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Studies on the Reactions of Heterocyclic Compounds. VIII.[1] 1,3-Dipolar Cycloaddition Reaction of Isoquinolinium Cyano(methoxycarbonyl)-methylide with Dimethyl Acetylenedicarboxylate: Structure and Reaction of the Adduct[2]

Teruo Kutsuma,[3a] Kazuo Fujiyama, and Yoshiro Kobayashi[3]

Tokyo College of Pharmacy[3]

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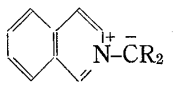
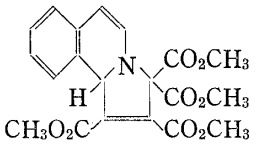
1,3-Dipolar cycloaddition of isoquinolinium cyano(methoxycarbonyl)methylide(V) and dimethyl acetylenedicarboxylate gave only one (VI) of the two possible primary adducts. Examination of the pyrolysis of this adduct revealed the structure of VI to have 10b-hydrogen and 3-ester group in *cis* configuration. Heating of VI afforded 2,3-dihydropyrroloisoquinoline(VIII), while its treatment with hydrogen chloride in benzene, followed by neutralization with potassium carbonate afforded the adduct (XIII) of two diastereoisomers(VIII and XIV). VIII was found to be unstable to acid and base, resulting in immediate hydrolysis of the ester group in its 3-position and decarboxylation to the diester (X). From the consideration of its reaction mechanism, the ester group in the 2- and 3-positions of VIII was determined to have a *cis* configuration and those in XIV, a *trans* configuration.

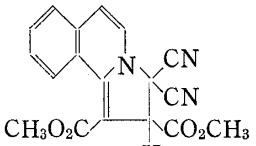
We previously reported that the 1,3-dipolar cycloaddition reaction of isoquinolinium bis(methoxycarbonyl)-methylide (I) and dicyano-methylide (II) with dimethyl acetylenedicarboxylate gave different products; *i.e.*, a primary adduct (III) from I and an isomerized product (IV) from II.[4] From the fact that the presence of a different substituent gave a different product, it seemed of interest to see what kind of a product would be formed by the reaction of isoquinolinium cyano(methoxycarbonyl)methylide[5] (V), which has both the ester group and cyano group, with dimethyl acetylenedicarboxylate, and the reaction was found to give a primary adduct (VI). The present paper describes the structural determination of this adduct and its reactivity.



I: R=CO_2CH_3
II: R=CN



III



IV

Reaction of V and dimethyl acetylenedicarboxylate in acetonitrile results in selective formation of a primary adduct (VI), as in the case of I. The nuclear magnetic resonance (NMR), ultraviolet (UV), and infrared (IR) spectra confirmed its structure. There can be two stereoisomers to the structure of VI, but the product obtained here was proved to be a

1) Part VII: Y. Kobayashi, I. Kumadaki, and H. Sato, *J. Org. Chem.*, in press.
2) Presented at the 90th Annual Meeting of Pharmaceutical Society of Japan, Sapporo, July 1970.
3) Location: *Kitashinjuku-3, Shinjuku-ku, Tokyo, 160, Japan.* (All requests are to be sent to this author); *a*) Present Address: *Research Laboratories, Ohta Seiyaku Co., Ltd., Namiki-cho, Kawaguchi, Saitama-ken, 332, Japan.*
4) T. Kutsuma, K. Fujiyama, Y. Sekine, and Y. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1558 (1972).
5) Y. Kobayashi, T. Kutsuma, K. Morinaga, M. Fujita, and Y. Hanazawa, *Chem. Pharm. Bull.* (Tokyo), **18**, 2489 (1970).

single entity from its NMR spectrum and the result of thin-layer chromatography (TLC) on a silica gel plate.

