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Synthesis of Methylpyridine Derivatives. XXVII.[1] Synthesis of 1,3-Disubstituted-4-oxo-quinolizine and 2,4-Disubstituted-1-oxo-benzo[*c*]quinolizine Derivatives

Tetsuzo Kato, Takuo Chiba, and Shigeru Tanaka

Pharmaceutical Institute, Tohoku University[2]

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Reaction of ethyl α-(dimethylaminomethylene)-2-pyridineacetate (I) with acetic anhydride gives ethyl 4-oxo-4*H*-quinolizine-1-carboxylate (Va). Similar reaction with acid anhydrides, such as propionic anhydride and *n*-butyric anhydride, affords the corresponding 3-substituted-quinolizine derivatives (Vc and Ve). Similarly, α-(dimethylaminomethylene)-2-pyridineacetonitrile (II) and quinolyl homologous (III and IV) react with acid anhydrides to give the corresponding 3-substituted-4-oxo-4*H*-quinolizine-1-carbonitrile (Vb, Vd and Vf), ethyl 2-substituted-1-oxo-1*H*-benzo[*c*]quinolizine-4-carboxylate (VIa, VIc and VIe) and 4-carbonitrile derivatives (VIb, VId, and VIf), respectively.

I reacts with diethyl malonate to give diethyl 4-oxo-4*H*-quinolizine-1,3-dicarboxylate (Vg). Similar reaction with esters, such as ethyl cyanoacetate, ethyl acetoacetate and ethyl 2-pyridineacetate, affords the corresponding 3-substituted-quinolizine derivatives (Vi, Vk, and Vm). II, III and IV react with esters to form quinolizine and benzoquinolizine derivatives (Vh, Vj, Vn, VIg, VIh, VIi, VIj, VIk, and VIl).

Reaction of III with esters affords ethyl 2-(2′-quinolyl)-1-oxo-1*H*-benzo[*c*]quinolizine-4-carboxylate (VII), besides the expected product (VIg, VIi, VIk).

Reaction of IV with ethyl acetoacetate gives ethyl 3-(2′-quinolyl)-6-methyl-2-pyridone-5-carboxylate (IX) as a main product (33%).

We have reported previously[3] that reaction of α-substituted pyridyl enamine such as ethyl α-(dimethylaminomethylene)-2-pyridineacetate (I) reacted with ketene and diketene giving ethyl 4-oxo-4*H*-quinolizine-1-carboxylate (Va) and ethyl 3-acetyl-4-oxo-4*H*-quinolizine-1-carboxylate (Vk), respectively. Similarly, α-(dimethylaminomethylene)-2-pyridineacetonitrile (II) and quinolyl homologous (III, IV) reacted with diketene to give corresponding quinolizine (VI) and benzoquinolizine derivatives (VIk, VIl).

This reaction might well involve the 1,4-dipolar cycloaddition reaction giving the quinolizine ring system. The present investigation was undertaken to see if a practical method could be worked out for synthesizing quinolizine derivatives by the reaction of such pyridyl or quinolyl enamine as described above with acid anhydrides or esters.

1. Reaction with Acid Anhydrides.

When ethyl α-(dimethylaminomethylene)-2-pyridineacetate (I) was heated with acetic anhydride, crystals of mp 118—119° were obtained. This was identified as ethyl 4-oxo-4*H*-quinolizine-1-carboxylate (Va) by the comparison of its infrared (IR) and nuclear magnetic resonance (NMR) spectra with those of an authentic sample prepared according to the literature.[4]

Similarly, α-(dimethylaminomethylene)-2-pyridineacetonitrile (II) reacted with acetic anhydride giving yellow prisms of mp 211—212° (Vb), whose IR spectrum ($CHCl_3$) showed carbonyl absorption at 1680 cm^{-1} and nitrile at 2230 cm^{-1}. The NMR spectrum ($CDCl_3$) showed signals in the range of 6.58—9.29 ppm ascribable to six aromatic protons. These spectral data are consistent with the structure 4-oxo-4*H*-quinolizine-1-carbonitrile (Vb).

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[1] Part XXVI: T. Kato and T. Niitsuma, *Yakugaku Zasshi*, **92**, 1024 (1972).

[2] Location: *Aobayama, Sendai*, 980, *Japan.*

[3] T. Kato and T. Chiba, *Yakugaku Zasshi*, **89**, 1464 (1969).

[4] V. Boekelheide and J.P. Lodge, Jr., *J. Am. Chem. Soc.*, 73, 3681 (1951).

Similar treatment of ethyl α-(dimethylaminomethylene)-2-quinolineacetate (III) and α-(dimethylaminomethylene)-2-quinolineacetonitrile (IV) with acetic anhydride afforded ethyl 1-oxo-1*H*-benzo[*c*]quinolizine-4-carboxylate (VIa) and 1-oxo-1*H*-benzo[*c*]quinolizine-4-carbonitrile (VIb), respectively. As previously reported, VIa and VIb were also prepared by the reaction of III and IV with ketene, but the use of acetic anhydride gave more satisfactory results.

Similarly, both *n*-propionic anhydride and *n*-butyric anhydride reacted with pyridyl and quinolyl enamines (I, II, III, IV) giving the corresponding 4-oxo-quinolizine and 1-oxo-benzoquinolizine derivatives (Vc, Vd, VIc, VId, Ve, Vf, VIe, VIf). These results are summarized in Table I.

