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Studies on Tertiary Amine Oxides. LXII.[1] A Novel Formation of Quinolinium Methylides by the Reaction of Quinoline 1-Oxides with Active Methylene Compounds in the Presence of an Acylating Agent

Kazuhisa Funakoshi,[2] Hirotsune Sonoda,[2a] Yoshiko Sonoda,[2b] and Masatomo Hamana[2]

Faculty of Pharmaceutical Sciences, Kyushu University 62[2]

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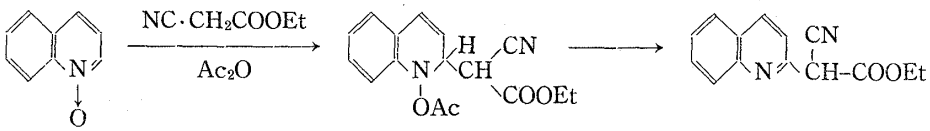
The reaction of quinoline 1-oxide with ethyl cyanoacetate and acetic anhydride in dimethylformamide (DMF) or dimethylsulfoxide (DMSO) at low temperatures was found to give quinolinium-ethoxycarbonylcyanomethylide as the main product besides the normal 2-substituted and 4-substituted products. This novel formation of N-ylide was examined under various conditions, and the following features were revealed.

Acetic anhydride was most effective as acylating agent, and DMF and DMSO seemed most suitable media for the N-ylide formation. In addition to ethyl cyanoacetate, malonodinitrile, methyl cyanoacetate and benzoylacetonitrile also produced the corresponding N-ylides, but other active methylene compounds such as malonates, ethyl acetoacetate and cyanoacetamide gave no ylide, only 2-substituted or/and 4-substituted products being formed. As for aromatic N-oxide, pyridine and isoquinoline N-oxides were inert to the N-ylide formation. On the other hand, quinoline 1-oxides bearing an electron-donating group at the 4-position, *i.e.*, lepidine, 4-methoxy- and 4-amino-quinoline 1-oxides, were highly reactive toward this type of N-ylide formation.

A likely reaction mechanism was proposed.

Keywords——N-acetoxy-1,2-dihydroquinoline intermediate; active methylene compound; nucleophilic reaction of aromatic N-oxide; a novel formation of N-ylide; substituent effect; solvent effect; aziridine intermediate

The reaction of aromatic N-oxide with active methylene compounds, such as ethyl cyanoacetate, in the presence of acetic anhydride is now recognized as one of the promising methods for introduction of carbon-substituents into the α-position of N-heteroaromatic ring, although its application suffers from some limitations.[3,4]



On the other hand, it is also well-known that nucleophilic reaction of aromatic N-oxide in the presence of an acylating agent is very varied depending upon the reaction conditions;[5,6] for example, γ-[5–7] or β-substitution[5–8] predominates in some cases. Taking account of this

1) Part LXI: M. Hamana, S. Takeo, and H. Noda, *Chem. Pharm. Bull.* (Tokyo), **25**, 79 (1977).
2) Location: *Maidashi, Higashi-ku, Fukuoka 812, Japan*; *a*) Present address; *Sato Pharm. Co., Higashi-Ohi, Shinagawa-ku, Tokyo 140, Japan*; *b*) *Kyoritsu Pharmaceutical College, Shibakoen, Minato-ku, Tokyo 105, Japan.*
3) *a*) M. Hamana and M. Yamazaki, *Chem. Pharm. Bull.* (Tokyo), **11**, 411 (1963); *b*) *Idem, ibid.*, **11**, 415 (1963).
4) J.D. Baty, G. Jones, and C. Moore, *J. Org. Chem.*, **34**, 3295 (1969).
5) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., Amsterdam, 1967, Chapter 7.
6) A.R. Katritzky and J.M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, London and New York, 1971, Chapter III-4.
7) *a*) M. Hamana and K. Funakoshi, *Yakugaku Zasshi*, **82**, 512 (1962); *b*) *Idem, ibid.*, **84**, 28 (1964).
8) M. Hamana and H. Noda, *Chem. Pharm. Bull.* (Tokyo), **15**, 474 (1967).

fact, the reaction of quinoline 1-oxide with ethyl cyanoacetate in the presence of an acylating agent was re-examined by varying the reaction conditions, especially the reaction medium, in hope of finding some other type of reaction. This paper deals with a novel formation of quinolinium-methylides encountered during the course of such studies.[9]

When ethyl cyanoacetate (ECA) was added dropwise to an ice-cooled solution of quinoline 1-oxide (**1**) and acetic anhydride in dimethylformamide (DMF), an exothermic reaction immediately occurred and the solution turned deep purple. After the reactants had been stirred with ice-cooling for 2—3 hr and then kept overnight at room temperatures, chromatographic separation of products on alumina gave ethyl α-cyano-2-quinolineacetate (**2a**),[3b] ethyl α-cyano-4-quinolineacetate (**3a**)[10] and quinolinium-ethoxycarbonylcyanomethylide (**4a**) in 32.0, 4.2 and 53.6% yields, respectively.

The main product **4a** was recrystallized from ethyl acetate to form purple needles of mp 203—204° (dec.). The elemental analysis and the mass spectrum (M^+: *m/e* 240) indicate that the molecular formula is $C_{14}H_{12}N_2O_2$. The infrared (IR) spectrum of **4a** exhibited a characteristic nitrile band at 2195 cm^{-1} and two strong bands at 1635 and 1620 cm^{-1} indicative of a highly ionic carbonyl group. The nuclear magnetic resonance (NMR) spectrum showed a one-proton doublet-doublet at δ 9.12 (J=6.0, 1.5 Hz) due to the C_2-proton of the quinoline ring bearing no substituent at the 3- and 4-positions. The ultraviolet (UV) spectrum in ethanol was quite different from that of the 2-substituted product **2a** and had a maximum around 445 nm, but the spectrum in 1 N hydrochloric acid was closely similar to that of quinoline methiodide[11] (Fig. 1 and 2).

