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Studies on the Reactions of Heterocyclic Compounds. IX.[1] Syntheses of 1,10b-Dihydropyrrolo[2,1-*a*]isoquinolines and 2,3-Dihydropyrrolo[2,1-*a*]isoquinolines[2]

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2-(Methoxycarbonylmethyl)- (I), 2-cyanomethyl- (VIII), and 2-phenacyl-isoquinolinium bromide (XII) react with dimethyl acetylenedicarboxylate, in the presence of triethylamine, and form the corresponding 1,10b-*cis*-1,10b-dihydropyrrolo[2,1-*a*]isoquinolines (IV, X, and XIV) and aromatized compounds (V, XI, and XV). Treatment of IV, X, and XIV with hydrogen chloride in benzene, with subsequent neutralization with potassium carbonate, results in isomerization to stable 2,3-*trans*-2,3-dihydropyrrolo[2,1-*a*]isoquinolines (VII, XX, and XXI).

We earlier isolated interesting products, including the so-called primary adduct, by the 1,3-dipolar cycloaddition reaction of disubstituted methylides of isoquinoline and dimethyl acetylenedicarboxylate, and reported that the kind of these products formed depended on the kind of a substituent present on the carbanion carbon of the ylides.[1,4]

In the present series of work, reaction between dimethyl acetylenedicarboxylate and ylides having one substituent on the carbanion carbon was examined and compounds differing from any of the products obtained to date were isolated.

Reaction of the ylide (II), obtained from 2-(methoxycarbonylmethyl)isoquinolinium bromide (I) and triethylamine, with dimethyl acetylenedicarboxylate afforded two kinds of a product, yellow crystals (IV) and colorless crystals (V), without the formation of a primary adduct (III). V was identified with trimethyl pyrrolo[2,1-*a*]isoquinoline-1,2,3-tricarboxylate reported in the preceding papers.[1,4] The physical properties of IV agreed with those of a compound which was obatined from the same reaction and assigned to a favored structure (VI) by Farnum and others.[5] However, the ultraviolet (UV), infrared (IR), and nuclear magnetic resonance (NMR) spectral patterns of IV were entirely different from those of trimethyl 2,3-*trans*-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,2,3-tricarboxylate (VII) we had reported earlier.[1,4] Consequently, if the structure assumed by Farnum and others were correct, IV must be the *cis* isomer of VII but, as will be discussed later, this assumption must be denied.

2-(Cyanomethyl)isoquinolinium bromide (VIII) and 2-phenacylisoquinolinium bromide (XII) also reacted with dimethyl acetylenedicarboxylate, in the presence of triethylamine, and formed yellow crystals (X and XIV) and aromatized products (XI[1,4] and XV). From the similarity of NMR spectra, IV, X, and XIV were considered to have similar structures (*cf.* Table II). In the reaction of XII, a product of orange-yellow crystals (XVI) was also

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[1] Part VIII: T. Kutsuma, K. Fujiyama, and Y. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1809 (1972).

[2] Presented at the Symposium on Heterocyclic Chemistry, Tokyo, November 1970.

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[4] T. Kutsuma, K. Fujiyama, Y. Sekine, and Y. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1558 (1972).

[5] D.G. Farnum, R.J. Alaimo, and J.M. Dunston, *J. Org. Chem.*, 32, 1130 (1967).

obtained, besides the above products, and XVI was identified with the ylide dimer[6] prepared by Kröhnke's method.[7]

Bubbling of dry hydrogen chloride into the benzene solutions of IV, X, and XIV resulted in the formation of oily products (XVII, XVIII, and XIX). UV spectrum of XVII ($R=CO_2CH_3$) was similar to that of 1-[bis(methoxycarbonyl)methyl]isoquinolinium bromide.[4] Neutralization of XVII, XVIII, and XIX with potassium carbonate afforded yellow crystals