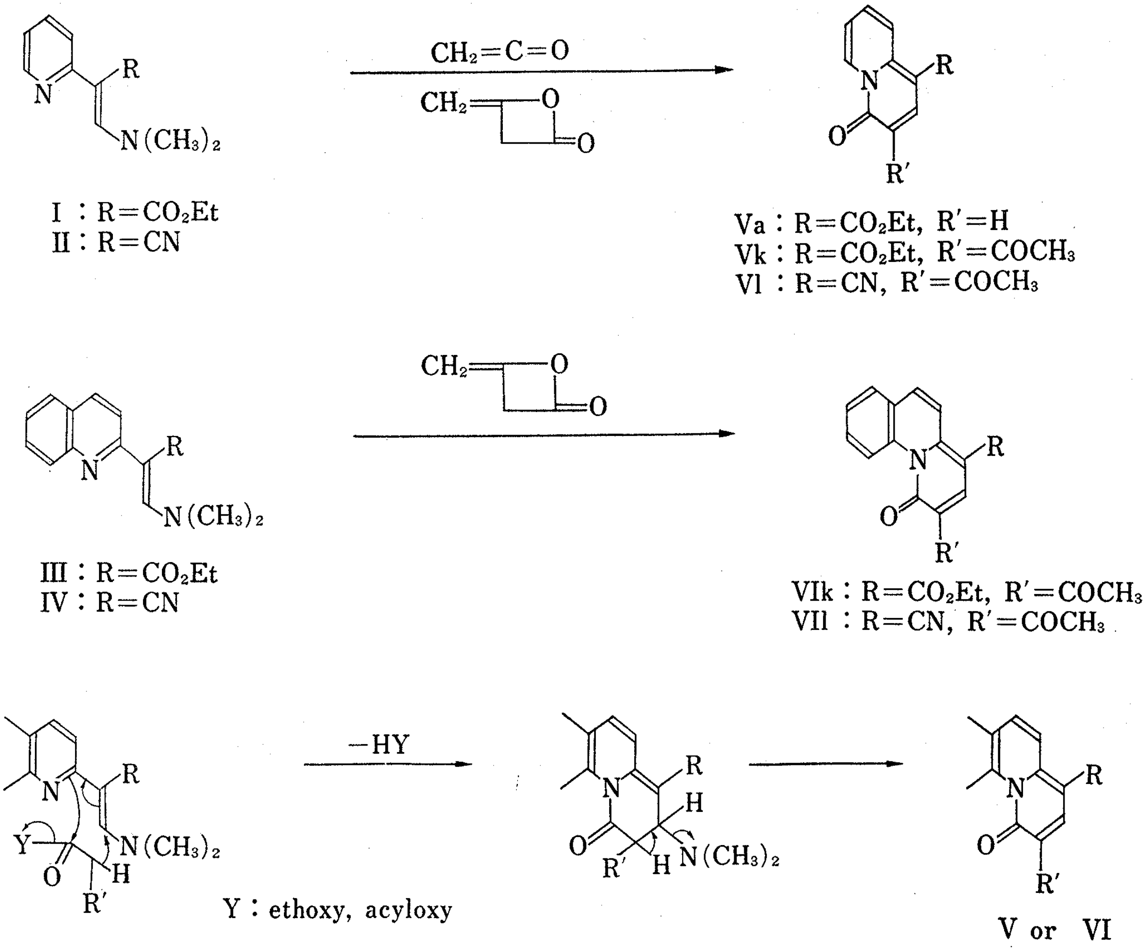

Chart 1

2. Reaction with Esters

Although heating of I with esters such as ethyl acetate or ethyl phenylacetate resulted in the recovery of I quantitatively, diethyl malonate reacted with I giving yellow crystals of mp 131—132° (Vg), whose IR spectrum ($CHCl_3$) showed carbonyl stretching at 1730, 1678 and 1670 cm^{-1}. NMR spectrum ($CDCl_3$) indicated the presence of two ethoxyl groups and five ring protons in the range of 7.20—9.56 ppm. These data are consistent with the structure diethyl 4-oxo-4*H*-quinolizine-1,3-dicarboxylate (Vg).[4]

Similarly, diethyl malonate reacted with II giving ethyl 1-cyano-4-oxo-4*H*-quinolizine-3-carboxylate (Vh) in 43% yield, which was identified by the mixed melting point test with an authentic sample prepared according to the literature.[5]

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5) G. Buchmann and W. Duchna, *Pharmazie*, 23, 301 (1968).

It was of interest to see that reaction of III with diethyl malonate gave orange prisms of mp 203—204°, $C_{25}H_{18}ON_2$ (VII), besides the expected product of diethyl 1-oxo-1*H*-benzo[*c*]quinolizine-2,4-dicarboxylate (VIg).

In the IR spectrum ($CHCl_3$) of VII, ester carbonyl and amide carbonyl absorptions could be observed at 1697 and 1658 cm^{-1}. NMR spectrum ($CDCl_3$) showed ethoxyl protons at 1.45 ppm (3H, t, $J=7.7$ Hz), 4.42 ppm (2H, q, $J=7.7$ Hz), and aromatic ring protons at 7.31—9.60 ppm.

These data suggested the structure being ethyl 2-(2′-quinolyl)-1-oxo-1*H*-benzo[*c*]quinolizine-4-carboxylate (VII), which, though melting point was different (lit.[6] mp 161—162°), was already reported by Clemo, *et al.*[6] According to the literature, ethyl 2-quinolineacetate (VIII) was treated with ethyl orthoformate giving orange prisms of mp 204—205°, whose IR spectrum was identical in every respects with that of VII.

Though the mechanism of the formation of VII is obscure for the present, a likely pathway may be shown by the reaction of III with ethyl 2-quinolineacetate, which is formed by hydrolysis of III during heating of reaction mixture.

