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Synthesis of Pyrazolone Derivatives. XXVI.[1] Reaction of 1-Methyl-2-phenyl-1,2,3,10-tetrahydro-4*H*-benzo[6,7]thiepino[3,4-*c*]pyrazole-3,4-dione with Dimethyl Acetylenedicarboxylate

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The Michael and the Diels-Alder reactions of 1-methyl-2-phenyl-1,2,3,10-tetrahydro-4*H*-benzo[6,7]thiepino[3,4-*c*]pyrazole-3,4-dione (**1**) with dimethyl acetylenedicarboxylate (**2**) were examined, and the fascinating reactions which gave two novel heterocycles were found: dimethyl 1,2-dihydro-1-methyl-3-oxo-2-phenyl-3*H*-benzothieno[3,2-*e*]indazole-9,10-dicarboxylate (**3**) and dimethyl 1,2-dihydro-4-hydroxy-1-methyl-3-oxo-2-phenyl-3*H*-[2]benzothiopyrano[4,3,2-*f*,*g*]indazole-8,9-dicarboxylate (**15**). The mechanisms of the formations of **3** and **15** were discussed.

For pharmacological evaluation some N,N-dimethylethylenediamine derivatives of **3** and **15** were synthesized.

We reported[3] earlier the synthesis of 1-methyl-2-phenyl-1,2,3,10-tetrahydro-4*H*-benzo-[6,7]thiepino[3,4-*c*]pyrazole-3,4-dione (**1**), which is of interest in its reactivity due to a new heterotricyclic ring system. During the investigation, the selective reduction of its α,β-unsaturated ketone and C=C double bond with sodium borohydride was found.[4] Such a reactivity of pyrazolone C=C double bond of **1** and its enolizable structure prompted us to study the reaction of **1** with dimethyl acetylenedicarboxylate (**2**). The presence of the enol-form (**1-b**) was supported by the ultraviolet (UV) spectrum of **1** in a basic medium.[5]

Thus, it appeared interesting for us to study whether the reaction of **1** with **2** in basic media would undergo (A) Michael addition of the active allylic methylene group of **1-a** to **2**, or (B) 1,4-addition(Diels-Alder reaction) or 1,2-addition of **2** to the enol-form (**1-b**). Furthermore, when we investigated the reaction of **1** with **2** in non-basic media, a nucleophilic attack by the 3d-orbital of the sulfur atom of **1** to the acetylenic carbon atom of **2** was caused.

In this paper we wish to report the results of the fascinating reaction of **1** with **2**, which gave two novel heterocycles according to conditions of the solvents used: dimethyl 1,2-dihydro-1-methyl-3-oxo-2-phenyl-3*H*-benzothieno[3,2-*e*]indazole-9,10-dicarboxylate (**3**) and dimethyl 1,2-dihydro-4-hydroxy-1-methyl-3-oxo-2-phenyl-3*H*-[2]benzothiopyrano[4,3,2-*f*,*g*]indazole-8,9-dicarboxylate (**15**).

The reaction of **1** with an excess of **2** at 170—180° for 30 min gave a compound of mp 280—282° (44.8% yield), to which the structure (**3**) was assigned from spectral data and the following experiments: elemental analysis and mass spectrum [*m/e*: 446 (M^+)] established the formula of $C_{24}H_{18}O_5N_2S$, which suggested that a molecule of H_2O was eliminated from the formula $C_{24}H_{20}O_6N_2S$ (an adduct of **1** and **2**). In contrast with the compound (**1**), the compound (**3**) showed no aryl ketone-absorption in the infrared (IR) spectrum and displayed no methylene-absorption in the nuclear magnetic resonance (NMR) spectrum. The NMR spectrum of **3** showed an N-methyl resonance at δ 3.18 ppm, two methyl ester resonances at δ 4.04

1) Part XXV: I. Ito, T. Ueda, and N. Oda, *Yakugaku Zasshi*, **95**, 879 (1975).
2) Location: *a*) *Tanabe-dori, Mizuho-ku, Nagoya*; *b*) *Hongo, Bunkyo-ku, Tokyo*.
3) I. Ito and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **18**, 1994 (1970).
4) I. Ito and T. Ueda, *Tetrahedron*, **30**, 1027 (1974).
5) P. Grossmann, *Z. Physik. Chem.* (Frankfurt), **109**, 305 (1924).

