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# Studies on Tertiary Amine Oxides. LXXV.[1] Reactions of Aromatic *N*-oxides with Meldrum's Acid in the Presence of Acetic Anhydride

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Reactions of quinoline, lepidine, 4-chloro-, 4-methoxy- and 4-morpholino-quinoline 1-oxides (**1a**—**e**) with Meldrum's acid (**2**) in acetic anhydride smoothly occurred at room temperature to afford the corresponding 5-(2-quinolyl)-Meldrum's acids (**3a**—**e**) in good yields. On the other hand, when the reactions were carried out in dimethylformamide containing 1.2 eq acetic anhydride the *N*-ylides (**4a**—**e**) were produced; while the reactions of **1a**, **d**, **e** yielded only *N*-ylides **4a**, **d**, **e**, **4b**, **c** were formed along with smaller amounts of **3b**, **c** in the reactions of **1b**, **c**. 3-Bromoquinoline 1-oxide (**1f**) gave only the *N*-ylide (**4f**) and isoquinoline 2-oxide (**6**) gave the 1-substituted isoquinoline (**7**) independently of the reaction conditions. Further, 5-alkyl-Meldrum's acids (**8a**—**c**) also reacted readily with **1a** in acetic anhydride to give the corresponding 2-substituted quinolines (**9a**—**c**) in good yields.

Heating of **3a**, **b** with conc. hydrochloric acid, 10% hydrochloric acid or methanol containing 10% hydrogen chloride gave 2-methylquinolines (**10a**, **b**), 2-quinolineacetic acids (**11a**, **b**) or their methyl esters (**12a**, **b**), respectively. Similarly, **9a**—**c** afforded 2-alkylquinolines (**14a**—**c**) in good yields upon being refluxed with conc. hydrochloric acid.

**Keywords**——aromatic *N*-oxide; Meldrum's acid; 5-(2-quinolyl)-Meldrum's acid; quinolinium-5-Meldrum's acid ylide; 5-(1-isoquinolyl)-Meldrum's acid; 2-alkylquinoline; 2-quinolineacetic acid; nucleophilic reaction; regioselectivity

Recently, we reported that reactions of quinoline *N*-oxide derivatives with barbituric acid in the presence of acetic anhydride afforded regioselectively 2-substituted quinolines or quinolinium-5-barbituric acid methylides, depending upon the nature of the *N*-oxides and the reaction conditions.[3] These results prompted us to examine reactions of quinoline *N*-oxides with Meldrum's acid[4] in the expectation that they might give 2-substituted quinolines or quinolinium methylides, depending upon the reaction conditions. This expectation was realized, and some interesting observations were obtained on the hydrolyses of 2-substituted quinolines thus formed.

When a solution of quinoline 1-oxide (**1a**) in acetic anhydride was added dropwise to a solution of Meldrum's acid (**2**) in acetic anhydride, an exothermic reaction occurred and a yellow solution was obtained. The reaction mixture was stirred at room temperature for 1 h, and yellow crystals precipitated. The reaction mixture was kept at room temperature overnight, then the precipitated crystals were filtered and recrystallized from ethanol to give 5-(2-quinolyl)-Meldrum's acid, 2,2-dimethyl-5-(2-quinolyl)-1,3-dioxane-4,6-dione (**3a**), yellow needles, mp 214—215°C (dec.), in 81% yield.

On the other hand, treatment of **1a** with **2** in dimethylformamide (DMF) containing 1.2 eq of acetic anhydride at room temperature gave rise to an orange solution, from which orange crystals began to precipitate after 1 h. The reaction mixture was kept at room temperature overnight, and the resulting crystals were filtered and recrystallized from ethanol to afford the quinolinium-5-Meldrum's acid ylide, quinolinium -5-(2,2-dimethyl-1,3-dioxane-4,6-dione)-methylide (**4a**), orange prisms, mp 262—263°C (dec.), in 63% yield (Chart 1).

Identification of **3a** and **4a** was performed by elemental analyses, spectral examinations (Tables II—V) and oxidation with hydrogen peroxide.

The infrared (IR) spectrum of **3a** exhibited a strong carbonyl band at 1705 $cm^{-1}$ and a

weak absorption at 3100 $cm^{-1}$ attributable to the NH group of the enamine form (**3a**—**B**). The nuclear magnetic resonance (NMR) spectrum in deuteriochloroform of **3a** showed two one-proton doublets at $\delta$ 8.90 and 8.10 ($J$=10.0 Hz), which could be assigned to the $C_3$- and $C_4$-protons of the quinoline ring, respectively,[5] but no signal due to the $C_2$-proton was observed. A broad singlet exchangeable with deuterium oxide was also seen at $\delta$ 15.15 which integrated to 0.8 proton and could be reasonably assigned to an NH group. These observations demon-

