

## Studies on the Synthesis of Indole Related Compounds. II.<sup>1)</sup> Diels-Alder Reaction of Phenacylidene Indolinone

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The Diels-Alder reactions of N-acetyl-3-phenacylidene-2-indolinone (VII) with dienes are reported. VII reacts with cyclohexadiene, cyclopentadiene and butadiene to afford VIII and IX, XIV and XV, and XIX, respectively. Mass spectra of VIII, IX, X and XII are recorded and discussed on their cleavages.

Ballantine, *et al.*<sup>3)</sup> reported that isatin was heated in a mixture of acetic anhydride and pyridine to give a purple crystalline, to which they gave the structure of I. In this reaction, they explained, the intermediate should be II, and the next stage might well involve an intramolecular Diels-Alder reaction in II to transformed into I. Subsequently, they<sup>4)</sup> reported the intermolecular Diels-Alder reaction of 3-acetonylidene-2-indolinone (III) to afford IV or V.

An attention in our laboratory was focused upon the Diels-Alder reaction of isatylidene compounds such as 3-phenacylidene-2-indolinone (VI) using it as a diene or dienophile. In this paper we report that VI reacts as a dienophile with the diene such as cyclohexadiene, cyclopentadiene or butadiene to give the spiro compounds.

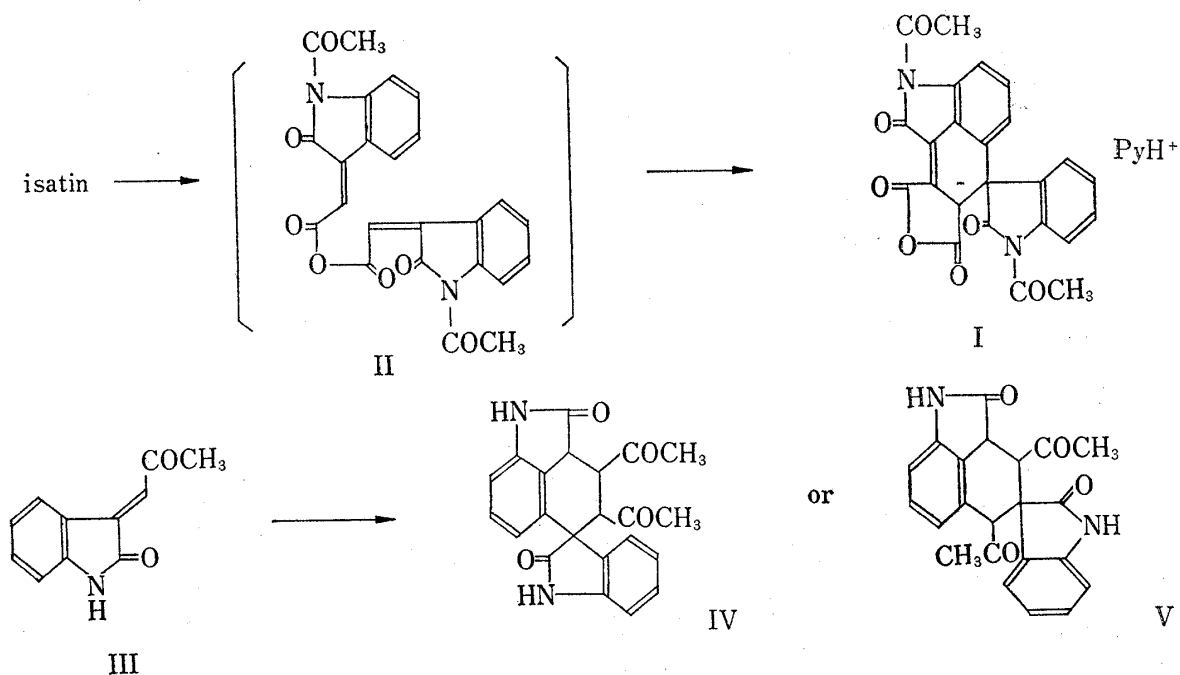


Chart 1

- 1) Part 1: T. Kato, H. Ichikawa, and M. Okita, *Yakugaku Zasshi*, **87**, 986 (1967).
- 2) Location: *Kita-4-bancho, Sendai*.
- 3) J. Ballantine, A.W. Johnson, and A.S. Kanter, *J. Chem. Soc.*, **1964**, 3323.
- 4) P. Bamfield, A.W. Johnson, and A.S. Kanter, *J. Chem. Soc.*, **1966**, 1028.

### Reaction of 3-Phenacylidene-2-indolinone (VI) with Cyclohexadiene

When 3-phenacylide-2-ineindolinone (VI) was heated with cyclohexadiene in a sealed tube, a crystalline substance,  $C_{22}H_{19}O_2N$  (X), was obtained. This empirical formula suggested the crystalline being an adduct between VI and cyclohexadiene, but two spots were observed on thin-layer chromatography. Although attempts to isolate these two spots by column chromatography or recrystallization were unsuccessful, X was converted, on acetylation with acetic anhydride, into two kinds of crystals, mp 145–147° (VIII) and mp 205–207° (IX), and both empirical formulae were established as  $C_{24}H_{21}O_3N$ .

On the other hand, the reaction of N-acetylphenacylidene-2-indolinone (VII), prepared from VI and acetic anhydride, with cyclohexadiene proceeded smoothly to give VIII and IX in good yield. Among some considerable structures four Diels–Alder type structures such as A–D will be given for the compounds VIII or IX, and on the basis of the spectral data described later, we assigned the structure of VIII and IX being A and B, respectively.