Steric structure of VI was determined from the following reaction. Heating of VI at 120° resulted in its foaming and methyl formate, dimethyl 3-cyanopyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate[4] (VII), and trimethyl 3-cyano-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,2,3-tricarboxylate (VIII) were formed. The reaction to form VII in the pyrolysis of VI can be explained by the internal 1,4-*cis*-elimination mechanism.[6] In this case, moreover, elimination of methyl formate is considered to be accelerated by the interaction between the ester group in 3-position and the hydrogen atom in 10b-position, which is related to the *cis*-configuration indicated by formula VI'. On the other hand, interaction between intramolecular hydrogen atom and an ester group is likely to be inhibited in a protic solvent. Therefore,

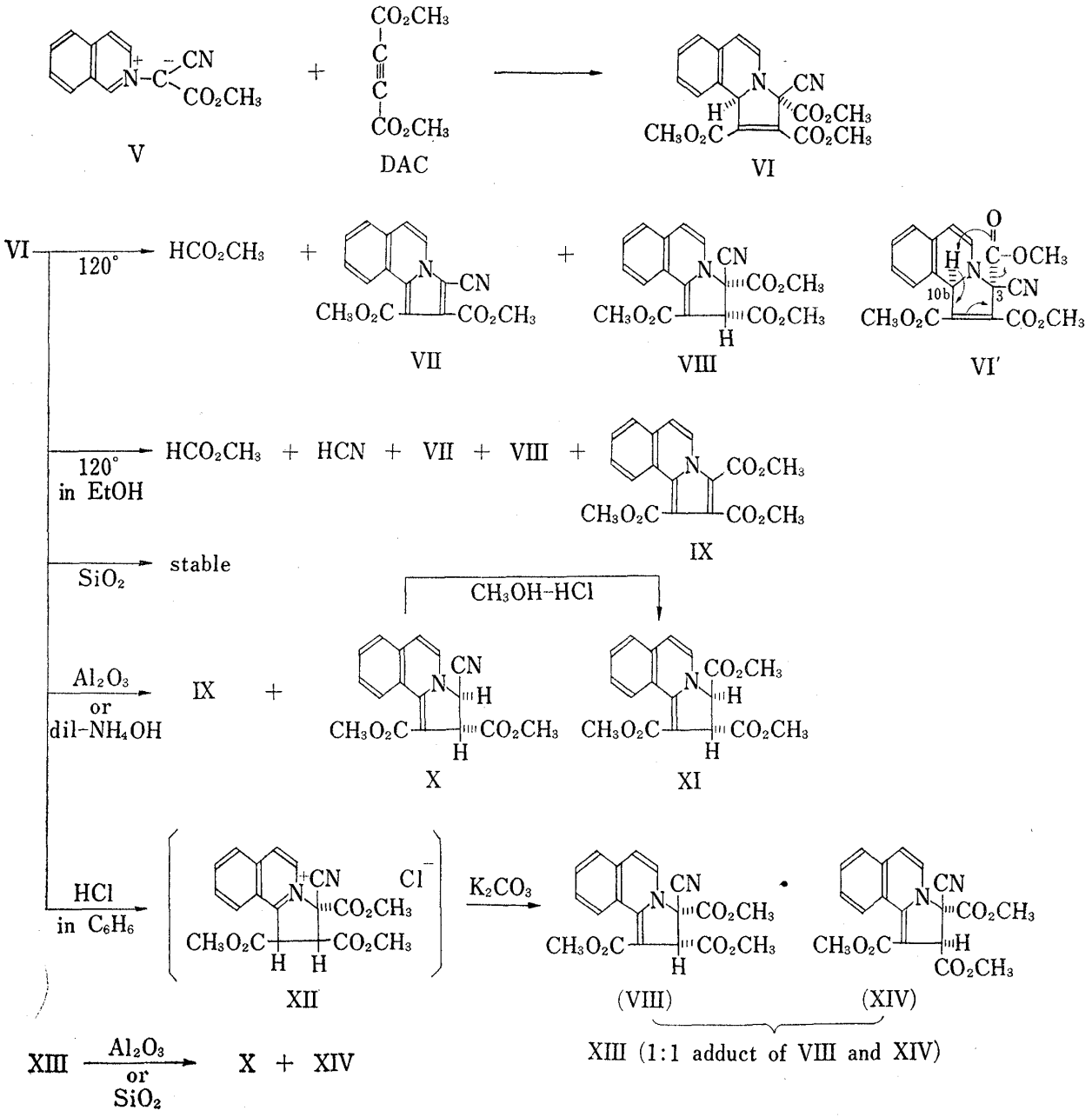


Chart 1

6) D.J. Cram. "Steric Effect in Organic Chemistry," ed. M.S. Newman, John Wiley & Sons, Inc., New York, 1956, pp. 305—314; R.B. Woodward and R. Hoffmann, *Angew. Chem.*, **81**, 797 (1969).

this pyrolysis was carried out in ethanol and, as was expected, liberation of hydrogen cyanide occurred rather than that of methyl formate, forming VII and the triester (IX) in *ca.* 1: 4.5 ratio.

VI is stable to silica gel but its passage through an alumina column or its treatment with dilute ammonia results in the formation of IX and 2,3-dihydro-diester (X), the latter compound seemingly formed by liberation of the ester group from VIII. This change from VIII to X will be explained later. The mechanism for formation of the triester (IX) may begin with extraction of the hydrogen atom at 10b-position in VI by base, followed by preferential elimination of the cyano group, which has a strong tendency to act as a leaving group.