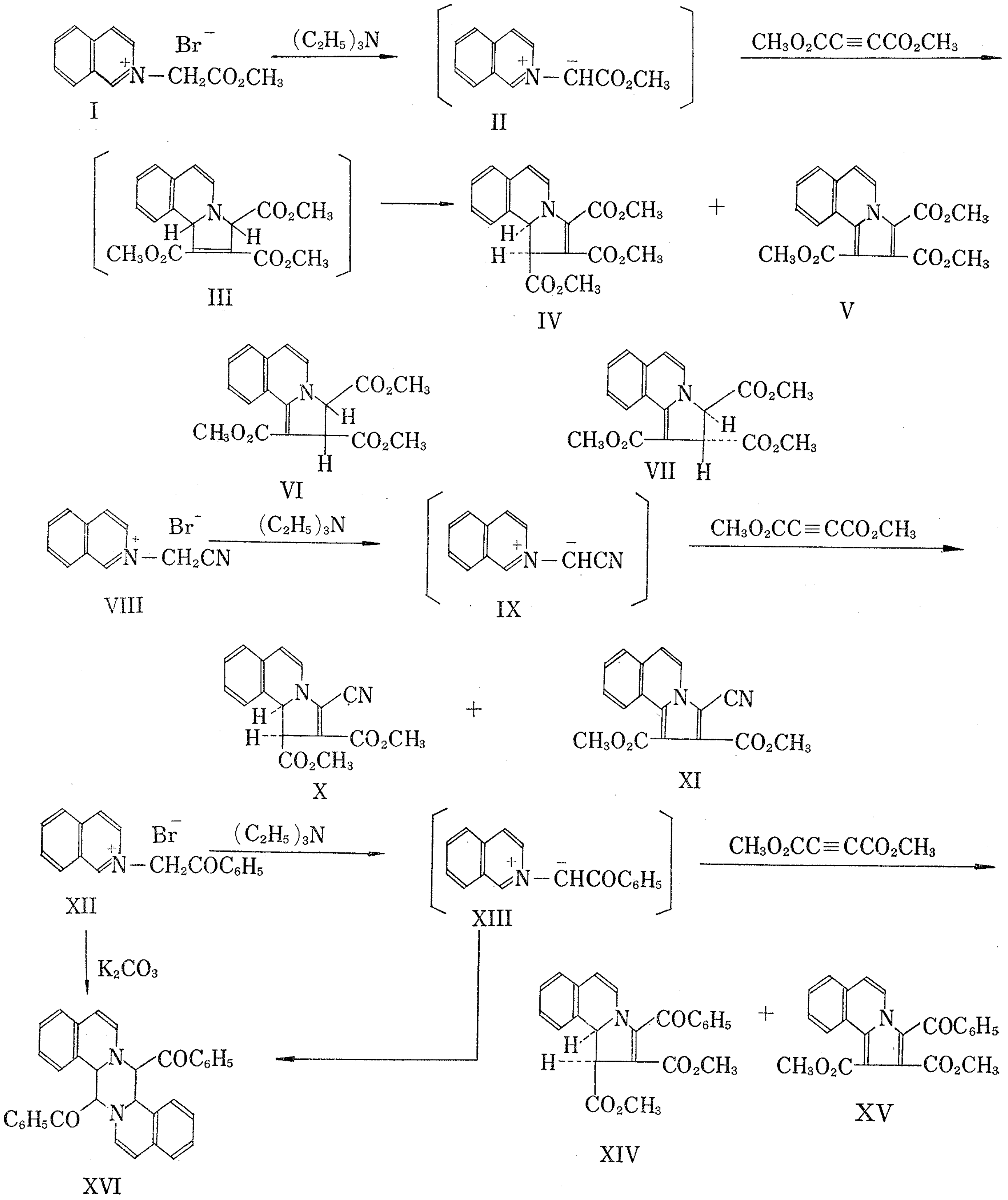

Chart 1

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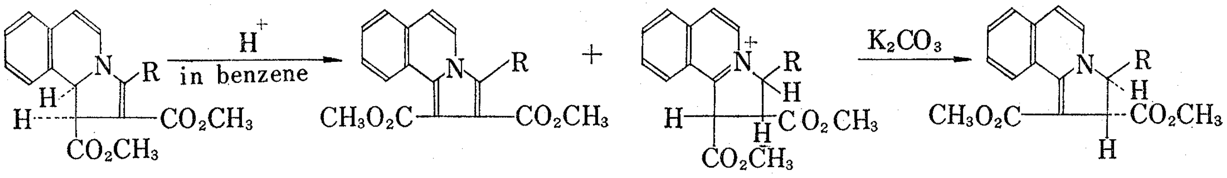
[6] H. Ahlbrecht, J. Fröhlich, U. Habermalz, and F. Kröhnke, *Tetrahedron Letters*, **1967**, 3649.
[7] *a*) F. Kröhnke, *Ber.*, **68**, 1177 (1935); *b*) F. Kröhnke and W. Zecker, *Chem. Ber.*, **95**, 1128 (1962).



IV : R=CO_2CH_3
X : R=CN
XIV : R=COC_6H_5

V : R=CO_2CH_3
XI : R=CN
XV : R=COC_6H_5

XVII : R=CO_2CH_3
XVIII : R=CN
XIX : R=COC_6H_5

VII : R=CO_2CH_3
XX : R=CN
XIX : R=COC_6H_5

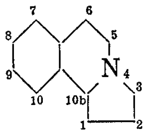
Chart 2

TABLE I. Ultraviolet and Infrared Spectra of 1,10b-Dihydropyrrolo[2,1-*a*]isoquinolines and 2,3-Dihydropyrrolo[2,1-*a*]isoquinolines

Compound	UV λ_{max}^{EtOH} nm ($\varepsilon_{max} \times 10^{-4}$)									IR (KBr) cm^{-1}			
										$\nu_{C=O}$		$\nu_{C=C}$	
IV	372	315	253							1748	1690	1678	1603
	(1.50)	(0.47)	(1.08)										
X	407	*320*[a]	309	*276*	272					1736	1683		1580
	(0.70)	(*0.33*)	(0.46)	(*0.66*)	(0.71)								
XIV	363	*296*	256							1746	1700	1690	1591
	(1.87)	(*0.79*)	(2.70)										
VII[b]	*440*	419	*400*	364	298	288	262	220		1753	1730	1655	1513