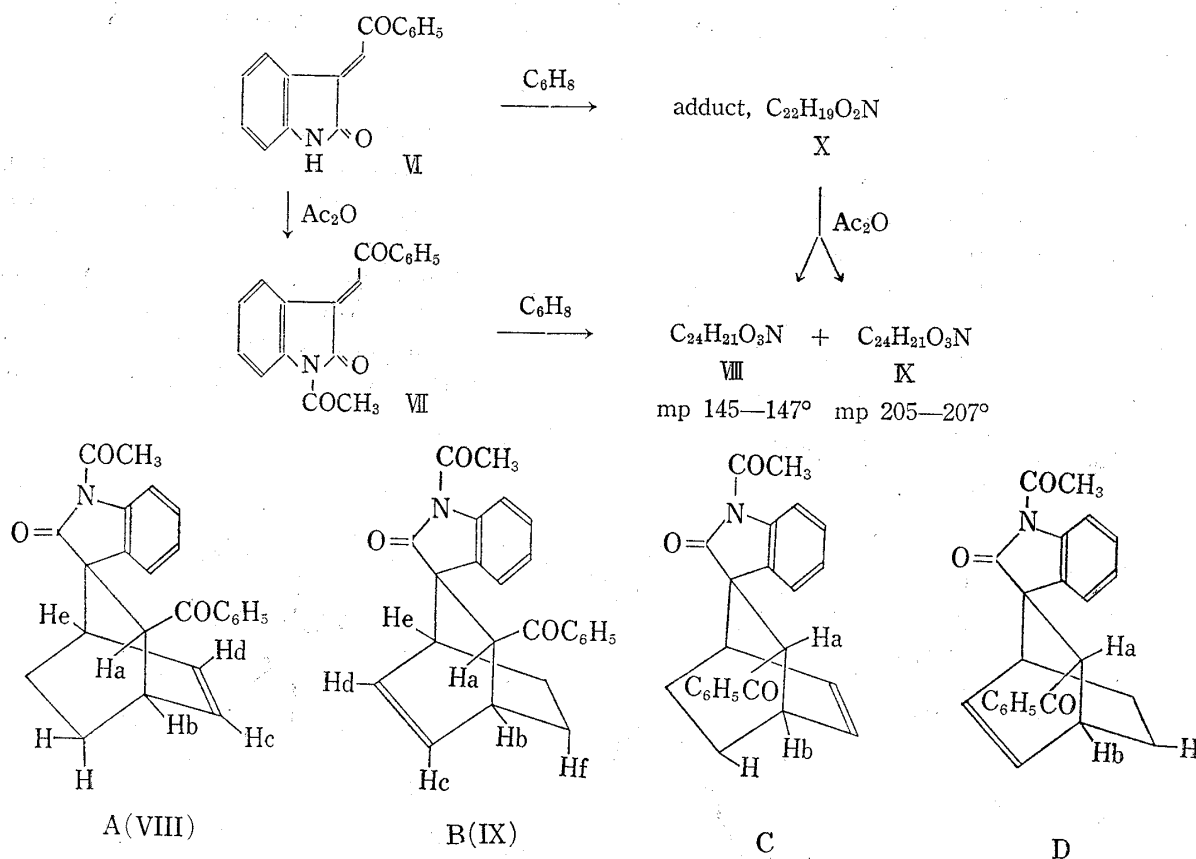
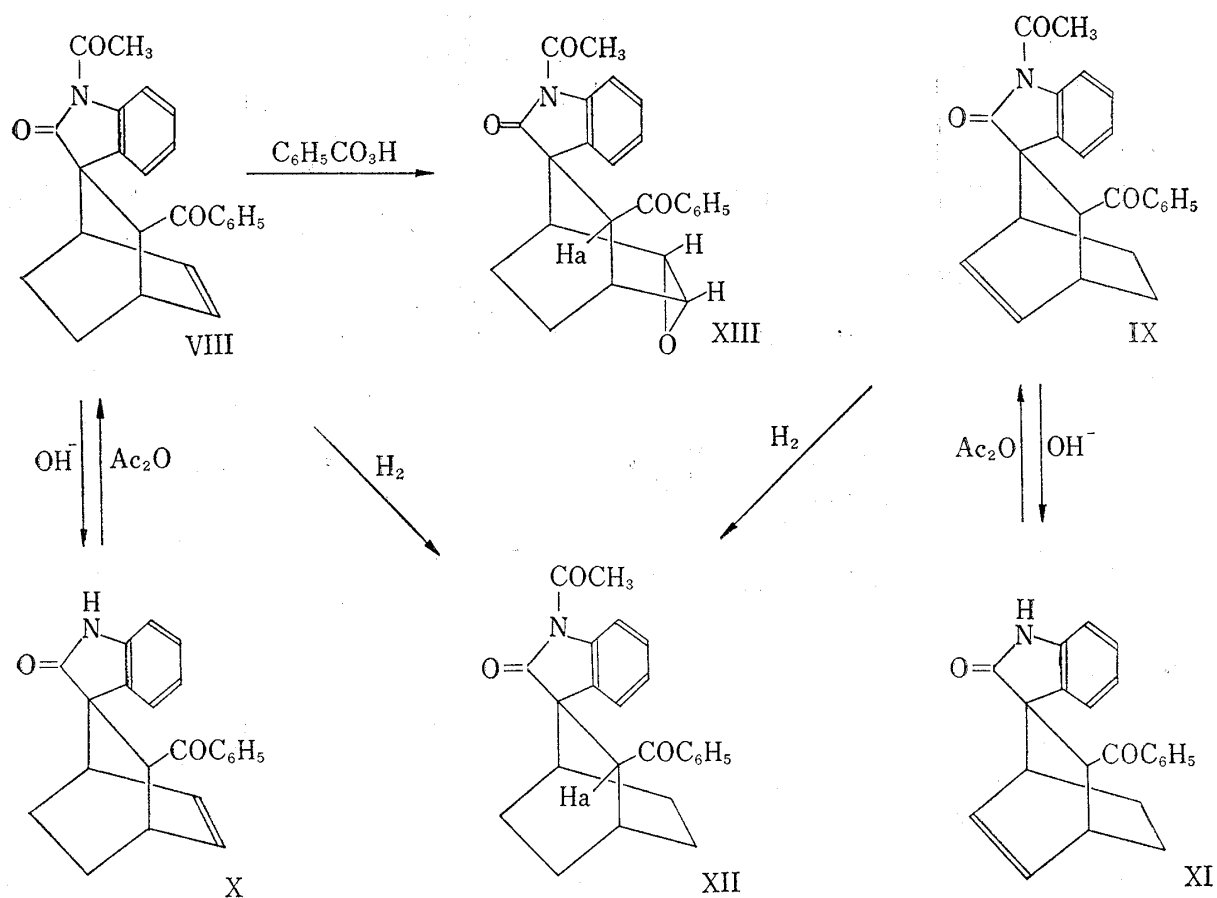


Chart 2

As shown in Chart 3, on treatment with alkali both VIII and IX were deacetylated to give X and XI, which were converted again by acetylation with acetic anhydride to VIII and IX, respectively. This observation suggested that the configuration of the benzoyl group did not change on treatment with alkali. On catalytic reduction with palladium both VIII and IX were converted to the same dihydro derivative (XII). Therefore, it is sure that VIII and IX are the structural isomers, in which the configuration of the benzoyl group is the same but the position of the double bond is different. This fact also suggests that one of the two groups, AB group and CD group, should be given for VIII and IX. On treatment with perbenzoic acid VIII was converted to the epoxide (XIII).