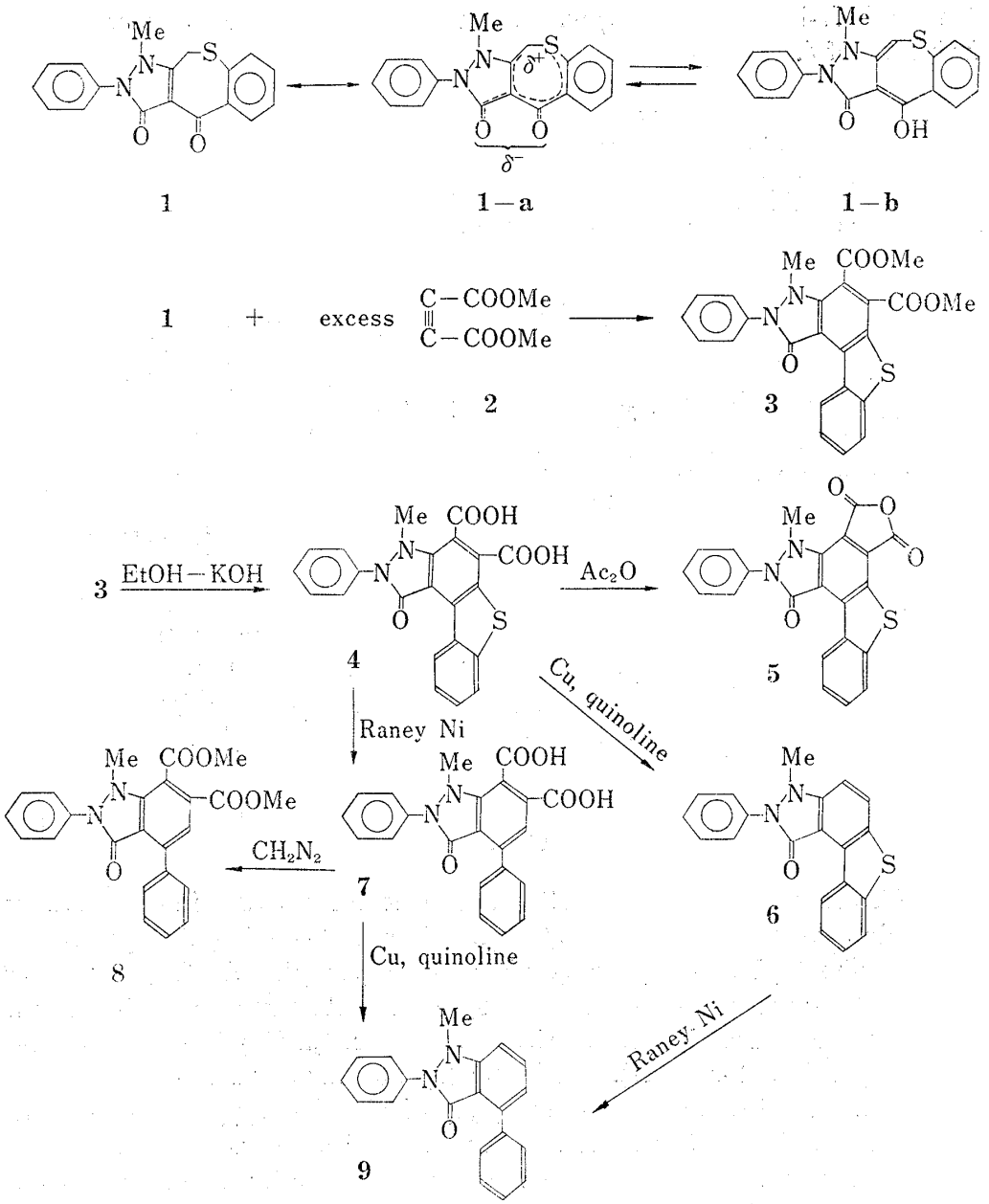


Chart 1

and 4.09 ppm, and nine aromatic protons at δ 7.20—7.90 ppm. In contrast with **1**, bathochromic shift in the UV spectrum of **3** indicated a formation of a new conjugate system. Hydrolysis of the diester (**3**) gave, 1,2-dihydro-1-methyl-3-oxo-2-phenyl-3*H*-benzothieno[3,2-*e*]-indazole-9,10-dicarboxylic acid (**4**), which was converted to 1,2-dihydro-1-methyl-3-oxo-2-phenyl-3*H*-benzothieno-[3,2-*e*]indazole-9,10-dicarboxylic anhydride (**5**) by refluxing in acetic anhydride. Decarboxylation of **4** with copper powder in quinoline afforded 1,2-dihydro-1-methyl-2-phenyl-3*H*-benzothieno[3,2-*e*]indazol-3-one (**6**). Its NMR spectrum showed the signals of eleven aromatic protons at δ 7.40—8.30 ppm and indicated that the two carboxylate groups had attached to an aromatic ring. Desulfurization of **4** in the presence of Raney nickel catalyst in an alkaline medium gave 1,2-dihydro-2,4-diphenyl-1-methyl-3-oxo-3*H*-indazole-6,7-dicarboxylic acid (**7**), whose treatment with diazomethane afforded dimethyl 1,2-dihydro-2,4-diphenyl-1-methyl-3-oxo-3*H*-indazole-6,7-dicarboxylate (**8**). The NMR spectrum of **8** showed the signals of eleven aromatic protons at δ 7.20—7.70 ppm and indicated that a sulfur atom was attached to two aromatic rings. Decarboxylation of **7** provided 1,2-dihydro-2,4-

diphenyl-1-methyl-3*H*-indazol-3-one (**9**) which was identical with the compound derived from the desulfurization of **6**.

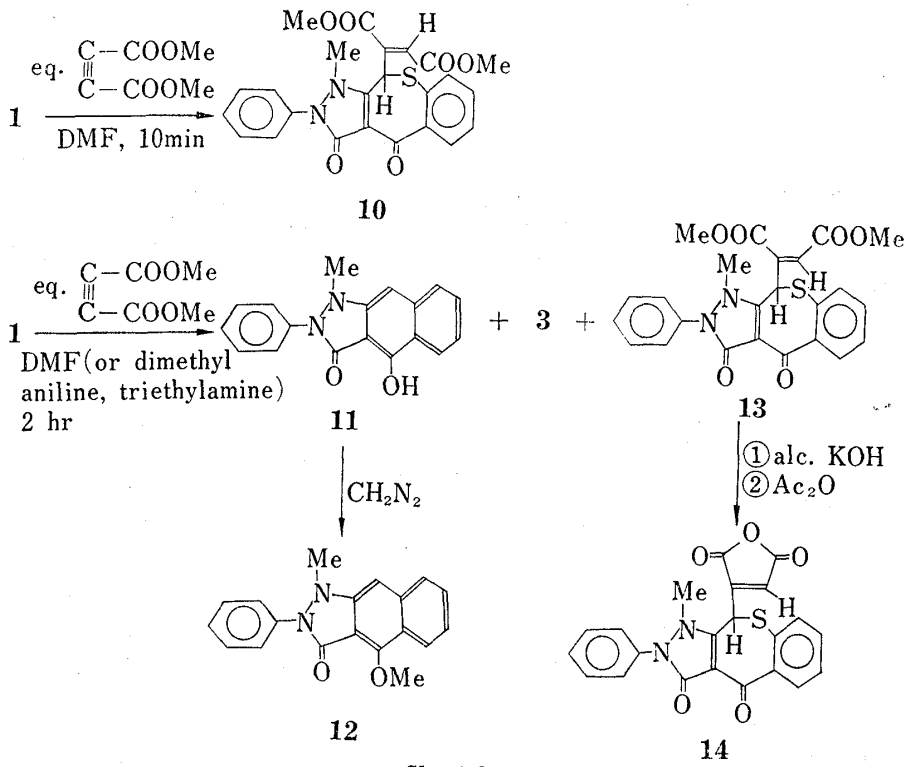


Chart 2

Reaction of **1** with an equimolar dimethyl acetylenedicarboxylate in dimethylformamide at 150° for 10 min gave an adduct ($C_{24}H_{20}O_6N_2S$) of mp 184—185° (6.5% yield) which was characterized as dimethyl 1,2-dihydro-3,4-dioxo-1-methyl-2-phenyl-1,2,3,10-tetrahydro-4*H*-benzo[6,7]thiepino[3,4-*c*]pyrazole-10-fumarate (**10**) by the elemental analysis, IR and NMR spectra. When the above reaction was carried out for 2 hr, 1,2-dihydro-4-hydroxy-1-methyl-2-phenyl-3*H*-benz[*f*]indazol-3-one (**11**), compound (**3**), and dimethyl 1,2-dihydro-3,4-dioxo-1-methyl-2-phenyl-1,2,3,10-tetrahydro-4*H*-benzo[6,7]thiepino[3,4-*c*]pyrazole-10-maleate (**13**) were obtained. The assignment of structure **11** was based on elemental analysis, IR, mass [*m/e*: 290 (M^+)], and NMR spectral data which located one N-methyl resonance at δ 3.20 ppm, a hydroxyl group at δ 8.55 ppm (disappeared on deuteration) and ten aromatic protons at δ 6.95—7.95 ppm. Treatment of **11** with diazomethane afforded 1,2-dihydro-4-methoxy-1-methyl-2-phenyl-3*H*-benzo[*f*]indazol-3-one (**12**). Compound (**11**) was also obtained when **1** was heated in dimethylformamide without **2**. Galt, *et al.*[6] obtained phenanthridines by thermal desulfurization of dibenzothiazepines. Thus, it seems that **11** was obtained by thermal desulfurization of **1** in refluxing dimethylformamide. Compound (**13**) was characterized by elemental analysis, IR and NMR spectra. Heindel, *et al.*[7] reported the chemical shift of the vinyl protons and methyl esters in an isomeric acetylenedicarboxylate adduct. Compound (**10**) displayed a vinyl proton resonance at δ 7.05 ppm and the ester methyls at δ 3.45 and δ 3.72 ppm, characteristic of the fumarate geometry. The esters themselves are in slightly different electronic environments from those of the maleate (**13**) which appear under the same peak at δ 3.80 ppm. The vinyl proton resonance of **13** was observed at δ 5.00 ppm by the shielding effects of the aromatic ring. Hydrolysis of the maleate (**13**) followed by reflux in acetic anhydride gave 1,2-dihydro-3,4-dioxo-1-methyl-2-phenyl-1,2,3,10-tetrahydro-4*H*-

6) R.H.B. Galt, J.D. Loudon, and A.D.B. Sloan, *J. Chem. Soc.*, **1588** (1958).
7) N.D. Heindel, V.B. Fish, M.F. Ryan, and A.R. Lepley, *J. Org. Chem.*, 32, 2678 (1967).

benzo[6,7-]thiepino[3,4-*c*]pyrazole-10-maleic anhydride (**14**), whose IR spectrum showed characteristic anhydride absorptions at 1850 and 1780 cm^{-1}. Its mass spectrum [*m/e*: 418 (M^+)] agreed with the assigned structure.

The reaction of **1** with an equimolar **2** in dimethylaniline or triethylamine also gave the compounds (**3**, **11**, and **13**), which were not obtained in the solvents such as xylene, decaline or dioxane. The mechanism of the formation of **3**, **10**, and **13** may be explained by the following reaction scheme (Chart 3).

