic ring are expected to be interesting not only because of their chemical properties but also because of their potential biological properties. Because such compounds had never been synthesized, the present authors synthesized some pyrazolyltropolones, starting from 4-cinnamoyltropolone (I) obtained by the condensation of 4-acetyltropolone and benzaldehyde,[1] and investigated their chemical natures.

4-(5-Phenyl-3-pyrazolyl)tropolone (II), the structure of which was established as mentioned below, was synthesized by the following three routes: i) The dehydrogenation of 4-(4, 5-dihydro-5-phenyl-3-pyrazolyl)tropolone (III) obtained by a reaction of I with hydrazine (a 24% over-all yield from I). ii) The reaction of 4-(α-bromocinnamoyl)tropolone (IV),[2] obtained by the bromination of I, with hydrazine (a 22% yield from I). iii) The ring formation of the hydrazone (VI) of 4-(2, 3-epoxy-3-phenylpropionyl)tropolone (V),[2] obtained by the oxidation of I with alkaline hydrogen peroxide (a 40% yield from I). The third method seemed to be the best. In the same way, 4-(1, 5-diphenyl-3-pyrazolyl)-tropolone (IX) and 4-[5-phenyl-1-(*p*-tolyl)-3-pyrozolyl] tropolone (X) were also obtained from phenylhydrazone (VII) and *p*-tolylhydrazone (VIII) of epoxide (V) in 98% and 87% yields respectively. Compounds II, III, IX and X were all proved to be tropolone derivatives by the facts that they were soluble in alkali, reacted positively to the ferric chloride test and formed a greenish-yellow copper chelate. The alkaline permanganate oxidation of II and IX gave 5-phenylpyrazole-3-carboxylic acid (XI)[3] and 1, 5-diphenylpyrazole-3-carboxylic acid (XII)[4] in good yields. The compound, III, was presumed to be a pyrazoline rather than a hydrazone derivative because of its stability to acid. The structures of II, III, IX and X were established by these facts, as is shown in the scheme.

The azo-coupling of II with *p*-toluenediazonium chloride gave an orange-colored 5-(*p*-tolylazo) derivative, the position of the azo group being inferred from analogy with the azo-coupling reaction of the other tropolones.[5] The methylation of II and IX with diazomethane afforded two kinds of methyl ethers, XIIIa and XIIIb, and XIVa and XIVb respectively. The structures of these ethers were inferred from their infrared spectra, in which a strong absorption appeared at 819 for XIIIa, 815 for XIVa, 797 for XIIIb and 795 cm^{-1} for XIVb in Nujol mull. These data suggest that these ethers possess the structures shown.[6] Furthermore, it was interesting to note that the ultraviolet absorption spectra of 4-substituted 2-methoxytropones (XIIIa and XIVa)



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[1] T. Nozoe, K. Takase and M. Ogata, *Chem. & Ind.*, **1957**, 1070.

[2] T. Nozoe, K. Takase, K. Suzuki and K. Sasaki, to be published.

[3] C. Beyer and L. Claisen, *Ber.*, **20**, 2185 (1887); A. Bschler, ibid., **25**, 3144 (1892).

[4] C. Bulow, ibid., **37**, 2200 (1904).

[5] T. Nozoe, *Fortschr. Chem. org. Naturst.*, **13**, 233 (1956).

[6] 2, 4-Disubstituted tropones show the characteristic absorption in the range 810~840 cm^{-1}, and 2, 6-disubstituted tropones show it in the range 770~800 cm^{-1}; T. Nozoe, K. Takase and M. Yasunami, to be published.

and 6-substituted isomers (XIIIb and XIVb) differed from each other remarkably in the long-wave region, as is shown in Fig. 1. Such was also the case in isomeric methyl ethers of styryltropolone⁷⁾ and in 3- and 4-phenyltropones,⁸⁾ this is probably due to the difference in the cross-conjugation system between the aromatic-ring and the unsaturated-ketone systems in a seven-membered ring.

