The Synthesis of 1-Methyl-5-(α-indolyl)imidazole and 1-Methyl-2-ethylthiol-5-(α-indolyl)imidazole

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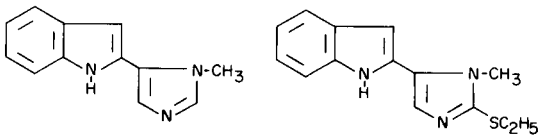
The pharmacological activity of some imidazole alkaloids (2,3), *i.e.* isomacrorine [1-methyl-5-(2′-quinolyl)-imidazole], has prompted us to synthesize an indole analogue (I) of these alkaloids. During the course of the synthesis 1-methyl-2-ethylthiol-5-(α-indolyl)imidazole (II) was also prepared.



(I) (II)

1-Methyl-5-acetylimidazole and 1-methyl-2-ethylthiol-5-acetylimidazole were prepared and converted into their respective phenylhydrazones from which I and II could be obtained by the general method of Fischer for the synthesis of indoles.

Imidazole ketones are compounds not readily available, because imidazoles fail to undergo the Friedel-Crafts synthesis (4). It was possible, however, to obtain the required methyl ketones through a malonic ester synthesis. Treatment of 1-methyl-5-imidazole carboxylic acid with phosphorus pentachloride gave the acid chloride which was reacted with the enolate from the reaction of sodium hydride and diethyl malonate. The product, a substituted malonic ester, was not isolated but hydrolyzed with mineral acid to an unstable β-ketodicarboxylic acid which decarboxylated under the experimental conditions to give 1-methyl-5-acetylimidazole.

1-Methyl-2-ethylthiol-5-acetylimidazole was prepared in a similar manner from 1-methyl-2-ethylthiol-5-imidazole carboxylic acid.

EXPERIMENTAL

UV absorption spectra refer to ethanol, and IR absorption spectra refer to chloroform solutions. The former was recorded on an Unicam S. P. 800 and the latter on a Perkin-Elmer Infracord 237 spectrophotometer. Unless otherwise specified, NMR spectra were determined in deuteriochloroform with T.M.S. as internal standard (τ 10.0) on a Varian A60 instrument and mass spectra with an A.E.I. MS-9 spectrometer using the direct insertion technique. Melting points were determined on a Kofler block. All samples were dried at 60°/0.001 mm for 3 hours before analysis.

Ethyl 1-Methyl-2-thiol-5-imidazole Carboxylate and 1-Methyl-5-imidazole Carboxylic Acid.

These two compounds were prepared from sarcosine by using the method of Jones (5).

Ethyl 1-Methyl-2-ethylthiol-5-imidazole Carboxylate (6).

To ethyl 1-methyl-2-thiol-5-imidazole carboxylate (150 g.) in absolute ethanol (1.5 l.) was added ethyl bromide (200 g.) and the mixture refluxed for 18 hours. Removal of the ethanol *in vacuo* and distillation of the residue yielded ethyl 1-methyl-2-ethylthiol-5-imidazole carboxylate as an oil (129 g.), b.p. 140°/4 mm.; NMR τ 2.31 (s, C_4 aromatic H), τ 5.7 and 8.62 (q and t respectively, J = 7 cps, $COOCH_2CH_3$), τ 6.80 and 8.67 (q and t respectively, J = 7 cps, SCH_2CH_3), τ 6.20 (s, NCH_3).

Anal. Calcd. for $C_9H_{14}N_2O_2S$: M. W. 214. Found: M^+ 214.

1-Methyl-2-ethylthiol-5-imidazole Carboxylic Acid.

Ethyl 1-methyl-2-ethylthiol-5-imidazole carboxylate (129 g.) was suspended in an aqueous solution of sodium hydroxide (60 g. in 250 ml. water) and the mixture refluxed for 3 hours. Neutralization of the solution with aqueous sulphuric acid (73.5 g. in 200 ml. water) caused precipitation of colourless crystals (66 g.) which were recrystallized from acetone-hexane as colourless needles, m.p. 138-139°; UV λ max (95% ethanol) 262 mμ (ε, 12,600), λ max (95% ethanol/hydrogen chloride) 268 mμ (ε, 11,700, ν max 1690 (s, CO).

Anal. Calcd. for $C_7H_{10}N_2O_2S$: C, 45.2; H, 5.4; N, 15.0. Found: C, 44.9; H, 5.3; N, 14.9.

1-Methyl-5-imidazole Carboxylic Acid Chloride.

Finely powdered 1-methyl-5-imidazole carboxylic acid (6.7 g.) was intimately mixed in a 250 ml. round-bottomed flask with phosphorus pentachloride (12.1 g.). A glass rod was used for this purpose. The flask was fitted with a reflux condenser and calcium chloride drying tubes and the mixture heated at 110° for 2 hours. Any phosphorus oxychloride which had not evaporated was then removed by heating the mixture under a stream of nitrogen for another 2 hours at 110°. The white residue was kept at room temperature under anhydrous conditions for use in the next step of the synthesis.

