Synthesis and Reaction of 2,7-Dimethylpyrrolo[1,2-*a*]quinoline with Electrophilic Reagents (1)

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2,7-Dimethylpyrrolo[1,2-*a*]quinoline (I) was synthesized from 2,6-dimethylquinoline and bromoacetone *via* a Tschitschibabin reaction. The electrophilic substitution reactions of I, namely, nitrosation, acylation, diazonium coupling, formylation, bromination, and nitration were studied.

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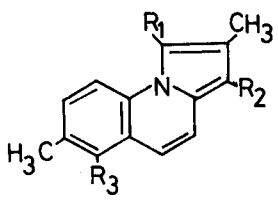
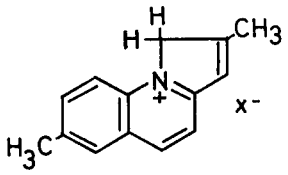
We report here the synthesis of 2,7-dimethylpyrrolo-[1,2-*a*]quinoline (I) and some electrophilic substitution reactions on I.

Reaction of 2,6-dimethylquinoline with bromoacetone in acetone, followed by treatment of the quarternary salt with a base, resulted in the formation of I in 12% yield. This is the first report of the synthesis of pyrrolo[1,2-*a*]-quinoline using Tschitschibabin's method. Although Tschitschibabin (2) prepared 2-methylpyrrolo[1,2-*a*]quinoline by reacting 2-methylquinoline with halogenoacetone, only a non-crystalline product was isolated and the experimental details were not available. Also, the efforts (3) to repeat the same gave only quinoline hydrohalide salts. The structure of I was assigned on the basis of its nmr and mass spectral data (see Experimental). The chemical shifts of H-1 and H-3 in I were indicated by a comparison of the nmr spectra of I and its dideutero derivative (III); the latter was prepared by the exchange reaction (4) with deuterium oxide on its perchlorate (II). The C-1 protonation in II is clearly seen in its broad singlet at δ 5.66 accounting for two protons.

Nitrosation, acylation, diazonium coupling, and formylation (Vilsmeier-Haack) reactions were carried out on I to give the 1-substituted derivatives (IV-VII), respectively. In the case of formylation of I by Reimer-Tiemann's method, the 1,3-diformyl derivative (VIII) was obtained. Treatment of I with bromine yielded 2,7-dimethylpyrrolo-[1,2-*a*]quinolinium bromide (IX) together with a green solid, the structure of which could not be determined due to its unstable nature.

It was observed that the green crystalline solids IV, VII and VIII behave similarly in that they turn to red on treatment with acid, a reaction also noticed with simple indolizines (5). In the case of IV, a red crystalline solid (X) was isolated upon addition of an equimolar quantity of perchloric acid in ethanolic medium. In its ir spectrum, X showed a broad band at 3050 cm^{-1} and its nmr spectrum exhibited a quartet at δ 7.22 (1H, J = 1.5 Hz, H-3) and a doublet at δ 2.75 (3H, J = 1.5 Hz, 2-CH_3). The corresponding signals in IV were only singlets. These data indicate that the red compounds have lost the indolizine nature and acquired the behavior of a quinolinium entity.





