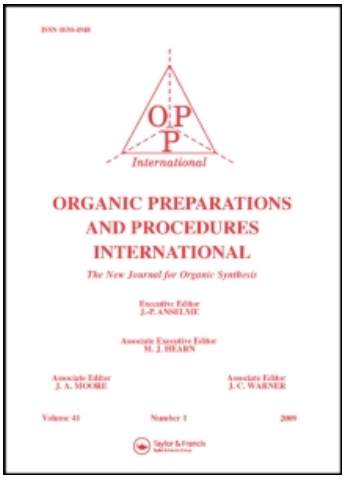

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2-SUBSTITUTED-3-METHYLQUINOLINES

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2-SUBSTITUTED-3-METHYLQUINOLINES

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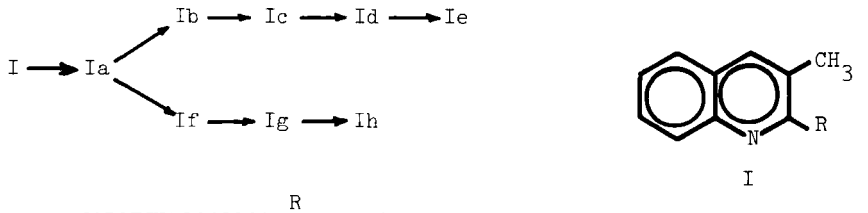
New 2-substituted-3-methylquinolines Ia-h[1] have been obtained by the sequences shown.



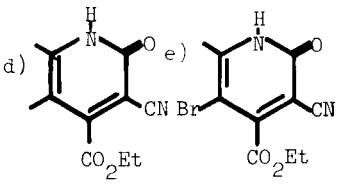
I

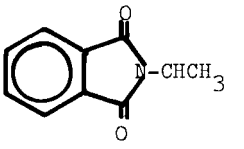
R

a) CH_3CHBr

b) CH_3CHOH

c) CH_3CO





g) CH_3CHNH_2

h) $CH_3CHNHCl$

EXPERIMENTAL

Melting points are uncorrected. Nmr spectra were obtained with a Varian Associates T-60 spectrometer using TMS as an internal reference. Mass spectra were obtained with a Varian Associates double focusing CH5 spectrometer. A mercury vapor ultraviolet lamp was used for irradiation.

2-Ethyl-3-methylquinoline.- The literature procedure[2] was used with some modifications. One-third equivalent of nitrobenzene was added before refluxing the mixture on the steam bath. After the reaction was completed, the mixture was extracted with ether. The product was distilled under vacuum and isolated as the sulfate salt mp. 186-188°, by dissolving the fraction boiling at 85-105°/1.2 mm in ethanol. Addition of sulfuric acid gave the sulfate salt.

Calcd for $C_{12}H_{15}NSO_4$: N, 5.20; C, 53.51; H, 5.61. Found: N, 5.14; C, 53.30; H, 5.58.

2-α-Bromoethyl-3-methylquinoline (Ia).- A solution of 2-ethyl-3-methylquinoline (142 g., 0.83 mole) in carbon tetrachloride (100 ml.) irradiated at reflux while bromine (102 g., 0.64 mole) was added portionwise. The progress of the bromination was followed by the visual consumption of bromine. The bromination ceased before all the bromine was added. After about 0.5 hr, a white precipitate began to separate. After the uptake of bromine ceased, reflux was continued for an additional 2 hrs. The mixture was filtered and the precipitate was washed with warm carbon tetrachloride. The washings were combined with the filtrate and evaporated to dryness. The crude product was crystallized from ethanol to give 63 g. of Ia, mp. 96-98° The mother liquor was concentrated to give an additional 30 g.
Nmr ($CDCl_3$): τ 7.80 d 3H, 7.40 s 2H, 4.39 q 1H, and 2.20 m 5H. Ia forms a picrate, mp. 168-171°.
Calcd for $C_{18}H_{15}N_4BrO_7$: N, 11.69; C, 45.11; H, 3.16. Found: N, 11.60; C, 45.36; H, 3.22.

The original precipitate was slurried in boiling water to give a red oil which was separated. When the aqueous extract was neutralized, it gave 51 g. of starting material. The red oil was dissolved in ethanol, treated with activated carbon and neutralized with concentrated ammonium hydroxide to give 22 g. of yellow crystals which by nmr proved to be a 1:1.5 mixture of the product and starting material. The total yield was 101 g., 90% based on unrecovered starting material.