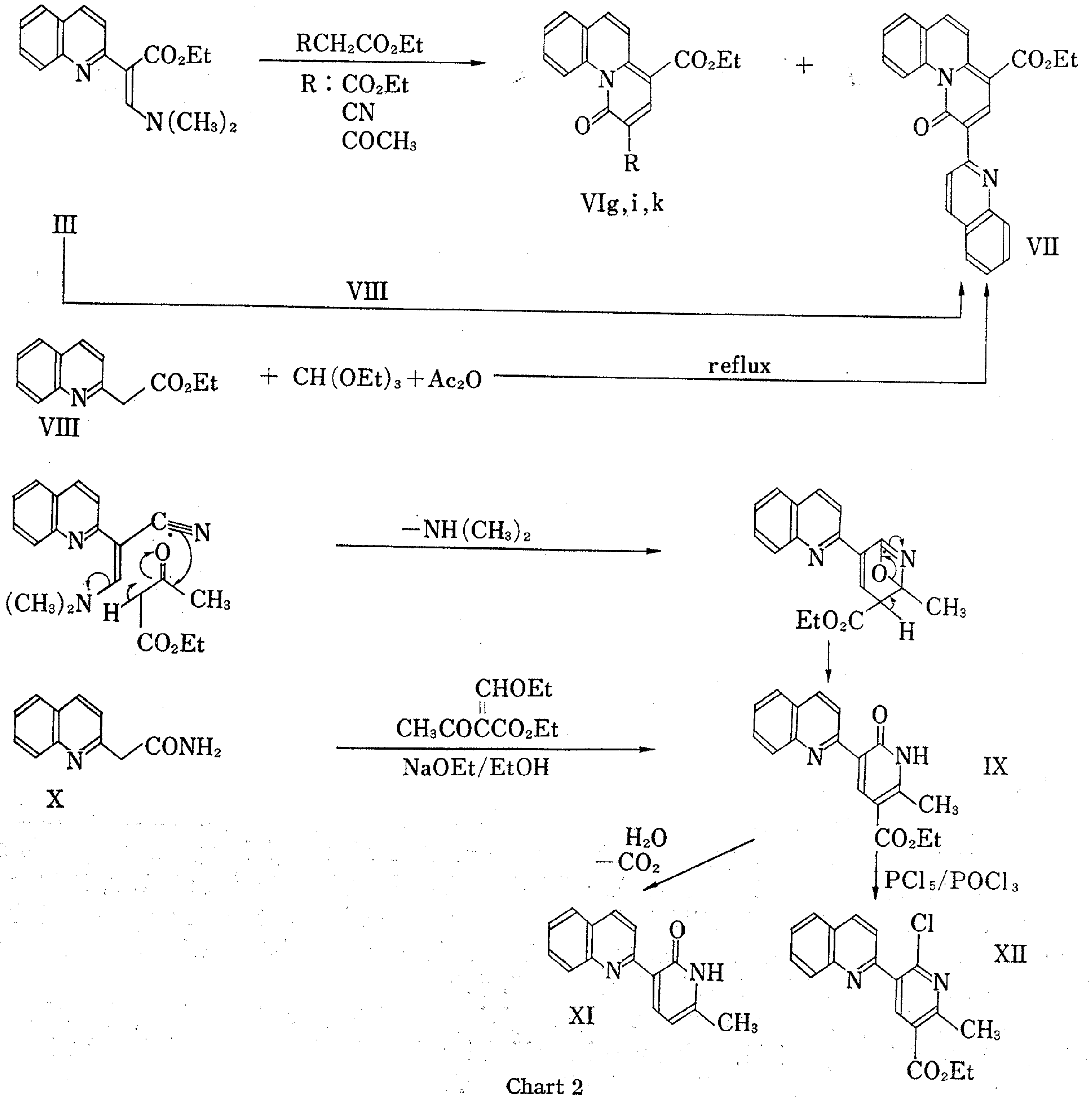

Chart 2

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[6] G.R. Clemo and B. Nath, *J. Chem. Soc.*, **1952**, 2196.

Actually ethyl 2-quinolineacetate reacted easily with such enamine, giving VII in 20% yield.

The formation of VII was also observed in the reaction of III with ethyl cyanoacetate or ethyl acetoacetate as described in experimental section.

Reaction of IV with diethyl malonate gave ethyl 4-cyano-1-oxo-1*H*-benzo[*c*]quinolizine-2-carboxylate (VIh) in 52% yield.

TABLE I

No.	R	R′	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found)			IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}	
						C	H	N		
Va	CO_2Et	H	22(64)	118—119[3,4] (117—118)	$C_{12}H_{11}O_3N$	66.35 (66.22	5.10 5.07	6.45 6.40)	1698	1665
Vb	CN	H	11(—)	211—212	$C_{10}H_6ON_2$	70.58 (70.53	3.55 3.76	16.46 16.62)	2230	1680
VIa	CO_2Et	H	72(37)	91— 92	$C_{16}H_{13}O_3N$	71.90 (71.86	4.90 5.19	5.24 5.34)	1700	1665
VIb	CN	H	65(9)	188—189	$C_{14}H_8ON$	76.36 (76.06	3.66 3.70	12.72 12.99)	2240	1673
Vc	CO_2Et	CH_3	51	114—115	$C_{13}H_{13}O_3N$	67.52 (67.79	5.67 5.90	6.09 6.07)	1690	1651
Vd	CN	CH_3	81	183—184	$C_{11}H_8ON_2$	71.72 (72.06	4.38 4.56	15.12 15.18)	2230	1657
VIc	CO_2Et	CH_3	86	106—107	$C_{17}H_{15}O_3N$	72.58 (72.37	5.37 5.64	4.98 4.79)	1695	1661
VId	CN	CH_3	90	228—229	$C_{15}H_{10}ON_2$	76.91 (76.58	4.30 4.49	11.96 11.87)	2230	1665
Ve	CO_2Et	Et	20	89— 90.5	$C_{14}H_{15}O_3N$	68.55 (68.69	6.16 6.29	5.71 5.60)	1685	1649
Vf	CN	Et	28	125—126	$C_{12}H_{10}ON_2$	72.72 (73.08	5.09 5.39	14.13 14.38)	2230	1660
VIe	CO_2Et	Et	81	106—107	$C_{18}H_{17}O_3N$	73.20 (73.05	5.80 5.76	4.74 4.85)	1697	1650
VIf	CN	Et	74	171—172	$C_{16}H_{12}ON_2$	77.40 (77.41	4.87 4.96	11.28 11.15)	2240	1662
Vg	CO_2Et	CO_2Et	50	131—133[4] (131—132)	$C_{15}H_{15}O_5N$	62.28 (62.21	5.23 5.22	4.84 4.87)	1730 1670	1678
Vh	CN	CO_2Et	43	177—179[5] (179)	$C_{13}H_{10}O_3N_2$	64.46 (64.37	4.16 4.35	11.57 11.93)	2240 1693	1710
VIg	CO_2Et	CO_2Et	33	120—121	$C_{19}H_{17}O_5N$	67.25 (67.39	5.01 5.34	4.13 4.14)	1735	1693
VIh	CN	CO_2Et	52	197—198	$C_{17}H_{12}O_3N_2$	69.85 (69.55	4.14 4.08	9.59 9.48)	2240 1705	1741
Vi	CO_2Et	CN	21	195—196[9] (197)	$C_{13}H_{10}O_3N_2$	64.46 (64.60	4.16 4.37	11.57 11.56)	2220 1700	1735
Vj	CN	CN	20	256—257[5] (256—258)	$C_{11}H_5ON_3$	67.69 (67.52	2.58 2.74	21.53 21.74)	2220	1700
VIi	CO_2Et	CN	17	175—176	$C_{17}H_{12}O_3N_2$	69.85 (69.58	4.14 4.22	9.59 9.57)	2270 1673	1730
VIj	CN	CN	23	314—316 (decomp.)	$C_{15}H_7ON_3$	73.47 (73.50	2.86 2.98	17.14 17.25)	2240	1678
Vl	CN	$COCH_3$	—(16)	(196—197)[3]	$C_{12}H_8O_2N_2$				(2240	1685)
VIk	CO_2Et	$COCH_3$	5(32)	180—181[3] (182—184)	$C_{18}H_{15}O_4N$				1703	1675
VIl	CN	$COCH_3$	trace (5)	(204—206)	$C_{16}H_{10}O_2N_2$				2240	1685
Vm	CO_2Et	2-Py	60	138—140[10] (140)	$C_{17}H_{14}O_3N_2$	69.37 (69.10	4.80 4.85	9.52 9.42)	1690	1650
Vn	CN	2-Py	32	214—215[5] (216)	$C_{15}H_9ON_3$	72.86 (72.85	3.67 3.77	17.00 17.00)	2200	1670