The value of the coupling constant ($J_{2,3}$=4.5 Hz)[7] in the NMR spectrum of X indicates that the hydrogen atoms in its 2- and 3-positions are in a *trans* configuration. Its structure was proved by deriving X to trimethyl 2,3-*trans*-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1, 2,3-tricarboxylate[4] (XI).

Treatment of VI with hydrogen chloride in benzene results in precipitation of a resinous oil (XII), whose neutralization with potassium carbonate gives yellow crystals (XIII), mp 122—123°. NMR spectrum of this product indicated it to be a 1: 1 adduct of VIII and XIV. Column chromatography of this adduct over silica gel or alumina afforded XIV and X, the latter having been formed from VIII. On the other hand, passage of hydrogen chloride through a dichloromethane solution of VI and washing of the reaction mixture with water afforded XIV from the dichloromethane layer. The aqueous solution separated from the organic layer was neutralized with potassium carbonate and extracted with dichloromethane, and X was obtained from this extract.

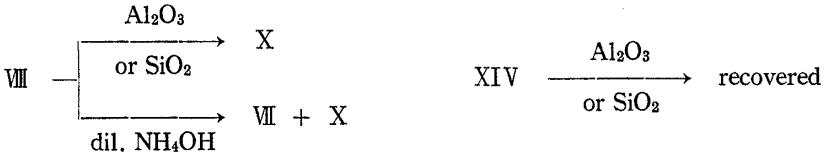


Chart 2

The foregoing experiments suggested that the diester (X) was formed *via* VIII and, in order to confirm this assumption, the dichloromethane solution of VIII, obtained by pyrolysis of VI, was passed through a column of silica gel or alumina from which the diester (X) was obtained. Further, treatment of VIII with dilute ammonia water gave the cyano compound (VII), formed by liberation of methyl formate, and the dihydro-ester (X) in *ca.* 2: 3 ratio.