2-α-Hydroxyethyl-3-methylquinoline (Ib).- 2-α-Bromoethyl-3-methylquinoline (63 g., 0.25 mole) was refluxed in acetic acid (500 ml.) containing sodium acetate (24 g.) for 1.5 hr. Most of the acetic acid was evaporated under

vacuum, then 10 N sodium hydroxide solution was added until the solution was basic to give a red oil. The basic aqueous solution was extracted with ether, and the ether was evaporated leaving a red oil which was dissolved in methanol (150 ml.). After addition of 10 N sodium hydroxide (30 ml.), the resulting solution was refluxed for 1.5 hr. Most of the methanol was evaporated under vacuum and the residue was extracted with ether. The extract was dried and evaporated to give 43.5 g. (92%) of Ib.

Nmr ($CDCl_3$): τ 8.51 d 3H, 7.62 s 3H, 4.85 q 1H, 4.65 broad signal 1H, and 2.23 m 5H.

Calcd for $C_{12}H_{13}NO$: N, 7.48; C, 76.77; H, 6.99. Found: N, 7.15; C, 76.23; H, 6.95. Ib forms a picrate, mp. 186-188°.

Calcd for $C_{18}H_{16}N_4O_8$: N, 13.46; C, 51.92; H, 3.87. Found: N, 13.54; C, 51.93; H, 3.87.

2-Acetyl-3-methylquinoline (Ic).- To a stirred solution of 2-α-hydroxyethyl-3-methylquinoline (43.5 g., 0.23 mole) in acetic acid (100 ml.) was added chromic anhydride (18 g., 0.18 mole) in portions over a period of about 2 hr. at 45-50°. The solution was stirred for an additional hr. and poured into ice water (600 ml.) with stirring to give 33 g. (77%) of Ia, mp. 61-63°.

Nmr ($CDCl_3$): τ 7.30 s 3H, 7.17 s 3H, 2.15 m 5H.

Calcd for $C_{12}H_{11}NO$: N, 7.55; C, 77.82; H, 5.97. Found: N, 7.36, C, 77.94; H, 6.12.

$[M]^+$ 96%, $[M-1]^+$ 17%, $[M-15]^+$ 3%, $[M-28]^+$ 44%, $[M-42]^+$ 100%

3-Cyano-4-Carboethoxy-6-(3-methyl-2-quinolinyl)-2-pyridone (Id).- Sodium (1.3 g., 0.056 mole) was added to ethanol (100 ml.). After all the sodium had dissolved, the solution was cooled to room temperature. Diethyl oxalate (7.9 g., 0.054 mole) was added followed by 2-acetyl-3-methylquinoline (10 g., 0.054 mole) and the solution was stirred for 24 hrs at room tem-

perature. Most of the alcohol was evaporated under vacuum and water (200 ml.) was added. The aqueous solution was extracted once with ether, acidified to pH 2 and again extracted with ether. The latter extract was washed with water, dried and evaporated to give a red oil. To this was added a solution of cyanoacetamide (4.5 g., 0.053 mole) in ethanol (150 ml.) followed by diethylamine (2 ml.) while stirring in a water bath at 45-50°. After 15 minutes, a yellow precipitate formed. It was filtered after stirring for 3 hrs and recrystallized from acetic acid to give 5 g. of Id (28%) mp. 246-248°.

Nmr (DMSO-d_6): τ 8.63 t 3H, 7.45 s 3H, 5.60 q 2H, 2.9 s 1H and 2.0 m 5H.

Calcd for $C_{19}H_{15}N_3O_3$: N, 12.60; C, 68.45; H, 4.53. Found: N, 12.53; C, 68.25; H, 4.72.

$[M]^+$ 82%, $[M-1]^+$ 27%, $[M-28]^+$ 16%, $[M-29]^+$ 71%, $[M-45]^+$ 6%, $[M-72]^+$ 21%, $[M-73]^+$ 100%

3-Cyano-4-carboethoxy-5-bromo-6-(3-methyl-2-quinolinyl)-2-pyridone (Ie).- 3-Cyano-4-carboethoxy-6-(3-methyl-2-quinolinyl)-2-pyridone (1 g., 0.003 mole) was dissolved in hot acetic acid (30 ml.) containing 0.3 g. of sodium hydroxide. The resulting solution was refluxed and irradiated while bromine (0.48 g., 0.003 mole) in acetic acid (10 ml.) was added portionwise. After 3 hrs of reflux, the mixture was concentrated under vacuum to about 10 ml. and poured into ice water to give a quantitative yield of Ie, mp. 253-254° after crystallization from isopropanol.