Reaction of ethyl cyanoacetate with enamines proceeded smoothly in similar fashion as in the case of diethyl malonate, giving the corresponding quinolizine derivatives (Vi, Vj, VIi, VIj).

As reported previously,[3] I reacted with ethyl acetoacetate to give ethyl 3-acetyl-4-oxo-4*H*-quinolizine-1-carboxylate (Vk) in 54% yield, however, when II was allowed to react with ethyl acetoacetate, the corresponding quinolizine derivative could not be obtained resulting in the recovery of starting materials. Both III and IV were transformed to the corresponding quinolizine derivatives (VIk, VIl) in poor yield.

Especially, in the reaction of IV with ethyl acetoacetate, the yield of VIl was very poor and colorless crystals of mp 239—240° (decomp.), $C_{18}H_{16}O_3N_2$ (IX), were obtained as a main product (33%). IR spectrum (KBr) indicated the presence of ester carbonyl and amide carbonyl at 1708 cm^{-1} and 1646 cm^{-1}. NMR spectrum ($CDCl_3$) showed characteristic signal owing to ethoxyl protons at 1.39 ppm (3H, t, $J=6.9$ Hz) and 4.34 ppm (2H, q, $J=6.9$ Hz), singlet signal due to methyl protons at 2.82 ppm (3H), multiplet signal presumably due to quinoline ring protons at 7.40—8.55 ppm (6H), singlet signal ascribable to pyridine ring proton at 9.18 ppm (1H), and a broad NH signal at 13.30 ppm.

As shown in Chart 2, IX was also prepared from 2-quinolineacetamide (X) and ethyl 2-ethoxymethyleneacetoacetate.

These observation suggested the structure of IX being ethyl 3-(2′-quinolyl)-6-methyl-2-pyridone-5-carboxylate. A probable pathway of the formation of IX is shown in Chart 2.

Lastly, reactions with ethyl pyridineacetates were carried out. Thus, ethyl 2-pyridineacetate was allowed to react with I and II in a similar manner as described above to give the corresponding quinolizine derivatives (Vm, Vn). However, in the reaction with ethyl 4-pyridineacetate the corresponding quinolizine derivatives could not be obtained, but reaction of I with ethyl 4-pyridineacetate afforded Vm, which was obtained by the reaction of I with ethyl 2-pyridineacetate. The formation of this product (Vm) from I and ethyl 4-pyridineacetate can be explained in the same way mentioned as in the formation of VIl by the reaction of III with esters.

Experimental[7]

Ethyl 4-Oxo-4*H*-quinolizine-1-carboxylate (Va)[3,4]——A mixture of ethyl α-(dimethylaminomethylene)-2-pyridineacetate (I) (0.5 g, 2.5 mmole) and acetic anhydride (1.0 g, 10 mmole) was heated at reflux on an oil bath at 160° for 2 hr. The reaction mixture was poured into a mixture of ice and water, made alkaline with K_2CO_3, and extracted with $CHCl_3$. After being dried over anhyd. K_2CO_3, the $CHCl_3$ layer was evaporated and the residue was chromatographed over alumina. The benzene eluted fraction on evaporation gave a crystalline solid, which was recrystallized from ether to give yellow needles of mp 118—119°. Yield, 0.12 g (22%). NMR ($CDCl_3$) ppm: 1.39 (3H, t, $J=7.0$ Hz, $C\underline{H}_3CH_2O$), 4.34 (2H, q, $J=7.0$ Hz, $CH_3C\underline{H}_2O$), 6.48 (1H, d, $J=11.25$ Hz, 3-H), 7.00—7.30 (1H, m, 7-H), 7.47—7.80 (1H, m, 8-H), 8.37 (1H, d, $J=11.25$ Hz, 2-H), 9.10—9.40 (2H, m, 6 and 9-H).

4-Oxo-4*H*-quinolizine-1-carbonitrile (Vb)——Following the procedure given for Va, α-(dimethylaminomethylene)-2-pyridineacetonitrile (II) (1.0 g) was treated with acetic anhydride (3.0 g), and the resulting residue was chromatographed over alumina. The fractions eluted with ether on evaporation gave Vb, which was recrystallized from benzene to give yellow prisms of mp 211—212°. Yield, 0.16 g (11%). NMR ($CDCl_3$): 6.58 (1H, d, $J=9.15$ Hz, 3-H), 7.14—8.20 (3H, m, 7, 8 and 9-H), 7.88 (1H, d, $J=9.15$ Hz, 2-H), 9.29 (1H, m, 6-H).