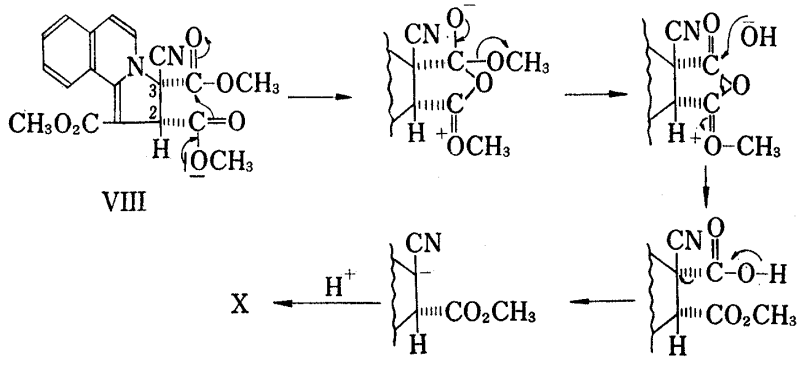


Chart 3

7) R. Huisgen, *Angew. Chem., Internat. Ed.*, **2**, 633 (1963); A. Hassner and M.J. Michelson, *J. Org. Chem.* **27**, 3974 (1962).

The formation of X by facile elimination of the ester group from VIII by merely passing through silica gel or alumina column may be explained in the following way. As shown in Chart 3, the ester group in 3-position activated by the cyano group[8] in 3-position is easily hydrolyzed by the neighboring group participation[9] of the ester group in 2-position, and this stimulates decarboxylation by steric acceleration to relieve the steric compression. Consideration of such a mechanism will also support the *cis* configuration of the ester groups in 2- and 3-positions of VIII.

Formation of VII by the treatment of VIII with aqueous ammonia also supports the *cis* configuration of the ester groups in 2- and 3-positions. In this case, the acidic hydrogen atom in 2-position was extracted by the base and VII was formed by *trans*-elimination. Therefore, the ester groups in 2- and 3-positions of VIII must be in *cis* configuration, and its diastereoisomer (XIV) stable to silica gel and alumina must have the ester groups in *trans* configuration.

The NMR spectra of dihydropyrrolo[2,1-*a*]isoquinolines are given in Table I and their UV and IR spectra in Table II.

Table I. NMR Spectra[a] of Dihydropyrrolo [2,1-*a*] isoquinolines

Compound	Chemical shift (δ)											Coupling constant (Hz)		
	H_2	H_3	H_5	H_6	H_7	H_8	H_9	H_{10}	H_{10b}		CH_3			
VI	—	—	6.33	6.00	7.25—6.85		(H_7-H_{10})[b]		6.01	4.00	3.91	3.85	$J_{5,6}$ 7.0	
VIII[c]	4.54	—	6.87	6.37	7.68—7.30		(H_7-H_9)[b]	9.75	—	3.95	3.84	3.70	$J_{5,6}$ 7.5	$J_{9,10}$ 7.5
X	4.42	5.24	6.82	6.34	7.65—7.30		(H_7-H_9)[b]	9.70	—	3.77	3.75		$J_{5,6}$ 7.5	$J_{9,10}$ 7.5
XIV[c]	4.75	—	6.76	6.37	7.68—7.30		(H_7-H_9)[b]	9.66	—	3.92	3.72	3.70	$J_{5,6}$ 7.5	$J_{9,10}$ 7.5

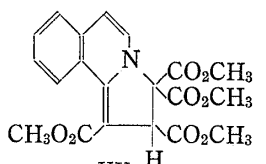
a) All the spectra were measured at 100 MHz by JNM-4H-100 Spectrometer (Japan Electron Optics Lab., Co., Ltd.) in *ca.* 5% (w/v) deuterio $CDCl_3$ solution with TMS as an internal standard.
b) multiplet
c) The spectrum of XIII agrees with the superimposed one of VIII and XIV.

Table II. UV and IR Spectra of Dihydropyrrolo [2,1-*a*] isoquinolines

Compound	UV[a] λ_{max} (nm) (ε_{max} $\varepsilon\times^{-3}$)									IR[b] $\nu_{C=O}$ (cm^{-1})		
VI	300	*250*[c]								1767	1745	
	9.10	*15.20*										
VIII	*436*	414	*396*	358	*340*	297.5	*288*	258	219	1772	1747	1672
	7.70	11.20	*9.40*	7.40	*6.40*	11.00	*9.70*	8.70	37.50			
X	*440*	418	*399*	361	*345*	298.5	*289*	263	218	1745	1662	
	7.70	11.30	*10.00*	8.50	*7.50*	12.90	*10.00*	12.30	19.20			
XIV	*438*	415	*396*	358	*344*	297.5	*288*	258	218.5	1778	1740	1679
	7.70	11.30	*9.20*	6.70	*5.80*	10.30	*8.50*	7.10	34.70			

a) All the spectra were measured in ethanol. *b*) All the spectra were measured in KBr disk. *c*) Italics indicate inflexion.