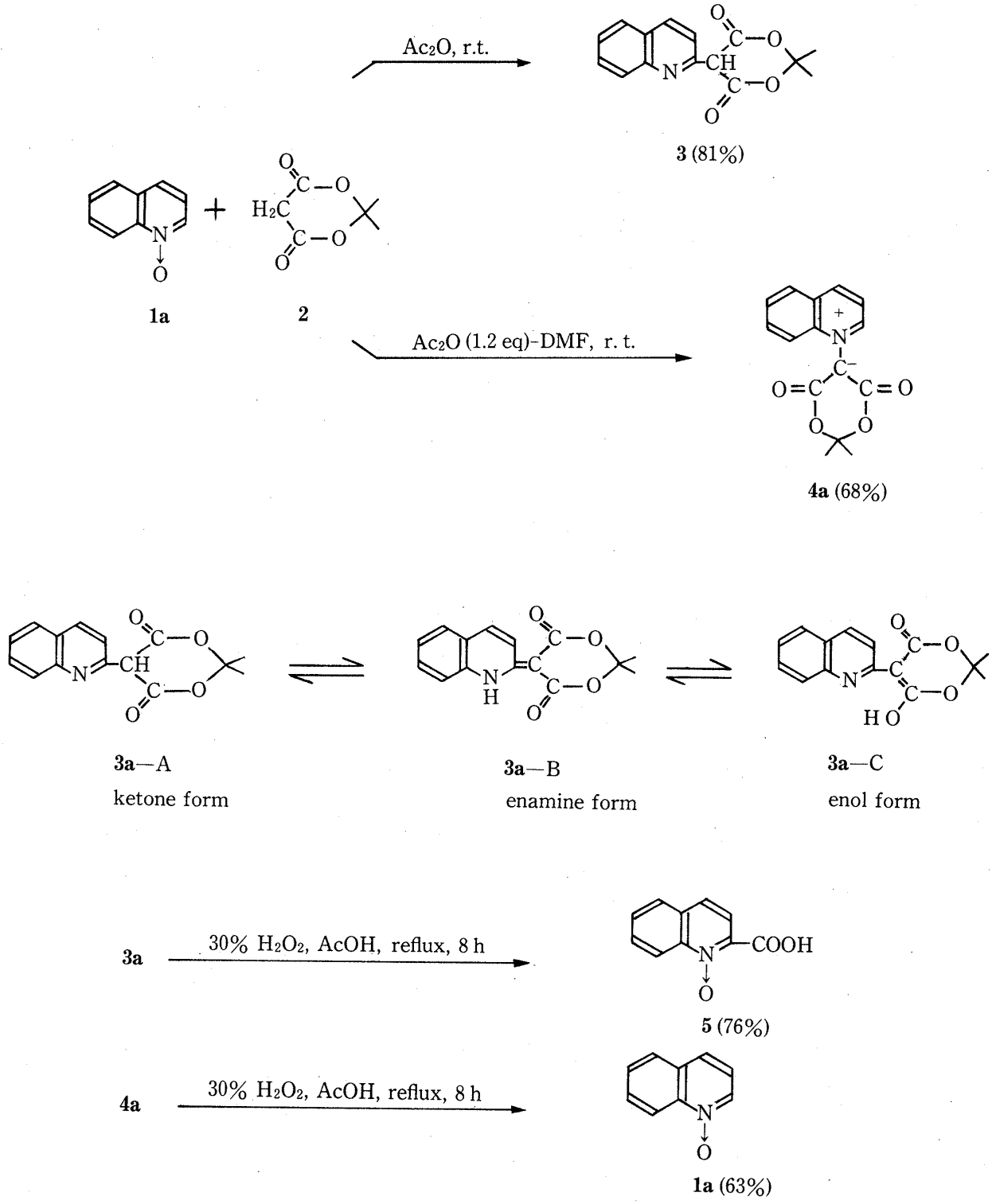



**Chart 1**

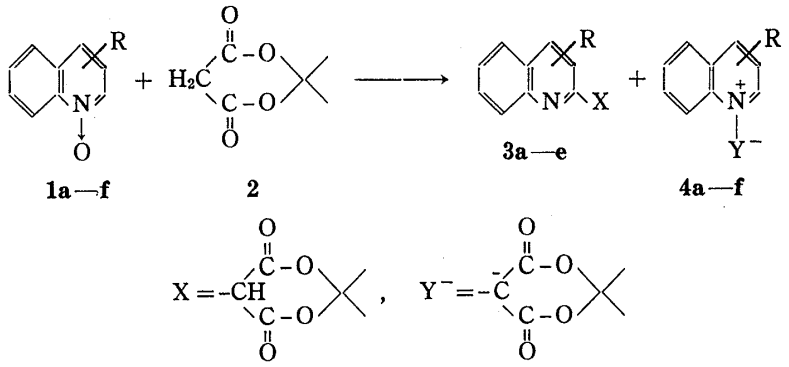
strate that **3a** exists as a tautomeric mixture of the ketone form (**3a—A**) and the enamine form (**3a—B**) in the ratio of 20:80 in deuteriochloroform; the contribution of the enol form (**3a—C**) seems negligible.

The IR spectrum of **4a** displayed a strong band at 1665 $cm^{-1}$, but lacked the NH absorption, and the $C_2$-proton appeared as a one-proton double doublet centered at $\delta$ 8.99 ($J$= 7.2, 1.4 Hz) in the NMR spectrum, which also showed a one-proton doublet ($J$=9.0 Hz) at $\delta$ 8.78 due to the $C_8$-proton, an aromatic multiplet at $\delta$ 7.73—8.32 resulting from five protons, and two methyl singlets at $\delta$ 1.88 and 1.99.

Oxidation of **3a** with 30% hydrogen peroxide in boiling acetic acid gave quinaldic acid 1-oxide (**5**) in 76% yield, as in the cases of other 2-substituted quinolines.[1,6,7] On the other hand, oxidaton of **4a** under the same conditions produced **1a** (63%), analogously with other *N*-ylides described previously.[3,8]

In order to explore the effects of substituents on the reaction course, reactions of some 4- and 3-substituted quinoline 1-oxides (**1b—f**) with **2** were carried out at room temperature in acetic anhydride alone or in acetic anhydride (1.2 eq)–dimethylformamide (DMF). The results thus obtained are listed in Table I.

TABLE I. Reactions of Quinoline 1-Oxides (**1a—f**) with Meldrum's Acid (**2**)




| 1 | R | Reaction conditions | Product, yield (%) 3 | 4 |
|---|---|---|---|---|
| **1a** | H | *a*) | **3a** : 81 | — |
| | | *b*) | — | **4a** : 68 |
| **1b** | 4-Me | *a*) | **3b** : 83 | — |
| | | *b*) | **3b** : 16 | **4b** : 64 |
| **1c** | 4-Cl | *a*) | **3c** : 72 | — |
| | | *b*) | **3c** : 12 | **4c** : 56 |
| **1d** | 4-OMe | *a*) | **3d** : 84 | — |
| | | *b*) | — | **4d** : 87 |
| **1e** | 4-N O | *a*) | **3e** : 79 | — |
| | | *b*) | — | **4e** : 89 |
| **1f** | 3-Br | *a*) | — | **4f** : 93 |
| | | *b*) | — | **4f** : 91 |

*a*) $Ac_2O$, r.t., 13—15 h. *b*) $Ac_2O$ (1.2 eq)–DMF, r.t., 13—15 h.