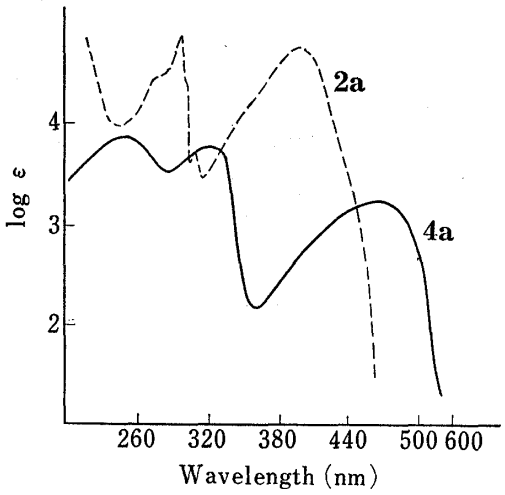


Fig. 1. UV Spectra of Quinolinium-ethoxycarbonylcyanomethylide (**4a**) and Ethyl α-Cyano-2-quinolineacetate (**2a**) in Ethanol

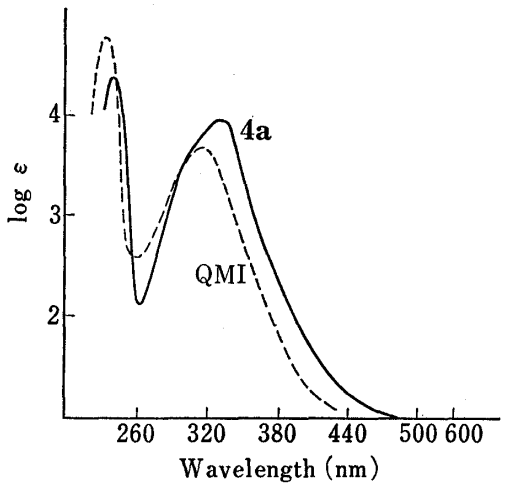


Fig. 2. UV Spectra of Quinolinium-ethoxycarbonylcyanomethylide (**4a**) and Quinoline Methiodide (QMI) in 1 N Hydrochloric Acid

Oxidation of **4a** with 30% hydrogen peroxide in hot acetic acid or in ethyl acetate at room temperatures afforded **1** or quinoline, respectively. Hydrolysis of **4a** with concentrated hydrobromic or hydrochloric acid gave N-carboxymethylquinolinium bromide (**5a**) or chloride (**5b**). The identity of **5a** was confirmed by direct comparison with an authentic sample prepared by hydrobromic acid hydrolysis of N-ethoxycarbonylmethylquinolinium

9) M. Hamana, *J. Heterocycl. Chem.*, **9**, S-51 (1972).
10) K. Golankiewiz, *Roczniki Chem.*, **36**, 625 (1962) [*C.A.* **59**, 570 (1963)].
11) D. Sutherland and C. Compton, *J. Org. Chem.*, **17**, 1257 (1952).

bromide (**6**) obtainable easily from quinoline and ethyl bromoacetate.[12] These reactions are formulated in Chart 1.

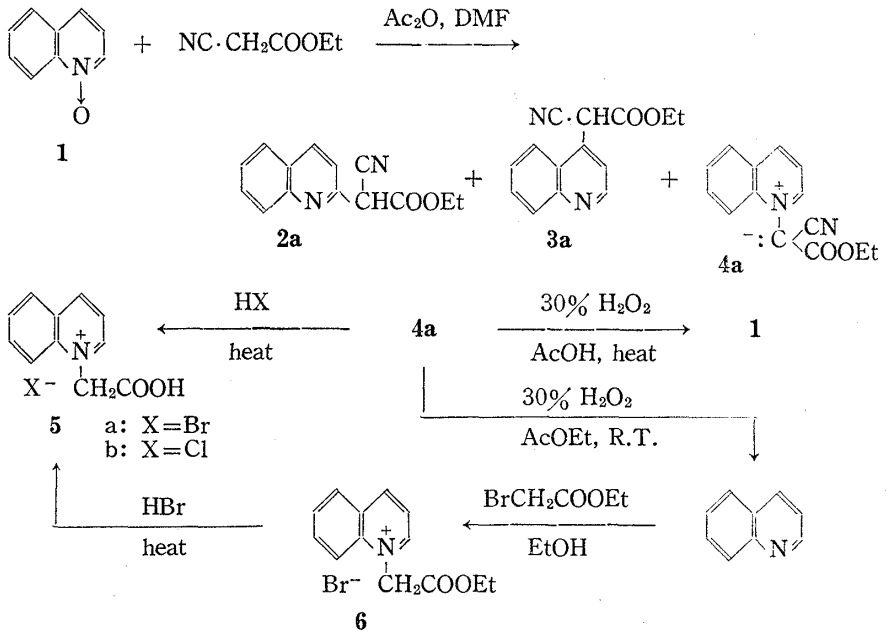


Chart 1

As a preliminary study of the influence of the nature of solvent as well as acylating agent on the formation of the ylide **4a**, various conditions were examined and the results shown in Table I were obtained. Apparently the nature of solvent is a very important factor for the formation of **4a**. DMF and dimethylsulfoxide (DMSO) seemed to be most suitable media, and interestingly **4a** was isolated also from the reaction in pyridine. No formation of **4a** was noticed when other solvents were used. As acylating agent, acetic anhydride was shown to be most effective; propionic anhydride, benzoic anhydride and acetyl chloride also gave **4a** but in lower yields. However notably, the use of benzoyl or tosyl chloride yielded no N-ylide.

Table I. Reaction of Quinoline 1-Oxide (**1**) with Ethyl Cyanoacetate (ECA)

Acylating agent	Solvent	Product (%)		
		2a	**3a**	**4a**
Ac_2O	H_2O	44.2	—	—
	MeOH	66.7	—	—
	Acetone	50.8	—	—
	AcOEt	62.4	—	—
	DMF	32.0	4.2	53.6
	DMSO	19.6	2.9	52.9
	Pyridine	22.0	0.9	17.1
AcCl	DMF	38.8	2.5	1.7
BzCl	DMF	45.7	2.1	—
TsCl	DMF	59.1	11.8	—
$(EtCO)_2O$	DMF	36.2	3.4	27.1
$(PhCO)_2O$	DMF	48.4	—	7.5
TsCl	DMF–NEt_3	46.2	20.5	—

12) *cf.* T.L. Gresham, J.E. Jansen, F.W. Shaver, R.A. Bankert, and F.T. Friedorek, *J. Am. Chem. Soc.*, **73**, 3168 (1951).