### Mass and NMR Spectra of VIII and IX

As shown in Fig. 1 and 2, both mass spectra of VIII and IX showed peaks at the following positions,  $M^+$  ( $m/e$  371, parent peak),  $M-80$  ( $m/e$  291), and  $M-122$  ( $m/e$  249). An  $m/e$  291 ion



should be considered as the fragment due to the retro Diels-Alder reaction, and an  $m/e$  249 fragment should come from the  $m/e$  291 ion from which ketene eliminated. Moreover, none of the peaks owing to the ions involving the elimination of ethylene, butadiene nor a cyclohexenyl radical appeared. These observation showed both VIII and IX being the Diels-Alder adducts.

In the mass spectrum of VIII the peaks were presented at  $m/e$  292 and  $m/e$  293, which were produced by the McLafferty rearrangement.<sup>5)</sup> This fact contradicted the structure of D, since in the structure D the benzoyl group and the amide carbonyl group are in the same side toward the double bond, therefore, such a rearrangement seems hardly to occur.

In the NMR spectrum (100 Mc,  $\text{CDCl}_3$ ) (Table 1) of IX the Ha proton appeared at 3.80 ppm as a triplet. This fact contradicted the structure D for IX, because in the structure D the Ha proton seems to couple difficultly except the Hb proton. Based on the data described above, the structure D was satisfied with neither VIII nor IX. Consequently, the structure of C is also deniable, because the configuration of the benzoyl group of both VIII and IX is the same.

The NMR spectrum of VIII exhibited the Ha proton at 4.17 ppm as a doublet ( $J=1.5$  cps), therefore, it will be reasonably concluded that the structure A is the most considerable one for the compound VIII. Accordingly, the compound IX must have the structure B. Also, in the structure A the configuration between Ha proton and the double bond is the *trans* structure, on the other hand, that of B is the *cis* configuration. As shown in Table II, the chemical shifts of Ha protons are well recognized for the above configurations.

5) H. Budzikiewicz, C. Djerassi, and D.H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc. San Francisco, 1967, p. 570.

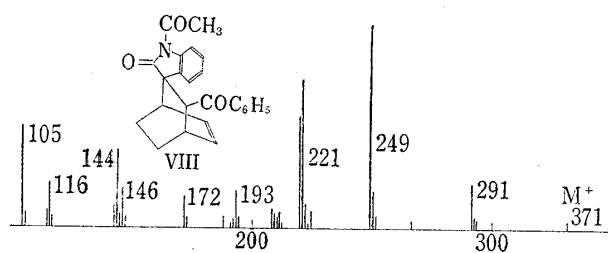


Fig. 1

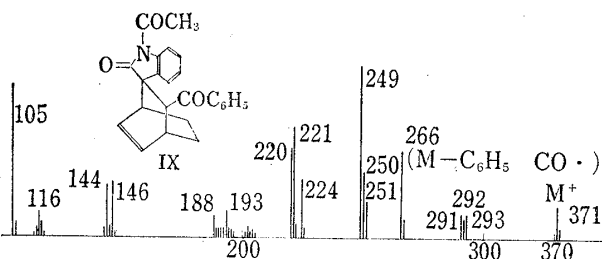


Fig. 2

TABLE I. NMR Spectra of VIII and IX (CDCl<sub>3</sub>)

	Chemical shift in ppm			Coupling const. (cps)	
	VIII	IX		VIII	IX
Ha	4.17 (d)	3.80 (t)	$J_{ab}$	1.5	1.5
Hb	3.21 (m)	3.30 (m)	$J_{af}$	—	1.5
Hc	6.98 (m)	6.65 (m)	$J_{bc}$	—	6.5
Hd	6.23 (m)	6.43 (m)	$J_{cd}$	<i>ca.</i> 6.0	8.5
He	2.50 (m)	2.39 (m)	$J_{de}$	6.0	6.0
			$J_{bd}$	—	1.4
			$J_{ce}$	—	1.4

TABLE II. Chemical Shift of Ha in ppm (CDCl<sub>3</sub>)