I $R_1=R_2=R_3=H$

II $X=ClO_4$

III $R_1=R_2=D$, $R_3=H$

IX $X=Br$

IV $R_1=NO$, $R_2=R_3=H$

V $R_1=COC_6H_5$, $R_2=R_3=H$

VI $R_1=NNC_6H_4\cdot CO_2Et(p)$, $R_2=R_3=H$

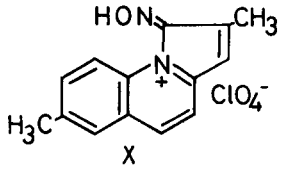
VII $R_1=CHO$, $R_2=R_3=H$

VIII $R_1=R_2=CHO$, $R_3=H$

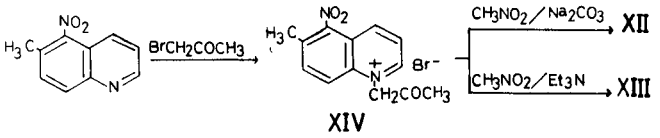
XI $R_1=NO_2$, $R_2=R_3=H$

XII $R_1=R_2=H$, $R_3=NO_2$

XIII $R_1=H$, $R_2=R_3=NO_2$



X



XIV

Nitration of I with nitric acid in acetic acid containing a trace amount of concentrated sulfuric acid (6) gave the 1-nitro derivative (XI) in 10% yield which could be enhanced to 33% in acetic anhydride. On the other hand, nitration of I with mixed acid at 0-5° gave the 6-nitro derivative (XII) in 70% yield. However, the 3,6-dinitro derivative (XIII) resulted on using two moles of nitric acid at 12-15°. The structures of XII and XIII were confirmed

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by an alternative synthesis (7) from quinolinium salt (XIV), obtained from 6-methyl-5-nitroquinoline and bromoacetone, *via* cyclization with nitromethane/sodium carbonate to give XII, and with nitromethane/triethylamine to give XIII.

In the electrophilic substitution reactions of *N*-bridgehead compounds, the reaction preferentially occurs at the carbon (C-1) adjacent to nitrogen atom. However, in the mixed acid medium, nitration of I occurs at C-6 (*i.e.*, XII). This is probably because in mixed acid medium, the nitronium ion preferentially attacked to C-6 as a result of C-1 protonation while in the other reaction medium, I existed in a free form and therefore reaction occurs at the position commonly susceptible to electrophilic attack (8).

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were measured with a Jasco IRA-1 spectrometer using the pressed potassium bromide discs and the nmr spectra were recorded on a Varian A-60-A spectrometer with tetramethylsilan as internal standard. The mass spectra were obtained with a Hitachi RMU-6 mass spectrometer.

2,7-Dimethylpyrrolo[1,2-*a*]quinoline (I).

A solution of 2,6-dimethylquinoline (15 g.) and bromoacetone (15 g.) in acetone (150 ml.) was refluxed for 2 hours. The resulting crystalline salt was filtered, washed with dry acetone, and dissolved in water (500 ml.). Sodium bicarbonate (50 g.) was added, and the mixture was stirred at 90° for 1 hour. After cooling, the reaction mixture was extracted with ether. The ethereal extracts were evaporated to dryness, and the residue was distilled. The fraction collected in the range of b.p. 144-147°/3 mm solidified on standing and was recrystallized from ethanol-water as colorless crystalline solid, I, 2.3 g. (12%), m.p. 71-73°; ms: m/e 195 (M^+); nmr (carbon tetrachloride): δ 2.25 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 6.18 (broad s, 1H, H-3), 6.75 (d, J = 9 Hz, 1H, H-4), 7.10 (d, J = 9 Hz, 1H, H-5), 7.15 (d, J = 8 Hz, 1H, H-8), 7.22 (broad s, 1H, H-6), 7.46 (broad s, 1H, H-1), 7.55 (d, J = 8 Hz, 1H, H-9).

Anal. Clacd. for $C_{14}H_{13}N$: C, 86.11; H, 6.71; N, 7.17. Found: C, 86.23; H, 6.49; N, 7.05.

2,7-Dimethylpyrrolo[1,2-*a*]quinolinium Perchlorate (II).

Perchloric acid (*d* = 1.67; 0.7 ml.) was added to a solution of I (1.0 g.) in ethanol (10 ml.) at room temperature. The precipitate obtained was filtered and recrystallized from ethanol to give II, 1.2 g. (82%), m.p. 195°; nmr (deuterotrifluoroacetic acid): δ 2.58 (d, J = 2 Hz, 3H, 2-CH_3), 2.72 (s, 3H, 7-CH_3), 5.66 (broad s, 2H, CH_2), 7.03 (q, J = 2 Hz, 1H, H-3), 7.70-8.10 (m, 4H, aromatic), 8.72 (d, J = 9 Hz, 1H, H-5).

Anal. Calcd. for $C_{14}H_{14}ClNO_4$: C, 56.86; H, 4.77; N, 4.74. Found: C, 56.65; H, 4.93; N, 4.66.

2,7-Dimethylpyrrolo[1,2-*a*]quinoline-1,3-d_2 (III).