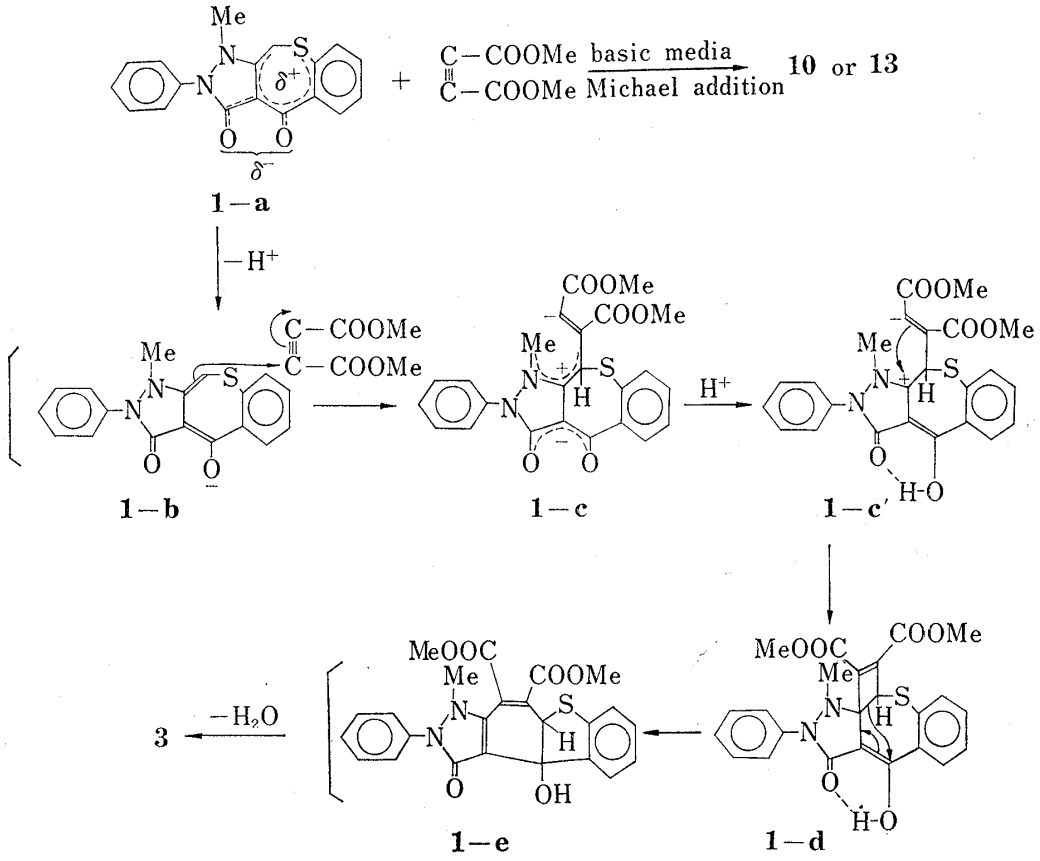


Chart 3

The formation of the adducts (**10**, **13**) appears to proceed by the Michael reaction of the active allylic methylene group of **1-a** with **2** in basic media. Diels-Alder adduct of **2** to the enol-form or diene-type (**1-b**) was not obtained but **3** was afforded. This fact indicates the mechanism of the formation of **3** may proceed predominantly by the 1,2-addition of **2** to the enamine-type (**1-c**), forming four-membered ring (**1-d**) which undergoes ring expansion to give **1-e**. Dehydration of **1-e** may give **3**.

The reaction of **1** with an equimolar **2** in refluxing xylene (or dioxane, decaline) gave red crystals of mp 215—217° (**15**) in 75.5% yield. The IR spectrum indicated the presence of hydroxyl group and the NMR spectrum showed two methyl ester resonances at δ 3.87 and δ 3.89 ppm, N-methyl at δ 3.12 ppm, hydroxyl group at δ 5.70 ppm (disappeared on deuteration), and eight aromatic protons at δ 6.90—8.00 ppm. Methylene or methine proton signal was not observed. High resolution mass spectral analysis indicated the formula $C_{24}H_{18}O_6N_2S$ (**15**), *m/e*: 462.0896 (M^+), suggesting that two hydrogen atoms were eliminated from the formula $C_{24}H_{20}O_6N_2S$ (an adduct of **1** and **2**). That the accounted aromatic hydrogen atoms were eight indicated the occurrence of a new substitution on a benzene ring. Hydrolysis of the ester (**15**) gave 1,2-dihydro-4-hydroxy-1-methyl-3-oxo-2-phenyl-3*H*-[2]benzothiopyrano[4,3,2-*f*,*g*]indazole-8,9-dicarboxylic acid (**16**), whose reflux in acetic anhydride afforded 4-acetoxy-