8) Tetraester (XV) was stable to silica gel and alumina.[4]



XV

9) B. Capon, *Quart. Review*, **18**, 45 (1964); T. Cohen and J. Lipowitz, *J. Am. Chem. Soc.*, **83**, 4866 (1961).

Experimental[10)]

Trimethyl 3-Cyano-3,10b-dihydropyrrolo[2,1-*a*]isoquinoline-1,2,3-tricarboxylate (10b-H, 3-CH_3O_2C, *cis*) (VI)——A solution of dimethyl acetylenedicarboxylate (1.42 g, 10 mmole) in 20 ml of MeCN was added to a solution of V (2.26 g, 10 mmole) in 20 ml of MeCN, with stirring under ice cooling, and the mixture was allowed to stand in an ice chamber overnight. The reaction mixture was concentrated in a reduced pressure below 40°; the residue was dissolved in 20 ml of MeOH and allowed to stand overnight. The bright yellow prismatic crystals formed were collected by filtration to 3.10 g, mp 115—120° (decomp.). Recrystallization from 20 ml of MeOH gave 2.75 g of bright yellow prisms (VI), mp 119—120° (decomp.). *Anal.* Calcd. for $C_{19}H_{16}O_6N_2$: C, 61.95; H, 4.38; N, 7.61. Found: C, 61.63; H, 4.40; N, 7.53.

Pyrolysis of VI——In a small flask fitted with a N_2 inlet tube and a gas outlet tube connected to a small trap immersed in a bath of ice and NaCl, 0.30 g of VI was placed and the flask was heated to 120° with gentle stream of N_2. The content in the flask first melted, then bubbled, and finally solidified. The flask was maintained at this temperature for 5 min. The small amount of irritating liquid that distilled into the trap was proved to be methyl formate from its IR spectrum.

The solid in the flask was treated with 5 ml of hot MeOH and separated into soluble and insoluble parts. The insoluble substance was recrystallized from 1,2-dichloroethane to 0.80 g of colorless crystals (VII), mp 224—225°. Its melting point and IR spectrum agreed with those of dimethyl 3-cyanopyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate.[4)]

The MeOH solution was allowed to cool and yellow crystals, mp 132—142°, were obtained. Their recrystallization from 3 ml of MeOH afforded 0.82 g of yellow needles (VIII), mp 141—144°. *Anal.* Calcd. for $C_{19}H_{16}O_6N_2$: C, 61.95; H, 4.38; N, 7.61. Found: C, 61.70; H, 4.35; N, 7.68.

Pyrolysis of VI in EtOH——A mixture of 0.040 g of VI and 5 ml of EtOH was sealed in a tube and heated at 120° for 5 min. When cooled, EtOH was evaporated and the residue was warmed with 1 ml of MeOH. A small amount of insoluble colorless crystals was collected by filtration to 0.0025 g of crystals, mp 220—223°, alone and in admixture with above VII.

The MeOH solution was allowed to cool at room temperature and 0.013 g of colorless needles (IX), mp 150—151°, thereby obtained agreed with trimethyl pyrrolo[2,1-*a*]isoquinoline-1,2,3-tricarboxylate[4)] in mp and IR spectrum.

The mother liquor left after separation of IX was cooled in ice and the yellow crystals that separated out were recrystallized from a small quantity of MeOH to 0.014 g of yellow needles, mp 142—144°, alone and in admixture with VIII obtained by the above described pyrolysis. Their IR spectra were also identical.