Perchlorate II (0.15 g.) was dissolved in deuterium oxide (4 ml.) and the dideutero compound was precipitated by addition of a slight excess of anhydrous sodium carbonate. The precipitate was filtered, and sublimed to give III, m.p. 68-70°. Comparison of the nmr data of I and III showed deuteration has occured in III at position 1 and 3.

Nitrosation of I to 1-Nitroso-2,7-dimethylpyrrolo[1,2-*a*]quinoline (IV).

A solution of sodium nitrite (0.7 g.) in water (5 ml.) was added dropwise to a stirred solution of I (1.9 g.) in hydrochloric acid (10%; 15 ml.) at 0-5°. After 30 minutes, the red solution was made alkaline by addition of sodium carbonate, and the green precipitate was filtered and recrystallized from methanol to give 2.0 g. (90%) as green crystalline solid, IV, m.p. 150-152°; ms: m/e 224 (M^+); nmr (deuterochloroform): δ 2.24 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 6.20 (s, 1H, H-3), 6.98-7.42 (m, 4H, aromatic), 9.14 (d, J = 8.5 Hz, 1H, H-9).

Anal. Calcd. for $C_{14}H_{12}NO_2$: C, 74.99; H, 5.38; N, 12.49. Found: C, 74.69; H, 5.15; N, 12.32.

Acylation of I to 1-Benzoyl-2,7-dimethylpyrrolo[1,2-*a*]quinoline (V).

A solution of I (1.0 g.) and benzoylchloride (0.7 g.) in benzene (5 ml.) was set aside overnight, then poured into aqueous sodium hydroxide (10%; 25 ml.) solution. The precipitate was filtered, washed with water and recrystallized from ether to give 0.6 g. (40%) of a yellow crystalline solid, V, m.p. 123-124°; ms: m/e 299 (M^+); nmr (deuterochloroform): δ 2.08 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 6.38 (s, 1H, H-3), 7.0-7.96 (m, 10H, aromatic).

Anal. Calcd. for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68. Found: C, 84.33; H, 5.70; N, 4.49.

Diazonium Coupling of I to 1-(4-Ethoxycarbonylphenylazo)-2,7-dimethylpyrrolo[1,2-*a*]quinoline (VI).

A solution of I (1.0 g.) in acetic acid (5 ml.) was added to a stirred solution of diazotized ethyl 4-aminobenzoate (0.85 g.) in acetic acid (50%; 10 ml.). The red precipitate was filtered, washed with water and recrystallized from ether to give 1.65 g. (90%) of a red crystalline solid, VI, m.p. 127-128°; nmr (deuterochloroform): δ 1.42 (t, J = 6.5 Hz, 3H, Et-CH_3), 2.46 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 4.42 (q, J = 6.5 Hz, 2H, Et-CH_2), 6.48 (s, 1H, H-3), 7.20-7.52 (m, 4H, aromatic), 7.82, 8.20 (each d, J = 7.5 Hz, each 2H, benzoyl), 9.28 (d, J = 8.5 Hz, 1H, H-9).

Anal. Calcd. for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.31. Found: C, 74.31; H, 5.52; N, 11.52.

Formylation of I to 1-Formyl-2,7-dimethylpyrrolo[1,2-*a*]quinoline (VII).

A solution of phosphorus oxychloride (1.7 g.) in dimethylformamide (10 ml.) was added dropwise during 30 minutes to a stirred solution of I (1.6 g.) in dimethylformamide (5 ml.). The temperature was maintained at 10-15° during the addition and at 55-60° for 1 hour. The mixture was then poured into aqueous sodium hydroxide (2*M*; 100 ml.). Crystallisation of the resulting product from petroleum ether gave 1.6 g. (70%) of green crystalline solid, VII, m.p. 78-80°; ms: m/e 223 (M^+); nmr (deuterochloroform): δ 2.45 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 6.38 (s, 1H, H-3), 7.25-7.46 (m, 4H, aromatic), 8.80 (d, J = 8.5 Hz, 1H, H-9), 9.95 (s, 1H, CHO).

Anal. Calcd. for $C_{15}H_{13}ON$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.87; H, 5.80; N, 6.01.