	(*0.86*)	(1.22)	(*1.00*)	(0.81)	(1.10)	(0.81)	(0.75)	(3.68)					
XX[c]	*440*	418	*399*	361	*345*	298.5	289	263	218	1745	1662		1523
	(*0.77*)	(1.13)	(*1.00*)	(0.85)	(*0.75*)	(1.29)	(1.00)	(1.23)	(1.92)				
XXI	*440*	422	*403*	364	298	290	249			1740	1695	1683	1510
	(*0.99*)	(1.32)	(*1.13*)	(1.10)	(1.49)	(1.19)	(3.12)						

a) italics indicate inflexion *b*) Ref. 4 *c*) Ref. 1

TABLE II. Nuclear Magnetic Resonance Spectra[a] of Dihydropyrrolo[2,1-*a*]isoquinolines



Compound	Chemical shift (δ)													Coupling constant (Hz)
	H_1	H_2	H_3	H_5	H_6	H_7	H_8	H_9	H_{10}	H_{10b}	CH_3			
IV	4.49	—	—	6.49	5.92	7.35—7.10 (H_7-H_{10})				5.33	3.99	3.88	3.73	$J_{1,10b}=13.3$ $J_{5,6}=7.5$
X	4.52	—	—	6.83	6.04	7.40—7.20 (H_7-H_{10})				5.35	3.90	3.83		$J_{1,10b}=14.0$ $J_{5,6}=7.5$
XIV	4.57	—	—	6.23	5.77	7.65—7.05 (H_7-H_{10})				5.43	3.88	3.43		$J_{1,10b}=13.0$ $J_{5,6}=7.5$
VII	—	4.33	4.87	6.80	6.27	7.52—7.33 (H_7-H_9)			9.80	—	3.80	3.74	3.70	$J_{2,3}=4.0$ $J_{5,6}=7.5$ $J_{9,10}=7.5$
XX	—	4.42	5.24	6.82	6.34	7.65—7.30 (H_7-H_9)			9.70	—	3.77	3.75		$J_{2,3}=4.5$ $J_{5,6}=7.5$ $J_{9,10}=7.5$
XXI	—	4.20	5.79	6.64	6.33	7.65—7.35 (H_7-H_9)			9.83	—	3.79	3.61		$J_{2,3}=4.0$ $J_{5,6}=7.5$ $J_{9,10}=7.5$