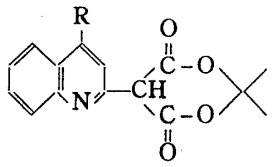
Reactions of 4-methoxy- and 4-morpholino-quinoline 1-oxides (**1d** and **1e**) gave results similar to those obtained with **1a**; the reactions in acetic anhydride gave the corresponding 2-substituted quinolines (**3d** and **3e**), and those in acetic anhydride–DMF gave only the corresponding *N*-ylides (**4d** and **4e**). However, while the reactions of lepidine and 4-chloroquinoline 1-oxides (**1b** and **1c**) using acetic anhydride alone as the reaction medium afforded the corresponding 2-substituted quinolines (**3b** and **3c**) as the sole product in each case, those in acetic anhydride (1.2 eq)–DMF gave the respective *N*-ylides (**4b** and **4c**) as the

main products but accompanied with smaller amounts of the 2-substituted quinolines, **3b** and **3c**; the separation of the mixtures into the respective components was easily effected in each case by fractional crystallization from methanol.

On the other hand, 3-bromoquinoline 1-oxide (**1f**) afforded only the corresponding ylide (**4f**) independently of the reaction conditions, no formation of the 2-substituted quinoline being observed.

The structures of **3b—e** and **4b—f** were unambiguously confirmed by the elemental analyses and the spectral examinations (Tables II—V). From the integrated areas of the NH signals at $\delta$ 14.6—15.15 in the NMR spectra, the ratios of the ketone form to the enamine form in **3b, c** were concluded to be approximately the same, 10: 90, in deuteriochloroform; on the other hand, both **3d** and **3e** were found to exist only in the ketone form.

TABLE II. 5-(2-Quinolyl)-Meldrum's Acids



**3a—e**

| Compound No. | R | Appearance | (°C) | Formula | Analyses (%) Calcd(Found) C | H | N |
|---|---|---|---|---|---|---|---|
| **3a** | H | Yellow needles | 214—215 (dec.) | $C_{15}H_{13}NO_4$ | 66.41 (66.40 | 4.83 4.97 | 5.16 5.17) |
| **3b** | Me | Yellow needles | 219—220 (dec.) | $C_{16}H_{15}NO_4$ | 67.36 (67.29 | 5.30 5.41 | 4.91 4.77) |
| **3c** | Cl | Yellow needles | 201—202 (dec.) | $C_{15}H_{12}ClNO_4$ | 58.94 (58.72 | 3.93 4.02 | 4.55 4.53) |
| **3d** | MeO | Yellow needles | 198—201 (dec.) | $C_{16}H_{15}NO_5$ | 63.78 (63.67 | 5.02 5.08 | 4.53 4.53) |
| **3e** |  | Yellow prisms | 224—225 (dec.) | $C_{19}H_{20}N_2O_5$ | 64.03 (63.98 | 5.66 5.57 | 7.87 7.69) |

Isoquinoline 2-oxide (**6**) also reacted readily with **2** in acetic anhydride at room temperature to afford the 1-substituted isoquinoline (**7**), yellow needles, mp 216—217°C (dec.), in 93% yield. However, the reaction in acetic anhydride–DMF gave not the *N*-ylide, but **7** in practically the same yield.

The analytical values and the spectral data of **7** were consistent with the assigned structures. The IR spectrum exhibited the carbonyl absorption at 1690 $cm^{-1}$ and a weak band at 3000 $cm^{-1}$ indicative of the presence of the enamine form. The NMR spectrum of **7** in deuteriochloroform showed a six-proton singlet at $\delta$ 1.88 due to two methyl groups, an aromatic five-proton multiplet at $\delta$ 7.30—7.82, a one-proton doublet at $\delta$ 8.36 ($J$=8.0 Hz) attributed to the $C_8$-proton of the isoquinoline ring and the NH resonance signal as a broad singlet exchangeable with deuterium oxide at $\delta$ 14.17 which integrated to one proton. Apparently, **7** exists overwhelmingly as the enamine form in deuteriochloroform (Chart 2).

Reactions with 5-methyl-, 5-ethyl- and 5-*n*-hexyl-Meldrum's acids (**8a**, **8b** and **8c**) were next examined, and it was found that these reactions occurred under somewhat stronger conditions. Thus, a solution of **1a** and **8a** in acetic anhydride was stirred at room temperature for 12 h and then heated at 90°C for 4 h to give 5-methyl-5-(2-quinolyl)-1,3-dioxane-4,6-dione (**9a**), colorless prisms, mp 140—141°C, in 79% yield. Similarly, the corresponding 5-ethyl and 5-*n*-hexyl derivatives (**9b** and **9c**) were obtained in 76 and 48% yields; the somewhat

lower yield of **9c** may be interpreted in terms of steric hindrance (Chart 3).

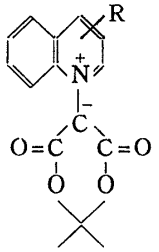
Products **9a**—**c** gave analytical values and spectral data in full agreement with the assigned structures. Their IR spectra showed two strong bands in the 1720—1735 and 1760—1765 $cm^{-1}$ regions attributable to two carbonyl groups of the Meldrum's acid ring. The methyl

TABLE III. Spectral Data for 5-(2-Quinolyl)-Meldrum's Acids **3a**—**e**

| Compound No. | MS $M^+$ (*m/e*) | IR ($cm^{-1}$, Nujol) | | NMR ($\delta$, $CDCl_3$) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | C=O | NH | $C_4$–H | $C_3$–H | Ar–H | NH[a] | $CH_3$ | Others |
| **3a** | 271 | 1705 | 3100 | 8.10 (1H, d, $J$=10Hz) | 8.90 (1H, d, $J$=10Hz) | 7.40—7.80 (4.2H, m) | 15.51 (0.8H, br s) | 1.78 (6H, s) | |
| **3b** | 285 | 1710 | 3200 | | 8.80 (1H, s) | 7.41—7.80 (4.1H, m) | 15.08 (0.9H, br s) | 1.78 (6H, s), 2.74 (3H, s) | |
| **3c** | 305 307 | 1700 | 3000 | | 8.42 (1H, s) | 7.52—7.88 (3.1H, m) | 15.10 (0.9H, br s) | 1.78 (6H, s) | |
| **3d** | 301 | 1700 | 3000 | | 8.40 (1H, s) | 7.30—7.78 (3H, m) 7.85 (1H, d) | 14.70 (1H, br s) | 1.78 (6H, s) | 4.16 (3H, s, OMe) |
| **3e** | 356 | 1710 | 3200 | | 8.40 (1H, s) | 7.22—7.80 (3H, m) | 14.60 (1H, | 1.78 (6H, s) | 3.40 (4H, t, $J$=4.8 Hz, $CH_2NCH_2$) 3.99 (4H, t, $J$=4.8 Hz, $CH_2OCH_2$) |

a) Each proton was exchangeable with deuterium oxide.