Formylation of I to 1,3-Diformyl-2,7-dimethylpyrrolo[1,2-*a*]-quinoline (VIII).

A solution of potassium hydroxide (12.5 g.) in water (15 ml.) was added with stirring to a boiling solution of I (1.0 g.) in chloroform (10 ml.) and ethanol (15 ml.) over a period of 2 hours; boiling was continued for a further 30 minutes and the mixture was then cooled. The inorganic salt was filtered off and the filtrate was evaporated to dryness. The residue was purified by chromatography on silica gel using chloroform as an eluent.

The eluate was evaporated and recrystallized from tetrahydrofuran to give 0.25 g. (19%) of a green crystalline solid, m.p. 154-156°; ms: m/e 251 (M^+); nmr (deuterochloroform): δ 2.45 (s, 3H, CH_3), 2.78 (s, 3H, CH_3), 7.42-8.68 (m, 5H, aromatic), 10.16 (s, 1H, CHO), 10.24 (s, 1H, CHO); ir: 1614 (C=O), 1675 (C=O) cm^{-1}.

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.30; H, 5.01; N, 5.71.

Bromination of I.

A solution of bromine (0.8 g.) in dry carbon tetrachloride (10 ml.) was added dropwise to a stirred solution of I (1.0 g.) in dry carbon tetrachloride (15 ml.) over 30 minutes and allowed to remain at room temperature for 5 hours. Solvent was removed, and the green oil was triturated with dry ether. The hydrobromide salt was filtered and recrystallized from ethanol-ether to give IX, 0.41 g. (29%) as a colorless crystalline solid, m.p. 226°; nmr (deuterotrifluoroacetic acid): δ 2.56 (d, J = 2 Hz, 3H, $2CH_3$), 2.68 (s, 3H, 7-CH_3), 5.65 (broad s, 2H, CH_2), 7.0 (q, J = 2 Hz, 1H, H-3), 7.86 (d, J = 8.5 Hz, 1H, H-4), 8.04 (m, 3H, aromatic), 8.90 (broad d, J = 8.5 Hz, 1H, H-5).

Anal. Calcd. for $C_{14}H_{14}BrN$: C, 60.88; H, 5.11; N, 5.07. Found: C, 61.05; H, 5.40; N, 5.31.

The mother liquor was concentrated to dryness, and to the residue was added a small amount of petroleum ether. The precipitate formed was collected to give a green solid. Attempts to purify this compound led only to a dark oil.

1-Isonitroso-2,7-dimethylpyrrolo[1,2-*a*]quinolinium Perchlorate (X).

Perchloric acid (0.7 ml.) was added to a solution of IV (1.2 g.) in ethanol (10 ml.) at room temperature. The red precipitate was filtered, washed with ether, and recrystallized from ethanol to give 1.49 g. (90%) as a red crystalline solid, X, m.p. 208°; nmr (deuterotrifluoroacetic acid): δ 2.68 (s, 3H, 7-CH_3), 2.75 (d, J = 1.5 Hz, 3H, 2-CH_3), 7.20 (q, J = 1.5 Hz, 1H, H-3), 7.72-9.46 (m, 5H, aromatic); ir: 3050 (broad, -OH).

Anal. Calcd. for $C_{14}H_{13}ClN_2O_5$: C, 51.78; H, 4.04; N, 8.63. Found: C, 51.53; H, 4.18; N, 8.36.

Nitration of I to 1-Nitro-2,7-dimethylpyrrolo[1,2-*a*]quinoline (XI).

a)

To a solution of I (1.0 g.) in acetic acid (15 ml.) was added concentrated sulfuric acid (2 drops) followed by nitric acid (*d* = 1.4; 0.6 ml.). The mixture was heated carefully over a flame until a vigorous reaction occurs which was allowed to continue for 2-3 minutes, the mixture was then poured into aqueous potassium hydroxide (40%; 40 ml.), and then extracted with ether. The dried ethereal extracts were evaporated to dryness. The residue on chromatography over silica gel and elution with benzene, yielded a solid which was recrystallized from ethanol to give a yellow crystalline solid, XI, 0.12 g. (10%), m.p. 155-157°; ms: m/e 240 (M^+); nmr (deuterochloroform): δ 2.42 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 6.22 (s, 1H, H-3), 7.02 (d, J = 7.5 Hz, 1H, H-8), 7.12 (d, J = 2.5 Hz, 1H, H-4 or H-5), 7.28 (d, J = 2.5 Hz, 1H, H-4 or H-5), 7.31 (s, 1H, H-6), 7.46 (d, J = 7.5 Hz, 1H, H-9).