Treatment of VI with Al_2O_3——A solution of 0.12 g of VI dissolved in CH_2Cl_2 containing a small quantity of MeOH was passed through a column of 10 g of Al_2O_3. From the first yellow fraction (20 ml of CH_2Cl_2), 0.095 g of a resinous substance was obtained and the second orange-yellow band (25 ml) afforded 0.012 g of yellow crystals. Recrystallization of the latter from a small quantity of MeOH gave yellow needles (X), mp 144—145°. *Anal.* Calcd. for $C_{17}H_{14}O_4N_2$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.80; H, 4.52; N, 9.09.

The resinous substance obtained from the first fraction was dissolved in 1 ml of MeOH and the solution was allowed to stand, from which 0.064 g of colorless needles, mp 150—151°, were obtained. This substance agreed with the triester(IX) obtained by pyrolysis in EtOH, by admixture. TLC (SiO_2–CH_2Cl_2) indicated the presence of IX and X in the mother liquor.

Treatment of VI with Aqueous NH_4OH——To a solution of 0.20 g of VI dissolved in 5 ml of MeOH with warming, 5 ml of 5% NH_4OH was added and 0.135 g of needle crystals, mp 144—147°, that formed immediately were collected by filtration. Recrystallization from 4 ml of MeOH gave 0.125 g of colorless needles, mp 150—151°, identified with IX by admixture and IR spectral comparison. TLC (SiO_2–CH_2Cl_2) examination indicated the presence of IX and X in the NH_4OH–MeOH filtrate.

Trimethyl 2,3-*trans*-2,3-Dihydropyrrolo[2,1-*a*]isoquinoline-1,2,3-tricarboxylate (XI)——Dry HCl was passed through the solution of 0.15 g of X dissolved in 15 ml of abs. MeOH until saturation and the mixture was allowed to stand at room temperature for 8 hr. The solvent was evaporated under a reduced pressure, the residue was dissolved in ice–water, and the solution was neutralized with aq. dil. K_2CO_3 solution. The yellow crystals that precipitated out were collected by filtration, washed with H_2O, and recrystallized from 7 ml of EtOH to 0.14 g of yellow prisms (XI), mp 154—155°, alone and in admixture with trimethyl 2,3-*trans*-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,2,3-tricarboxylate.[4)] Their IR spectra were also identical.

Adduct (XIII) of Trimethyl 3-Cyano-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,2,3-tricarboxylate (2,3-Di(methoxycarbonyl), *cis*) (VIII) and (2,3-Di(methoxycarbonyl), *trans*) (XIV)——Dry HCl gas was passed through a solution of 2.00 g of VI dissolved in 50 ml of dehyd. benzene with ice cooling. The oily precipitate (XII) was separated from the benzene layer by decantation and dissolved in CH_2Cl_2, and the solution was washed with dil. K_2CO_3 solution. The organic layer was dried over anhyd. Na_2SO_4 and evaporated, and

10) All the melting points are uncorrected.

the residue was recrystallized from MeOH to 1.48 g of yellow prisms (XIII), mp 122—123°. *Anal.* Calcd. for $C_{19}H_{16}O_6N_2$: C, 61.95; H, 4.38; N, 7.61. Found: C, 61.92; H, 4.43; N, 7.60.

Treatment of VI with HCl in CH_2Cl_2——Dry HCl was passed through a solution of 0.20 g of VI dissolved in 20 ml of CH_2Cl_2 until saturation, 20 ml of ice-water was added, and the mixture was shaken thoroughly. The CH_2Cl_2 layer was washed with dil. K_2CO_3 solution, dried over anhyd. Na_2SO_4, and evaporated. To 0.14 g of a resinous residue thereby obtained, MeOH was added and the solid formed was recrystallized from 3 ml of MeOH to 0.085 g of yellow needles (XIV), mp 139—141°. *Anal.* Calcd. for $C_{19}H_{16}O_6N_2$: C, 61.95; H, 4.38; N, 7.61. Found: C, 61.94; H, 4.36; N, 7.64.