a) All the spectra were measured at 100 Hz by JNM-4H-100 spectrometer (Japan Electron Optics Lab. Co., Ltd.) in *ca.* 5% (w/v) deuterochloroform solution with TMS as an internal standard.

(VII, XX, and XXI). VII and XX were respectively identified as trimethyl 2,3-*trans*-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,2,3-tricarboxylate and dimethyl 2,3-*trans*-3-cyano-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate by comparison with authentic samples.[1,4] From the similarity of UV and NMR spectra of XXI with those of VII and XX, XXI was determined as dimethyl 2,3-*trans*-3-benzoyl-2,3-dihydropyrrolo[2.1-*a*]isoquinoline-1,2-dicarboxylate. From the benzene layer left after removal of the oily substance (XVII, XVIII, and XIX), aromatized products (V, XI, and XV) were respectively isolated. The UV and IR spectra of all these compounds are given in Table I, and their NMR spectra in Table II.

We have already reported that the UV spectra of 2,3-dihydropyrrolo[2,1-*a*]isoquinoline derivatives are not affected by the substituent in their 3-position.[1,4] In contrast, the absorptions in the longest wavelength region of the UV spectra of IV, X, and XIV were found to be markedly affected by the substituent in their 3-position, and their absorption bands are present in a considerably shorter wavelength region. These facts suggest that the carbon-carbon double bond in IV, X, and XIV is present in 2—3 position rather than in 1—10b position.

In the NMR spectra, the strong deshielding effect of the ester group at 1-position on the hydrogen atom at 10-position was observed in the aromatized compounds[1,4,8] and the 2,3-dihydro compounds,[1,4] but not in IV, X, and XIV (*cf.* Table II). This fact also supports the presence of a double bond at 2—3 position in these compounds. Consequently, these compounds must be the derivatives of 1,10b-dihydropyrrolo[2,1-*a*]isoquinoline, and the structure assumed by Farnum and others[5] would not be correct. From the value of coupling constant (J=13.0—14.0 Hz), *cis* configuration was assigned to the hydrogen atoms at 1- and 10b-positions.[9]

We have also reported[1] on the characteristic absorptions in IR spectra of 2,3-dihydropyrrolo[2,1-*a*]isoquinolines due to the enamino-ester grouping.[10] In the IR spectra of 1,10b-dihydropyrrolo[2,1-*a*]isoquinolines (IV, X, and XIV), absorptions due to the conjugated ester (1678—1690 cm^{-1}) and the carbon–carbon double bond (1580—1603 cm^{-1}, the strongest absorption band) were observed. The latter absorption appeared in a higher wave number region than that in 2,3-dihydro compounds.

