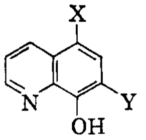
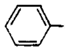
TABLE I

HALOGEN DERIVATIVES OF 8-QUINOLINOL COMPOUNDS



| No. | X (5 position) | Y (7 position) | Yield, % | Solvent | Form[a] | M.p., °C. | Formula | Anal. N, % Calcd. | Anal. N, % Found |
|---|---|---|---|---|---|---|---|---|---|
| I[b] | CH$_3$—CO— | I | 90 | EtOH | Needles | 183 (dec.) | $C_{11}H_8INO_2$ | 4.47 | 4.44 |
| II[b] | -CO- | I | 90 | EtOH | Plates | 209–210 | $C_{16}H_{10}INO_2$ | 3.73 | 3.60 |
| III[c] | Cl—CH$_2$—CO— | I | 95 | Glacial AcOH | Needles | 227 (dec.) | $C_{11}H_7ClINO_2$ | 4.03 | 3.97 |
| IV[d] | I—CH$_2$—CO— | H | 96 | $C_6H_6$ | Plates | 135 (dec.) | $C_{11}H_8INO_2$ | 4.47 | 4.56 |
| V[e] | CCl$_3$—CH(OH)— | I | 96 | 50% AcOH | Prisms | 192 (dec.) | $C_{11}H_7Cl_3INO_2$ | 3.35 | 3.26 |
| VI[f] | EtOOC— | I | 98 | EtOH | Needles | 199–200 | $C_{12}H_{10}INO_3$ | 4.08 | 4.21 |
| VII[f] | BuOOC— | I | 98 | EtOH | Plates | 155 | $C_{14}H_{14}INO_3$ | 3.77 | 3.78 |
| VIII[g] | HOOC— | I | 70 | EtOH | Prisms | 228–229 (dec.) | $C_{10}H_6INO_3$ | 4.44 | 4.43 |
| IX[h] | Cl | NO$_2$ | 80 | EtOH | Needles | 197 (dec.) | $C_9H_5ClN_2O_3$ | 12.47 | 12.90 |
| X[i] | Cl | NH$_2$ | 86 | Et$_2$O | Slightly brown prisms | 162–163 | $C_9H_7ClN_2O$ | 14.40 | 14.20 |
| XI[j] | Cl | NHCOCH$_3$ | 76 | $C_6H_6$ | Colorless needles | 201–202 (dec.) | $C_{11}H_9ClN_2O_2$ | 11.84 | 11.36 |

[a] Unless otherwise stated all crystal colors are orange. [b] Iodinated by method A-A1. [c] Iodinated by method B. [d] Prepared by method E. [e] Prepared by method C. [f] Iodinated by method A-A2. [g] Iodinated by method D. [h] Prepared by the addition of concentrated nitric acid (63%, 1 ml.) to a mixture of 5-chloro-8-quinolinol (1.8 g.) and glacial acetic acid (25 ml.) below 25°. [i] Made by stirring a mixture of IX (0.6 g.) pyridine (5 ml.) sodium hydrosulfite (4 g.) and water (20 ml.) at room temperature. [j] Made by allowing a mixture of X (0.4 g.) acetic anhydride (0.22 g.) freshly fused sodium acetate (0.4 g.) and ether (20 ml.) to stand at room temperature for 2 days.

## EXPERIMENTAL

*Method of Iodination.* (A) 0.1 *N* Iodine–potassium iodide solution (20 ml.) was added dropwise into a solution of 5-substituted-8-quinolinol (0.001 mol.) and sodium acetate (0.25 g.) in methanol (40 ml.) at about 10° during 0.5 hr. After standing, excess iodine was destroyed by sulphur dioxide.

A1. The reaction mixture was evaporated on water bath to one-half volume and then made up to the original volume by addition of water. The resulting solid was crystallized from solvent.

A2. The product separated upon adding water (100 ml.) to the reaction mixture.