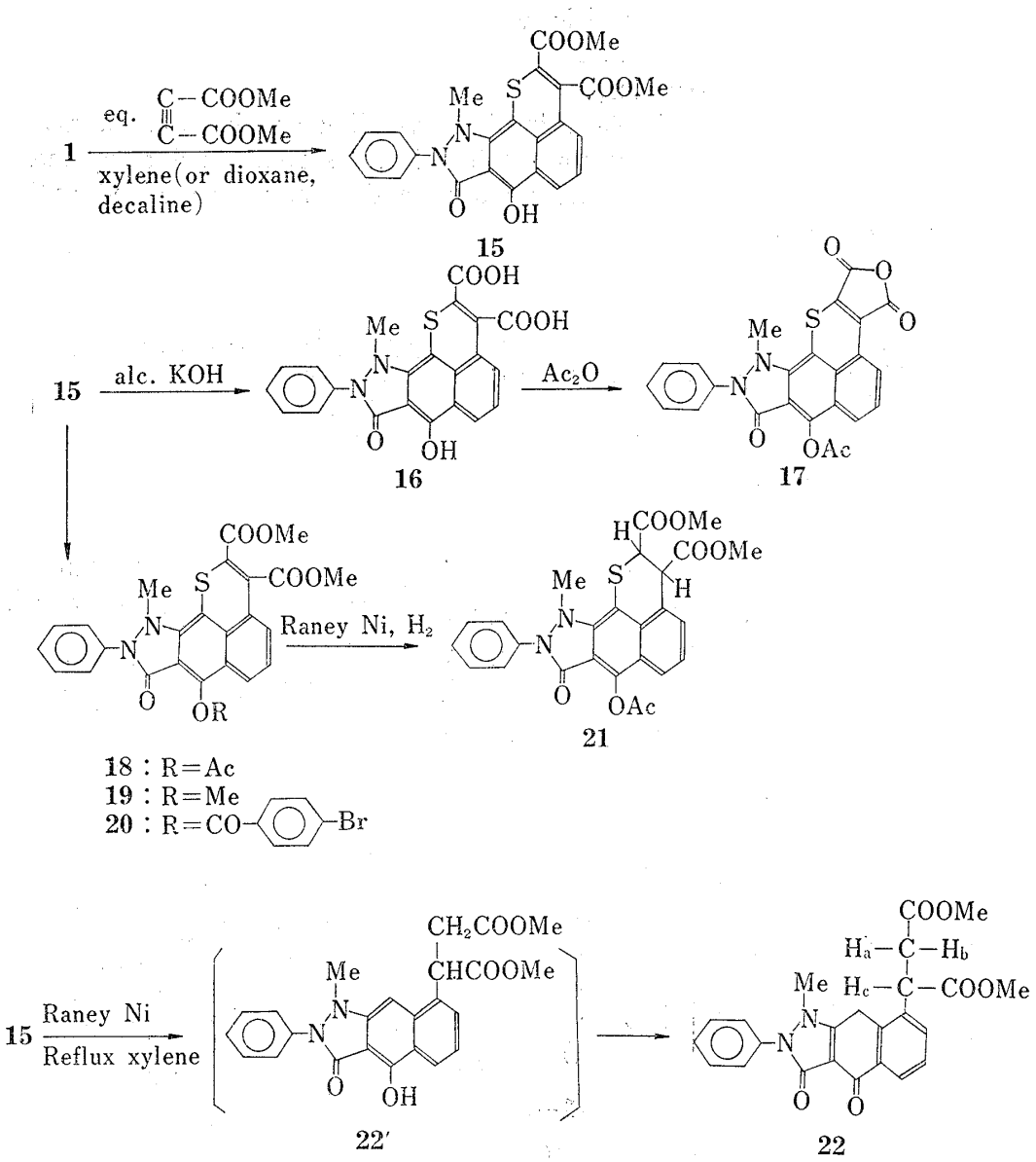


Chart 4

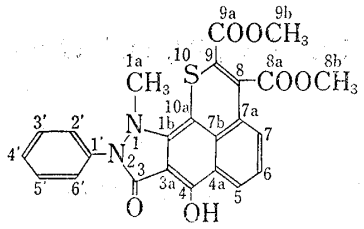
1,2-dihydro-1-methyl-3-oxo-2-phenyl-3*H*-[2]benzothiopyrano[4,3,2-*f*,*g*]indazole-8,9-dicarboxylic anhydride (**17**). Reflux of **15** in acetic anhydride presented dimethyl 4-acetoxy-1,2-dihydro-1-methyl-3-oxo-2-phenyl-3*H*-[2]-benzothiopyrano[4,3,2-*f*,*g*]indazole-8,9-dicarboxylate (**18**). Treatment of **15** with diazomethane gave dimethyl 1,2-dihydro-4-methoxy-1-methyl-3-oxo-2-phenyl-3*H*-[2]benzothiopyrano[4,3,2-*f*,*g*]indazole-8,9-dicarboxylate (**19**) which was identical with the compound derived from **16**. Hydrogenation of **18** in the presence of Raney nickel catalyst gave dimethyl 4-acetoxy-1-methyl-3-oxo-2-phenyl-1,2,8,9-tetrahydro-3*H*-[2]benzothiopyrano[4,3,2-*f*,*g*]indazole-8,9-dicarboxylate (**21**). Desulfurization of **15** in the presence of Raney nickel catalyst in refluxing xylene afforded dimethyl 3,4-dioxo-1-methyl-2-phenyl-1,2,4,9-tetrahydro-3*H*-indazole-8-succinic acid (**22**).

The structure of **15** was supported by its ^{13}C NMR spectrum (Table I). However, the final structural confirmation was carried out by the X-ray crystallographic analysis of the *p*-bromobenzoate (**20**) of **15**. A detailed account of the X-ray work will be reported later.

Formation of **15** from **1** may be rationalized by the following reaction mechanism (Chart 5).

In the reaction of **1** with **2** in non-basic media, initially the acetylenic carbon atom of **2** appears to undergo nucleophilic attack by the 3d-orbital of the sulfur atom of **1** to give **1-f**,

TABLE I. ^{13}C NMR Spectrum of **15**



Observed shift (ppm)	Carbon atom	Observed shift (ppm)	Carbon atom
37.6	1 a	128.7	4 a
52.9	9 b (or 8 b)	129.2	5, 6 and 7 b
53.2	8 b (or 9 b)	133.4	9
102.0	3 a	134.6	1′
105.2	1 b	138.2	7 a
122.2	2′ and 6′	142.7	10 a
122.5	8	149.8	4
124.7	4′	161.9	9 a (or 8 a)
125.0	7	162.5	8 a (or 9 a)
126.2	3′ and 5′	167.4	3

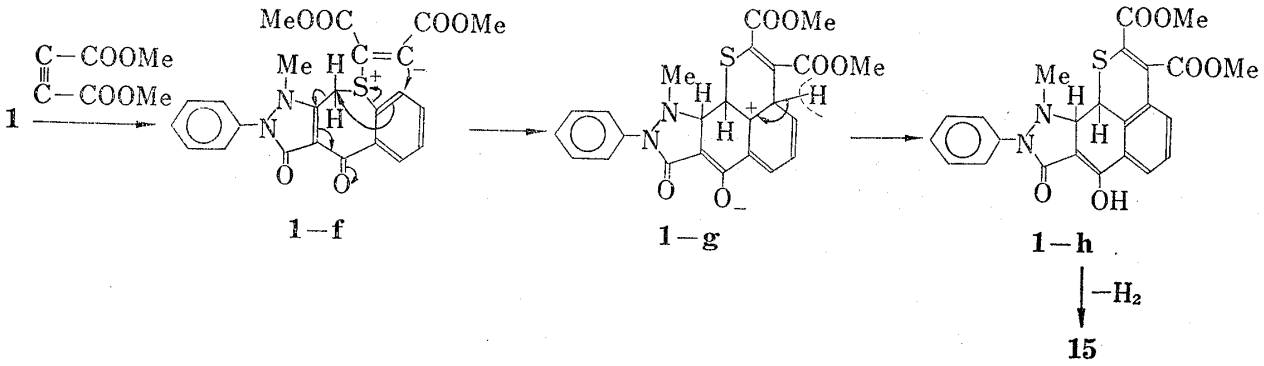


Chart 5

which may subsequently undergo intramolecular attack of the anion (S_Ni reaction) at the aromatic carbon atom of the *ortho* position of the sulfur atom to afford **1-g**. Formation of **15** may be explained by the aromatization of **1-h**.

Compound (**19**) was hydrolyzed with ethanolic potassium hydroxide to give the crude dicarboxylic acid (**23**), which was washed with ether. Evaporation of the ether from the washings gave a small amount of the anhydride (**24**), which was identical with the compound obtained by the reaction of **23** with acetic anhydride. Its NMR spectrum indicated the presence of ethoxyl group instead of methoxyl group. Thus the compound (**24**) was assigned the structure, 4-ethoxy-1,2-dihydro-1-methyl-3-oxo-2-phenyl-3*H*-[2]benzothiopyrano[4,3,2-*f*,*g*]-indazole-8,9-dicarboxylic anhydride.

When **19** was treated with methanolic potassium hydroxide followed by reflux with acetic anhydride, 4-methoxy-1,2-dihydro-1-methyl-3-oxo-2-phenyl-3*H*-[2]benzothiopyrano[4,3,2-*f*,*g*]indazole-8,9-dicarboxylic anhydride (**26**).

The reaction of **24** or **26** with N,N-dimethylaminoethylenediamine gave 8,10-dioxo-9-(2-dimethylamino)ethyl-4-ethoxy-1-methyl-2-phenyl-1,2,8,9,10-pentahydro-3*H*-[2]benzothiopyrano[2,3-*c*]pyrrolo[6,5,4-*f*,*g*]indazol-3-one (**27**) or 8,10-dioxo-9-(2-dimethylamino)ethyl-4-methoxy-1-methyl-2-phenyl-1,2,8,9,10-pentahydro-3*H*-[2]-benzothiopyrano[2,3-*c*]pyrrolo[6,5,4-*f*,*g*]indazol-3-one (**28**). Similarly, 9,11-dioxo-10-(2-dimethylamino)ethyl-1-methyl-2-phenyl-

1,2,9,10,11-pentahydro-3*H*-[1]benzothieno[3,2-*e*]pyrrolo[3,4-*g*]indazol-3-one (**29**) was prepared from **5**.

The pharmacological evaluation of **27**, **28**, and **29** are now under investigation.