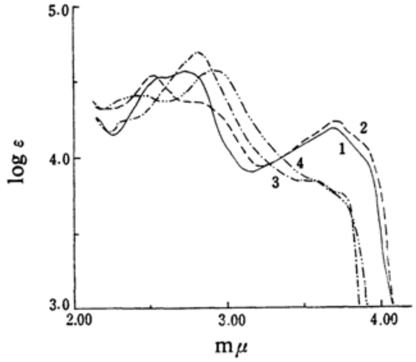
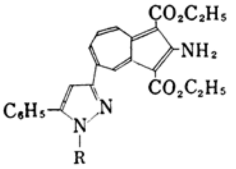
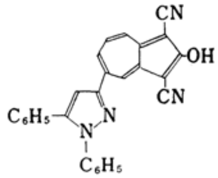


Fig. 1. Ultraviolet absorption spectra of
1: 2-Methoxy-4-(5-phenyl-3-pyrazolyl)tropone (XIIa),
2: 2-Methoxy-4-(1,5-diphenylpyrazolyl)tropone (XIVa),
3: 2-Methoxy-6-(5-phenylpyrazolyl)tropone (XIIIb) and
4: 2-Methoxy-6-(1,5-diphenylpyrazolyl)tropone (XIVb)
in methanol.

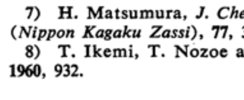
Methyl ethers (XIIIa, b and XIVa, b) were easily hydrolyzed to the original tropolones with alkali. They also gave, by the action of ethyl cyanoacetate in the presence of sodium ethoxide, pyrazolylazulene derivatives (XV, XVI and XVIIa),⁹⁾ the structures of which were inferred from their analytical data and their ultraviolet and infrared absorption spectra. These properties of pyrazolyltropolones, e. g., the formation of two kinds of reactive methyl ethers, were quite similar to those of usual monocyclic tropolones rather than those of tropolones fused with aromatic nuclei, e. g., benzotropolone¹⁰ᵃ⁾ or pyridotropolones.¹⁰ᵇ⁾



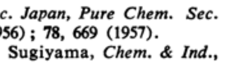
XIIIa: R=H
XIVa: R=C₆H₅



XIIIb: R=H
XIVb: R=C₆H₅



XV: R=H
XVI: R=C₆H₅



XVII

Experimental¹¹⁾

4-(4,5-Dihydro-5-phenyl-3-pyrazolyl)tropolone (III).—A mixture of 4-cinnamoyltropolone (I) (500 mg.), ethanol (4 ml.), 80% hydrazine hydrate (0.2 ml.) and glacial acetic acid (5 drops) was heated under reflux for 5 min. The crystals thereby formed were collected and recrystallized from ethanol to give III (430 mg.) as yellow prisms, m. p. 132~133°C.

Found: C, 71.82; H, 4.91; N, 10.64. Calcd. for $C_{16}H_{14}O_2N_2$: C, 72.16; H, 5.30; N, 10.52%.

$\lambda_{max}^{\text{MeOH}}$ mμ (log ε); 235 (4.29), 320 (4.31), 365~390 (4.15).

N-Acetate.—M. p. 181°C, pale yellow micro-needles (from ethanol).

Found: C, 69.32; H, 5.05; N, 8.96. Calcd. for $C_{18}H_{16}O_3N_2$: C, 70.11; H, 5.23; N, 9.09%.

4-(5-Phenyl-3-pyrazolyl)tropolone (II).—*a) From III.*—A mixture of III (270 mg.), chloranil (370 mg.), and glacial acetic acid (2 ml.) was heated under reflux for 3 hr. After the crystals (dihydrochloranil) which separated out on cooling had been filtered off, the solvent was removed from the filtrate and the residue was recrystallized from ethanol, affording II (80 mg.), m. p. 186~187°C. Further recrystallization from ethanol gave cream yellow silky needles, m. p. 190~191°C.

Found: C, 72.45; H, 4.65; N, 10.63. Calcd. for $C_{16}H_{12}O_2N_2$: C, 72.71; H, 4.58; N, 10.60%.

$\lambda_{max}^{\text{MeOH}}$ mμ (log ε); 280 (4.61), 390 (3.93).

b) From 4-(α-Bromocinnamoyl)tropolone (IV).—To a suspension of IV (1.36 g.) in methanol (10 ml.), 80% hydrazine hydrate (0.4 ml.) was added, and the mixture was heated under reflux for 20 min. The crystals thereby formed were collected and recrystallized from ethanol to give II (655 mg.) as cream-yellow silky needles, m. p. 190~191°C.

c) From 4-(2,3-Epoxy-3-phenylpropionoyl)tropolone (V).—A mixture of V (1.54 g.), ethanol (50 ml.) and 80% hydrazine hydrate (0.5 ml.) was heated under reflux for 1 hr. and then cooled to give the hydrazone (VI) (820 mg.), m. p. 194°C (decomp.). Recrystallization from ethanol afforded yellow plates, m. p. 204°C (decomp.).