TABLE IV. Quinolinium-5-Meldrum's Acid Ylides



**4a**—**f**

| Compound No. | R | Appearance | mp. (°C) | Formula | Analyses (%) Calcd (Found) | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| **4a** | H | Orange prisms | 262—263 (dec.) | $C_{15}H_{13}NO_4$ | 66.41 (66.52 | 4.83 4.91 | 5.16 5.23) |
| **4b** | 4-Me | Yellow needles | 253—254 (dec.) | $C_{16}H_{15}NO_4$ | 67.36 (67.42 | 5.30 5.28 | 4.91 5.03) |
| **4c** | 4-Cl | Orange needles | 212—214 (dec.) | $C_{15}H_{12}ClNO_4$ | 58.94 (59.03 | 3.93 3.96 | 4.55 4.46) |
| **4d** | 4-OMe | Yellow prisms | 212—213 | $C_{16}H_{15}NO_5$ | 63.78 (63.82 | 5.02 5.11 | 4.65 4.71) |
| **4e** | 4-N O | Yellow needles | 247 (dec.) | $C_{19}H_{20}N_2O_5$ | 64.03 (63.97 | 5.66 5.74 | 7.86 7.93) |
| **4f** | 3-Br | Orange needles | 199—201 (dec.) | $C_{15}H_{12}BrNO_4$ | 51.42 (51.49 | 3.43 3.51 | 4.00 3.95) |

TABLE V. Spectral Data for Quinolinium-5-Meldrum's Acid Ylides **4a—f**

| Compound No. | MS $M^+$ ($m/e$) | IR($cm^{-1}$, Nujol) C=O | NMR ($\delta$, $CDCl_3$) $C_2$–H | $C_3$–H | Ar–H | –$CH_3$ | Others |
|---|---|---|---|---|---|---|---|
| **4a** | 271 | 1665 | 8.99 (1H, dd, $J$=7.2 Hz, 1.4 Hz) | | 7.73—8.32 (5H, m) 8.78 (1H, d, $J$=9 Hz, $C_8$–H) | 1.88 (3H, s) 1.99 (3H, s) | |
| **4b** | 285 | 1685 | 8.82 (1H, d, $J$= | 7.46 (1H, d, $J$=7.2 Hz) | 7.78—8.39 (4H, m) | 1.85 (3H, s), 1.97 (3H, s), 2.99 (3H, s) | |
| **4c** | 305 307 | 1690 | 8.97 (1H, d, $J$=7.2 Hz) | 7.22 (1H, d, $J$=7.2 Hz) | 7.42—8.57 (4H, m) | 1.80 (3H, s) 1.98 (3H, s) | |
| **4d** | 301 | 1685 | 8.73 (1H, d, $J$=7.4 Hz) | 7.12 (1H, d, $J$=7.4 Hz) | 7.43—8.42 (4H, m) | 1.85 (3H, s) 1.95 (3H, s) | 4.22 (3H, s, –$OCH_3$) |
| **4e** | 356 | 1690 | 8.39 (1H, d, $J$=7.2 Hz) | 6.94 (1H, d, $J$=7.2 Hz) | 7.40—8.20 (4H, m) | 1.85 (3H, s) 1.92 (3H, s) | 3.72 (4H, t, $J$=4.8 Hz, $CH_2$–N–$CH_2$), 3.99 (4H, t, $J$=4.8 Hz, $CH_2$–O–$CH_2$) |
| **4f** | 349 | 1685 | 8.92 (1H, s) | | 7.70—8.30 (4H, m), 9.12 (1H, d, $C_8$–H) | 1.86 (3H, s), 1.96 (3H, s) | |

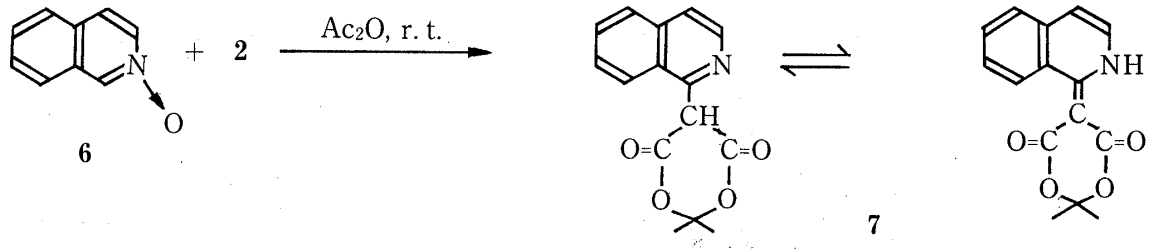



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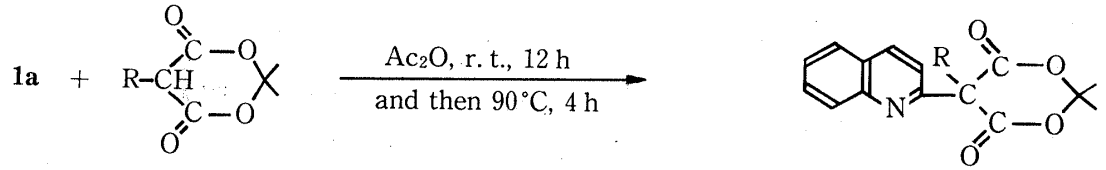
Chart 2



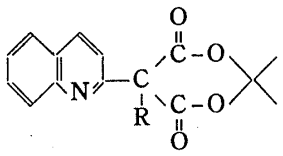

8 9

**8a** : R=Me
**8b** : R=Et
**8c** : R=$n$-$C_6H_{13}$

**9a** : R=Me (79%)
**9b** : R=Et (76%)
**9c** : R=$n$-$C_6H_{13}$ (48%)

Chart 3

Table VI. 5-Alkyl-5-(2-Quinolyl)-Meldrum's Acids



**9a—c**

| Compound No. | R | Yield % | Appearance | mp (°C) | Formula | Analyses (%) Calcd (Found) C | H | N |
|---|---|---|---|---|---|---|---|---|
| **9a** | Me– | 79 | Colorless prisms | 140—141 | $C_{16}H_{15}NO_4$ | 67.36 (67.28 | 5.30 5.35 | 4.91 4.87) |
| **9b** | $C_2H_5$– | 76 | Colorless prisms | 132 | $C_{17}H_{17}NO_4$ | 68.21 (68.32 | 5.73 5.79 | 4.68 4.72) |
| **9c** | $n$-$C_6H_{13}$– | 48 | Colorless scales | 112 | $C_{21}H_{25}NO_4$ | 70.96 (71.01 | 7.09 7.23 | 3.94 3.87) |