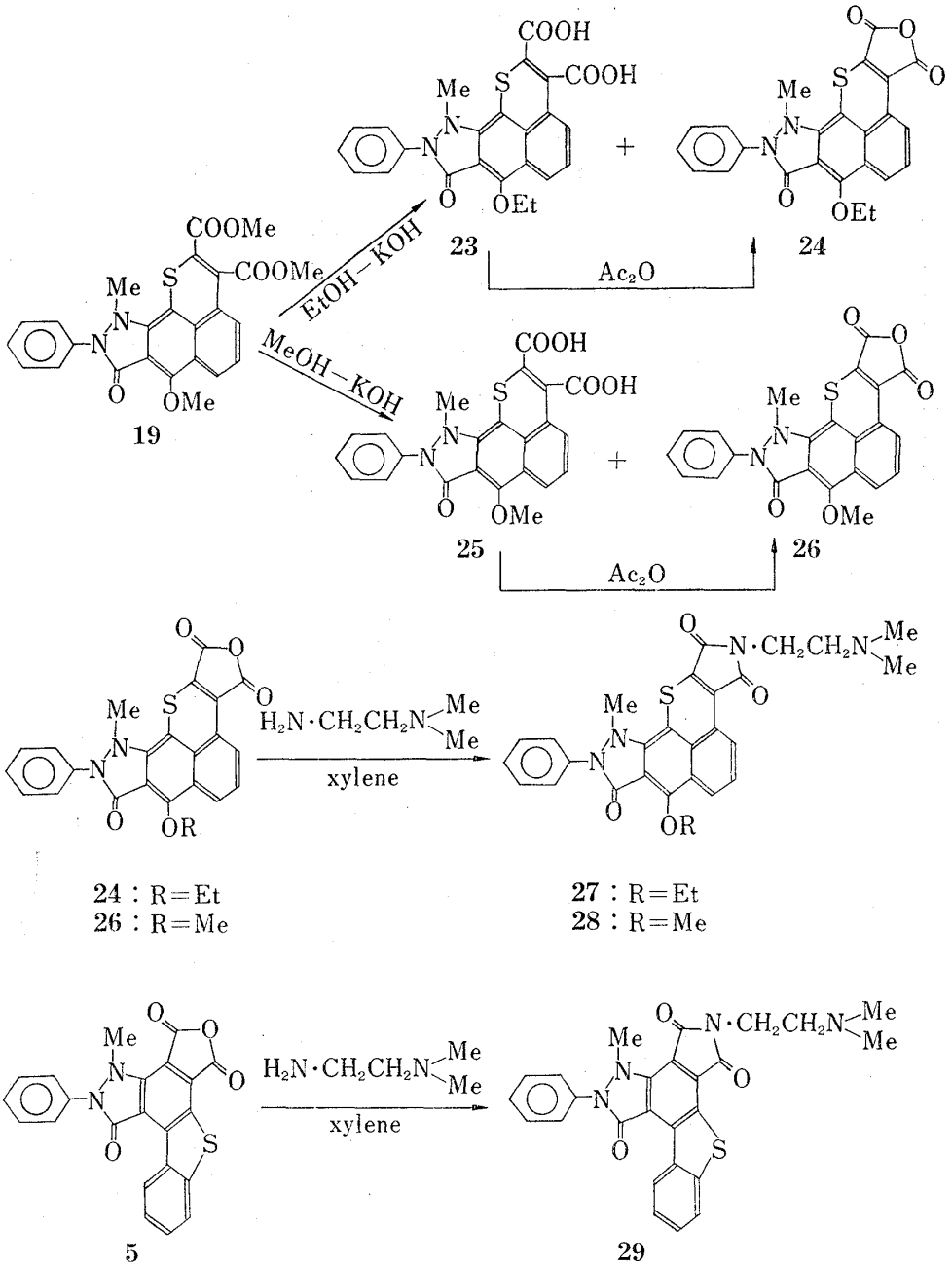


Chart 6

Experimental

All the melting points were determined on a Yanagimoto Micro Melting Point apparatus and are not corrected. The UV spectra were recorded with a Hitachi Recording Spectrophotometer EPS-3T, and the IR spectra were measured with a Nihon Bunko Spectroscopic Co. Ltd. Model IR-S. The NMR spectra were measured with a Japan Electron Optics Laboratory Co., JNM-100 spectrometer using tetramethylsilane as internal standard. Mass spectra were evaluated on a Hitachi Mass Spectrometer, Model RMU-6E, equipped with a double focusing system. High resolution mass spectral analysis was carried out with a Japan Electron Optics Laboratory Co. JMS-D 100 Mass Spectrometer. ^{13}C NMR spectrum was measured at 25.149 MHz using a JNM-PS-100 NMR spectrometer operating in the Fourier transform (F. T.) mode. The spectrum

was run in $CDCl_3$ solution using TMS standard. The spectral width was 12.5 μ sec (45°) and 4095 data points were used.

UV Spectra of **1**: λ_{max}^{EtOH} mμ (log ε): 240 (4.17), 325 (3.99), $\lambda_{max}^{EtOH\text{-}1\%NaOH(100:1)}$ mμ (log ε): 325 (4.08), $\lambda_{max}^{EtOH\text{-}1\%NaOH(10:1)}$ mμ (log ε): 325 (4.20).

Dimethyl 1,2-Dihydro-1-methyl-3-oxo-2-phenyl-3*H*-benzothieno[3,2-*e*]indazole-9,10-dicarboxylate (3)——A mixture of **1** (0.5 g) and dimethyl acetylenedicarboxylate (2 g) was heated at 170—180° in an oil-bath for 30 min. On cooling yellow crystals appeared, which were washed with a small amount of $CHCl_3$. Yellow prisms of mp 280—282° (from $CHCl_3$). Yield 310 mg (44.8%). IR ν_{max}^{KBr} cm^{-1}: 1735 (ester C=O). NMR $\delta_{ppm}^{CDCl_3}$: 3.18 (3H, singlet, N–Me), 4.04 (3H, singlet, –COOMe), 4.09 (3H, singlet, –COOMe), 7.20—7.90 (9H, multiplet, aromatic protons). UV λ_{max}^{EtOH} mμ (log ε): 231 (4.20), 276 (4.03), 357 (3.80). Mass Spectrum *m/e*: 446 (M^+). *Anal.* Calcd. for $C_{24}H_{18}O_5N_2S$: C, 64.56; H, 4.06; N, 6.27. Found: C, 64.40; H, 4.01; N, 6.05.

1,2-Dihydro-1-methyl-3-oxo-2-phenyl-3*H*-benzothieno[3,2-*e*]indazole-9,10-dicarboxylic Acid (4)——Compound **3** (0.5 g) was dissolved in 10 ml of ethanolic KOH which contained 370 mg of KOH. The mixture was refluxed for 30 min. EtOH was distilled and the residue was dissolved in water. An insoluble substance was filtered off and the filtrate was neutralized with 10% H_2SO_4 to obtain precipitates, which were dissolved in saturated $NaHCO_3$ solution and the resulting solution was neutralized with 10% H_2SO_4 to obtain precipitates. Prisms of mp>270° (from EtOH). Yield 386 mg (82.3%). IR ν_{max}^{KBr} cm^{-1}: 3180—2300, 1730 (–COOH). *Anal.* Calcd. for $C_{22}H_{14}O_5N_2S$: C, 63.15; H, 3.37; N, 6.70. Found: C, 62.98; H, 3.16; N, 6.52.

1,2-Dihydro-1-methyl-3-oxo-2-phenyl-3*H*-benzothieno[3,2-*e*]indazole-9,10-dicarboxylic Anhydride (5)——Compound **4** (200 mg) was dissolved in cetic anhydride (3 ml) and the solution was refluxed for 3 hr. After cooling red crystals were collected by filtration. Needles of mp>270° (from Ac_2O). Yield 156 mg (81.7%). IR ν_{max}^{KBr} cm^{-1}: 1850, 1670. *Anal.* Calcd. for $C_{22}H_{12}O_4N_2S$: C, 65.99; H, 3.02; N, 7.00. Found: C, 65.75; H, 3.02; N, 6.83.

1,2-Dihydro-1-methyl-2-phenyl-3*H*-benzothieno[3,2-*e*]indazol-3-one (6)——A mixture of **4** (300 mg), copper powder (50 mg), and quinoline (2 ml) was heated in an oil-bath (180—200°) for 7 hr. Copper powder was filtered off and the filtrate was evaporated to dryness. The residue was washed with saturated $NaHCO_3$ solution and was column-chromatographed on silica-gel (Mallinckrodt, 100 mesh). From $CHCl_3$-eluate prisms were obtained. Recrystallization from EtOH gave needles of mp 163—164°. Yield 47 mg (19.8%). IR ν_{max}^{KBr} cm^{-1}: 1670 (amide C=O). NMR $\delta_{ppm}^{CDCl_3}$: 3.42 (3H, singlet, N–Me), 7.40—8.30 (11H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{20}H_{14}ON_2S$: C, 72.70; H, 4.27; N, 8.48. Found: C, 72.63; H, 4.25; N, 8.49.