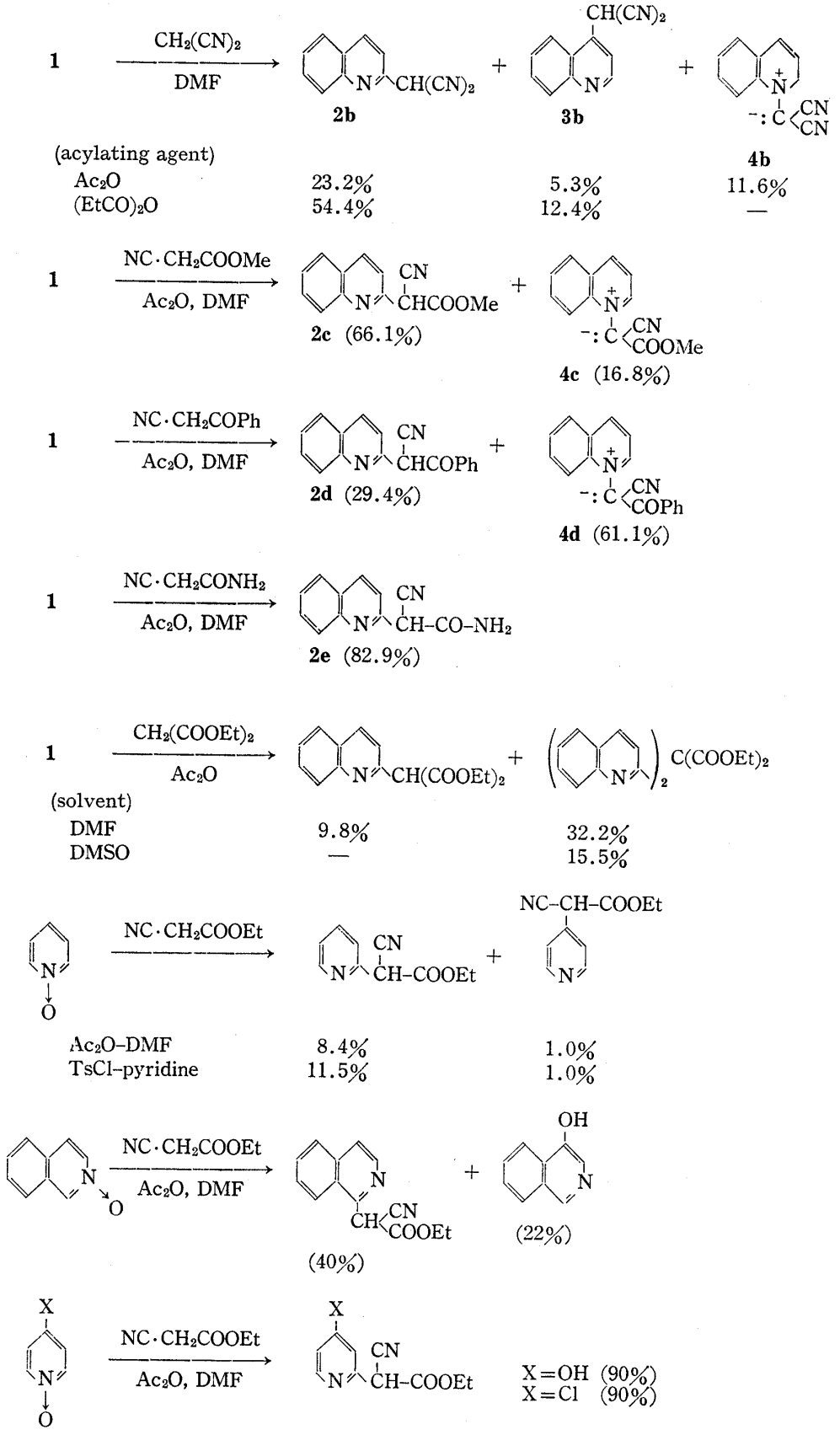


Chart 2

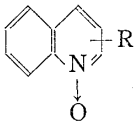
Subsequently in order to explore the scope of this type of N-ylide formation and, if possible, to gain some insight into the reaction mechanism, reactions of **1** as well as pyridine and isoquinoline N-oxides with some typical active methylene compounds were tried in DMF using mainly acetic anhydride as the acylating agent.

Malonodinitrile (MN) similarly reacted with **1** in the presence of acetic anhydride, giving the 2-, 4- and N-substituted products (**2b**,[13] **3b**[14] and **4b**) in somewhat lower yields of 23.2, 5.3 and 16.8%, respectively. However, the use of propionic anhydride in place of acetic anhydride afforded not N-ylide **4b** but only products **2b** and **3b**, indicating that propionic anhydride is less effective than acetic anhydride and MN is not so reactive as ECA in the formation of N-ylide (Chart 2). Conversion of **4b** into quinoline, its N-oxide **1** and N-carboxymethylquinolinium halides (**5**) were effected in the similar way as the case of **4a**.

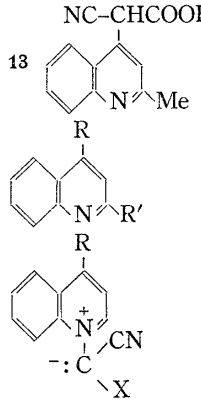
In addition to ECA and MN, methyl cyanoacetate (MCA) and benzoylacetonitrile (BAN) were found to react with **1** to give 2-substituted (**2c**,[4] 66.1% and **2d**, 29.4%) and N-substituted products (**4c**, 16.8% and **4d**,[15] 61.1%), no 4-substituted product being isolated in these cases.