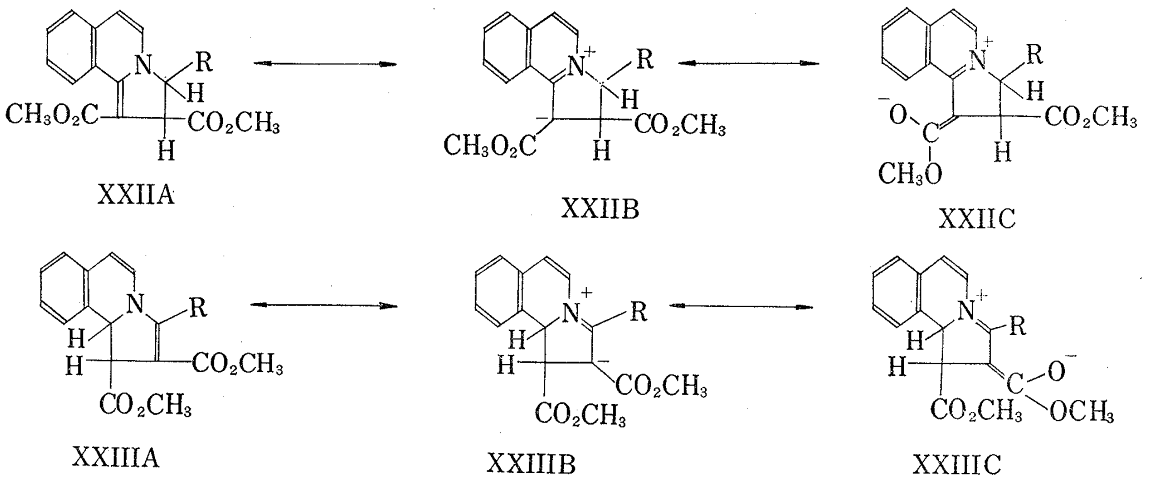


Chart 3

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[8] R.M. Acheson and D.A. Robinson, *J. Chem. Soc.* (*C*), **1968**, 1633.

[9] R. Huisgen, *Angew. Chem. Interal. Edit.*, **2**, 633 (1963); A. Hassner and M.J. Michelson, *J. Org. Chem.*, **27**, 3974 (1962).

[10] R. Huisgen, K. Herbig, A. Siegel, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966); Z. Horii, K. Morikawa, and I. Ninomiya, *Chem. Pharm. Bull.* (Tokyo), **17**, 2230 (1969).

The characteristic UV and IR spectra of 2,3-dihydro compounds with ester groups in 1- and 2-positions are due to the resonance hybrid structure indicated by XXII A, B, C, and the contribution of a similar structure (XXIII A, B, C) can be considered for the 1,10b-dihydro compounds. The fact that the absorption band in the UV spectra of 2,3-dihydro compounds appears in a considerably longer wavelength region than that in the UV spectra of 1,10b-dihydro compounds may indicate that XXII has a system with a more stable isoquinolinoid structure[5] (XXII B and XXII C) than the resonance hybrid system of XXIII. Actually, the 2,3-dihydro compounds are stable under recrystallization conditions but a part of 1,10b-dihydro compounds undergoes conversion to aromatized compounds[5] under the same condition.

Experimental[11]

Trimethyl 1,10b-*cis*-1,10b-Dihydropyrrolo[2,1-*a*]isoquinoline-1,2,3-tricarboxylate (IV) and Trimethyl Pyrrolo[2,1-*a*]isoquinoline-1,2,3-tricarboxylate (V)——These compounds were synthesized from I and dimethyl acetylenedicarboxylate according to the method of Farnum and others.[5] IV: Yellow cubes, mp 142—144° (reported,[5] mp 142.5—145°). V: Colorless needles, mp 150—151° (reported,[5] mp 151.5—152°). V was identified by mixed fusion with authentic specimens.[4]

Dimethyl 1,10b-*cis*-3-Cyano-1,10b-dihydropyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (X) and Dimethyl 3-Cyanopyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (XI)——Triethylamine (0.222 g, 2.2 mmole) was added to a stirring solution of a mixture of finely pulverized bromide[12] (VIII) (0.498 g, 2 mmole), dimethyl acetylenedicarboxylate (0.284 g, 2 mmole), and CH_3CN (15 ml), and the mixture was stirred at room temperature for 3 hr. Insoluble matter was removed by filtration, CH_3CN was evaporated, and the residue was warmed with 3 ml of acetone, affording 0.074 g of an insoluble colorless powder (XI), mp 222—223°, alone and in admixture with the authentic specimen.[1,4] Leaving of the acetone filtrate gave 0.119 g of orange-yellow crystals whose recrystallization from acetone afforded orange prisms (X), mp 153—154°. *Anal.* Calcd. for $C_{17}H_{14}O_4N_2$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.42; H, 4.71; N, 9.17.