Compd.	VIII	XIII	XII	IX
	4.17	4.28	4.26	3.80

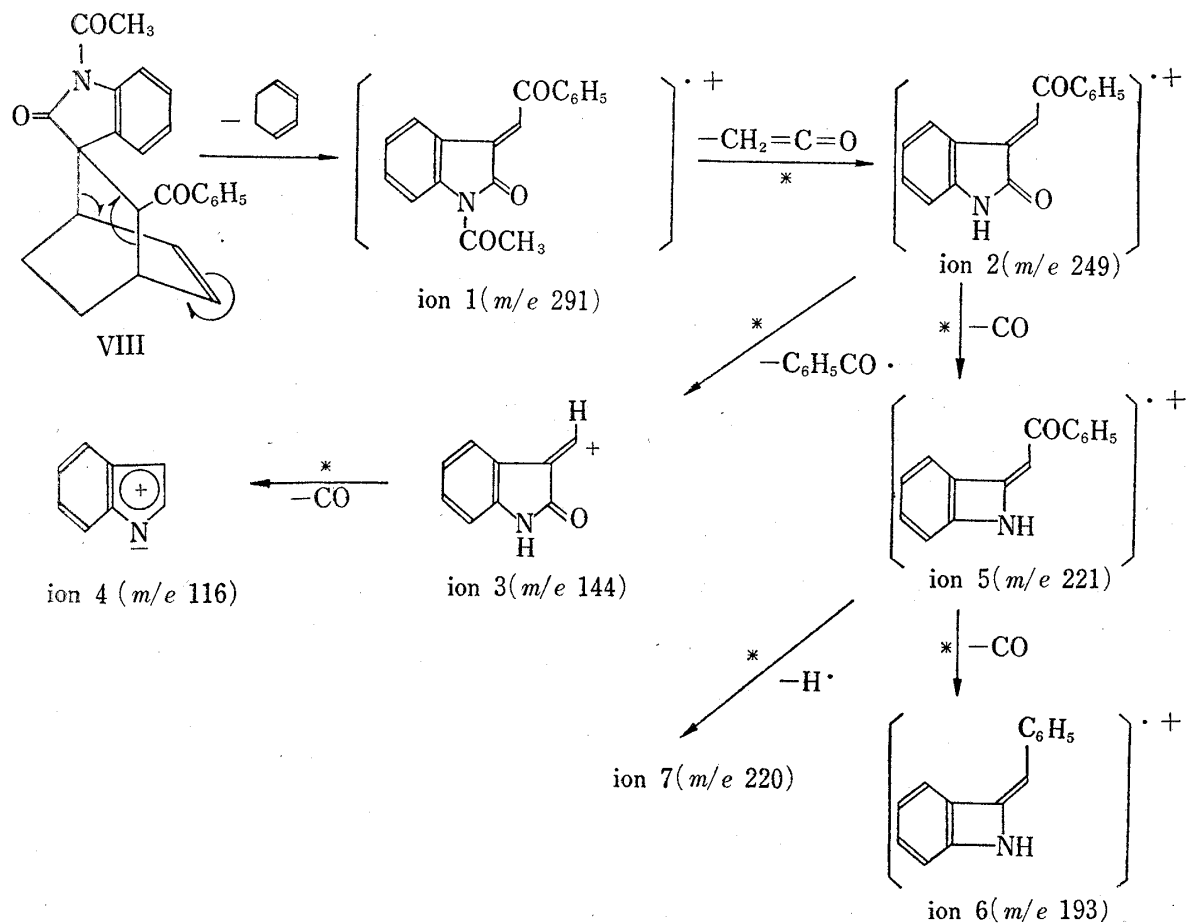


Chart 4

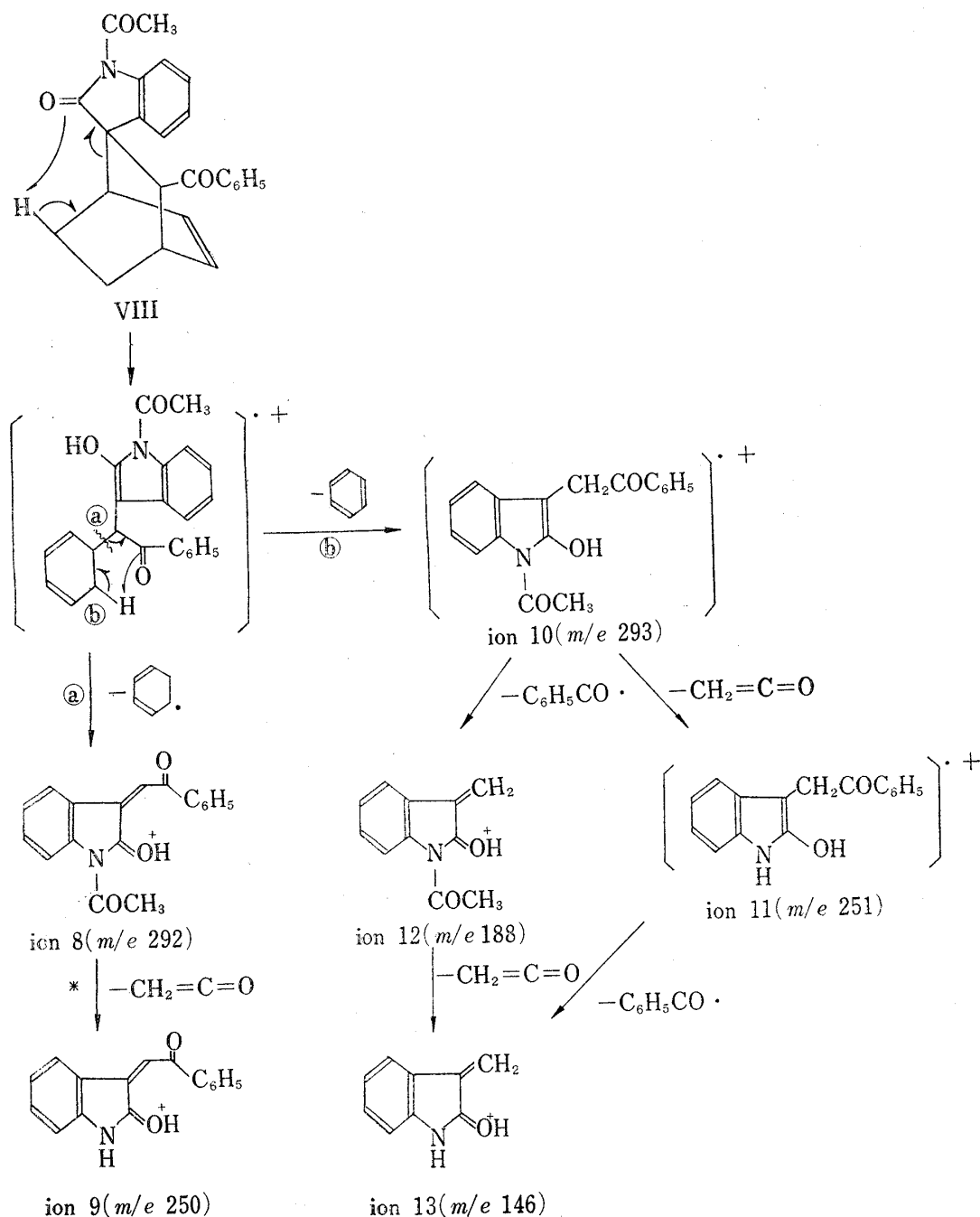


Chart 5

The important fragmentations in the mass spectrum of VIII (Fig. 1) is shown in Chart 4 and 5. Chart 4 shows the fragmentation *via* the retro Diels-Alder reaction. A peak at  $m/e$  213 can be regarded as a metastable ion transited from ion 1 ( $m/e$  291) to ion 2 ( $m/e$  249) by the loss of ketene (Calcd. for 291→249; 213.1). Also, the appearance of metastable ion at  $m/e$  83.5 (Calcd. for 249→144; 83.3) and 93.5 (Calcd. for 144→116; 93.4) supports the route listed in Chart 4 (ion 2→ion 3→ion 4). The other metastable ions presented at  $m/e$  196 (Calcd. for 249→221; 196.1) and  $m/e$  168.5 (Calcd. for 221→193; 168.6), which suggested the appropriateness of the fission of ion 2 to give ion 6 *via* ion 5.