B. 0.1 *N* Methanolic iodine solution (20 ml.) was used and other conditions similar to that of A-A2.

C. One-half normal methanolic iodine solution (80 ml.) was added to a solution of 5-($\alpha$-hydroxy-$\beta$-trichloroethyl)-8-quinolinol (0.02 mol.) and sodium acetate (10 g.) in methanol (800 ml.) at about 10° during 1 hr.

Sulphur dioxide was added, if necessary, after the reaction mixture had stood overnight.

Most of the methanol was evaporated in vacuo below 50°. The product separated upon adding water (250 ml.) to the residual paste.

D. 0.1 *N* Iodine-iodide solution (20 ml.) was added dropwise with stirring to a solution of 5-carboxy-8-quinolinol (0.001 mol.) and sodium hydroxide (0.001 mol.) in water (50 ml.) at about 15° during 0.5 hr. The reaction mixture was acidified with acetic acid, the resulting solid filtered and dissolved in dilute sodium carbonate. The undissolved diiodo-8-quinolinol (0.05 g., m.p. 192–200°) which was formed as a byproduct was filtered off. The product separated upon adding acetic acid to the filtrate. It can be recrystallized from ethanol or glacial acetic acid.

E. A normal solution (4 ml.) of sodium iodide in acetone was added a little at a time to a mixture of 5-chloroacetyl-8-quinolinol (0.004 mol.) and acetone (30 ml.) with stirring at room temperature. After standing for a few hours, most of acetone was removed in vacuo. The product separated upon adding water to the residue.

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# Chalcone-Type 8-Quinolinol Compounds

KONOMU MATSUMURA, MOTOKO ITO, AND SHEN TSO LEE

*Received April 6, 1959*

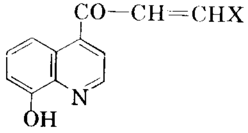
The compounds were prepared by condensation of 5-acetyl-8-quinolinol with aromatic aldehydes in the presence of potassium hydroxide or hydrochloric acid. None of them possessed any notable antituberculous or antiamebicidal activity.

## EXPERIMENTAL

*Method of condensation. A. In methanolic potassium hydroxide.* To a solution of 5-acetyl-8-quinolinol (0.38 g., 0.002 mol.) and aromatic aldehyde (0.002 mol.) in methanol (6 ml.) was added a solution of potassium hydroxide (1 g.) in water (2 ml.) with stirring. The resulting solution was allowed to stand at room temperature or gently refluxed on a water bath. Then the reaction mixture was diluted with water, acidified with acetic acid, the separated solid filtered on standing and recrystallized.