Dimethyl 1,10b-*cis*-3-Benzoyl-1,10b-dihydropyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (XIV), Dimethyl 3-Benzoylpyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (XV), and Ylide Dimer (XVI)——Dimethyl acetylenedicarboxylate (0.426 g, 3 mmole) and triethylamine (0.808 g, 8 mmole) were added to the suspension of the bromide[7a] (XII) (0.984 g, 3 mmole) in CH_2Cl_2 (30 ml) and the mixture was refluxed for 8 hr. After cooling, orange-yellow needles (XVI) (0.320 g, mp 194—195°), were collected by filtration and identified by admixture with ylide dimer[6] prepared by the method of Kröhnke.[7]

The CH_2Cl_2 filtrate was washed with water and dried over Na_2SO_4, and the solvent was evaporated. The residue was dissolved in 7 ml of MeOH, the solution was allowed to cool, and 0.070 g of yellowish orange crystals, mp 155—157°, was obtained. Recrystallization from MeOH gave slightly yellow needles (XV), mp 158—159°. *Anal.* Calcd. for $C_{23}H_{17}O_5N$: C, 71.31; H, 4.42; N, 3.62. Found: C, 71.03; H, 4.30; N, N, 3.28.

First and second recrystallization mother liquor left after removal of XV was combined and concentrated, the residue was dissolved in benzene–AcOEt (19:1), and the solution was passed through a column of SiO_2 (30 g). The initially eluted pale yellow fraction gave 0.019 g of XV. The next orange yellow fraction afforded 0.320 g of resinous orange substance which was dissolved in 3 ml of MeOH. After standing for while, 0.210 g of yellow crystals (XIV), mp 94—96°, was obtained. Recrystallization from MeOH gave yellow needles, mp 96—97°. *Anal.* Calcd. for $C_{23}H_{19}O_5N$: C, 70.94; H, 4.92; N, 3.60. Found: C, 70.89; H, 4.86; N, 3.61.

Treatment of IV with HCl——Dry HCl gas was passed through a solution of IV (0.200 g) dissolved in dehyd. benzene (10 ml) by which a pale orange oil separated. The benzene layer was decanted, the oily substance was dissolved in CH_2Cl_2, and the solution was shaken with K_2CO_3 solution. The pale yellow organic solvent layer turned yellow. This layer was collected and dried over Na_2SO_4, and CH_2Cl_2 was evaporated, leaving 0.110 g of a resinous yellow substance which crystallized on addtion of MeOH. Recrystallization from MeOH gave 0.091 g of yellow prisms (VII), mp 156—157°, alone and in admixture with an authentic specimen.[4]

The benzene layer separated from the oily substance was washed with H_2O and dried over Na_2SO_4, and the solvent was evaporated to leave 0.083 g of pale yellow resinous substance. Recrystallization from MeOH gave 0.042 g of colorless to pale yellow needles (V), mp 150—151°, identified with the authentic specimen by admixture.

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[11] All melting points are not corrected.

[12] F. Bamberger, *Ber.*, **20**, 3344 (1887).

Treatment of X with HCl——A solution of X (0.60 g) dissolved in dehyd. benzene (40 ml) was treated in the same way as for above IV, and 0.175 g of yellow needles (XX), mp 144—145°, was obtained from the oily substance, and 0.150 g of colorless crystals (XI), mp 222—223°, from the benzene layer. These two compounds were identified with respective authentic specimens[1] by admixture.

Treatment of XIV with HCl——A solution of XIV (0.080 g) dissolved in benzene–cyclohexane (1:1, 20 ml) was treated in the same way as for IV. The precipitated oily substance afforded 0.046 g of yellow needles (XXI), mp 194—195°. *Anal.* Calcd. for $C_{23}H_{19}O_5N$: C, 70.94; H, 4.92; N, 3.60. Found: C, 70.65; H, 5.08; N, 3.65.

The benzene–cyclohexane layer afforded 0.026 g of pale yellow needles (XV), mp 158—159°, alone and in admixture with a specimen derived from XII and dimethyl acetylenedicarboxylate mentioned above.

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