Dimethyl 1,2-Dihydro-2,4-diphenyl-1-methyl-3-oxo-3*H*-indazole-6,7-dicarboxylate (8)——Compound **4** (300 mg) was dissolved in 10% NaOH solution. Raney nickel catalyst (1 g) was added and the mixture was heated in an autoclave for 5 hr under a pressure of 80 kg/cm^2 of H_2 at 60°. The catalyst was filtered off, and the filtrate was neutralized with 10% H_2SO_4 to obtain precipitates, which were dissolved in 50 ml of diazomethane–ether solution (1.3 g of diazomethane was generated from 5 g of N-nitrosomethylurea). Evaporation of ether gave needles of mp 176—177° (from EtOH). Yield 43 mg (14.3%). Negative sulfur-test. IR ν_{max}^{KBr} cm^{-1}: 1740, 1700 (ester C=O). NMR $\delta_{ppm}^{CDCl_3}$: 3.27 (3H, singlet, N–Me), 3.95 (3H, singlet, –COOMe), 4.03 (3H, singlet, –COOMe), 7.20—7.70 (11H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{24}H_{20}O_5N_2$: C, 69.22; H, 4.84; N, 6.73. Found: C, 68.99; H, 4.77; N, 6.82.

1,2-Dihydro-2,4-diphenyl-1-methyl-3*H*-indazol-3-one (9)——(a) A mixture of **4** (200 mg), ethanolic KOH (20 ml) and Raney nickel catalyst (2 g) were refluxed for 10 hr. The solvent was distilled and the residue was dissolved in water. The aqueous solution was neutralized with 10% H_2SO_4 to obtain precipitates, which were collected by filtration. A mixture of the crude compound (**7**) thus obtained, copper powder (50 mg), and quinoline (2 ml) was refluxed in an oil-bath for 10 hr. Quinoline was distilled and the residue was extracted with $CHCl_3$. The condensed extract was column-chromatographed on silica-gel (Mallinckrodt, 100 mesh). From $CHCl_3$-eluate crystals were obtained. Recrystallization from EtOH gave prisms of mp 196—197°. Yield 16 mg (11.3%). NMR $\delta_{ppm}^{CDCl_3}$: 3.20 (3H, singlet, N–Me), 7.20—8.00 (13H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{20}H_{16}ON_2$: C, 79.98; H, 5.37; N, 9.33. Found: C, 80.11; H, 5.20; N, 9.51.

(b) A mixture of **4** (300 mg), copper powder (50 mg), and quinoline (2 ml) was refluxed in an oil-bath for 7 hr. Raney nickel catalyst (2 g) and EtOH (100 ml) were added, and the mixture was refluxed for 5 hr. The mixture was filtered and the filtrate was evaporated to dryness, and was column-chromatographed on silica-gel (Wako-gel, C–200). From ether-eluate crystals were obtained. Recrystallization from EtOH gave 11 mg (5.2%) of mp 195—197°. IR spectrum of this compound was identical with that prepared by the method (a), and the mixed melting point did not show any depression.

Dimethyl 1,2-Dihydro-3,4-dioxo-1-methyl-2-phenyl-1,2,3,10-tetrahydro-4*H*-benzo[6,7]thiepino[3,4-*c*]-pyrazole-10-fumarate (10)——A mixture of **1** (322 mg), **2** (142 mg), and dimethylformamide (2 ml) was heated 150° in an oil-bath for 10 min. Dimethylformamide was distilled off and the remained residue was column-chromatographed on silica-gel (Mallinckrodt, 100 mesh). From the first $CHCl_3$-eluate, crystals of mp 184—185° (from EtOH) were obtained in 6.5% yield (30 mg). IR ν_{max}^{KBr} cm^{-1}: 1740 (ester C=O), 1680 (aryl C=O), 1650 (amide C=O). NMR $\delta_{ppm}^{CDCl_3}$: 3.36 (3H, singlet, N–Me), 3.45 (3H, singlet, –COOMe), 3.72 (3H, singlet, –COOMe), 5.08 (1H, singlet, –CH–S–), 7.05 (1H, singlet, –C=CH–), 7.10—8.20 (9H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{24}H_{20}O_6N_2S$: C, 62.06; H, 4.34; N, 6.03. Found: C, 62.13; H, 4.11; N, 5.84.

1,2-Dihydro-4-hydroxy-1-methyl-2-phenyl-3*H*-benz[*f*]indazol-3-one (11)——A mixture of **1** (322 mg), **2** (142 mg), and dimethylformamide (2 ml) was heated at 150—160° in an oil-bath for 2 hr. Dimethylformamide was distilled. The residue was column-chromatographed on silica-gel (Mallinckrodt, 100 mesh). $CHCl_3$-eluate was collected and $CHCl_3$ was evaporated to obtain tarry residue, which was extracted with ether and the extracts were column-chromatographed on silica-gel (Wako-gel, C-200). From ether-eluate 100 mg (34.5% yield) of orange yellow crystals of mp 175—176° (from EtOH) were isolated. IR ν_{max}^{KBr} cm^{-1}: 3300 (OH), 1665, 1645 (amide C=O). NMR δ $^{CDCl_3}_{ppm}$: 3.20 (3H, singlet, N-Me), 6.95—7.95 (10H, multiplet, aromatic protons), 8.55 (1H, broad singlet, -OH, disappeared on deutration). UV λ_{max}^{EtOH} mμ (log ε): 262 (4.51), 269 (5.51), 384 (4.17). Mass Spectrum *m/e*: 290 (M^+). *Anal.* Calcd. for $C_{18}H_{14}O_2N_2$: C, 74.47; H, 4.86; N, 9.65; O, 11.02. Found: C, 74.42; H, 4.85; N, 9.46; O, 11.23. From the insoluble fraction in ether, **3** and **13** were obtained.

1,2-Dihydro-4-methoxy-1-methyl-2-phenyl-3*H*-benz[*f*]indazol-3-one (12)——Compound **11** (289 mg) was dissolved in 50 ml of diazomethane-ether solution (1.3 g of diazomethane was prepared from 5 g of N-nitrosomethylurea). Evaporation of ether gave orange yellow crystals of mp 169—170° (from EtOH). Yield 300 mg (98.7%). NMR δ $^{CDCl_3}_{ppm}$: 3.17 (3H, singlet, N-Me), 4.40 (3H, singlet, -OMe), 7.23—8.38 (10H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{19}H_{16}O_2N_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 74.96; H, 5.37; N, 9.15.

Dimethyl 1,2-Dihydro-3,4-dioxo-1-methyl-2-phenyl-1,2,3,10-tetrahydro-4*H*-benzo[6,7]thiepino[3,4-*c*]-pyrazole-10-maleate (13)——A mixture of **1** (322 mg), **2** (142 mg), and dimethylformamide (2 ml) or dimethylaniline (2 ml) was heated at 150—160° in an oil-bath for 2 hr and the solvent was distilled. The residue was washed with ether, and column-chromatographed on silica-gel. From the first $CHCl_3$-eluate a small amount of **3** was obtained. From the succeeding $CHCl_3$-eluate white fine needles of mp 254—255° (from EtOH), yield 51 mg (10.9%), were isolated. IR ν_{max}^{KBr} cm^{-1}: 1750 (shoulder), 1730, 1650. NMR δ $^{CDCl_3}_{ppm}$: 3.22 (3H, singlet, N-Me), 3.80 (6H, singlet, 2 × COOMe), 5.00 (1H, singlet, vinyl proton), 5.15 (1H, singlet, -CH-S-), 6.85—8.05 (9H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{24}H_{20}O_6N_2S$: C, 62.06; H, 4.34; N, 6.03. Found: C, 62.05; H, 4.09; N, 5.73.