On the other hand, the fragmentations *via* the McLafferty rearrangement is shown in Chart 5. The existences of the peaks at  $m/e$  251,  $m/e$  250 and  $m/e$  146, which can not be observed in the spectrum of VII supports the above fragmentations. Though a peak at  $m/e$  266 (M-

$\text{C}_6\text{H}_5\text{CO}$ ) is obscure, the spectrum of IX is essentially the same with that of VIII, and another fragmentations listed below might be considerable.

The McLafferty rearrangement in the case of IX (Chart 6) has been observed more clearly in the mass spectrum of the deacetyl compound (X) (Fig. 3). The strong peaks at  $m/e$  251 (ion 10),  $m/e$  250 (ion 9) and  $m/e$  146 (ion 13) can be regarded as the fragments decomposed similarly *via* the McLafferty rearrangement as shown in Chart 6.

Fig. 4 shows the mass spectrum of the dihydro compound (XII), and the fragmentations will be reasonably given as shown in Chart 7.

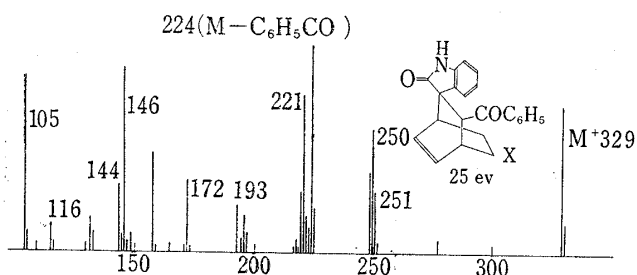


Fig. 3

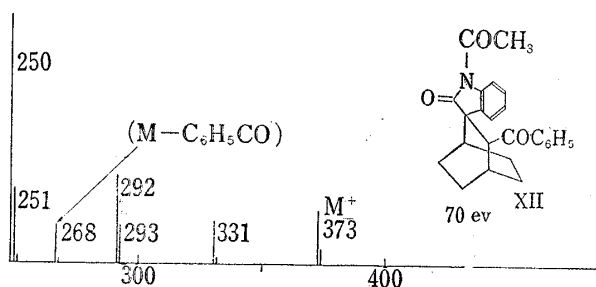
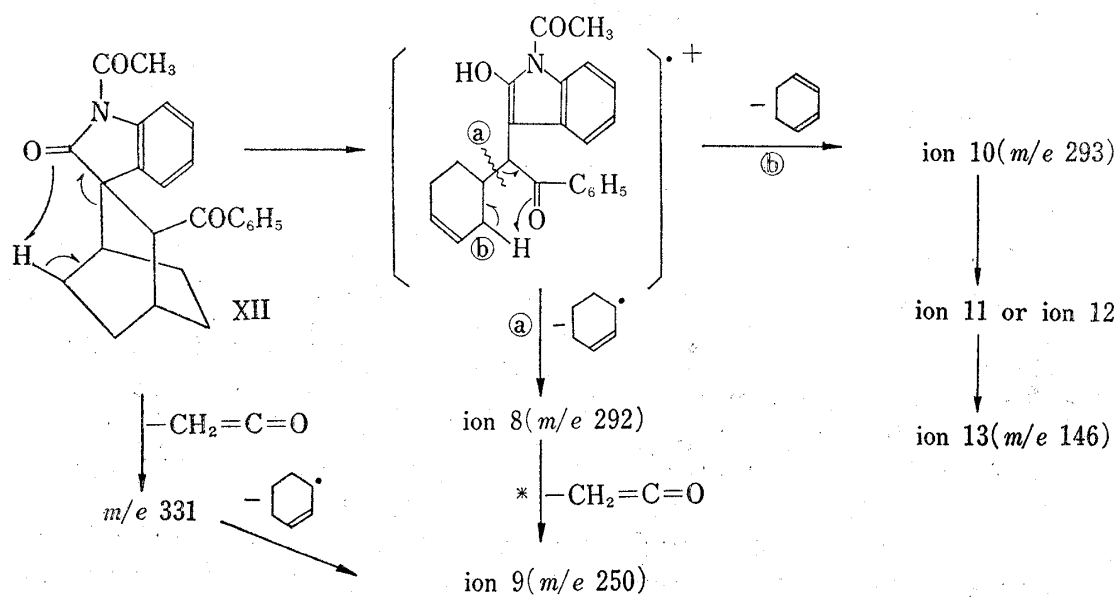
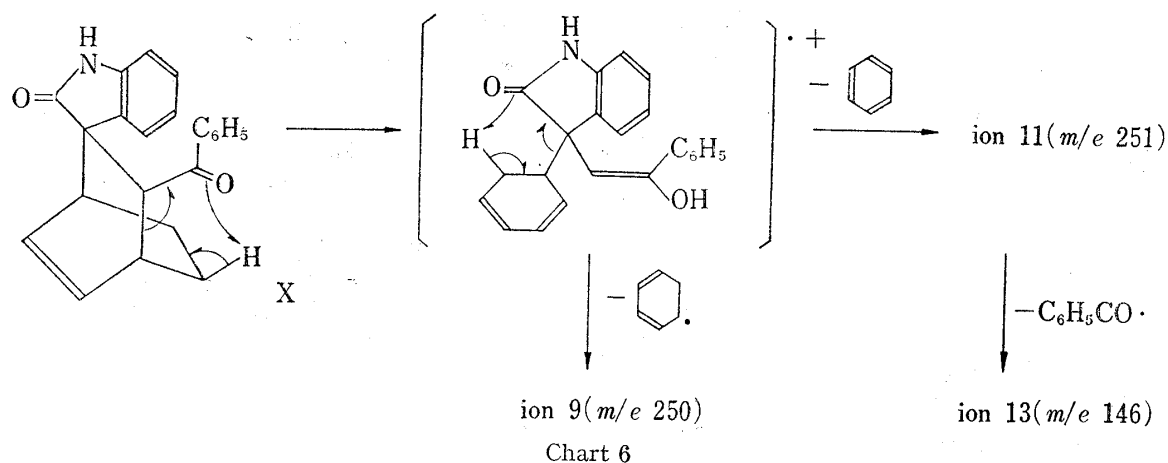