Table VII. Spectral Data for 5-Alkyl-5-(2-Quinolyl)-Meldrum's Acids **9a—c**

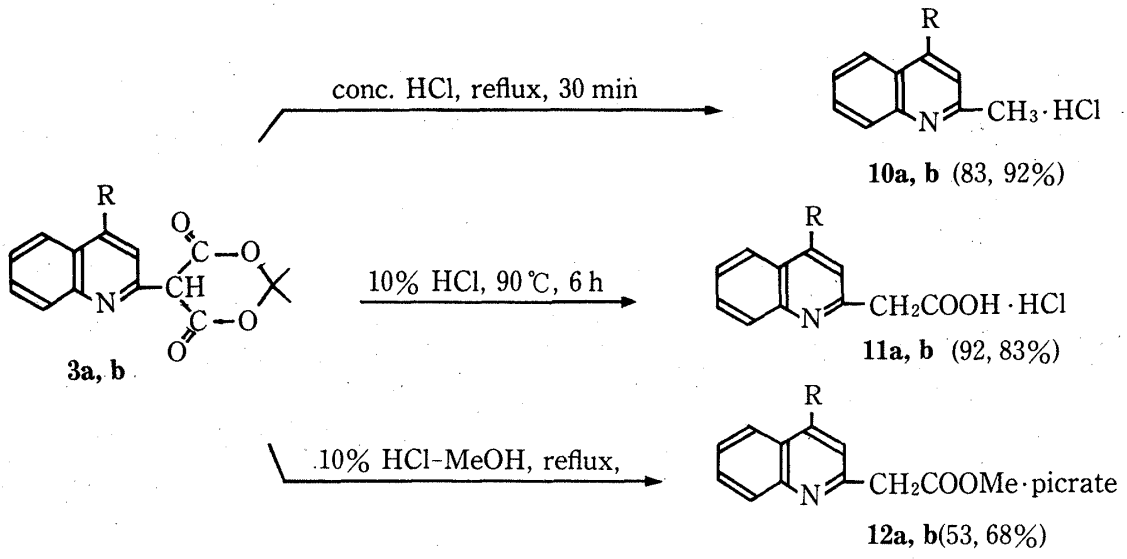
| Compound No. | MS $M^+$ ($m/e$) | IR ($cm^{-1}$, Nujol) C=O | NMR ($\delta$, $CDCl_3$) Ar–H | –$CH_3$ | Others |
|---|---|---|---|---|---|
| **9a** | 285 | 1725, 1760 | 7.40—8.10 (5H, m), 8.25 (1H, d) | 1.58 (3H, s), 1.80 (3H, s), 2.11 (3H, s) | |
| **9b** | 299 | 1735, 1765 | 7.42—8.01 (6H, m) | 1.1 (3H, t), 1.78 (3H, s), 1.80 (3H, s) | 2.61 (2H, q, $C\underline{H}_2$–$CH_3$) |
| **9c** | 369 | 1720, 1760 | 7.42—8.00 (5H, m) 8.21 (1H, d) | 0.88 (3H, t), 1.78 (3H, s), 1.80 (3H, s) | 1.2—1.60 (8H, m, –(–$CH_2$–)$_n$–, 2.59 (2H, q, –$C\underline{H}_2$–$CH_3$) |

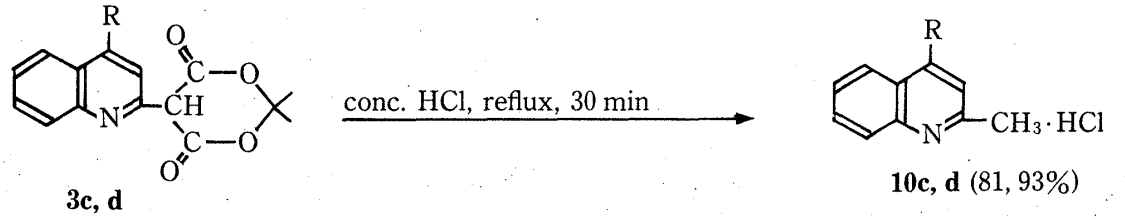
protons appeared as two singlets at $\delta$ 1.80 and 2.11 in the NMR spectrum of **9a**, and at $\delta$ 1.78 and 1.80 in those of **9b** and **9c** (Tables VI and VII).

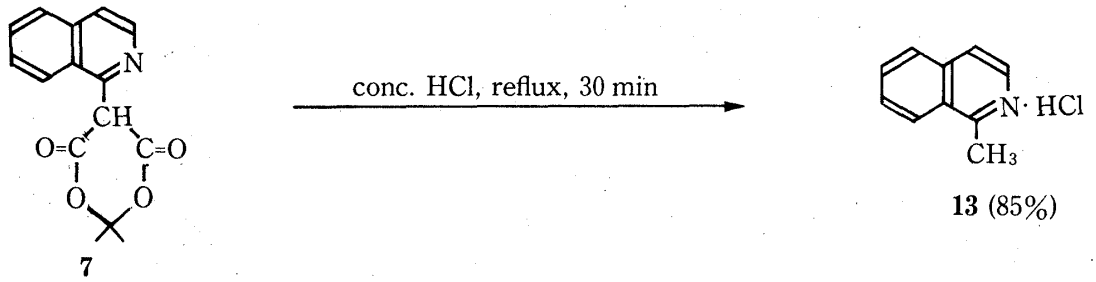
Subsequently, acid hydrolyses of the products were investigated, and interesting results were obtained.