1,2-Dihydro-3,4-dioxo-1-methyl-2-phenyl-1,2,3,10-tetrahydro-4*H*-benzo[6,7]thiepino[3,4-*c*]pyrazole-10-maleic Anhydride (14)——A mixture of **13** (200 mg) and ethanolic KOH (10 ml) was refluxed in a water-bath for 30 min. EtOH was distilled. The residue was dissolved in water and neutralized with 10% H_2SO_4 to obtain precipitates which were collected by filtration and dried. A mixture of the substance thus obtained and Ac_2O (2 ml) was refluxed for 1 hr in an oil-bath (140—150°). Ac_2O was distilled, and the residue was column-chromatographed on silica-gel. From the $CHCl_3$-eluate crystals of mp 205° (decomp.) (from Ac_2O), yield 14 mg (7.8%) were isolated. IR ν_{max}^{KBr} cm^{-1}: 1850, 1780, 1740, 1650. Mass Spectrum *m/e*: 418 (M^+). *Anal.* Calcd. for $C_{22}H_{14}O_5N_2S$: C, 63.15; H, 3.37; N, 6.70. Found: C, 63.41; H, 3.32; N, 6.48.

Dimethyl 1,2-Dihydro-4-hydroxy-1-methyl-3-oxo-2-phenyl-3*H*-[2]benzothiopyrano[4,3,2-*f*,*g*]indazole-8,9-dicarboxylate (15)——A mixture of **1** (644 mg), **2** (300 mg), and xylene (50 ml) was refluxed on a mantle-heater for 5 hr. Xylene was distilled and the residue was washed with ether to obtain red crystals, yield 700 mg (75.8%), which were recrystallized from $CHCl_3$, mp 215—217°. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1750 (ester C=O), 1680 (amide C=O). NMR δ $^{CDCl_3}_{ppm}$: 3.12 (3H, singlet, N-Me), 3.87 (3H, singlet, -COOMe), 3.98 (3H, singlet, -COOMe), 5.70 (1H, singlet, -OH, disappeared on deuteration), 6.90—8.00 (8H, multiplet, aromatic protons). UV λ_{max}^{EtOH} mμ (log ε): 266 (4.11), 300 (3.82), 438 (3.59). Mass Spectrum *m/e*: 462.0896 (M^+). *Anal.* Calcd. for $C_{24}H_{18}O_6N_2S$: C, 62.33; H, 3.92; N, 6.06. Found: C, 62.39; H, 4.10; N, 5.95.

4-Acetoxy-1,2-dihydro-1-methyl-3-oxo-phenyl-3*H*-[2]benzothiopyrano[4,3,2-*f*,*g*]indazole-8,9-dicarboxylic Anhydride (17)——Compound **15** (0.5 g) was dissolved in 10 ml of ethanolic KOH solution which contained 370 mg of KOH. The mixture was refluxed for 30 min. EtOH was distilled and the residue was dissolved in water. An insoluble substance was filtered off and the filtrate was neutralized with 10% H_2SO_4 to obtain precipitates, which were collected, dried, and dissolved in Ac_2O (5 ml). The mixture was refluxed on a mantle-heater for 1 hr. Ac_2O was distilled and the residue was column-chromatographed on silica-gel (Mallinckrodt, 100 mesh). From benzene-eluate crystals of mp (decomp.) 185—190° (from Ac_2O) were obtained, yield 130 mg (26.2%). IR ν_{max}^{KBr} cm^{-1}: 1850, 1775, 1690. NMR δ $^{CDCl_3}_{ppm}$: 2.57 (3H, singlet, $-COCH_3$), 3.15 (3H, singlet, N-Me), 7.17—8.20 (8H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{24}H_{14}O_6N_2S$: C, 62.88; H, 3.08; N, 6.11. Found: C, 26.77; H, 3.00; N, 6.07.

Dimethyl 4-Acetoxy-1,2-dihydro-1-methyl-3-oxo-2-phenyl-3*H*-[2]benzothiopyrano[4,3,2-*f*,*g*]indazole-8,9-dicarboxylate (18)——A mixture of **15** (0.6 g) and Ac_2O (20 ml) was refluxed on a mantle-heater for 3 hr. Ac_2O was distilled and the residue was recrystallized from EtOH to obtain orange prisms of mp 206—207°, yield 515 mg (94.3%). IR ν_{max}^{KBr} cm^{-1}: 1780, 1745, 1700. NMR δ $^{CDCl_3}_{ppm}$: 2.55 (3H, singlet, $-OCOCH_3$), 3.17 (3H, singlet, N-Me), 3.93 (3H, singlet, -COOMe), 4.00 (3H, singlet, -COOMe), 6.97—7.85 (8H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{16}H_{20}O_7N_2S$: C, 61.90; H, 4.00; N, 5.55. Found: C, 61.83; H, 3.88; N, 5.54.

Dimethyl 1,2-Dihydro-4-methoxy-1-methyl-3-oxo-2-phenyl-3*H*-[2]benzothiopyrano[4,3,2-*f*,*g*]indazole-8,-9-dicarboxylate (19)——(a) A solution of **15** (0.5 g) in dioxane (10 ml) was added to 50 ml of diazomethane-ether solution (1.3 g of diazomethane was prepared from 5 g of N-nitrosomethylurea), and the mixture was allowed to stand overnight. Evaporation of the solvents gave crystals of mp 172—173° (from EtOH), yield

490 mg (95.2%). IR ν_{max}^{KBr} cm^{-1}: 1740, 1690. NMR $\delta_{ppm}^{CDCl_3}$: 3.08 (3H, singlet, N–Me), 3.87 (3H, singlet, –COOMe), 3.95 (3H, singlet, –COOMe), 4.27 (3H, singlet, –OMe), 6.90—8.10 (8H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{25}H_{20}O_6N_2S$: C, 62.94; H, 4.23; N, 5.87. Found: C, 62.80; H, 4.25; N, 5.71.

(b) Compound **15** (0.5 g) was dissolved in 10 ml of ethanolic KOH solution which contained 370 mg of KOH. The mixture was refluxed for 30 min. EtOH was distilled and the residue was dissolved in water. An insoluble substance was filtered off and the filtrate was neutralized with 10% H_2SO_4 to obtain precipitates, which were dissolved in 50 ml of diazomethane–ether solution (1.3 g of diazomethane was prepared from 5 g of N–nitrosomethylurea). Evaporation of ether gave crystals of mp 172—173° (from EtOH), yield 215 mg (41.7%).

Dimethyl 4-(*p*-Bromobenzoyl)oxy-1,2-dihydro-1-methyl-3-oxo-2-phenyl-3*H*-[2]benzothiopyrano[4,3,2-*f*,*g*]indazole-8,9-dicarboxylate (20)——A mixture of **15** (462 mg), $CHCl_3$ (5 ml), pyridine (5 ml), and *p*-bromobenzoyl chloride (131 mg) was allowed to stand overnight. After addition of excess 10% H_2SO_4, the mixture was extracted with $CHCl_3$. The extract was washed with 5% $NaHCO_3$ solution, and then with water. Evaporation of $CHCl_3$, followed by recrystallization from benzene gave red crystals of mp 237—238°. X–Ray analysis disclosed that the crystals contain benzene in a ratio of the compound **20**: benzene (2: 1). IR ν_{max}^{KBr} cm^{-1}: 1750, 1700. *Anal.* Calcd. for $2\times(C_{31}H_{21}N_2O_7SBr)\cdot C_6H_6$: C, 59.66; H, 3.53; N, 4.09. Found: C, 59.26; H, 3.34; N, 4.31.