Fig. 4



### Reaction of N-Acetyl-3-phenacylidene-2-indolinone (VII) with Cyclopentadiene and 1,3-Butadiene

When a solution of N-acetyl-3-phenacylidene-2-indolinone (VII) and cyclopentadiene in benzene was allowed to stand overnight at room temperature, two kinds of the adducts were obtained. Both two substances have the same empirical formula  $C_{23}H_{19}O_3N$  and melting point of 143–144°, but they are apparently different on thin-layer chromatography and on admixture test.

As described before, the structures of the Diels–Alder adducts from VII and cyclohexadiene were assigned as A and B, therefore, the configuration of the starting VII must be, *trans*. On the other hand, it is reported that  $\beta$ -carbonyl isatilidenes usually existed in the *trans* form at room temperature.<sup>6)</sup> Based on the above facts, the adducts obtained from VII and cyclopentadiene must have the similar type structures such as XIV or XV, which are corresponded to A or B structure. Upon catalytic reductions, XIV and XV transited to the dihydro compounds of XVI and XVII, respectively.

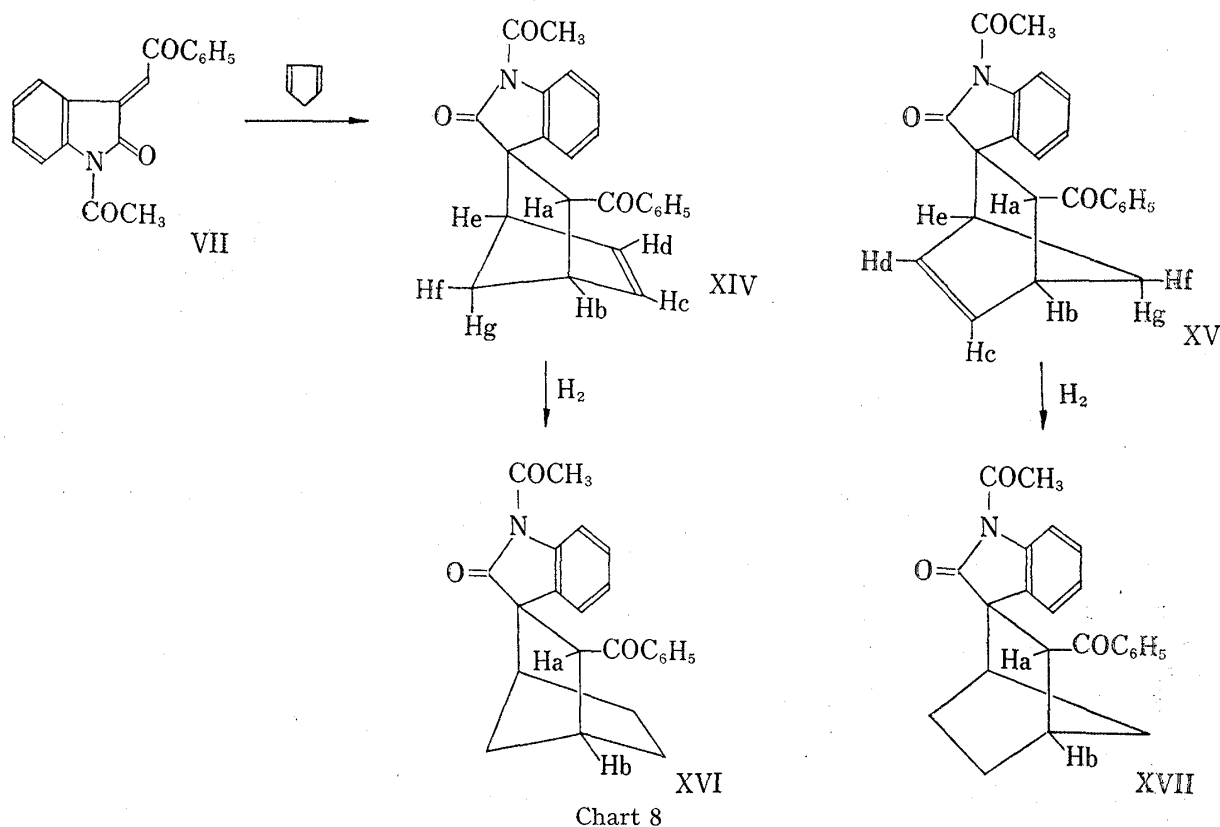


TABLE III. NMR Spectra of XIV and XV (Chemical Shift in ppm) ( $CDCl_3$ )

	Ha	Hb	Hc	Hd	He	Hf	Hg
XIV	3.80	3.30	6.98	6.08	3.00	2.42	1.41
XV	3.01	3.38	6.58	6.19	2.79	2.35	1.63

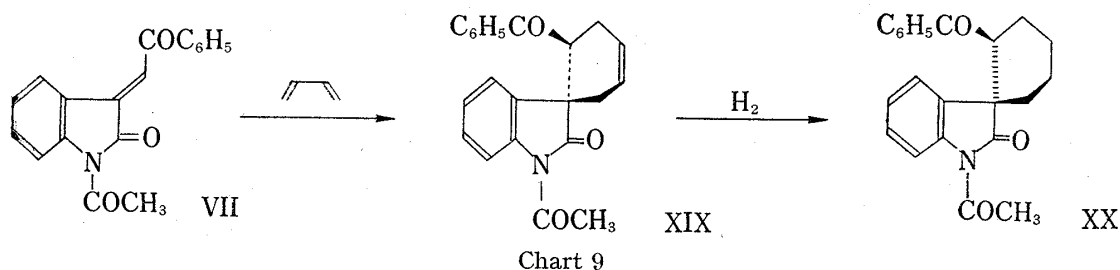
Chemical shifts of each protons in the NMR spectra of XIV and XV, after determinating by the spin decoupling, are shown in Table III. Although the difference of the splitting between the Ha proton of XIV and that of XV, which had been a useful method for the assignment of the structures between VIII and IX, was obscure, the chemical shifts of Ha