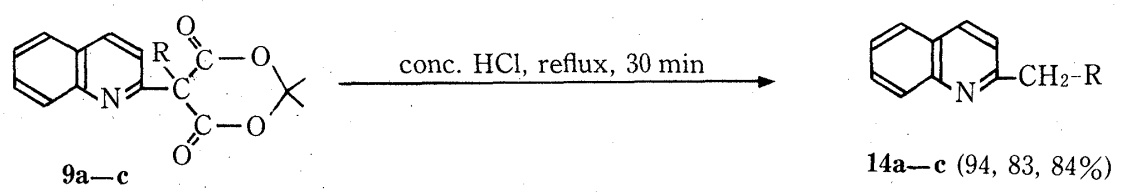
The behavior of **3a** was first examined. A suspension of **3a** in concentrated hydrochloric acid was refluxed for 30 min to give an almost colorless solution, which on evaporation afforded quinaldine hydrochloride (**10a**) in 83% yield. On the other hand, when a suspension of **3a** in 10% hydrochloric acid was heated at 90°C for 6 h, 2-quinolineacetic acid hydrochloride (**11a**) was isolated in 92% yield. Further, methanolysis of **3a** was carried out by refluxing a solution in dry methanol containing 10% hydrogen chloride for 6 h. Evaporation of the resulting solution led to a highly hygroscopic crystalline product, which was converted by the action of sodium picrate into methyl 2-quinolineacetate picrate (**12a**) in 53% yield. In a similar manner, the 2-substituted lepidine (**3b**) was transformed into 2,4-dimethylquinoline hydrochloride (**10b**), 4-methyl-2-quinolineacetic acid hydrochloride (**11b**) and methyl 4-methyl-2-quinolineacetate picrate (**12b**) in 92, 83 and 68% yields, respectively (Chart 4).

It was further found that not only the other 2-substituted quinoline (**3e, d**) and the 1-substituted isoquinoline (**7**) but also 5-alkyl-Meldrum's acid derivatives (**9a—c**) were smoothly converted into the corresponding hydrochlorides of 2-methylquinolines (**10c, d**), 1-methylisoquinoline (**13**) and the picrates of 2-alkylquinolines (**14a—c**), respectively, in good yields as shown in Chart 4.




**9a** : R=Me
**9b** : R=Et
**9c** : R=*n*-$C_6H_{13}$

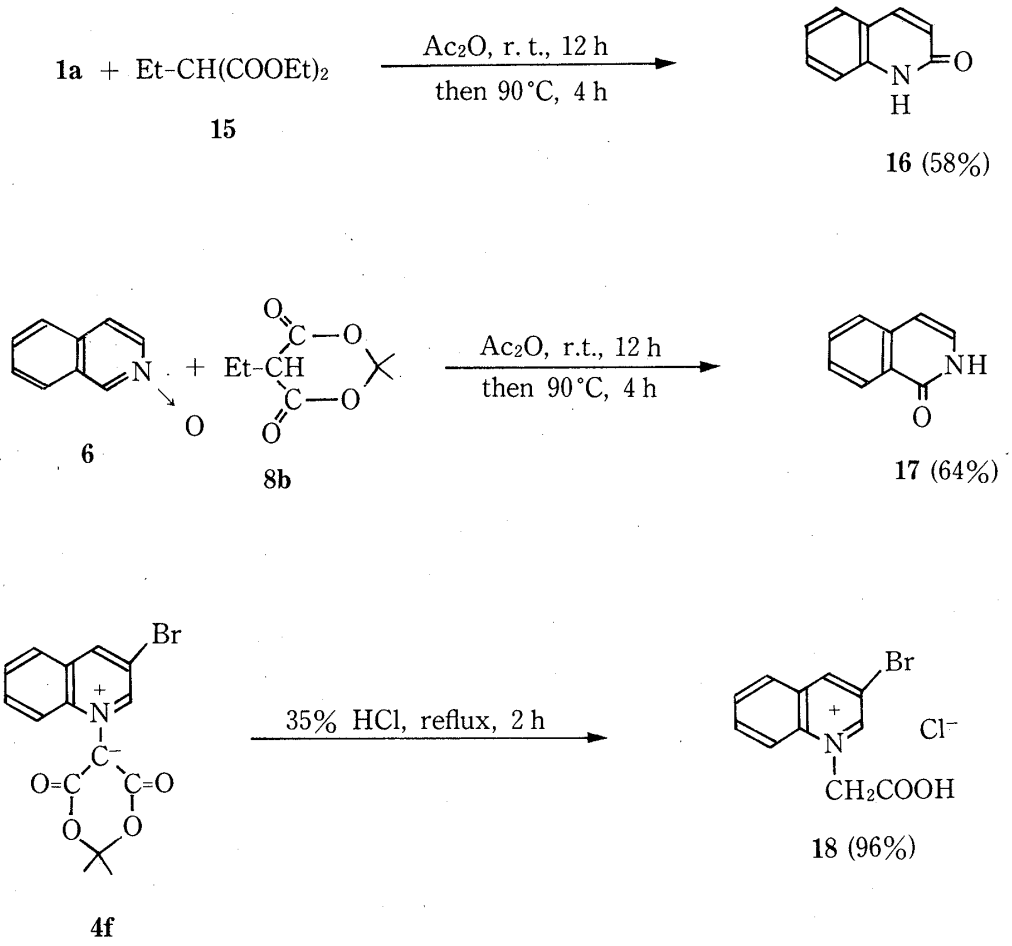
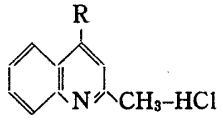



Chart 4

These results suggest that the reaction of quinoline 1-oxides with 5-alkyl-Meldrum's acid followed by acid hydrolyses of the products is a novel and promising route to 2-alkylquinolines. In this connection, the reaction of **1a** with diethyl ethylmalonate (**15**) as well as that of **6** with **8b** was examined. Treatment of **1a** with **15** in acetic anhydride at room temperature for 12 h and then at 90°C for 4 h gave no alkylated quinolines but instead

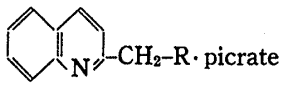
Table VIII. 2-Methylquinoline Hydrochlorides



**10a—d**

| Compound No. | R | Yield % | Appearance | MS $M^+$ ($m/e$) — HCl | mp (°C) | Formula | Analyses Calcd (Found) C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| **10a** | H | 83 | Colorless needles | 143 | 199 (dec.) | $C_{10}H_{10}ClN$ | 66.84 (66.68 | 5.56 5.62 | 7.79 7.83) |
| **10b** | Me | 92 | Pale pink prisms | 157 | 210 (dec.) | $C_{11}H_{12}ClN$ | 68.21 (67.96 | 6.20 6.32 | 7.23 7.26) |
| **10c** | Cl | 81 | Pale pink prisms | 177, 179 | 218—219 (dec.) | $C_{10}H_9Cl_2N$ | 56.07 (56.12 | 4.20 4.18 | 6.54 6.43) |
| **10d** | MeO– | 93 | Colorless prisms | 163 | 179 (dec.) | $C_{11}H_{12}ClNO$ | 63.00 (62.87 | 5.72 5.83 | 6.68 6.76) |