Found: C, 67.84; H, 5.07; N, 9.83. Calcd. for $C_{16}H_{14}O_3N_2$: C, 68.07; H, 5.00; N, 9.92%.

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7) H. Matsumura, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zassi*), **77**, 330 (1956); **78**, 669 (1957).

8) T. Ikemi, T. Nozoe and H. Sugiyama, *Chem. & Ind.*, **1960**, 932.

9) Cf. T. Nozoe, S. Seto, S. Matsumura and Y. Murase, This Bulletin, **35**, 1179 (1962).

10) a) T. Nozoe et al., "Dai Yuki Kagaku (Comprehensive Organic Chemistry)," Vol. 13, Asakura-Shoten, Tokyo (1960), Chapter 14.

b) T. Nozoe et al., ibid., Chapter 26.

11) All melting points are uncorrected.

λ_{max}^{MeOH} mμ (log ε); 237 (4.23), 320 (4.33), 370 (4.12).

A mixture of the hydrazone (VI) (640 mg.), ethanol (50 ml.) and 6 N hydrochloric acid (3 drops) was heated under reflux for 1 hr. and then cooled to give II (470 mg.) as cream-yellow silky needles m. p. 190∼191°C.

4-(1, 5-Diphenyl-3-pyrazolyl)tropolone (IX). — A mixture of epoxide (V) (1.35 g.), ethanol (40 ml.) and phenylhydrazine (0.8 ml.) was heated under reflux for 1 hr. and then concentrated to a small volume and allowed to cool to give the phenylhydrazone (VII) (1.69 g.), m. p. 199∼201°C. Recrystallization from ethanol-dioxane afforded orange-yellow micro-needles, m. p. 207∼209°C.

Found: C, 73.69; H, 4.94; N, 7.45. Calcd. for $C_{22}H_{18}O_3N_2$: C, 73.73; H, 5.06; N, 7.82%.

A mixture of the phenylhydrazone (VII) (1.69 g.), ethanol (70 ml.) and 6 N hydrochloric acid (10 drops) was heated under reflux for 40 min. and then concentrated to a small volume and allowed to cool to give IX (1.36 g.), m. p. 170∼172°C. Recrystallization from ethanol afforded cream-yellow prisms, m. p. 171∼172°C.

Found: C, 77.74; H, 4.56; N, 8.08. Calcd. for $C_{22}H_{16}O_2N_2$: C, 77.63; H, 4.74; N, 8.23%.

λ_{max}^{MeOH} mμ (log ε); 252 (4.45), 292 (4.50), 393 (3.91).

4-[5-Phenyl-1-(*p*-tolyl)-3-pyrazolyl]tropolone (X). — A mixture of epoxide (V) (270 mg.), ethanol (7 ml.) and *p*-tolylhydrazine (180 mg.) was heated under reflux for 40 min. and allowed to cool to give the *p*-tolylhydrazone (VIII) (350 mg.), m. p. 188∼189°C. Recrystallization from ethanol-dioxane formed reddish orange prisms, m. p. 192∼193°C.

Found: C, 73.74; H, 5.33; N, 7.36. Calcd. for $C_{23}H_{20}O_3N_2$: C, 74.17; H, 5.41; N, 7.52%.

A mixture of this *p*-tolylhydrazone (90 mg.), ethanol (5 ml.) and 6 N hydrochloric acid (1 drop) was heated under reflux for 1 hr. and then allowed to cool to give X (80 mg.), m. p. 166∼168°C. Recrystallization from ethanol afforded cream-yellow needles, m. p. 169.5∼170°C.

Found: C, 77.72; H, 4.97; N, 7.30. Calcd. for $C_{23}H_{18}O_2N_2$: C, 77.95; H, 5.12; N, 7.91%.

λ_{max}^{MeOH} mμ (log ε); 252 (4.45), 292 (4.46), 393 (3.90).