1-Methyl-2-ethylthiol-5-imidazole Carboxylic Acid Chloride.

From 1-methyl-2-ethylthiol-5-imidazole carboxylic acid (20 g.) and phosphorus pentachloride (24.5 g.) the acid chloride was prepared using the same procedure as for 1-methyl-5-imidazole

carboxylic acid chloride.

1-Methyl-5-acetylimidazole.

Ethyl malonate (16 g.) was dissolved with cooling in THF (150 ml.) in a flask fitted with a reflux condenser. To the mixture was added sodium hydride (4.8 g.) at such a rate that the THF refluxed steadily. A clear solution resulted which was added to a suspension of the acid chloride (ex 6.7 g. acid) in THF (100 ml.). The reaction flask was fitted with a mechanical stirrer, a reflux condenser, and drying tubes and the mixture then stirred for 2 hours at room temperature and 3 hours at reflux temperature. A yellow precipitate formed. The THF was removed *in vacuo* and water (200 ml.) containing sulphuric acid (15 ml.) added to the precipitate. The acid solution was then refluxed for 10 hours, cooled, and extracted with chloroform (4 x 100 ml.) to remove any unchanged ester. The acid solution was basified with potassium carbonate to pH $>$ 10 and extracted with chloroform (4 x 50 ml.). The chloroform was dried over sodium sulphate and evaporated to give hygroscopic colourless crystals (2.0 g.), m.p. 54-56°, b.p. 84°/2.5 mm; NMR τ 2.23, 2.42 (s,s, aromatic) τ 6.09 (s, NCH_3), τ 7.55 (s, $COCH_3$); UV λ max (95% ethanol) 255 mμ (ϵ, 14,950), λ max (95% ethanol/hydrogen chloride) 235 mμ (ϵ, 12,250); ν max 1670 (s, CO); mass spectrum m/e 124 (M^+), 109 (M-CH_3), 81 (M-$COCH_3$).

1-Methyl-5-acetylimidazole Hydrochloride.

Hydrogen chloride was bubbled through a solution of 1-methyl-5-acetylimidazole (200 mg.) in methanol (2 ml.) for 10 seconds. Ether (100 ml.) was added to the solution, the precipitate filtered off and crystallized from acetone-hexane to give colourless needles, m.p. 196-202°.

Anal. Calcd. for $C_6H_8N_2O$·HCl: C, 44.9; H, 5.7; N, 17.5. Found: C, 44.9; H, 5.6; N, 17.3.

1-Methyl-2-ethylthiol-5-acetylimidazole.

1-Methyl-2-ethylthiol-5-imidazole carboxylic acid chloride (ex 20 g. acid) was added to THF (300 ml.) containing the enolate prepared from sodium hydride (9.6 g.) and diethyl malonate (33.0 g.). The experimental procedure used for the preparation of 1-methyl-5-acetylimidazole was followed to give yellowish crystals of 1-methyl-2-ethylthiol-5-acetylimidazole (6.8 g.) m.p. 48-50°, b.p. 120°/2.5 mm; UV λ max (95% ethanol) 290 mμ (ϵ, 15,400), λ max (95% ethanol/hydrogen chloride) 286 mμ (ϵ, 11,550); ν max 1660 (s, CO); NMR τ 2.27 (s, aromatic), τ 6.18 (s, NCH_3), τ 7.58 (s, $COCH_3$), τ 6.75 and 8.60 (q and t respectively, J = 8 cps, SCH_2CH_3).

Anal. Calcd. for $C_8H_{12}N_2OS$: M. W. 184. Found: M^+ 184.

1-Methyl-2-ethylthiol-5-acetylimidazole Hydrochloride.

The hydrochloride, prepared in the same manner as that of 1-methyl-5-acetylimidazole hydrochloride, crystallized from acetone-hexane as colourless needles, m.p. 145° (dec.).

Anal. Calcd. for $C_8H_{12}N_2OS$·HCl: C, 43.5; H, 5.9; N, 12.7. Found: C, 43.6; H, 5.8; N, 12.8.

1-Methyl-5-acetylimidazole Phenylhydrazone.

A mixture of 1-methyl-5-acetylimidazole (1.5 g.), freshly distilled phenylhydrazine (2.5 ml.) and ethanol 25 ml.) was heated on a water-bath for 15 minutes. The ethanol was removed *in vacuo* and the residue heated in a metal bath at 100° for 1 hour and at 140° for 15 minutes. Ethyl acetate-hexane was added to the cooled residue. Colourless crystals (0.85 g.) which were difficult to purify, were deposited, m.p. 163-164°.

Anal. Calcd. for $C_{12}H_{14}N_4$: M. W. 214. Found: M^+ 214.

1-Methyl-2-ethylthiol-5-acetylimidazole Phenylhydrazone.