However curiously, the reaction with cyanoacetamide (CAA) produced only 2-substituted product (**2e**)[4] in a high yield of 82.9%, and no N-ylide was detected.

Table II. Reactions of Quinoline 1-Oxides with Active Methylene Compounds and Acetic Anhydride in DMF

	Active methylene[a]	Product (%)		
		2-Substituted	4-Substituted	N-Substituted
7 (R=2-Me)	ECA	—	**13** (49.0)	—
	ECA	**14a** (38.6)	—	**15a** (24.5)
8 (R=4-Me)	MN	**14b** (27.4)	—	**15b** (11.6)
	BAN	**14d** (6.3)	—	**15d** (66.0)
	ECA	**16a** (4.57)	—	**17a** (39.0)
9 (R=4-OMe)	MN	**16b** (11.3)	—	**17b** (43.2)
	BAN	**16d** (19.1)	—	**17d** (16.4)
	ECA	**18a** (1.0)	—	**19a** (90.1)
10 (R=4-NH_2)	MN	—	—	**19b** (35.9)
	BAN	—	—	**19d** (82.3)
11 (R=4-OH)	ECA	**20a** (84.5)	—	—
	MN	**20b** (77.3)	—	—
12 (R=4-Cl)	ECA	**21a** (59.1)	—	—

a) ECA=NC·CH_2COOEt, MN=$CH_2(CN)_2$, BAN=PhCOCH_2CN



14: R=Me, **16**: R=OMe, **18**: R=NHAc, **20**: R=OH, **21**: R=Cl
a: R′=CH(CN)COOEt, **b**: R′=$CH(CN)_2$, **d**: R′=CH(CN)COPh

15: R=Me, **17**: R=OMe, **19**: R=NHAc, **19′**: R=NH_2
a: X=COOEt, **b**: X=CN, **d**: X=COPh

13) *a*) A.L. Borror and A.F. Haeberer, *J. Org. Chem.*, **30**, 243 (1965); *b*) A.R. Katritzky and E. Lunt, *Tetrahedron*, **25**, 4291 (1969).
14) H.J. Richter, N.E. Rustad, and R.L. Dressler, *J. Org. Chem.*, **32**, 1635 (1967).
15) R.A. Abramovitch, G. Grins, R.B. Rogers, and I. Shinkai, *J. Am. Chem. Soc.*, **98**, 5671 (1976).

N-Ylide formation was not noticed at all in any of reactions with other active methylene compounds such as diethyl malonate, ethyl acetoacetate and acetylacetone; furthermore yields of 2- and 4-substituted products were much more lower as compared with the original process in acetic anhydride,[3] as exemplified by the case of diethyl malonate shown in Chart 2.

Unlike quinoline 1-oxide, N-oxides of pyridine and isoquinoline resisted the N-ylide formation and attempted reactions with ECA under various conditions resulted in the formation of only α- and γ-substitution in rather ow yields. However interestingly, the reactions of 4-hydroxy- and 4-chloro-pyridine 1-oxides were found to give the corresponding 2-substituted products in high yields as shown in Chart 2.

Further ECA, MN and BAN were applied to some substituted quinoline 1-oxides in DMF using acetic anhydride as the acylating agent. Table II shows the results thus obtained.

The reaction of quinaldine 1-oxide (**7**) with ECA gave only 4-substituted product (**13**) in 49% yield with no visible sign of the N-ylide formation. Quinoline 1-oxide having an electron-donating substituent at the 4-position, that is, N-oxides of lepidine (**8**), 4-methoxy- (**9**) and 4-amino-quinoline (**10**) were disclosed to be substantially reactive toward the N-ylide formation. All reactions of these N-oxides with ECA, MN and BAN produced the respective N-ylides (**15**, **17** and **19**) in fair to excellent yields together with varing amounts of the corresponding 2-substituted products (**14**, **16** and **18a**). Particularly the high reactivity of **10** is very noticeable, and the corresponding 4-acetamidoquinolinium N-ylide (**19a**, **19b** and **19d**) were obtained in 90.1, 35.9 and 82.3% yields, respectively; furthermore, only from the reaction with ECA was isolated a product **18a** conceivable as 2-substituted one in a poor yield of 1.0%, no 2-substituted derivative being formed with MN or BAN. Deacetylation of 4-acetamidoquinolinium N-ylides, **19a** and **19d**, was effected by treatment with hot potassium hydroxide solution, giving the corresponding 4-amino derivatives, **19'a** and **19'd**, respectively. On the other hand, no ylide formation was observed in the reactions of 4-quinolinol 1-oxide (**11**) and 4-chloroquinoline 1-oxide (**12**), the respective 2-substituted products being produced in good yields.

In contrast with the reaction of 4-aminoquinoline 1-oxide (**10**), that of 2-aminoquinoline 1-oxide with ECA and acetic anhydride was found to follow a different course, giving ethyl