Ethyl 1-Oxo-1*H*-benzo[*c*]quinolizine-4-carboxylate (VIa)——a) Following the same procedure as mentioned above, a mixture of ethyl α-(dimethylaminomethylene)-2-quinolineacetate (III) (1.4 g) and acetic anhydride (1.5 g) was treated to give a crystalline residue. Recrystallization from ether gave 0.8 g (72%) of VIa as yellow needles, mp 91—92°. NMR ($CDCl_3$): 1.39 (3H, t, $J=7.20$ Hz, $C\underline{H}_3CH_2O$), 4.35 (2H, q,

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[7] All melting points were uncorrected. NMR spectra were determined on a Hitachi-Perkin Elmer R-20 spectrometer at 60 MHz. Values are given in parts per million relative to tetramethylsilane as an internal standard. Symbols are described of follows: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. IR spectra were taken on a Nippon-bunko Model IR-S spectrophotometer.

$J=7.20$ Hz, $CH_3C\underline{H}_2O$), 6.58 (1H, d, $J=9.75$ Hz, 2-H), 7.38—7.75 (3H,m, 7, 8 and 9-H), 7.53 (1H, $J=9.75$ Hz, 6-H), 8.12 (1H, d, $J=9.75$ Hz, 3-H), 8.81 (1H, d, $J=9.75$ Hz, 6-H), 8.12 (1H, m, 10-H).

b) Ketene, generated by the pyrolysis of acetone according to the Hauford and Sauer's method[8] (the amount of ketene produced per hour was 0.33 mole) was passed into a solution of III (1.5 g) in acetone (20 ml) for 110 sec (corresponding to 0.06 g of ketene). The reaction mixture was allowed to stand in the refrigerator overnight. After evaporation of acetone, a crystalline solid was recrystallized from ether to yield 0.5 g (37%) of VIf as fluorescent and yellow needles mp 91—93°, undepressed on admixture with the specimen (VIa) obtained in the above run a).

1-Oxo-1*H*-benzo[*c*]quinolizine-4-carbonitrile (VIb)——a) A mixture of α-(dimethylaminomethylene)-2-quinolineacetonitrile (IV) (1.1 g) and acetic anhydride (1.5 g) was treated similarly as mentioned above, and the residue was recrystallized from acetone to give 0.72 g (65%) of VIb as fluorescent and yellow needles, mp 187—188°. NMR ($CDCl_3$): 6.59 (1H, d, $J=9.38$ Hz, 2-H), 7.43—7.80 (6H, m, ring proton), 9.57—9.86 (1H, m, 10-H).

b) Ketene was passed into a solution of IV (1.1 g) in acetone (20 ml) for 110 sec (corresponding to 0.06 g of ketene). The reaction mixture was kept in the refrigerator overnight. After concentration of the solution crystals separated were purified by recrystallization to give 0.1 g (9%) of VIb as yellow needles (acetone), mp 188—189°, undepressed on admixture with the compound obtained in the above run a).

Ethyl 3-Methyl-4-oxo-4*H*-quinolizine-1-carboxylate (Vc)——A mixture of I (0.5 g) and propionic anhydride (1.0 g) was refluxed on an oil bath at 200° for 2 hr. The reaction mixture was poured into ice water, made alkaline with K_2CO_3, and extracted with $CHCl_3$. After drying over anhyd. K_2CO_3, the $CHCl_3$ solution was evaporated and the residue was chromatographed over alumina. The benzene eluted fraction on evaporation gave 0.3 g (51%) of Vc as yellow needles (ether). NMR ($CDCl_3$): 1.40 (3H, t, $J=7.0$ Hz, $C\underline{H}_3CH_2O$), 2.32 (3H, s, $C\underline{H}_3$), 4.37 (2H, q, $J=7.0$ Hz, $CH_3C\underline{H}_2O$), 6.95—7.70 (2H, m, 7 and 8-H), 8.30 (1H, s, 2-H), 9.05—9.35 (2H, m, 6 and 9-H).

3-Methyl-4-oxo-4*H*-quinolizine-1-carbonitrile (Vd)——A mixture of II (1.0 g) and propionic anhydride (4.0 g) was treated similarly as mentioned above, and the resulting crystalline substance was chromatographed over alumina and from the fraction eluted with benzene 1.25 g (81%) of Vd was obtained as yellow needles (benzene), mp 183—184°. NMR ($CDCl_3$): 2.33 (3H, s, $C\underline{H}_3$), 7.04—8.07 (3H, m, 7, 8 and 9-H), 7.77 (1H, s, 2-H), 9.10—9.30 (1H, m, 6-H).

Ethyl 2-Methyl-1-oxo-1*H*-benzo[*c*]quinolizine-4-carboxylate (VIc)——A mixture of III (1.4 g) and propionic anhydride (1.8 g) was treated similarly as mentioned above. The crystalline mass was recrystallized from ether to give 1.2 g (86%) of VIc as yellow and fluorescent needles, mp 106—107°. NMR ($CDCl_3$): 1.41 (3H, t, $J=6.75$ Hz, $C\underline{H}_3CH_2O$), 2.32 (3H, s, $C\underline{H}_3$), 4.35 (2H, q, $J=6.75$ Hz, $CH_3C\underline{H}_2O$), 7.42—7.62 (3H, m, 7, 8 and 9-H), 7.45 (1H, d, $J=10.35$ Hz, 6-H), 8.03 (1H, s, 3-H), 8.74 (1H, d, $J=10.35$ Hz, 5-H), 9.40—9.65 (1H, m, 10-H).

2-Methyl-1-oxo-1*H*-benzo[*c*]quinolizine-4-carbonitrile (VId)——A mixture of IV (1.1 g) and propionic anhydride (1.8 g) was treated similarly as above, and the resulting crystalline mass was recrystallized from benzene to give 1.05 g (90%) of VId as yellow needles mp 228—229°. NMR (CF_3COOH): 2.45 (3H, s, $C\underline{H}_3$), 7.57—8.00 (6H, m, ring proton), 9.48—9.72 (1H, m, 10-H).