Dimethyl 4-Acetoxy-1-methyl-3-oxo-2-phenyl-1,2,8,9-tetrahydro-3*H*-[2]benzothiopyrano[4,3,2-*f*,*g*]indazole-8,9-dicarboxylate (21)——A mixture of **18** (0.5 g), Raney nickel catalyst (1 g), and EtOH (100 ml) was agitated under the hydrogen atmosphere for 3 hr. The catalyst was filtered off and the filtrate was evaporated to dryness. The residue was recrystallized from EtOH. Yield 380 mg (75.7%), mp 235—237°. IR ν_{max}^{KBr} cm^{-1}: 1780 ($OCOCH_3$), 1780 (ester C=O). NMR $\delta_{ppm}^{CDCl_3}$: 2.58 (3H, singlet, $-OCOCH_3$), 3.29 (3H, singlet, N–Me), 3.64 (3H, singlet, –COOMe), 3.75 (3H, singlet, –COOMe), 4.68 and 4.85 (2H, AB quartet, J=4 Hz, –CH–CH–), 7.25—8.15 (8H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{26}H_{22}O_7N_2S$: C, 61.65; H, 4.38; N, 5.53. Found: C, 61.67; H, 4.33; N, 5.25.

Dimethyl 3,4-Dioxo-1-methyl-2-phenyl-1,2,4,9-tetrahydro-3*H*-benz[*f*]indazole-8-succinate (22)——A mixture of **15** (0.3 g), Raney nickel catalyst (3 g), and xylene (100 ml) was refluxed for 3 hr. The mixture was filtered and the filtrate was evaporated to dryness. The residue was recrystallized from EtOH to obtain colorless needles of mp 170—171°, yield 72 mg (25.5%). IR ν_{max}^{KBr} cm^{-1}: 1750 (ester C=O), 1640 (amide C=O). NMR $\delta_{ppm}^{CDCl_3}$: 2.85 (1H, doublet doublet, J_{ab}=18 Hz, J_{ac}=8 Hz), 3.37 (1H, doublet doublet, J_{ba}=18 Hz, J_{bc}=6 Hz), 4.48 (1H, doublet doublet, J_{ca}=8 Hz, J_{cb}=6 Hz), 3.20 (3H, singlet, N–Me), 3.69 (3H, singlet, –COOMe), 3.70 (3H, singlet, –COOMe), 4.13 (2H, singlet, $-CH_2-$), 7.10—8.32 (7H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{24}H_{22}O_6N_2$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.39; H, 5.33; N, 6.06.

4-Ethoxy-1,2-dihydro-1-methyl-3-oxo-2-phenyl-3*H*-[2]benzothiopyrano[4,3,2-*f*,*g*]indazole-8,9-dicarboxylic Anhydride (24)——A mixture of **19** (500 mg) and ethanolic KOH (20 ml of EtOH and 700 mg of KOH) was refluxed for 1 hr. EtOH was distilled and the residue was dissolved in water. The solution was neutralized with 10% H_2SO_4 to obtain precipitates, which were collected by filtration, dried, and washed with ether (from ether extract a small amount of anhydride **24** was obtained). The crude dicarboxylic acid thus obtained was dissolved in Ac_2O and was refluxed for 1 hr. Ac_2O was distilled to obtain anhydride (24). Yield 410 mg (87%), mp (decomp.) 200°. IR ν_{max}^{KBr} cm^{-1}: 1850, 1775, 1700 (C=O). NMR $\delta_{ppm}^{CDCl_3}$: 1.50 (3H, triplet, J=6 Hz, $-CH_2-\underline{CH_3}$), 4.60 (2H, quartet, J=6 Hz, $-\underline{CH_2}-CH_3$), 3.05 (3H, singlet, N–Me), 7.20—8.25 (8H, multiplet, aromatic protons). This compound was used to the next procedure without further purification.

1,2-Dihydro-4-methoxy-1-methyl-3-oxo-2-phenyl-3*H*-[2]benzothiopyrano[4,3,2-*f*,*g*]indazole-8,9-dicarboxylic Anhydride (26)——A mixture of **19** (500 mg) and methanolic KOH (20 ml of MeOH and 700 mg of KOH) was refluxed for 1 hr, and the mixture was treated by the same procedure as that for the synthesis of **24**, mp (decomp.) 250°. IR ν_{max}^{KBr} cm^{-1}: 1850, 1780, 1700 (C=O). This compound was used to the next reaction without further purification.

8,10-Dioxo-9-(2-dimethylamino)ethyl-4-ethoxy-1-methyl-2-phenyl-1,2,8,9,10-pentahydro-3*H*-[2]benzothiopyrano[2,3-*c*]pyrrolo[6,5,4-*f*,*g*]indazol-3-one (27)——A mixture of **24** (300 mg), N,N-dimethylethylenediamine (0.5 ml), and xylene (10 ml) was refluxed for 5 hr. Xylene was distilled and the residue was purified by column-chromatography on silica–gel (Wako–gel, C-200). From ether–eluate deep green needles of mp 199—200° (from EtOH), 42 mg (12.1%) were obtained. IR ν_{max}^{KBr} cm^{-1}: 1770, 1710 (C=O). NMR $\delta_{ppm}^{CDCl_3}$: 1.50 (3H, triplet, J=6 Hz, $-CH_2-\underline{CH_3}$), 2.25 (6H, singlet, $-N(Me)_2$), 2.52 (2H, triplet, J=6 Hz, $-N-CH_2-\underline{CH_2}-N(Me)_2$), 3.05 (3H, singlet, N–Me), 3.70 (2H, triplet, J=6 Hz, $-N-\underline{CH_2}-CH_2-N(Me)_2$), 4.60 (2H, quartet, J=6 Hz, $-\underline{CH_2}-CH_3$), 7.20—8.30 (8H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{28}H_{26}O_4N_4S$: C, 65.35; H, 5.09; N, 10.89. Found: C, 65.43; H, 5.24; N, 10.68.

8,9-Dioxo-9-(2-dimethylamino)ethyl-4-methoxy-1-methyl-2-phenyl-1,2,8,9,10-pentahydro-3*H*-[2]benzothiopyrano[2,3-*c*]pyrrolo[6,5,4-*f*,*g*]indazol-3-one (28)——A mixture of **26** (300 mg), N,N-dimethylethylenediamine (0.5 ml), and xylene (10 ml) was refluxed for 5 hr, and the mixture was treated by the same procedure as that for the synthesis of **27**, mp 215—217° (from MeOH). IR ν_{max}^{KBr} cm^{-1}: 1770, 1710 (C=O). NMR $\delta_{ppm}^{CDCl_3}$: 2.30 (6H, singlet, $-N(Me)_2$), 2.55 (2H, triplet, J=6 Hz, $-N-CH_2-\underline{CH_2}-N(Me)_2$), 3.05 (3H, singlet, N–Me), 3.70 (2H, triplet, J=6 Hz, $-N-\underline{CH_2}-CH_2-N(Me)_2$), 4.30 (3H, singlet, –OMe), 7.20—8.30 (8H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{27}H_{24}O_4N_4S$: C, 64.79; H, 4.83; N, 11.19. Found: C, 64.51; H, 4.41; N, 11.03.

9,11-Dioxo-10-(2-dimethylamino) ethyl-1-methyl-2-phenyl-1,2,9,10,11-pentahydro-3*H*-benzothieno[3,2-*e*]pyrrolo[3,4-*g*]indazol-3-one (29)——A mixture of **5** (300 mg), N,N-dimethylethylenediamine (0.5 ml), and xylene (10 ml) was refluxed for 5 hr to obtain a clear solution. After cooling orange crystals were obtained. Recrystallization from benzene gave needles of mp 227—229°. Yield 326 mg (92.6%). IR ν_{max}^{KBr} cm^{-1}: 1765, 1680 (C=O). NMR $\delta_{ppm}^{CDCl_3}$: 2.30 (6H, singlet, $-N(Me)_2$), 3.62 (3H, singlet, N–Me), 2.65 (2H, triplet, $J=6$ Hz, $-N-CH_2-C\underline{H}_2-N$), 3.80 (2H, triplet, $J=6$ Hz, $-N-\underline{C}H_2-CH_2-N$), 7.20—7.80 (9H, multiplet, aromatic protons). *Anal.* Calcd. for $C_{26}H_{22}O_3N_4S$: C, 66.37; H, 4.71; N, 11.91. Found: C, 66.12; H, 4.80; N, 11.67.

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