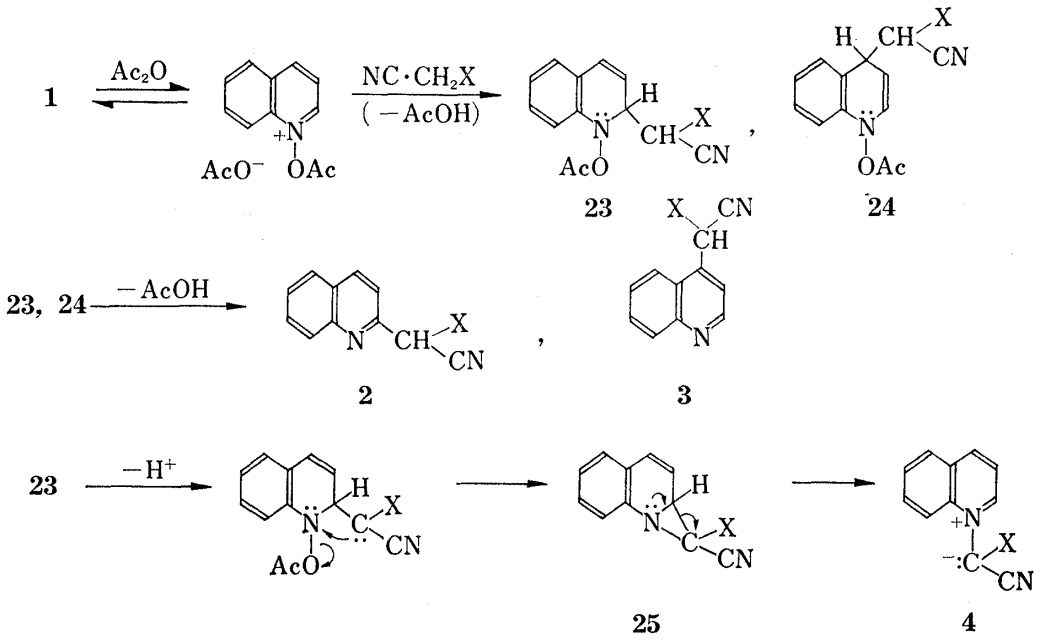
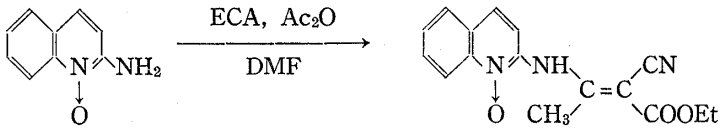


Chart 3

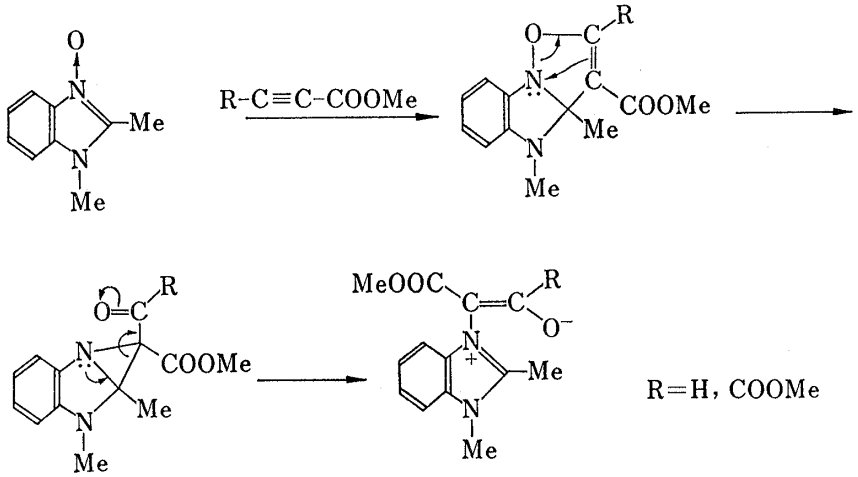
α-cyano-β-(1-oxido-2-quinolylamino)crotonate (**22**). This and related reactions will be reported shortly.



The formation of 2- and 4-substituted products, for example **2** and **3**, can be well explained by liberation of the acetic acid component from the 1,2- and 1,4-dihydroquinoline intermediate (**23** and **24**) in the usual way (Chart 3).

Although the details of the mechanism have not been established, the N-ylide formation seems likely to follow the course shown in Chart 3. The 1,2-dihydroquinoline intermediate (**23**) looses a proton, followed by extrusion of acetoxy anion and aziridine formation, and the aziridine intermediate (**25**) isomerizes to the ylide **4**.

A somewhat similar course has been suggested as one of the possible mechanism for the betaine formation from the 1,3-dipolar cycloaddition between some acetylenic compounds and aromatic N-oxide[15–18] as exemplified below, but its detailed mechanism is also not yet clarified.



Although cyanoacetamide forms no N-ylide, all the active methylene compounds capable of giving the N-ylide have at least one cyano group (ECA, MN, MCA and BAN), and this feature seems essential for the N-ylide formation, but the details of this aspect are not yet clear. The acidity of the active methylene compounds is apparently an important factor for the mode of reaction, however the above-mentioned results cannot be rationalized only by this factors; for instance, acetylacetone and ethyl acetoacetate give no N-ylide, but their pK_a values are approximately the same with those of ECA and MN, respectively.[19]

Further work on extending the scope of this type of reaction is in progress.

Experimental

Melting points are uncorrected. IR spectra were recorded on JASCO DS-301, IR-S and IR-E spectrophotometer, and NMR spectra were measured with JNM C-60H spectrophotometer at 60 MHz using tetramethylsilane as internal reference.

16) *a*) S. Takahashi and H. Kano, *J. Org. Chem.*, **30**, 1118 (1965); *b*) *Idem*, *Chem. Pharm. Bull.* (Tokyo), **16**, 142 (1968).
17) *a*) R.M. Acheson, A.S. Bailey, and I.A. Selby, *Chem. Commun.*, **1966**, 835; *b*) *Idem*, *J. Chem. Soc.* (*C*), **1976**, 2066.
18) R. Huisgen, H. Seidl, and J. Wulff, *Chem. Ber.*, **102**, 915 (1969).
19) H.O. House, "Modern Synthetic Reaction," W.A. Benjamin, INC., Menlo Park, California, 1972, Chapter 9.