Table IX. 2-Alkylquinoline·picrates



**14a—c**

| Compound No. | R | Yield % | Appearance | mp (°C) | Formula | Analyses (%) Calcd (Found) C | H | N |
|---|---|---|---|---|---|---|---|---|
| **14a** | Me | 94 | Yellow needles | 158 | $C_{11}H_{11}N \cdot C_6H_3N_3O_7$ | 52.71 (52.83 | 3.41 3.52 | 14.56 14.47) |
| **14b** | $C_2H_5$– | 83 | Yellow needles | 163—164 | $C_{12}H_{13}N \cdot C_6H_3N_3O_7$ | 53.86 (53.91 | 4.23 4.25 | 13.96 14.07) |
| **14c** | *n*-$C_6H_{13}$– | 84 | Yellow needles | 105—106 | $C_{16}H_{21}N \cdot C_6H_3N_3O_7$ | 57.89 (57.70 | 5.30 5.45 | 12.28 12.12) |

provided carbostyril (**16**) as the sole product in 58% yield. Quite similarly, the reaction of **6** with **8b** under the same conditions gave only isocarbostyril (**17**) in 64% yield with no visible sign of the formation of the 1-substituted isoquinoline. Thus, the above route was proved to be an excellent one for the preparation of 2-alkylquinolines (Chart 4).

Finally, hydrolysis of the *N*-ylide **4f** was explored. When a solution of **4f** in 35% hydrochloric acid was refluxed for 2 h, 3-bromo-*N*-carboxymethylquinolinium chloride (**18**) was formed in 96% yield.

## Experimental

All melting points are uncorrected. IR spectra were recorded on a JASCO IR-E spectrometer. NMR spectra were measured with a JEOL PS-100 spectrometer at 100 MHz using tetramethylsilane (TMS) as an internal reference. Mass spectra (MS) were obtained on a JMS 01SG spectrometer.

**Reactions of Quinoline 1-Oxides (1a—e) with Meldrum's Acid (2) in $Ac_2O$**——A solution of a quinoline 1-oxide (**1a—e**) (6 mmol) in $Ac_2O$ (5 ml) was added dropwise to a stirred solution of Meldrum's acid (**2**) (0.86 g, 6 mmol) in $Ac_2O$ (6 ml) while being cooled with an ice-bath. An exothermic reaction occurred and crystals began to separate from the reaction mixture after 2—3 h. The ice-bath was then removed and the reaction mixture was kept at room temperature overnight. The resulting crystals were filtered and recrystallized from EtOH to give **3a—e** in high yields.

The results and some physical and spectral data of **3a—e** are shown in Tables II and III.

**Reactions of 1a, d, e with 2 in DMF containing 1.2 Equivalents of $Ac_2O$**——A solution of **1a, d, e** (5 mmol) in DMF (5 ml) and $Ac_2O$ (0.9 g, 7 mmol) was added dropwise to a stirred solution of **2** (0.72 g, 5 mmol) in DMF (5 ml) at room temperature. Crystals began to separate from the reaction mixture after 2—3 h. The reaction mixture was kept at room temperature overnight, and the resulting crystals were filtered and recrystallized from EtOH to give **4a, d, e** in high yields.

The results and some physical and spectral data of **4a, d, e** are shown in Tables IV and V.

**Reactions of 1b, c with 2 in DMF-$Ac_2O$ (1.2 eq)**——A solution of **1b, c** (5 mmol) in DMF (5 ml) and $Ac_2O$ (0.9 g, 7 mmol) was added dropwise to a stirred solution of **2** (0.72 g, 5 mmol) in DMF (5 ml) at room temperature. Crystals began to separate from the reaction mixture after 3 h. The reaction mixture was kept at room temperature overnight, and the resulting crystals were filtered and dried to give a mixture of **3** and **4**. The ratios of **3** to **4** were estimated from the NMR spectra of the reaction products in deuteriochloroform; the ratios of **3b** to **4b** and **3c** to **4c** were 21:79 and 35:65, respectively. Separation of the components was easily effected by fractional crystallization. When the mixture of **3b** and **4b** was dissolved in boiling MeOH and then cooled, only **4b** readily separated out. Conversely, **3c** precipitated from the similarly prepared MeOH solution of **3c** and **4c**. The other isomer in each case, that is **3b** and **4c**, was obtained as fine crystals by concentrating and then cooling the filtrates.

**Reaction of 3-Bromoquinoline 1-Oxide (1f) with 2**——1) A solution of **1f** (1.17 g, 5 mmol) in $Ac_2O$ (6 ml) was added dropwise to a solution of **2** (0.72 g, 5 mmol) in $Ac_2O$ (5 ml). An orange solution was obtained and orange crystals began to separate from the reaction mixture after 3 h. The reaction mixture was kept at room temperature overnight, and the resulting crystals were filtered and recrystallized from EtOH to give 1.61 g (93%) of **4f**.

The results and some physical and spectral data of **4f** are shown in Tables IV and V.

2) A solution of **1f** (1.17 g, 5 mmol) in DMF (5 ml) and $Ac_2O$ (0.9 g, 7 mmol) was added dropwise to a stirred solution of **2** (0.72 g, 5 mmol) in DMF (5 ml) at room temperature. An orange solution was obtained and orange crystals began to separate from the reaction mixture after 2 h. The reaction mixture was kept at room temperature overnight, and the resulting crystals were filtered and recrystallized from EtOH to give 1.55 g of **4f** (91%).

**Oxidation of 3a to Quinaldic Acid 1-Oxide (5)**——A solution of **3a** (0.5 g) in AcOH (20 ml) and 30% $H_2O_2$ (25 ml) was refluxed for 8 h to give an almost colorless solution. The solution was concentrated under reduced pressure, and cold water (20 ml) was added. The deposited crystals were filtered and recrystallized from MeOH to give 0.19 g of **5** (76%), mp 169—170°C (dec.). It was identified by direct comparison with an authentic sample.