Ethyl 3-Ethyl-4-oxo-4*H*-quinolizine-1-carboxylate (Ve)——A mixture of I (0.5 g) and butyric anhydride (1.2 g) was treated similarly as above. Crystals isolated by alumina chromatography (benzene) were recrystallized from ether to yield 0.12 g (20%) of Ve as fluorescent and yellow prisms, mp 89—90.5°. NMR ($CDCl_3$): 1.29 (3H, t, $J=7.35$ Hz, $C\underline{H}_3CH_2$), 1.31 (3H, t, $J=6.9$ Hz, $C\underline{H}_3CH_2O$), 2.76 (2H, q, $J=7.35$ Hz, $CH_3C\underline{H}_2$), 4.37 (2H, q, $J=6.9$ Hz, $CH_3C\underline{H}_2O$), 6.95—7.75 (2H, m, 7 and 8-H), 8.29 (1H, s, 2-H), 9.05—9.37 (2H, m, 6 and 9-H).

3-Ethyl-4-oxo-4*H*-quinolizine-1-carbonitrile (Vf)——A mixture of II (1.0 g) and butyric anhydride (4.8 g) was treated similarly as above, and resulting crystals were recrystallized from acetone to give 0.45 g (28%) of Vf as yellow needles, mp 125—126°. NMR ($CDCl_3$): 1.26 (3H, t, $J=7.35$ Hz, $C\underline{H}_3CH_2$), 2.23 (2H, q, $J=7.35$ Hz, $CH_3C\underline{H}_2$), 7.00—8.05 (3H, m, 7, 8 and 9-H), 7.72 (1H, s, 2-H), 9.08—9.30 (1H, m, 6-H).

Ethyl 2-Ethyl-1-oxo-1*H*-benzo[*c*]quinolizine-4-carboxylate (VIe)——In a similar fashion as above, a mixture of III (1.4 g) and butyric anhydride (2.4 g) was treated and the resulting crystalline mass was recrystallized from ether to give 1.19 g (81%) of VIe as fluorescent and yellow prisms, mp 106—107°. NMR ($CDCl_3$): 1.29 (3H, t, $J=7.2$ Hz, $C\underline{H}_3CH_2$), 1.41 (3H, t, $J=6.75$ Hz, $C\underline{H}_3CH_2O$), 2.73 (2H, q, $J=7.2$ Hz, $CH_3C\underline{H}_2$), 4.35 (2H, q, $J=6.75$ Hz, $CH_3C\underline{H}_2O$), 7.40—7.60 (3H, m, 7, 8 and 9-H), 7.42 (1H, d, $J=9.75$ Hz, 6-H), 7.98 (1H, s, 3-H), 8.71 (1H, d, $J=9.75$ Hz, 5-H), 9.33—9.58 (1H, m, 10-H).

2-Ethyl-1-oxo-1*H*-benzo[*c*]quinolizine-4-carbonitrile (VIf)——In a similar fashion as above, a mixture of IV (1.1 g) and butyric anhydride (2.4 g) was treated and the resulting crystalline substance was recrystallized from acetone to yield 0.88 g (74.5%) of VIf as yellow needles, mp 171—172°. NMR ($CDCl_3$): 1.27 (3H, t, $J=7.2$ Hz, $C\underline{H}_3CH_2$), 2.70 (2H, q, $J=7.2$ Hz, $CH_3C\underline{H}_2$), 7.40—7.68 (6H, m, ring proton), 9.55—9.79 (1H, s, 10-H).

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8) W. Hauford and H. Sauer, "Org. Reactions," Vol. 3, John Wiley & Sons, Inc., London, 1946, p. 132.

Diethyl 4-Oxo-4*H*-quinolizine-1,3-dicarboxylate (Vg)[4]——A mixture of I (1.1 g, 5 mmole) and diethyl malonate (0.8 g, 5 mmole) was refluxed on an oil bath at 240° for 1 hr. After cooling, the reaction mixture was washed with petroleum ether, dissolved in benzene, and purified by alumina chromatography to give 0.7 g (50%) of Vg (benzene) as yellow needles, mp 131—132° (lit.[4] mp 131—132°). NMR ($CDCl_3$): 1.43 (6H, t, $J=7$ Hz, $2\times C\underline{H}_3CH_2O$), 4.40 (2H, q, $J=7$ Hz, $CH_3C\underline{H}_2O$), 4.45 (2H, q, $J=7$ Hz, $CH_3C\underline{H}_2O$), 7.20—7.50 (1H, m, 7-H), 7.70—8.05 (1H, m, 8-H), 9.19 (1H, s, 2-H), 9.40 (1H, m, 9-H), 9.56 (1H, m, 6-H).

Ethyl 1-Cyano-4-oxo-4*H*-quinolizine-3-carboxylate (Vh)[5]——Following the procedure given for Vg, the reaction of II (0.69 g) with diethyl malonate (0.6 g) gave 0.2 g (21%) of Vh. Recrystallization from benzene gave yellow needles of mp 177—179° (lit.[5] mp 179°). NMR ($CDCl_3$): 1.41 (3H, t, $J=7$ Hz, $C\underline{H}_3CH_2O$), 4.42 (2H, q, $J=7$ Hz, $CH_3C\underline{H}_2O$), 7.30—7.49 (1H, m, 7-H), 7.97—8.10 (2H, m, 8 and 9-H), 8.61 (1H, s, 2-H), 9.47 (1H, m, 6-H).

Reaction of III with Diethyl Malonate——A mixture of III (1.4 g) and diethyl malonate (0.8 g) was refluxed on an oil bath at 200° for 2 hr, and the mixture was concentrated under reduced pressure to give an oily residue, which was purified by alumina-chromatography. From the benzene elution 0.55 g (33%) of yellow needles (ether), mp 120—121° (VIg), and small amount of orange-red prisms, mp 203—204° (VII), were isolated.