Table III. Some Properties of New Products of Quinoline Series

No.	Formula	mp (°C)	Appearance (Recryst. solv.)	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
4a	$C_{14}H_{12}N_2O_2$	203—204	Red violet needles (AcOEt)	69.99	5.03	11.66	70.24	5.16	11.82
5a	$C_{11}H_{10}BrNO_2$	222—223	Yellow needles (EtOH–MeOH)	49.27	3.76	5.22	49.11	4.08	5.25
5b	$C_{11}H_{10}ClNO_2$	201—202	Yellow needles (EtOH)	59.07	4.51	6.26	59.10	4.48	6.21
6	$C_{13}H_{14}BrNO_2$	183—185	Golden yellow scales (EtOH–ether)	52.72	4.76	4.73	52.80	4.87	4.57
4b	$C_{12}H_7N_3$	223—224	Red needles (MeOH)	74.60	3.65	21.75	74.39	3.58	21.53
4c	$C_{13}H_{10}N_2O_2 \cdot H_2O$	184—187	Red needles (AcOEt)	63.92	4.95	11.47	64.03	4.74	11.19
2d	$C_{18}H_{12}N_2O$	204—206	Yellow needles (MeOH)	79.49	4.34	10.15	79.36	4.29	10.11
4d[15]	$C_{18}H_{12}N_2O$	224—226	Red prisms (MeOH)	79.49	4.34	10.15	79.36	4.44	10.29
13	$C_{15}H_{14}N_2O_2$	210—211	Yellow scales (acetone)	70.85	5.55	11.02	71.07	5.65	10.83
15a	$C_{15}H_{14}N_2O_2$	212—213	Red scales (EtOH–AcOEt)	70.85	5.55	11.02	71.12	5.73	10.96
14b	$C_{13}H_9N_3$	307—308	Yellow needles (AcOEt)	75.34	4.38	20.28	75.25	4.50	20.32
15b	$C_{13}H_9N_3$	201—202	Red needles (AcOEt)	75.34	4.38	20.28	75.33	4.68	20.29
14d	$C_{19}H_{14}N_2O$	175—176	Yellow needles (MeOH)	79.70	4.93	9.78	79.51	4.88	9.76
15d	$C_{19}H_{14}N_2O$	227—228	Red needles (EtOH)	79.70	4.93	9.78	79.41	4.86	9.65
16a	$C_{15}H_{14}N_2O_3$	171—173	Yellow needles (acetone–MeOH)	66.65	5.22	10.37	66.49	5.28	10.30
17a	$C_{15}H_{14}N_2O_3$	186—187	Orange red needles (AcOEt)	66.65	5.22	10.37	66.56	5.22	10.21
16b	$C_{13}H_9N_3O$	288—293	Yellow needles (MeOH)	67.23	4.34	18.10	67.25	4.19	18.35
17b	$C_{13}H_9N_3O$	226—228	Orange scales (MeOH)	69.94	4.06	18.83	69.86	3.94	18.56
16d	$C_{19}H_{14}N_2O_2$	278—280	Colorless prisms (MeOH)	75.48	4.67	9.27	75.20	4.41	9.57
17d	$C_{19}H_{14}N_2O_2$	209—210	Orange red prisms (AcOEt)	75.48	4.67	9.27	75.62	4.58	8.99
19a	$C_{16}H_{15}N_3O_3$	279—280	Red pillars (AcOH–H_2O)	64.63	5.09	14.14	64.64	5.13	14.09
19'a	$C_{14}H_{13}N_3O_2$	276—278	Yellow needles (EtOH)	65.87	5.13	16.46	65.71	5.06	16.29
19b	$C_{14}H_{10}N_4O$	265—266	Red needles (MeOH)	67.19	4.03	22.39	67.12	4.08	22.06
19d	$C_{20}H_{15}N_3O_2$	286—288	Red needles (AcOH)	72.93	4.59	12.76	72.97	4.63	12.73
19'd	$C_{18}H_{13}N_3O$	268—270	Yellow needles (EtOH)	70.80	4.95	13.79	71.04	4.97	13.92
20a	$C_{14}H_{17}N_2O_3$	279—280	Colorless needles (MeOH)	65.62	4.72	10.93	65.59	4.72	10.78
20b	$C_{12}H_7N_3O$	217—218	Yellow needles (MeOH)	68.89	3.37	20.09	68.76	3.41	20.11
21a	$C_{11}H_{11}ClN_2O_2$	140—141	Yellow needles (MeOH)	61.20	4.03	10.19	61.35	3.85	10.08

Table IV. IR and NMR Spectral Data of N-Ylides

No.	IR (cm^{-1})		NMR							
			Chemical shift (δ)						Coupling constant	
	$\nu_{C\equiv N}$	$\nu_{C=O}$	C_2–H	C_3–H	$C_{5,6,7,8}$–H	CH_2 (q)[a]	CH_3 (t)[a]	Others[b]	$J_{2,3}$(Hz)	Solvent[c]
4a	2195	1632 1620	9.12 (dd)	7.77 (dd)	7.8—8.8	4.25	1.34	8.66 (dd)	6.0	A
4b	2200 2175		9.43 (dd)	7.95 (dd)	7.9—8.9	—	—	9.12 (dd)	6.0	B
4c	2200	1630 1620								
4d	2200	1688 1650 1615								
15a	2200	1650	8.95 (d)	7.64 (d)	7.6—8.5	4.23	1.30	2.08 (s)	6.5	A
15b	2240 2200	1650	8.90 (d)	7.54 (d)	7.6—8.5	—	—	2.90 (s)	6.0	A
15d	2200	1600	9.30 (d)	7.44 (d)	7.5—8.2	—	—	3.00 (s)	6.4	B
17a	2200	1630 1610	8.85 (d)	7.10 (d)	7.5—8.6	3.90	1.25	4.40 (s)	6.4	C
17b	2200 2180		9.34 (d)	7.50 (d)	7.7—8.5	—	—	4.30 (s)	7.6	B
17d	2200	1600	9.18 (d)	7.40 (d)	7.5—8.6	—	—	4.34 (s)	7.4	B
19a	2200	1730 1620								
19′a	2200	1670	8.95 (d)	6.76 (d)	7.6—8.3	4.01	1.20	—	7.5	B
19b	2240 2200		9.12 (d)	7.84 (d)	7.9—9.0	—	—	4.42 (s)	6.6	B
19d	2200	1720 1625								
19′d	2200	1680 1640								

a) Signals of $\overset{+}{\underset{}{N}}-\overset{-}{C}(CN)(COOCH_2CH_3)$.
b) Signals of C_4–H or a substitutent on the 4-position of quinoline ring.
c) A: $CDCl_3$, B: DMSO-d_6, C: CCl_4.

Melting points, appearance and analytical values of products are listed in Table III, and the IR and NMR spectral data of N-ylides are summarized in Table IV.