6) R.L. Autrey and F.C. Tahk, *Tetrahedron*, **23**, 901 (1967).

proton provided that the structures of XIV and XV, after comparing with those of VIII and IX. Namely, as shown in Table II, the chemical shift of the Ha proton, which located the same side with the double bond such as the compound IX is presented at higher field than that of double bond isomers. Therefore, the structure of the compound having the chemical shift of Ha at 4.58 ppm should be XIV and the other being XV. The mass spectra of XVI and XVII were almost the same and it was unsuccessful to distinguish the structures between XVI and XVII.

When N-acetyl-3-phenacylidene-2-indolinone (VII) was treated with 1,3-butadiene in benzene at room temperature, a crystalline of mp 166–167° was obtained in good yield. Elemental analysis provided its empirical formula as  $C_{22}H_{19}O_3N$  (XIX), the adduct between VII and butadiene. Upon catalytic reduction, XIX was reduced to the dihydro compound  $C_{22}H_{21}O_3N$  (XX).

As discussed before, the configuration of VII is already determined, therefore, the most reasonable structure of this adduct is considered as XIX which is shown in Chart 9.



### Experimental

**N-Acetyl-3-phenacylidene-2-indolinone (VII)**—A mixture of 3-phenacylidene-2-indolinone (2.5 g), AcONa (2.5 g) and  $Ac_2O$  (20 ml) was warmed on a water bath at 80° for 30 min with occasional stirring. After cooling, the reaction mixture was poured into 400 ml of water to give a crystalline precipitate, which was recrystallized from EtOH to give yellow needles. mp 121°. Yield, 2.4 g (86%). *Anal.* Calcd. for  $C_{18}H_{13}O_3N$  (VII): C, 74.21; H, 4.50; N, 4.81. Found: C, 74.23; H, 4.60; N, 4.60. IR  $\nu_{max}^{KBr}$   $cm^{-1}$ : 1741, 1724, 1664.

**Reaction of 3-Phenacylidene-2-indolinone (VI) with Cyclohexadiene**—A mixture of 3-phenacylidene-2-indolinone (VI) (5 g), cyclohexadiene (5 ml) and toluene (30 ml) was placed in a sealed tube, and heated at 150° for 50 hr. After cooling, a precipitate was collected. Recrystallization from AcOH gave colorless prisms (X), mp 234–236. Yield, 2.65 g. (38%). *Anal.* Calcd. for  $C_{22}H_{19}O_2N$  (X): C, 80.22; H, 5.81; N, 4.25. Found: C, 79.85; H, 6.12; N, 4.11.

On thin-layer chromatography using silicagel as an absorbent and a mixture of benzene–ether (1:1) as a solvent, two spots was observed, but attempts to isolate were unsuccessful. The mixture of the adduct (0.1 g) and  $Ac_2O$  (2 ml) was refluxed for 50 min, and poured into icewater (20 ml) to give a precipitate which was purified by the preparative thin-layer chromatography (Merck Co. Kiesel gel G. 7731; solvent, benzene) to give two kinds of crystals. Recrystallizations from acetone and methanol of these two afforded VIII (mp 145–147°, 0.075 g) and IX (mp 205–207°, 0.02 g). *Anal.* Calcd. for  $C_{24}H_{21}O_3N$  (VIII): C, 77.60; H, 5.70; N, 3.77. Found: C, 77.46; H, 5.69; N, 3.77. *Anal.* Calcd. for  $C_{24}H_{21}O_3N$  (IX): C, 77.60; H, 5.70; N, 3.77. Found: C, 77.44; H, 5.67; N, 3.83. IR  $\nu_{max}^{KBr}$   $cm^{-1}$  (VIII): 3040, 2941, 2882, 1739, 1706, 1681. (IX) 3030, 2950, 2874, 1742, 1706, 1681.

**Reaction of N-Acetyl-3-phenacylidene-2-indolinone (VII) with Cyclohexadiene**—A mixture of N-acetyl-3-phenacylidene-2-indolinone (VII) (5 g) and cyclohexadiene (5 ml) in dry benzene (20 ml) was refluxed for 20 hr, and then condensed. To the residue EtOH (20 ml) was added to give a white precipitate, which was recrystallized from AcOH to give colorless prisms of mp 177–185°. Yield, 4 g (63%). Further purification of this compound (0.5 g) by column chromatography (silicagel; Mallinckrodt Co. 7081, 100–200 mesh, 10 g) using *n*-hexane and benzene as a solvent afforded VII (0.2 g) and IX (0.13 g), which were characterized on admixture test and the comparison of IR spectra with those obtained in the above run.

**Hydrogenation of VIII and IX**—1) A solution of VIII (50 mg) in tetrahydrofuran (3 ml) was shaken in  $H_2$  in the presence of Pd-black (5 mg). After 30 min 4.0 ml of  $H_2$  absorbed, and the catalyst was filtered off. The filtrate was condensed, and the residue was purified by recrystallization from EtOH–acetone to give colorless prisms of mp 181–182°. Yield, 48 mg (95%). *Anal.* Calcd. for  $C_{24}H_{23}O_3N$  (XII): C, 77.19; H, 6.12; N, 3.75. Found: C, 77.23; H, 6.36; N, 3.79. IR  $\nu_{max}^{KBr}$   $cm^{-1}$ : 3026, 2907, 2857, 1739, 1709, 1627.



2) Following the similar fashion described above, IX (50 mg) afforded, on catalytic reduction, the dihydro compound, undepressed on admixture with a sample of XII obtained in the above run. Yield, 45 mg (89%).