The Oxidation of II.—Into a solution of II (530 mg.) in a mixture of 6 N potassium hydroxide solution (2.5 ml.) and water (60 ml.), powdered potassium permanganate (2.80 g.) was stirred in small portions at room temperature; 2.56 g. of potassium permanganate were consumed rapidly. After stirring was continued for a further 3 hr., the excess permanganate was decomposed by the addition of methanol, the manganese dioxide which separated out was filtered off, and the filtrate was acidified to pH 2 with 6 N hydrochloric acid and extracted with ether. After the solution had been dried over anhydrous sodium sulfate, the solvent was removed from the extract to leave colorless crystals (330 mg.), m. p. 230∼234°C. Recrystallization from aqueous methanol afforded 5-phenylpyrazole-3-carboxylic acid (XI) as colorless needles, m. p. 234∼235°C (decomp.); it was identified by admixture with an authentic specimen[3] and also by a comparison of their infrared spectra.

Found: C, 63.42; H, 3.96; N, 14.47. Calcd. for $C_{10}H_8O_2N_2$: C, 63.82; H, 4.29; N, 14.89%.

The Oxidation of IX.—To a solution of IX (680 mg.) in a mixture of 6 N potassium hydroxide solution (5.5 ml.) and water (180 ml.), powdered potassium permanganate (2.95 g.) was added in small portions; the reaction mixture was treated in a manner similar to that above to give colorless crystals (430 mg.), m. p. 175∼182°C. Recrystallization from aqueous methanol afforded 1,5-diphenylpyrazole-3-carboxylic acid (XII) as colorless needles, m. p. 183∼184°C; it was identified by admixture with an authentic specimen[4] and by a comparison of their infrared spectra.

Found: C, 73.29; H, 4.96; N, 10.47. Calcd. for $C_{16}H_{12}O_2N_2$: C, 72.71; H, 4.58; N, 10.60%.

The *p*-Tolylazo Compound of II. — Into a solution of II (260 mg.) in pyridine (1.7 ml.), a solution of *p*-toluenediazonium chloride prepared from *p*-toluidine (120 mg.) by the usual method, was stirred under cooling. The mixture was then stirred for an additional 2 hr. and allowed to stand overnight. The crystals so obtained were collected by filtration and washed with a small amount of benzene to give 4-(5-phenyl-3-pyrazolyl)-5-(*p*-tolylazo)tropolone (250 mg.) as orange crystals, m. p. 220.5∼221°C.

Found: C, 72.02; H, 4.47; N, 14.78. Calcd. or $C_{23}H_{18}O_2N_4$: C, 72.23; H, 4.74; N, 14.65%.

λ_{max}^{MeOH} mμ (log ε); 255 (4.57), 422 (4.50).

Methyl Ethers of II: 2-Methoxy-4-(5-phenyl-3-pyrazolyl)tropone (XIIIa) and 2-Methoxy-6-(5-phenyl-3-pyrozolyl)tropone (XIIIb).—To a solution of II (800 mg.) in ethyl acetate (150 ml.), an ethereal solution of diazomethane (13 ml.) was added. After additional stirring for 3 hr., the mixture was concentrated to a small volume to give crystals (690 mg.); m. p. 207∼213°C. Recrystallization from methanol gave XIIIb (330 mg.) as cream-yellow needles, m. p. 252∼253°C.

Found: C, 73.27; H,. 4.92; N, 9.71. Calcd. for $C_{17}H_{14}O_2N_2$: C, 73.36; H, 5.07; N, 10.07%.

λ_{max}^{MeOH} mμ (log ε); 280 (4.67).

The crystals, obtained from the mother liquor by the removal of the solvent, were fractionally recrystallized from methanol to give XIIIa (180 mg.) as cream-yellow plates, m. p. 235°C.

Found: C, 73.05; H, 4.99; N, 9.71. Calcd. for $C_{17}H_{14}O_2N_2$: C, 73.36; H, 5.07; N, 10.07%.

λ_{max}^{MeOH} mμ (log ε); 273 (4.55), 368 (4.17).

The heating of XIIIa or XIIIb with a dilute potassium hydroxide solution in aqueous ethanol gave II in a 60% yield.