### TABLE I

### CONDENSATION OF 5-ACETYL-8-QUINOLINOL WITH AROMATIC ALDEHYDE



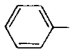
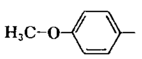
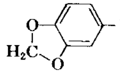
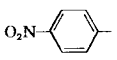
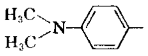
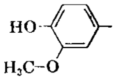
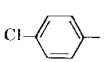
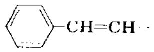
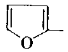
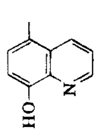
| X | Reaction |  |  | Yield, % | Solvent | Form | M.P., °C. | Color in Concd. $H_2SO_4$ | Formula | Nitrogen, % |  |
|---|---|---|---|---|---|---|---|---|---|---|---|
|  | Method | Temp., °C. | Time |  |  |  |  |  |  | Calcd. | Found |
|  | A<br>B | 30<br>60 | 24 hr.<br>4 | 73<br>73 | EtOH | Plates | 143–144 | Orange yellow | $C_{18}H_{13}NO_2$ | 5.09 | 5.32 |
| Hydrochloride |  |  |  |  | EtOH-HCl | Plates | 252–254 (dec.) |  | $C_{18}H_{13}NO_2 \cdot HCl$ | 4.49 | 4.34 |
|  | A<br>B | 60<br>60 | 5<br>3 | 80<br>64 | Glacial AcOH | Needles | 193–194 | Red | $C_{19}H_{15}NO_3$ | 4.59 | 4.99 |
| Hydrochloride |  |  |  |  | EtOH-HCl | Needles | 271 (dec.) |  | $C_{19}H_{15}NO_3 \cdot HCl$ | 4.10 | 3.92 |
|  [a] | A<br>B | 20<br>8 | 24<br>12 days | 94<br>59 | EtOH | Prisms | 180–181 | Red |  |  |  |
| Hydrochloride |  |  |  |  | EtOH-HCl | Needles | 256 |  |  |  |  |
|  | A<br>B | 25<br>60 | 24 hr.<br>17 | 75<br>89 | EtOH | Prisms | 224 | Orange yellow | $C_{18}H_{12}N_2O_4$ | 8.75 | 8.55 |
| Hydrochloride |  |  |  |  | EtOH-HCl | Plates | 280 |  | $C_{18}H_{12}N_2O_4 \cdot HCl$ | 7.85 | 7.63 |
|  | A<br>B | 60<br>60 | 10<br>35 | 31<br>74 | EtOH | Prisms | 191–192 | Wine red | $C_{20}H_{18}N_2O_2$[b] | 8.81 | 9.01 |
| Dihydrochloride |  |  |  |  | 20% HCl | Needles | 263–265 (dec.) |  | $C_{20}H_{18}N_2O_2 \cdot 2HCl$ | 7.16 | 7.04 |
|  | A<br>B[c] | 80<br>30 | 3<br>48 | 0<br>70 | EtOH | Prisms | 180–181 | Red | $C_{19}H_{15}NO_4$ | 4.36 | 4.33 |
| Hydrochloride |  |  |  |  | Dil. HCl | Needles | 268 (dec.) |  | $C_{19}H_{15}NO_4 \cdot HCl$ | 3.92 | 3.81 |
|  | A | 60 | 3 | 76 | EtOH | Cubes | 193–195 | Orange | $C_{18}H_{12}Cl\ NO_2$ | 4.52 | 4.52 |
|  | A<br>B | 80<br>8 | 3<br>3 days | 0<br>70 | EtOH | Prisms | 147 | Purple red | $C_{20}H_{15}NO_2$ | 4.65 | 4.45 |
| Hydrochloride |  |  |  |  | EtOH-HCl | Needles | 257 (dec.) |  | $C_{20}H_{15}NO_2 \cdot HCl$ | 4.15 | 4.17 |
|  | A | 8 | 24 hr. | 89 | EtOH | Plates | 155–155.5 | Reddish brown | $C_{16}H_{11}NO_3$ | 5.28 | 5.15 |

TABLE I (*Continued*)

| X | Reaction Method | Reaction Temp., C°. | Reaction Time | Yield, % | Solvent | Form | M.P., °C. | Color in Concd. $H_2SO_4$ | Formula | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
|  | A<br>B | 80<br>60 | 3<br>17 | 0<br>80 | $C_6H_6$ | Needles | 271 | Red | $C_{21}H_{14}N_2O_3$[d] | 8.18 | 8.08 |
| Dihydrochloride | | | | | Dil. HCl | Prisms | 267 (dec.) | | $C_{21}H_{14}N_2O_3 \cdot 2HCl$ | 6.75 | 6.77 |

[a] Lit. m.p. 178–179°, K. Matsumura and C. Sone, *J. Am. Chem. Soc.*, *53*, 1492 (1931). [b] Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.47; H, 5.66. Found: C, 75.19; H, 5.72. [c] In one lot, from the filtrate of recrystallization another isomer [yellow prisms, m.p. 276° (dec.), yield 20%, a red color in concd. $H_2SO_4$ · ] was isolated, but not successfully repeated.

*Anal.* Calcd. for $C_{19}H_{15}NO_4$: N, 4.36. Found: N, 4.37. *The hydrochloride* crystallized EtOH-HCl as yellow needles, m.p. 273–274° (dec.).