**Reaction of VIII with Perbenzoic Acid**—To a solution of VIII (0.1 g 0.37 mmole) in  $\text{CHCl}_3$  (1 ml) was added perbenzoic acid (0.37 mmole in  $\text{CHCl}_3$  (1 ml)). After being allowed to stand for a week, the mixture was washed with 5%  $\text{K}_2\text{CO}_3$  and  $\text{H}_2\text{O}$  dried over  $\text{Na}_2\text{SO}_4$ , and then filtered. The filtrate was condensed to give a crystalline residue, which was purified by recrystallization from benzene-*n*-hexane to give colorless prisms of mp 227–229° (XIII). Yield, 75 mg (72%). *Anal.* Calcd. for  $\text{C}_{24}\text{H}_{21}\text{O}_4\text{N}$  (XIII): C, 74.40; H, 5.46; N, 3.62. Found: C, 74.51; H, 5.69; N, 3.48. IR  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 3049, 2941, 1739, 1715, 1678, 1266.

**Hydrolysis of VIII and IX**—1) A mixture of VIII (60 mg) in ethanolic NaOH (NaOH 0.1 g, EtOH 5 ml,  $\text{H}_2\text{O}$  2 ml) was refluxed for 3 hr, and was allowed to stand overnight. A crystalline substance precipitated was collected, and recrystallized from EtOH giving colorless prisms of mp 233–233.5°. Yield, 40 mg (73%). *Anal.* Calcd. for  $\text{C}_{22}\text{H}_{19}\text{O}_2\text{N}$  (X): C, 80.22; H, 5.81; N, 4.25. Found: C, 80.49; H, 5.98; N, 4.25.

2) Employing the similar manner described above, IX (0.1 g) was hydrolyzed with ethanolic NaOH giving XI (mp 218–221°, colorless needles (Yield, 37 mg 68%)). *Anal.* Calcd. for  $\text{C}_{22}\text{H}_{19}\text{O}_2\text{N}$  (XI): C, 80.22; H, 5.81; N, 4.25. Found: C, 80.01; H, 6.22; N, 4.37.

**Acetylation of X and XI**—1) A mixture of X (50 mg), AcONa (50 mg) and  $\text{Ac}_2\text{O}$  (3 ml) was refluxed for 30 min, and then poured into  $\text{H}_2\text{O}$  (20 ml) to give a precipitate, which was collected, purified by recrystallization from MeOH-acetone to give colorless needles of mp 146–147°, undepressed on admixture with a specimen of VIII obtained in the run described above. 39 mg (70%).

2) According to the similar manner described above, XI (60 mg) was treated with  $\text{Ac}_2\text{O}$ -AcONa to give IX. Yield, 45 mg (66%).

**Reaction of N-Acetyl-3-phenacylidene-2-indolinone (VII) with Cyclopentadiene**—A solution of N-acetyl-3-phenacylidene-2-indolinone (VII: 1.5 g) and cyclopentadiene was allowed to stand overnight at room temperature, and condensed below 40° *in vacuo*. The residue was purified on silicagel column chromatography using *n*-hexane and benzene as a solvent to give two kinds of crystallines (XIV and XV), having the same melting point, mp 143–144°, but the mixed melting point was depressed to 130°. Yield of XIV, 0.8 g (37%); XV, 0.3 g (14%). *Anal.* Calcd. for  $\text{C}_{23}\text{H}_{19}\text{O}_3\text{N}$  (XIV): C, 77.29; H, 5.36; N, 3.92. Found: C, 77.53; H, 5.54; N, 3.78. IR (XIV)  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 3077, 2976, 2899, 1754, 1709, 1667. *Anal.* Calcd. for  $\text{C}_{23}\text{H}_{19}\text{O}_3\text{N}$  (XV): C, 77.29; H, 5.36; N, 3.92. Found: C, 77.30; H, 5.69; N, 4.11. IR (XV)  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 3058, 3033, 2941, 1748, 1706, 1678.

**Reduction of XIV and XV**—1) A mixture of XIV (50 mg) and Pd-black (5 mg) in tetrahydrofuran (5 ml) was shaken in  $\text{H}_2$  for 30 min until about an equimolar equivalent of  $\text{H}_2$  (3.9 ml) absorbed. The catalyst was filtered off, and the filtrate was condensed. The residue was purified by recrystallization from MeOH-acetone to give colorless plates of mp 153–154°. Yield, 40 mg (80%). *Anal.* Calcd. for  $\text{C}_{23}\text{H}_{21}\text{O}_3\text{N}$  (XVI): C, 76.86; H, 5.89; N, 3.90. Found: C, 76.66; H, 6.07; N, 3.91.

2) Employing the similar fashion described as above, the reduction of XV (50 mg) gave its dihydro derivative (XVII), mp 150–151°. Yield, 43 mg (86%). *Anal.* Calcd. for  $\text{C}_{23}\text{H}_{21}\text{O}_3\text{N}$  (XVII): C, 76.86; H, 5.89; N, 3.90. Found: C, 76.66; H, 5.87; N, 3.92.

**Reaction of N-Acetyl-3-phenacylidene-2-indolinone (VII) with 1,3-Butadiene**—A solution of VII (2.0 g) and excess butadiene (*ca.* 10 ml at –10°) in benzene (50 ml) was placed in a sealed tube, and heated at 60° for 10 hr. After evaporation of the solvent and excess butadiene, 20 ml of EtOH was added to the residue. A crystalline solid precipitated was collected and recrystallized from acetone and EtOH to give colorless prisms of mp 166–167°. Yield, 1.5 g (63%). *Anal.* Calcd. for  $\text{C}_{22}\text{H}_{19}\text{O}_3\text{N}$  (XIX): C, 76.50; H, 5.55; N, 4.06. Found: C, 77.05; H, 5.72; N, 4.21.

**Reduction of XIX to give XX**—A mixture of XIX (0.2 g) and Pd-black (0.01 g) in tetrahydrofuran (20 ml) was shaken in  $\text{H}_2$  until 8.0 ml (at 10°) of  $\text{H}_2$  absorbed. After removal of the catalyst by suction, the filtrate was condensed. The residue was purified by recrystallization from EtOH affording colorless prisms of mp 160–162°. Yield, 0.17 g (85%). *Anal.* Calcd. for  $\text{C}_{22}\text{H}_{21}\text{O}_3\text{N}$  (XX): C, 76.06; H, 6.09; N, 4.03. Found: C, 76.55; H, 5.72; N, 3.90.

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