A mixture of 1-methyl-2-ethylthiol-5-acetylimidazole (1.057 g.), phenyl hydrazine (0.83 g., 1 mole eq.), sodium acetate (1.2 g.) and acetic acid (1 ml.) in water (10 ml.) in a stoppered flask was protected from light and mechanically shaken for 18 hours. A reddish brown oil separated from the mixture. Water (50 ml.) and sodium carbonate (2 g.) were added and the mixture extracted with methylene chloride (3 x 50 ml.). The combined extracts were dried over sodium sulphate, filtered and the methylene chloride removed *in vacuo* to give a brown oil (1.92 g.) which darkened on standing and which could not be purified.

Anal. Calcd. for $C_{14}H_{18}N_4S$: M. W. 274. Found: M^+ 274.

1-Methyl-5-(α-indolyl)imidazole.

To 1-methyl-5-acetylimidazole phenylhydrazone (760 mg.) in 2-methyl naphthalene (15 g.) freshly powdered fused zinc (3.1 g.) was added. The mixture was heated between 140° and 190° for 1.5 hours and then at 150° for another 1.5 hours. The mixture was cooled, hydrochloric acid (10% w/v, 25 ml.) was added and the mixture heated on a water-bath for 15 minutes. The acid solution was diluted with water (75 ml.) and extracted with ether (4 x 50 ml.). The aqueous solution was filtered and basified to pH $>$ 10 with concentrated aqueous potassium hydroxide. Extraction with methylene chloride (3 x 50 ml.), drying over sodium sulphate, filtration and removal of solvent *in vacuo* yielded an oil (260 mg.). Preparative thin layer chromatography on silica with 19:1 methylene chloride-ethanol as mobile phase led to the isolation of an oil (230 mg.) which gave a positive Ehrlich test for indoles and crystallized from acetone-hexane as amber needles m.p. 180°-181°; NMR (in acetone-d_6 with TMS τ 10.0), τ 2.3-3.1 (m, 6 aromatic protons), τ 3.35 (s, showing further splitting, β-indole proton), τ 6.12 (NCH_3), τ 6.8 (s, NH, disappears on equilibration with deuterium oxide); UV λ max (95% ethanol) 222 (ϵ, 16,600), 305 (ϵ, 20,500), 320 mμ (ϵ, 12,700), λ max (95% ethanol/hydrogen chloride), 221 (ϵ, 20,500), 294 mμ (ϵ, 17,550); ν max 3470 (m, NH); mass spectrum m/e 197 (M^+).

Anal. Calcd. for $C_{12}H_{11}N_3$: C, 73.1; H, 5.6; N, 21.3. Found: C, 72.8; H, 5.7; N, 20.9.

1-Methyl-2-ethylthiol-5-(α-indolyl)imidazole.

1-Methyl-2-ethylthiol-5-acetylimidazole (570 mg.) was mixed with freshly powdered zinc chloride (3 g.) and the mixture heated in a stoppered test tube between 140° and 180° for 30 minutes. The mixture was cooled and digested on a water-bath with concentrated hydrochloric acid (20 ml.). The solution was diluted with water (50 ml.) and basified with solid sodium carbonate to pH $>$ 10. Extraction with methylene chloride (3 x 50 ml.), drying over sodium sulphate, filtration and removal of solvent *in vacuo* yielded a brown semi-crystalline residue (500 mg.). Chromatography on silica (25 g.) and elution with 100:1 methylene chloride-methanol led to the separation of a brownish oil (460 mg.) which was crystallized from chloroform-hexane as light brown needles, m.p. 150-153°; NMR τ 2.3-3.1 (m, 5 aromatic protons), τ 3.45 (s, showing further splitting, β-indole proton), τ 6.30 (s, NCH_3), τ 6.89, 8.67 (q and t respectively, J = 7 c.p.s., SCH_2CH_3) τ 8.15 (s, NH, disappears on equilibration with deuterium oxide); UV λ max (95% ethanol) 314 (ϵ, 23,600), 328 mμ (ϵ, 12,800), λ max (95% ethanol/hydrogen chloride) 221 (ϵ, 21,600), 302 mμ (ϵ, 18,900); ν max 3470 (m, NH); mass spectrum m/e 257 (M^+).

Anal. Calcd. for $C_{14}H_{15}N_3S$: C, 65.3; H, 5.9; N, 16.3. Found: C, 65.2; H, 5.8; N, 16.3.

REFERENCES

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(6) Note added in proof: The evidence that the compound is *S*-ethyl and not *N*-ethyl is given by the fact that it fails to give the typical yellow colour with sulphur dioxide (4 p. 85) and by its basic character as could be shown by the isolation of a crystalline hydrochloride, m.p. 102-104°. (No hydrochloride could be obtained from ethyl 1-methyl-2-thio-5-imidazole carboxylate). While no odour is discernable when 1-methyl-2-thio-5-imidazole carboxylic acid is heated with solid sodium hydroxide, a mercaptan odour is noticed when the analogous 2-ethylthio-acid is treated in the same manner.

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