Nmr ($CDCl_3$): τ 8.63 t 3H, 7.56 s 3H, 5.49 q 2H and 2.18 m 6H.

Calcd for $C_{19}H_{14}N_3O_3Br$: N, 10.18; C, 55.35; H, 3.42. Found: N, 10.02; C, 55.28; H, 3.23.

$[M]^+$ 83%, $[M-28]^+$ 16%; $[M-29]^+$ 68%, $[M-45]^+$ 10%, $[M-79]^+$ 65%, $[M-107]^+$ 100%, $[M-152]^+$ 77%, $[M-153]^+$ 41%

2-α-Phthalimidoethyl-3-methylquinoline (If).- 2-α-Bromoethyl-3-methylquinoline (24 g., 0.096 mole) was heated with potassium phthalimide (17.8 g., 0.096 mole) in dimethylformamide (60 ml.) at 120-130° for 50 min. The mixture was poured into ice water (600 ml.) to give an off-white precipitate, which was extracted with chloroform, dried and concentrated to one-fifth its volume. Hexane was added to give a dark yellow oil which solidified upon seeding with the product. The yield was 23 g. (76%), mp. 105-106°.

Nmr ($CDCl_3$): τ 8.00 d 3H, 7.59 s 3H, 4.18 q 1H, 2.32 m 9H.

Calcd for $C_{20}H_{16}N_2O_2$: N, 8.86; C, 75.93; H, 5.10. Found: N, 8.93; C, 75.70; H, 5.05.

2-α-Chloroaminoethyl-3-methylquinoline (Ih).- 2-α-Phthalimidoethyl-3-methylquinoline (7 g., 0.02 mole) in methanol (75 ml.) was refluxed on a steam bath with 85% hydrazine hydrate (2 1/2 ml.) for 1 hr. Most of the methanol was evaporated under vacuum, water (30 ml.) was added followed by conc. hydrochloric acid (25 ml.) to give an immediate white precipitate. The mixture was heated on a steam bath for 1 hr., filtered, neutralized and extracted with methylene chloride. The methylene chloride extract was stirred with 1 N sodium hypochlorite solution (50 ml.) for 0.5 hr. The aqueous layer was removed (water aspirator), another 50 ml. of fresh sodium hypochlorite was added and stirred for another 0.5 hr. The mixture was separated and the methylene chloride was washed with water. The methylene chloride extract was dried and evaporated to dryness to give an orange solid which was crystallized from ethanol. The yield of Ih was 3.4 g. (76%), mp. 112-114°.

Nmr ($CDCl_3$): τ 8.65 d 3H, 7.60 s 3H, 5.46 broad signal 1H, 4.20 broad signal 1H, 2.30 m 5H.

($CDCl_3/D_2O$): τ 8.65 d 3H, 7.60 s 3H, 5.65 q 1H, 2.30 m 5H

Calcd for $C_{12}H_{13}N_2Cl$: N, 12.69; C, 65.29; H, 5.94. Found: N, 12.58; C, 65.49; H, 5.97

$[M^+]$ 27%, $[M-15]^+$ 100%, $[M-35]^+$ 63%, $[M-49]^+$ 23%, $[M-50]^+$ 64%, $[M-77]^+$ 97%, $[M-98]^+$ 43%, $[M-104]^+$ 30%, $[M-105]^+$ 74%

2-α-Aminoethyl-3-methylquinoline (Ig).- 2-α-Chloroaminoethyl-3-methylquinoline (1 g., 0.0045 mole) in 98% sulfuric acid (10 ml.) was irradiated at 40° for 3 hrs. The mixture was poured into ice water (150 ml.) and extracted with ether. The aqueous layer was treated with 40% sodium hydroxide solution until strongly basic and extracted with ether. The ethereal extract was washed with water, dried and evaporated to give 0.6 g. of crude Ig.

Nmr ($CDCl_3$): τ 8.6 d 3H, 7.58 s 3H, 7.39 s 2H (exchangable), 5.59 q 1H, 2.26 m 5

$[M]^+$ 61%, $[M-15]^+$ 98%, $[M-42]^+$ 37%, $[M-43]^+$ 100%, $[M-44]^+$ 17%, $[m-71]^+$ 25%

Ig forms a dihydrochloride salt, mp. 272° (dec.).

Calcd for $C_{12}H_{16}N_2Cl_2$: N, 10.80; C, 55.58; H, 6.22. Found: N, 10.46; C, 55.57; H, 6.18.

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†. Taken from the Ph.D. dissertation of Hassan A. El-Sayad, University of North Carolina, Chapel Hill, 1974.

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