**Oxidatin oof 4a to 1a**——A mixture of **4a** (0.6 g) in AcOH (25 ml) and 30% $H_2O_2$ (30 ml) was refluxed for 8 h to give an almost colorless solution. The solution was concentrated under reduced pressure, and the residue was treated with 10% $Na_2CO_3$ and extracted with $CHCl_3$ to give 0.21 g of **1a** (63%), which was identified as the picrate, yellow needles, mp 144—145°C.

**Reaction of 1a with 5-Alkyl-Meldrum's Acid (8)**——A solution of **1a** (0.78 g, 5 mmol) in $Ac_2O$ (6 ml) was added dropwise to a stirred solution of **8a—c** (5 mmol) in $Ac_2O$ (6 ml) at room temperature. The whole was kept at room temperature for 12 h then heated at 90°C for 4 h. The reaction mixture was concentrated under reduced pressure and the residual solid mass was recrystallized from EtOH to give **9a—c**.

The results and some physical and spectral data of **9a—c** are shown in Tables VI and VII.

**Reactions of Isoquinoline 2-Oxide (6) with 2**——A solution of **6** (0.78 g, 5 mmol) in $Ac_2O$ (6 ml) was added dropwise to a stirred solution of **2** (0.72 g, 5 mmol) in $Ac_2O$ (6 ml) at room temperature. Yellow crystals began to separate from the reaction mixture after 2 h. The reaction mixture was kept at room temperature overnight, then the crystals were filtered and recrystallized from EtOH to give 1.16 g of **7** (93%), yellow needles, mp 216—217°C (dec.). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3000 (NH), 1690 (C=O). MS *m/e*: 271, ($M^+$). *Anal.* Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.38; H, 4.78; N, 5.12.

**Reaction of 1a with Diethyl Ethylmalonate**——A solution of **1a** (0.78 g, 5 mmol) in $Ac_2O$ (6 ml) was added dropwise to a stirred solution of diethyl ethylmalonate (0.94 g, 5 mmol) in $Ac_2O$ (6 ml) at room temperature. The whole was kept at room temperature overnight and then heated at 90°C for 4 h. The solution was concentrated under reduced pressure and the residue was recrystallized from EtOH to give 0.45 g (58%) of carbostyril (**16**), pale brown needles, mp 199—201°C.

**Reaction of 6 with 8b**——A solution of **6** (0.78 g, 5 mmol) in $Ac_2O$ (6 ml) was added dropwise to a stirred solution of **8b** (0.86 g, 5 mmol) in $Ac_2O$ (6 ml) at room temperature. The whole was kept at room temperature overnight and then heated at 90°C for 4 h. The solution was concentrated under reduced pressure and the residue was recrystallized from EtOH to give 0.49 g of isocarbostyril (**17**) (64%), pale brown needles mp 212—213°C. It was identified by direct comparison with an authentic sample.

**Hydrolyses of 3a—d to 2-Methylquinolines Hydrochlorides (10a—d)**——A suspension of **3a—d** (2 mmol) in conc. HCl (30 ml) was refluxed for 30 min to give an almost colorless solution. The solution was concentrated under reduced pressure and the residual crystals were dissolved in EtOH. The solution was filtered and then mixed with ether. On cooling, the product 2-methylquinoline hydrochloride (**10a—d**) separated as fine crystals.

The results and some physical and spectral data of **10a—d** are shown in Table VIII.

**Hydrolysis of 3a to 2-Quinolineacetic Acid Hydrochloride (11a)**——A suspension of **3a** (0.54 g, 2 mmol) in 10% HCl (30 ml) was heated at 90°C for 6 h to give an almost colorless solution. The solution was concentrated under reduced pressure and the residual crystals were dissolved in EtOH. The solution was filtered and then mixed with ether to give 0.41 g of **11a** (92%), mp 219—220°C. *Anal.* Calcd for $C_{11}H_{10}ClNO_2$: C, 59.06; H, 4.47; N, 6.26. Found: C, 59.13; H, 4.58; N, 6.28.

**Methanolysis of 3a to Methyl 2-Quinolineacetate (12)**——A solution of **3a** (0.54 g, 2 mmol) in dry MeOH containing 10% HCl was refluxed for 6 h. The solution was concentrated to give highly hygroscopic crystals, which were dissolved in $H_2O$ and treated with aqueous sodium picrate. The resulting solid was filtered and recrystallized from MeOH to give 0.49 g (53%) of **12a**·picrate, yellow needles, mp 171—172°C. *Anal.* Calcd for $C_{12}H_{11}NO_2 \cdot C_6H_3N_3O_7$: C, 50.24; H, 3.28; N, 13.02. Found: C, 50.19; H, 3.36; N, 12.83.

**Hydrolysis of 7 to 1-Methylisoquinoline Hydrochloride (13)**——A suspension of **7** (0.54 g, 2 mmol) in conc. HCl (30 ml) was refluxed for 30 min to give a colorless solution. The solution was concentrated under reduced pressure, and the residue was dissolved in MeOH while hot, filtered, and then mixed with ether. The product **13** separated as colorless prisms, mp 206°C. *Anal.* Calcd for $C_{10}H_9N \cdot HCl \cdot 2H_2O$: C, 55.68; H, 6.48; N, 6.48. Found: C, 55.84; H, 6.42; N, 6.33.

**Hydrolyses of 9a—c to 2-Alkylquinolines (14a—c)**——A suspension of **9a—c** (2 mmol) in conc. HCl was refluxed for 30 min to give a colorless solution. The solution was concentrated under reduced pressure to give highly hygroscopic crystals, which were dissolved in $H_2O$ and treated with aqueous sodium picrate. The precipitated yellow mass was collected and recrystallized from MeOH to give **14a—c**·picrate in high yields.

The results and some physical properties of the picrates are shown in Table IX.

**Hydrolysis of 4f to *N*-Carboxymethyl-3-bromoquinolinium Chloride (18)**——A solution of **4f** (0.7 g, 2 mmol) in 35% HCl was refluxed for 2 h to give a colorless solution. The solution was concentrated under reduced pressure, and the residual crystals were recrystallized from EtOH to give 0.58 g of **18** (96%), colorless prisms, mp 245°C (dec.). *Anal.* Calcd for $C_{11}H_9BrClNO_2$: C, 43.63; H, 2.97; N, 4.62. Found: C, 43.49; H, 3.17; N, 4.57.

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