VIg: NMR ($CDCl_3$): 1.42 (6H, t, $J=7.0$ Hz, $2\times C\underline{H}_3CH_2O$), 4.40 (2H, q, $J=7.0$ Hz, $CH_3C\underline{H}_2O$), 4.45 (2H, q, $J=7.0$ Hz, $CH_3C\underline{H}_2O$), 7.47—7.90 (3H, m, 7, 8 and 9-H), 7.78 (1H, d, $J=9.75$ Hz, 6-H), 8.92 (1H, d, $J=9.75$ Hz, 5-H), 8.95 (1H, s, 3-H), 9.30—9.50 (1H, m, 10-H). VII: *Anal.* Calcd. for $C_{25}H_{18}O_3N_2$ (VII): C, 76.13; H, 4.60; N, 7.10. Found: C, 76.50; H, 4.39; N, 7.09. IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 1697 (ester CO), 1658 (amide CO). NMR ($CDCl_3$): 1.45 (3H, t, $J=7.7$ Hz, $C\underline{H}_3CH_2O$), 4.42 (2H, t, $J=7.7$ Hz, $CH_3C\underline{H}_2O$), 7.31—8.00 (7H, m, ring proton), 8.20 (2H, d, $J=8.75$ Hz), 8.53 (1H, d, $J=8.75$ Hz, 4′-H), 8.92 (1H, d, $J=9.43$ Hz, 5-H), 9.25 (1H, s, 3-H), 9.37—9.60 (1H, m, 10-H).

Ethyl 4-Cyano-1-oxo-1*H*-benzo[*c*]quinolizine-2-carboxylate (VIh)——A mixture of IV (1.1 g) and diethyl malonate (0.8 g) was heated on an oil bath at 200° for 2 hr. After coloing, the reaction mixture was washed with ether and the residue was recrystallized form acetone to yield 0.72 g (52%) of VIh as yellow needles, mp 197—198°. NMR ($CDCl_3$): 1.42 (3H, t, $J=7.0$ Hz, $C\underline{H}_3CH_2O$), 4.44 (2H, q, $J=7.0$ Hz, $CH_3C\underline{H}_2O$), 7.55—8.10 (5H, m, ring proton), 8.45 (1H, s, 3-H), 9.45—9.70 (1H, m, 10-H).

Ethyl 3-Cyano-4-oxo-4*H*-quinolizine-1-carboxylate (Vi)[9]——According to the procedure given for Vg, a mixture of I (1.1 g) and ethyl cyanoacetate (0.5 g) was heated to give a crystalline solid, which was purified by recrystallization from acetone to give yellow needles of mp 195—196° (Vi) (lit.[9] mp 197°). Yield, 0.5 g (43%). NMR ($CDCl_3$): 1.43 (3H, t, $J=7$ Hz, $C\underline{H}_3CH_2O$), 4.41 (2H, q, $J=7$ Hz, $CH_3C\underline{H}_2O$), 7.37—7.62 (1H, m, 7-H), 7.88—8.16 (1H, m, 8-H), 8.73 (1H, s, 2-H), 9.46 (2H, m, 6 and 9-H).

4-Oxo-4H-quinolizine-1,3-dicarbonitrile (Vj)[5]——Similar treatment of II (0.69 g) with ethyl cyanoacetate (0.4 g) gave 0.5 g (20%) of Vj as yellow needles (acetone), mp 256—257° (lit.[5] mp 256—258°). NMR ($CDCl_3$–CF_3COOH): 7.62—8.00 (1H, m, 7-H), 8.28—8.40 (2H, m, 8 and 9-H), 8.43 (1H, s, 2-H), 9.58 (1H, m, 6-H).

Reaction of III with Ethyl Cyanoacetate——According to the method given for VIg, a mixture of III (1.4 g) and ethyl cyanoacetate (0.6 g) was treated. The resulting crystalline product was purified by alumina-chromatography. Recrystallization from acetone gave 0.24 g (17%) of ethyl 2-cyano-1-oxo-1*H*-benzo[*c*]quinolizine-4-carboxylate (VIi) as yellow needles, mp 175—176°, and 0.14 g (7%) of VII, mp 203—204°, undepressed on admixture with an authentic sample of VII. VIi: NMR ($CDCl_3$): 1.42 (3H, t, $J=7.0$ Hz, $C\underline{H}_3CH_2O$), 4.40 (2H, q, $J=7.0$ Hz, $CH_3C\underline{H}_2O$), 7.40—8.00 (3H, m, 7, 8 and 9-H), 7.88 (1H, d, $J=9.75$ Hz, 6-H), 8.59 (1H, s, 3-H), 9.00 (1H, d, $J=9.75$ Hz, 5-H), 9.40—9.67 (1H, m, 10-H).

Ethyl 2-(2′-Quinolyl)-1-oxo-1*H*-benzo[*c*]quinolizine-4-carboxylate (VII)[6]——A mixture of ethyl 2-quinolineacetate (2.1 g), ethyl orthoformate (2.2 g) and acetic anhydride (2 g) was refluxed for 2 hr. After cooling, crystals separated were collected, recrystallized from benzene to yield 1.6 g (41%) of VII as orange prisms, mp 204—205°, whose IR was identical with that of a specimen obtained in the above run.

1-Oxo-1*H*-benzo[*c*]quinolizine-2,4-dicarbonitrile (VIj)——A mixture of IV (1.1 g) and ethyl cyanoacetate (0.6 g) was refluxed on an oil bath at 200° for 2 hr, the resulting crystalline residue was washed with ether and benzene, and recrystallized from benzene to give 0.3 g (23%) of VIj as yellow plate, mp 314—316° (decomp.). NMR (CF_3COOH): 7.87—8.62 (5H, m, ring proton), 8.55 (1H, s, 3-H), 9.70—9.98 (1H, m, 10-H).

Reaction of III with Ethyl Acetoacetate——A mixture of III (2.8 g) and ethyl acetoacetate (1.4 g) was refluxed on an oil bath at 200° for 2 hr, and concentrated under reduced pressure. The residue was washed with benzene. The benzene washing was chromatographed over alumina. The benzene eluted fraction was condensed and the crystals separated were collected by suction. Recrystallization from benzene gave 0.15 g (5%) of VIk as yellow needles, mp 180—181° (lit.[3] mp 182—184°), and 0.16 g (4%) of VII, mp 203—204°. Mixed melting point of VIk with the authentic sample showed no depression. VIk: NMR ($CDCl_3$): 1.42 (3H, t, $J=6.75$ Hz, $C\underline{H}_3CH_2O$), 2.78 (3H, s, $C\underline{H}_3CO$), 4.39 (2H, q, $J=6.75$ Hz, $CH_3C\underline{H}_2O$), 7.47—7.90 (4H, m, ring proton), 8.93 (1H, s, 3-H), 8.95 (1H, d, $J=9.75$ Hz, 5-H), 9.27—9.45 (1H, m, 10-H).