General Procedure for Reaction of Quinoline 1-Oxides with Active Methylene Compounds——An active methylene compound (0.012 mol) was added to a solution of a quinoline 1-oxide (0.01 mol) and Ac_2O (0.024 mol) in DMF (10 ml) with stirring at −15° to −10°. After the reactants had been stirred at the same temperature for 2—3 hr, the reaction mixture was kept at room temperatures overnight, and worked up by methods (A) or (B).

Method (A): The reaction mixture was poured into AcOEt (80 ml), and washed with two 50 ml portions of 10% Na_2CO_3 and five 80 ml portions of saturated NaCl solution to remove DMF. The AcOEt layer was extracted with 10% HCl. From the AcOEt solution, 2-substituted or/and 4-substituted products were obtained. The acidic solution was made alkaline with Na_2CO_3 solution and extracted with $CHCl_3$ or AcOEt to afford N-ylide. Purification of products was performed by chromatography on silica gel or alumina column and recrystallization.

Method (B): The reaction mixture was poured into H_2O (100 ml), and the deposites were filtered and washed with three 10 ml portions of 10% HCl to give the crude 2-substituted or/and 4-substituted products. From the HCl solution, the N-ylide were isolated in the same way with method (A).

Reaction of Quinoline 1-Oxide (1) with Ethyl Cyanoacetate (ECA)——1) ECA (1.35 g) was added to a solution of **1** (1.45 g) and Ac_2O (2.45 g) in DMF (10 ml) with stirring at −15°, and the reactants were stirred at −10——15° for 2 hr, kept at room temperature overnight, and worked up by method (A). The AcOEt solution was dried and evaporated, and the residue was chromatographed on silica gel. The first fraction

eluted with benzene was recrystallized from acetone to give 0.77 g (32.0%) of ethyl α-cyano-2-quinolineacetate (**2a**),[3b] yellow prisms, mp 166—167°. The second fraction eluted with AcOEt was recrystallized from MeOH to afford 0.11 g (4.2%) of ethyl α-cyano-4-quinolineacetate (**3a**),[10] red needles, mp 174—176°. The 10% HCl solution was made alkaline with 10% Na_2CO_3 and extracted with $CHCl_3$. The residue from the extract was chromatographed on silica gel with AcOEt and recrystallized from AcOEt to give 1.29 g (53.6%) of quinolinium-ethoxycarbonylcyanomethylide (**4a**), violet needles, mp 203—204° (dec.). Picrate: yellow prisms, mp 172—173°. *Anal.* Calcd. for $C_{20}H_{15}N_5O_9$: C, 51.18; H, 3.32; N, 14.92. Found: C, 51.18; H, 3.22; N, 15.11. Products **2a** and **3a** were identified by comparison with the respective authentic samples.

2) A solution of **1** (1.45 g), Ac_2O (2.45 g) and ECA (1.35 g) in DMSO (10 ml) was stirred at room temperature for 12 hr. To the reaction mixture was added AcOEt (50 ml), and the whole was washed with 10% Na_2CO_3 and saturated NaCl solution to remove DMSO [method (A)]. The AcOEt solution was evaporated, and the residue was chromatographed on alumina column. The first fraction eluted with benzene gave 0.47 g of **2a**. Subsequent elution with AcOEt successively afforded 0.07 g of **3a** and 1.27 g of N-ylide **4a**.

3) A solution of **1** (1.45 g), Ac_2O (2.45 g) and ECA (1.35 g) in pyridine (10 ml) was stirred at −15° for 2 hr and then at room temperatures overnight. The reaction mixture was evaporated *in vacuo*, and the residue was dissolved in AcOEt (50 ml). Processing as described in 2) gave 0.53 g of **2a**, 0.02 g of **3a** and 0.41 g of **4a**.

Reactions of Quinolinium-ethoxycarbonylcyanomethylide (4a)——1) Hydrolysis: (a) A solution of **4a** (1.0 g) in 40% HBr (10 ml) was refluxed for 2 hr and evaporated *in vacuo*. The residue was recrystallized from EtOH–MeOH to give 0.6 g (63.6%) of N-carboxymethylquinolinium bromide (**5a**), yellow needles, mp 222—223° (dec.).

(b) Similar hydrolysis of **4a** with 35% HCl afforded 0.55 g (58.2%) of N-carboxymethylquinolinium chloride (**5b**), pale yellow needles (EtOH), mp 201—202° (dec.).

2) Oxidation: (a) A solution of **4a** (0.6 g) and 30% H_2O_2 (3 ml) in AcOH (5 ml) was heated on a water-bath for 3 hr and evaporated *in vacuo*. The residue was treated with 10% Na_2CO_3 and extracted with $CHCl_3$ to give 0.21 g (58.0%) of **1**, which was identified as picrate, yellow needles, mp 144—146°.

(b) A solution of **4a** (0.6 g) and 30% H_2O_2 (2 ml) in AcOEt (10 ml) was stirred at room temperature for 15 hr. The reaction mixture was shaken with 10% $NaHSO_3$ and H_2O, dried and evaporated to give 0.17 g (52.5%) of quinoline (picrate: yellow needles, mp 200—201°).

N-Carboxymethylquinolinium Bromide (5a)——A solution of quinoline (1.29 g) and ethyl bromoacetate (1.0 g) in anhyd. EtOH (10 ml) was allowed to stand at room temperature for 4 days. Addition of ether (100 ml) gave a precipitate, which was recrystallized from anhyd. EtOH–ether to give 1.14 g (37.6%) of N-ethoxycarbonylmethylquinolinium bromide (**6**), golden yellow scales, mp 183—185° (dec.).

Hydrolysis of **6** (1.0 g) with 40% HBr (10 ml) afforded 0.63 g (69.8%) of **5a**.

Reaction of Pyridine 1-Oxide with ECA——A solution of pyridine 1-oxide (0.95 g), Ac_2O (2.45 g) and ECA (1.35 g) in DMF (10 ml) was treated in the same way as the reaction of **1** to give 0.16 g (8.4%) of ethyl α-cyano-2-pyridineacetate,[3b] yellow needles, mp 106—107° (acetone) and 0.02 g (1.0%) of the 4-substituted product, colorless needles, mp 170—173° (acetone). *Anal.* Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.64; H, 5.17; N, 14.70.