The aqueous solution separated from the CH_2Cl_2 layer was neutralized with dil, K_2CO_3 solution, the insoluble matter thereby formed was extracted with CH_2Cl_2, and the extract was evaporated after drying over anhyd. Na_2SO_4. Recrystallization of 0.040 g of resinous residue from MeOH afforded 0.022 g of yellow needles, mp 144—145°, alone and in admixture of X obtained by treatment of VI with alumina. Their IR spectra were also identical.

Treatment of the Adduct(XIII) with Silica Gel——A solution of 0.2 g of XIII dissolved in 1,2-dichloroethane was passed through a column of 20 g of SiO_2 and the column was eluted with 1,2-dichloroethane. The yellow effluent was collected in 40-ml fractions and 0.085 g of yellow crystals was obtained from fractions 2 and 3. Recrystallization of this product from a small quantity of MeOH gave 0.035 g of yellow needles, mp 139—141°, which was identified with XIV, obtained by treatment of VI with HCl in CH_2Cl_2, by admixture and IR spectral comparison.

TLC (SiO_2-1,2-dichloroethane) of the recrystallization mother liquor of XIV and fractions 4—7 gave very closely positioned two spots, indicating insufficient separation by column chromatography. These solutions were combined and 0.140 g of crystals thereby obtained was dissolved in 5 ml of ether. Ice cooling of ether solution precipitated some yellow crystals whcih were recrystallized from *ca.* 1 ml of MeOH to 0.063 g of yellow needles, mp 144—145°, alone and in admixture with X. Their IR spectra were also identical.

Treatment of the Adduct(XIII) with Al_2O_3——A solution of 0.20 g of XIII dissolved in a mixture of 1,2-dichloroethane and EtOH (*ca.* 49:1) was passed through a column of 10 g of Al_2O_3. The effluent was evaporated and the crystalline solid thereby obtained was recrystallized from 3 ml of EtOH to 0.082 g of yellow needles, mp 144—145°, identified with X by mixed fusion and IR spectral comparison.

The mother liquor was concentrated to about 1 ml in volume and allowed to stand. The first crops of crystals were collected before the precipitation of the second crop and recrystallized from MeOH to 0.025 g of yellow needles, mp 139—141°, identified with XIV by admixture and IR spectral comparison.

Treatment of VIII with Al_2O_3——A solution of 0.030 g of VIII dissolved in a mixture of 1,2-dichloroethane and EtOH (*ca.* 49:1) was passed through a column of 2 g of Al_2O_3. The effluent was concentrated and 0.023 g of yellow crystals, which showed one spot in TLC (SiO_2–1,2-dichloroethane), was recrystallized from 1 ml of EtOH to yellow needles, mp 144—145°, identified with X by admixture and IR spectral comparison.

Treatment of VIII with Silica Gel——A solution of 0.020 g of VIII dissolved in 1,2-dichloroethane was passed through a column of 2 g of SiO_2, the effluent was concentrated, and yellow crystals thereby obtained were recrystallized from 1 ml of EtOH to 0.011 g of yellow needles, identified with X by admixture and IR spectral comparison.

Treatment of VIII with Aq. NH_4OH——To a solution of 0.020 g of VIII dissolved in 1 ml of warm MeOH, 0.3 ml of 10% NH_4OH solution was added, followed by 30 ml of CH_2Cl_2. The organic layer was separated, washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated. The residue was mixed with 3 ml of warm MeOH and the insoluble white crystals were collected by filtration and recrystallized from 0.5 ml of 1,2-dichloroethane to 0.006 g of colorless crystals, mp 222—224°, identified with VII by admixture and IR spectral comparison.

The MeOH filtrate was evaporated, the residue was warmed with 0.5 ml of EtOH, and the EtOH solution was allowed to cool, from which 0.009 g of yellow needles, mp 144—145°, were obtained and identified with X by admixture and IR spectral comparison.

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