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9) T. Govindachari, S. Rajadural, and M. Subramanian, *J. Chem. Soc.*, **1957**, 3839.

Reaction of IV with Ethyl Acetoacetate——A mixture of IV (2.2 g) and ethyl acetoacetate (1.4 g) was heated at 200° for 2 hr. After cooling, the reaction mixture was washed with petroleum-ether and ether. The residue was recrystallized from AcOEt to give 1.01 g (33%) of IX as colorless needles, mp 239—240° (decomp.). The petroleum-ether and ether soluble layer was purified by alumina-chromatography. From the benzene eluted fraction a trace of VII was obtained, mp 200—203°, undepress on admixture with a sample obtained before. IX: *Anal.* Calcd. for $C_{18}H_{16}O_3N_2$ (IX): C, 70.11; H, 5.23; N, 9.09. Found: C, 70.19; H, 5.23; N, 8.94.

Ethyl 6-Methyl-3-(2′-quinolyl)-2-pyridone-5-craboxylate (IX)——A mixture of 2-quinolineacetoamide (X) (0.2 g) and ethyl 2-ethoxymethyleneacetoacetate (0.2 g) in EtOH (20 ml) in the presence of NaOEt was allowed to stand at room temperature for 45 hr. The mixture was condensed to give an oily residue, to which was added water and extracted with $CHCl_3$. After drying over anhyd. K_2CO_3, the $CHCl_3$ solution was evaporated and the residue was recrystallized from AcOEt to give 0.15 g (50%) of IX as colorless needles, mp 241—242° (decomp.), whose IR spectrum was identical with that of sample obtained in the above run.

Ethyl 3-(2′-Pyridyl)-4-oxo-4*H*-quinolizine-1-carboxylate (Vm)[10]——A mixture of I (1.1 g) and ethyl 2-pyridineacetate (0.8 g) was heated at 240° for 1 hr. After cooling, the reaction mixture was washed with petroleum-ether and the residue was purified by alumina-chromatography to give 0.8 g (60%) of Vm as yellow needles, mp 138—140° (lit.[10] mp 140°). NMR ($CDCl_3$): 1.43 (3H, t, $J=7$ Hz, $C\underline{H}_3CH_2O$), 4.42 (2H, q, $J=7$ Hz, $CH_3C\underline{H}_2O$), 7.10—7.40 (2H, m), 7.50—7.92 (2H, m), 8.50—8.80 (2H, m), 9.38 (2H, m, 9-H), 9.53 (1H, s, 2-H), 9.52 (1H, m, 6-H).

3-(2′-Pyridyl)-4-oxo-4*H*-quinolizine-1-carbonitrile (Vn)[5]——Following the procedure give for Vm, II (0.69 g) was heated with ethyl 2-pyridineacetate (0.8 g) to give Vn, which was purified by recrystallization from acetone to give yellow needles of mp 214—215° (lit.[5] mp 216°). Yield, 0.3 g (32%). NMR ($CDCl_3$): 7.10—7.50 (2H, m), 7.60—8.20 (3H, m), 8.55—8.80 (2H, m), 9.12 (1H, s, 2-H), 9.47 (1H, m, 6-H).

Reaction of I with Ethyl 4-Pyridineacetate——A mixture of I (0.5 g) and ethyl 4-pyridineacetate (0.4 g) was treated similarly as in the above run, giving 0.08 g (6%) of Vm as yellow needles (benzene).

3-(2′-Quinolyl)-6-methyl-2-pyridone (XI)——IX (0.45 g) was added to polyphosphoric acid (10 ml), and the mixture was heated at 170° for 2 hr, poured into cold water, made alkaline with K_2CO_3, and extracted with $CHCl_3$. After drying over anhyd. K_2CO_3, the $CHCl_3$ layer was condensed and crystals separated were recrystallized from benzene to yield as colorless needles, mp 244—245° (decomp.). Yield, 0.28 g (82%). *Anal.* Calcd. for $C_{15}H_{12}ON_2$ (XI): C, 76.25; H, 5.12; N, 11.86. Found: C, 75.97; H, 5.02; N, 11.85. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1643 (amide C=O). NMR (CF_3COOH): 2.73 (3H, s, $C\underline{H}_3$), 7.00 (1H, d, $J=7.8$ Hz), 7.90—8.52 (5H, m, ring proton), 8.87 (1H, d, $J=7.8$ Hz), 9.00 (1H, d, $J=9.15$ Hz).

Ethyl 2-Methyl-6-chloro-5-(2′-quinolyl)-pyridine-3-carboxylate (XII)——A mixture of IX (0.6 g), PCl_5 (0.4 g) and $POCl_3$ (10 ml) was heated for 4 hr evaporated under reduced pressure, and residue was poured into water, made alkaline with K_2CO_3, extracted with ether, subsequently with $CHCl_3$ and both fractions were dried over anhyd. K_2CO_3. The ether fraction was condensed and the residue was purified by recrystallization from ether and petroleum-ether (1: 1) to give XII as colorless needles, mp 137—138°. Yield, 0.15 g (24%). From the $CHCl_3$ extract, 0.23 g (40%) of the starting material (IX) was recovered. XII: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (ester CO). NMR ($CDCl_3$): 1.39 (3H, t, $J=7.2$ Hz, $C\underline{H}_3CH_2O$), 2.89 (3H, s, $C\underline{H}_3$), 4.38 (2H, q, $J=7.2$ Hz, $CH_3C\underline{H}_2O$), 7.50—8.32 (6H, m, ring proton), 8.58 (1H, s, 4-H).

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10) G.R. Clemo, R.W. Fox, and R. Raper, *J. Chem. Soc.*, **1954**, 2673.