Methyl Ethers of IX: 2-Methoxy-4-(1, 5-diphenyl-3-pyrazolyl)tropone (XIVa) and 2-Methoxy-6-(1, 5-diphenyl-3-pyrozolyl)tropone (XIVb).—Into a solution of IX (1.00 g.) in ethyl acetate (70 ml.), an ethereal solution of diazomethane (15 ml.) was stirred under cooling. After additional stirring for 4 hr., the mixture was allowed to stand overnight to give XIVb (440 mg.), m. p. 220∼221°C, which was recrystallized from methanol as cream-colored needles, m. p. 223∼224°C.

Found: C, 77.81; H, 4.88; N, 7.87. Calcd. for $C_{23}H_{18}O_2N_2$: C, 77.95; H, 5.12; N, 7.91%.

λ_{max}^{MeOH} mμ (log ε); 247 (4.40), 292 (4.56).

Removing the solvent from the mother liquor afforded crystals, from which XIVa (260 mg.) was obtained as pale yellow micro-needles, m. p. 168~169°C, after recrystallization from methanol.

Found: C, 77.71; H, 4.89; N, 7.94. Calcd. for $C_{23}H_{18}O_2N_2$: C, 77.95; H, 5.12; N, 7.91%.

λ_{max}^{MeOH} mμ (log ε); 252 (4.54), 370 (4.22).

The heating of XIVa or XIVb with a 2 N potassium hydroxide solution in aqueous ethanol afforded IX in a 60% yield.

Diethyl 2-Amino-5-(5-phenyl-3-pyrozolyl)azulene-1,3-dicarboxylate (XV). — To a sodium ethoxide solution, prepared by dissolving sodium (300 mg.) in anhydrous ethanol (2 ml.), ethyl cyanoacetate (300 mg.) and then a solution of XIIIa (300 mg.) in anhydrous ethanol (50 ml.) were added. After having been allowed to stand for one day, the mixture was diluted with water (150 ml.) and extracted with benzene. The removal of the solvent from the extract left an oily substance, which was crystallized by the addition of a small amount of methanol, giving XV (170 mg.) as orange micro-crystals, m. p. 237~238°C.

Found: C, 69.92; H, 5.19; N, 9.36. Calcd. for $C_{25}H_{23}O_4N_3$: C, 69.91; H, 5.40; N, 9.76%.

λ_{max}^{MeOH} mμ (log ε); 259 (4.61), 343 (4.91), 462 (3.45). IR (KBr); 3420, 3290 (NH_2); 3200 (NH); 1667 (C=O) cm^{-1}.

Diethyl 2-Amino-5-(1,5-diphenyl-3-pyrazolyl)azulene-1,3-dicarboxylate (XVI) and 1,3-Dicyano-2-hydroxy-5-(1,5-diphenyl-3-pyrozolyl)azulene (XVII). —Into a suspension of ethyl sodiocyanoacetate in ethanol, prepared from sodium (30 mg.), anhydrous ethanol (2 ml.) and ethyl cyanoacetate (250 mg.), a solution of methyl ether (a mixture of XIVa and XIVb) (250 mg.) in a mixture of anhydrous ethanol (15 ml.) and dry dioxane (10 ml.) was stirred. After having been allowed to stand for one day, the mixture was diluted with water and extracted with benzene. The removal of the solvent from the extract afforded XVI (190 mg.) as orange prisms, m. p. 179°C, after recrystallization from methanol.

Found: C, 73.89; H, 5.16; N, 8.18. Calcd. for $C_{31}H_{27}O_4N_3$: C, 73.64; H, 5.39; N, 8.31%.

λ_{max}^{MeOH} mμ (log ε); 253 (4.58), 346 (4.96), 462 (3.50). IR (KBr); 3440, 3310 (NH_2); 1658 (C=O) cm^{-1}.

An aqueous layer was acidified with 6 N hydrochloric acid and extracted with benzene. The solvent was removed from the extract and the residue was recrystallized from ethanol to give XVII (50 mg.) as orange micro-crystals, m. p. over 280°C.

Found: C, 78.64; H, 3.68; N, 13.22. Calcd. for $C_{27}H_{16}ON_4$: C, 78.60; H, 3.88; N, 13.59%.

λ_{max}^{MeOH} mμ (log ε); 233 (4.64), 345 (4.96), 393 (4.00), 470 (3.54). IR (KBr); 3010 (broad) (OH); 2210 (C≡N) cm^{-1}.

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