Reaction of Isoquinoline 2-Oxide with ECA——A solution of isoquinoline 2-oxide (1.45 g), Ac_2O (2.45 g) and ECA (1.35 g) in DMF (10 ml) was stirred at −15° for 2 hr and at room temperature overnight. The reaction mixture was worked up by method (A). The AcOEt solution afforded 0.96 g (40.0%) of ethyl α-cyano-1-isoquinolineacetate, yellow needles, mp 138—140° (MeOH). *Anal.* Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.83; H, 4.98; N, 11.69. From the HCl solution, 0.32 g (22.0%) of 4-isoquinolinol,[20] yellow scales, mp 214—216° (dec.) (EtOH) was obtained.

Reaction of 4-Pyridinol 1-Oxide with ECA——A solution of the N-oxide (1.1 g), Ac_2O (2.5 g) and ECA (1.5 g) in DMF (10 ml) was stirred at −15° for 2 hr and at room temperature overnight. The reaction mixture was poured into H_2O, made alkaline with Na_2CO_3 and extracted with CH_2Cl_2. The extract was washed several times with NaCl solution and evaporated. The residue was chromatographed on alumina with benzene to give 1.85 g (90%) of ethyl α-cyano-4-hydroxy-2-pyridineacetate, pale red needles, mp 245—246° (EtOH). *Anal.* Calcd. for $C_{10}H_{10}NO_3$: C, 58.25; H, 4.89; N, 13.58. Found: C, 58.39; H, 4.84; N, 13.24.

Reaction of 4-Chloropyridine 1-Oxide with ECA——4-Chloropyridine 1-oxide (1.3 g) was treated with Ac_2O (2.5 g) and ECA (1.5 g) in DMF (10 ml) under the same conditions to give 2.0 g (90%) of ethyl α-cyano-4-chloro-2-pyridineacetate, yellow needles, mp 131—132° (acetone). *Anal.* Calcd. for $C_{10}H_9ClN_2O_2$: C, 53.46; H, 4.04; N, 12.40. Found: C, 53.35; H, 4.03; N, 12.51.

Reaction of 4-Methoxyquinoline 1-Oxide (9) with ECA——To a solution of **9** (1.75 g) and Ac_2O (2.1 g) in DMF (10 ml), ECA (1.45 g) was added dropwise at −15°, and the reactants were stirred with ice-cooling for 2 hr and then at room temperature overnight. The reaction mixture was worked up by method (A), giving 0.68 g (39.0%) of the N-ylide **17a**, orange red needles, mp 186—187° (AcOEt) and 0.08 g (4.57%) of the 2-substituted product **16a**, yellow needles, mp 171—173° (MeOH or acetone).

20) M.M. Robison and E.L. Robison, *J. Am. Chem. Soc.*, **80**, 3443 (1958).

Reaction of 4-Aminoquinoline 1-Oxide (10) with ECA——A solution of **10** (1.6 g), Ac_2O (2.5 g) and ECA (1.45 g) in DMF (10 ml) was stirred at −15° for 2 hr and then kept at room temperature overnight. Addition of H_2O (80 ml) to the reaction mixture gave a precipitate, which was filtered and recrystallized from diluted AcOH to give 2.67 g (90.1%) of the N-ylide **19a**, red pillars, mp 279—280° (dec.). From the mother liquor, a minute amount (*ca.* 0.03 g) of the 2-substituted product **18a** was isolated.

Hydrolysis of 4-Acetamidoquinolinium-ethoxycarbonylcyanomethylide (19a)——A solution of **19a** (1.0 g) in 40% KOH (10 ml) was heated on a water-bath for 1 hr. To the cooled solution was added NH_4Cl (5 g), and that solution was extracted with $CHCl_3$ to give 0.58 g (67.5%) of the corresponding 4-aminoquinolinium ylide (**19'a**), yellow needles, mp 276—278° (EtOH).

Reaction of 4-Quinolinol 1-Oxide (11) with ECA——A solution of **11** (1.61 g), Ac_2O (2.5 g) and ECA (1.5 g) in DMF (10 ml) was treated in the same way as the reaction of 4-pyridinol 1-oxide to give 2.5 g of ethyl α-cyano-4-acetoxy-2-quinolineacetate, yellow needles, mp 155—156° (acetone). *Anal.* Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.27; H, 4.74; N, 9.29.

The above product was heated with 10% HCl on a water-bath for 2 hr gave almost quantitatively ethyl α-cyano-4-hydroxy-2-quinolineacetate (**20a**), colorless needles, mp 279—280° (MeOH).

Conversion of Ethyl α-Cyano-4-hydroxy-2-quinolineacetate (20a) to Ethyl α-Cyano-2-quinolineacetate (2a) and Ethyl α-Cyano-4-methoxy-2-quinolineacetate (16a) through Ethyl α-Cyano-4-chloro-2-quinolineacetate (21a)——1) A mixture of **20a** (1.0 g), PCl_5 (1.0 g) and $POCl_3$ (1 ml) was refluxed for 3 hr. The reaction mixture was made alkaline with 10% Na_2CO_3 and extracted with $CHCl_3$. The extract was passed through a silica gel column to give 0.78 g (72.5%) of ethyl α-cyano-4-chloro-2-quinolineacetate (**21a**).

2) Compound **21a** (0.8 g) was hydrogenated in AcOH (5 ml)–MeOH (15 ml) over 5% Pd-C (0.3 g). After absorption of 1 mol hydrogen, the catalyst was filtered and the filtrate was evaporated. The residue was recrystallized from MeOH to give 0.49 g (71.3%) of **2a**.

3) A solution of **21a** (1.0) and NaOMe–MeOH (prepared from 0.15 g of Na and 15 ml of MeOH) was refluxed for 5 hr. The reaction mixture was evaporated and treated with NH_4Cl solution to give 0.61 g of **16a**.

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