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.73; H, 5.30; N, 11.45.

b)

To a stirred ice-cold, solution of I (1.0 g.) in acetic anhydride (20 ml.) was added dropwise a mixture of fuming nitric acid (*d* = 1.5; 2.0 g.) and acetic anhydride (5 ml.). The mixture was stirred for a further 30 minutes and processed as in a) above, to get the product, XI, 0.39 g. (33%) (mixed m.p. and ir).

Nitration of I to 6-Nitro-2,7-dimethylpyrrolo[1,2-*a*]quinoline (XII).

A mixture of nitric acid (*d* = 1.4; 1.2 ml.) and concentrated sulfuric acid (5 ml.) was added dropwise to a stirred solution of I (1.9 g.) in concentrated sulfuric acid (5 ml.) maintained at 0-5°. After 10 minutes, the mixture was poured into crushed ice, and the precipitate filtered, washed with water and recrystallized from ethanol to give a red crystalline solid, XII, 0.84 g. (70%), m.p. 153-155°. It was proved to be identical (mixed m.p. and ir) with a sample prepared by another route described below.

Nitration of I to 3,6-Dinitro-2,7-dimethylpyrrolo[1,2-*a*]quinoline (XIII).

To a stirred solution of I (1.9 g.) in concentrated sulfuric acid (8 ml.) maintained at 10-12° was added dropwise of nitric acid (*d* = 1.4; 2.4 ml.) and concentrated sulfuric acid (8 ml.). After 15 minutes, the mixture was poured into crushed ice, extracted with chloroform, and evaporated to dryness. The resulting residue was chromatographyed on silica gel. Elution with chloroform afforded a solid which was recrystallized from dioxane to give a yellow crystalline solid, XIII, 0.25 g. (25%), m.p. 260°, which was identical (mixed m.p. and ir) with a sample prepared by another route, described below.

Synthesis of XII and XIII from XIV.

N-Acetonyl-6-methyl-5-nitroquinolinium Bromide (XIV).

A solution of 6-methyl-5-nitroquinoline (5.5 g.) and bromoacetone (4.2 g.) in acetone (50 ml.) was refluxed for 2 hours. The solid obtained was recrystallized from ethanol to give a colorless crystalline solid, XIV, 6.3 g. (70%), m.p. 208-210°.

A solution of XIV (3.3 g.) in nitromethane (40 ml.) and sodium carbonate (6 g.) was refluxed for 8 hours. The inorganic salts were removed and evaporated to dryness. Purification over a silica gel column using chloroform as solvent let to a solid which recrystallized from ethanol to give XII, 0.15 g. (6.2%), m.p. 154-155°; ms: m/e 240 (M^+); nmr (deuterochloroform): 2.32 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 6.40 (broad s, 1H, H-3), 6.74, 7.30 (each d, J = 9.5 Hz, each 1H), 7.28, 7.75 (each d, J = 9.0 Hz, each 1H), 7.60 (broad s, 1H, H-1).

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.75; H, 5.15; N, 11.72.

A solution of XIV (3.3 g.) in nitromethane (6 ml.) and triethylamine (5 ml.) in methanol (30 ml.) was refluxed for 6 hours and worked up as above to give XIII, 1.1 g. (39%), m.p. 260°; ms: m/e 285 (M^+).

Anal. Calcd. for $C_{14}H_{11}N_3O_4$: C, 58.94; H, 3.89; N, 14.73. Found: C, 59.10; H, 3.70; N, 14.92.

REFERENCES AND NOTES

(1) This constitutes Part 49 of a series entitled "Studies on Heterocyclic Compounds". Part 48: H.-S. Kuo, K. Hotta, M. Yogo and S. Yoshina, *Synthesis*, submitted.

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(8) From the result of nmr, it is known that compound I caused no protonation in acetic acid.