*Anal.* Calcd. for $C_{19}H_{15}NO_4 \cdot HCl$: N, 3.92. Found: N, 4.11.

[d] Calcd. for $C_{21}H_{14}N_2O_3$: C, 73.68; H, 4.09. Found: C, 73.92; H, 4.40.

In the case of furfural, *N* sodium hydroxide (8 ml.) was added dropwise to a cooled solution of the components.

*B. In concentrated hydrochloric acid.* A mixture of 5-acetyl-8-quinolinol (0.38 g., 0.002 mol.) aromatic aldehyde (0.002 mol.) and concentrated hydrochloric acid (5 ml.) was allowed to stand in a sealed tube. After different periods of reaction time, the tube was opened, acid fume removed *in vacuo*, the product filtered, dissolved in water, and free base precipitated by adding sodium acetate to it.

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# 5-Carboxy-8-quinolinol Derivatives

MOTOKO ITO AND KONOMU MATSUMURA

*Received April 16, 1959*

This note describes the preparation of several derivatives of 5-carboxy-8-quinolinol in the hope that they may be of tuberculostatic activity. None of them, however, possessed any notable antituberculous activity *in vitro*.

## EXPERIMENTAL

*Condensation of 8-quinolinol with carbon tetrachloride. The Lippmann and Fleissner method*[1] *was followed.* Starting from 20 g. of 8-quinolinol and with 13 hr. refluxing, 5.7 g. (22%) of 5-carboxy-8-quinolinol [m.p. 272° (dec.)] was isolated as the final product.

From dirty matter which was insoluble in dilute sodium carbonate, 4.7 g. of unreacted 8-quinolinol (m.p. 70–74°) was recovered by distillation with steam and 1.2 g. of 5-carboethoxy-8-quinolinol (m.p. 124.5–125.5°) isolated by carbon tetrachloride extraction of the residue of steam distillation and recrystallization of the extract from ethanol, the identity being ascertained by mixed m.p. method with an authentic specimen of 5-carboethoxy-8-quinolinol.

*The hydrochloride* formed light yellow needles, m.p. 263° (dec.).

*Anal.* Calcd. for $C_{12}H_{11}NO_3 \cdot HCl$: N, 5.53. Found: N, 5.71.

The carbon tetrachloride insoluble dark solid (*ca.* 5 g.) after three recrystallizations from dilute hydrochloric acid gave pure hydrochloride. It produced 0.62 g. of the free base on treating with dilute sodium carbonate.

It formed colorless prisms, m.p. 282–283° when recrystallized from nitrobenzene and then glacial acetic acid. The analytical figures corresponded to those of *bis*-8-quinolinol-5-yl ketone.

*Anal.* Calcd. for $C_{19}H_{12}N_2O_3$: C, 72.15; H, 3.80; N, 8.86. Found: C, 72.26; H, 3.79; N, 8.61.

*The hydrochloride* crystallized from dilute hydrochloric acid as light yellow columns, m.p. 309–311° (dec.).

*Anal.* Calcd. for $C_{19}H_{12}N_2O_3 \cdot 2HCl$: N, 7.20. Found: N, 7.02.

*Diacetyl derivative* crystallized from dilute acetic acid as colorless prisms, m.p. 201–202°. In dilute ethanol, it gives no color reaction with ferric chloride but develops a green color on standing or warming.

*Anal.* Calcd. for $C_{23}H_{16}N_2O_5$: N, 7.00. Found: N, 7.21.

*8-Hydroxy-*(XII) *and 8-chloro-*(XIII) *5-carbamoylquinoline.* A mixture of 5-carboxy-8-quinolinol (1.9 g., 0.01 mol.), phosphorus pentachloride (2.2 g., 0.011 mol.) and phosphorus oxychloride (2.9 g.) was heated at 100–105°

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[1] E. Lippmann and F. Fleissner, *Ber.*, 19, 2467 (1886).