Synthesis of some 2,4-diamino-pyrrolo-pyrimidines

J R MERCHANT and SUNEEL Y DIKE
Department of Organic Chemistry, Institute of Science, Bombay 400 032

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Abstract. Some new 2, 4-diamino-pyrrolo-pyrimidines have been synthesized. Their structures are established on the basis of spectral-analytical data.

Keywords. N-B-cyanoethyl-phenyl glycine ethyl esters; 3-amino-4-cyano-3-pyrrolines; 2,4-diamino-6-phenyl-6,7-dihydro-pyrrolopyrimidines; 4-amino-6,7-dihydropyrrolopyrimidine-3, oxide.

1. Introduction

A number of substituted pyrrolo (3, 4-d) pyrimidines have been synthesised for biological evaluation (Southwick and Hofmann 1963, Sheradsky and Southwick 1965, Cavalla 1964, Cavalla and Willis 1967). In view of the interesting antimalarial activity of these types of compounds the synthesis of some new 2, 4-diamino-pyrrolopyrimidines was undertaken utilising cyanoethylation as an intermediate step.

2. Synthesis of pyrrolo (3, 4-d) pyrimidine derivatives

Condensation of p-toluidine with acrylonitrile in the presence of catalytic amounts of acetic acid afforded the corresponding propionitrile 2b. The latter on reaction with ethyl bromoacetate in alcohol furnished N-β-cyanoethyl (4-methylphenyl)-glycine ethyl ester 3b which on a Dieckmann cyclization with sodium ethoxide and subsequent treatment with excess of ammonium formate yielded a pasty material which on trituration with a little alcohol gave 3-amino-(4-methyl)-4-cyano-3-pyrrolone 4b in 50% yield. Its structure and analytical data were fully consistent with the assigned structure.

The above pyrroline derivative was then converted to 2, 4-diamino-6-(3-methylphenyl)-6, 7-dihydro-5H-pyrrolo-(3, 4-d) pyrimidine 5b by refluxing it with guanidine carbonate in 2-ethoxyethanol in 37% yield.

The syntheses of other pyrrolo-pyrimidines were effected on similar lines as described, starting from m-toluidine, 3,4-dimethylaniline and p-phenetidine. (Scheme I) In general, 3-amino-4-cyano-3-pyrrolines showed a characteristic spectral pattern: given in the experimental section.

The spectral characteristics of 2, 4-diaminopyrrolo-(3, 4-d) pyrimidines were similar to those of pyrrolines except that the signal for two amino groups (4 protons) was observed at δ 8.3.
In a different synthesis of pyrimidines 3-amino-(3, 4-dimethylphenyl)-4-cyano-3-pyrroline 4d obtained from 3, 4-dimethylaniline following the series of reactions described above was reacted with triethyl orthoformate and acetic anhydride to afford the corresponding 3-ethoxymethyleneimino pyrroline 6d as a yellow crystalline solid whose structure was in full agreement with its spectral analytical data.

The pyrroline was converted to the corresponding 4-amino-6,7-dihydro-5H-pyrrolo (3, 4-d) pyrimidine-3-oxide (7d) by reaction with hydroxylamine hydrochloride and pyridine in moderate yield.

The structure of the latter was assigned on the basis of analytical and spectroscopic evidence, which is as follows:

3. Experimental

All melting points reported herein are uncorrected. IR spectra were run on a Perkin-Elmer spectrophotometer. The NMR spectra were recorded on a Varian A-60 spectrometer. Chemical shifts are quoted in δ values relative to tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on a Varian Mat CH-7 mass spectrometer.

3.1.1. Starting materials

3.1.1a. β-(3-methylanilino) propionitrile
3.1.1b. β-(4-methylanilino) propionitrile
3.1.1c. β-(4-ethoxyanilino) propionitrile
3.1.1d. β-(3, 4-dimethylanilino) propionitrile
A solution of alkyl or alkoxyaniline (0·1 mole) acrylonitrile (0·1 mole) in glacial acetic acid (2·5 ml) was heated on a water bath for 20-24 hr. The mixture was taken in chloroform and the solvent layer was washed thoroughly with water, then with saturated sodium bicarbonate solution and water. It was then dried over anhydrous sodium sulphate. Evaporation of the solvent afforded the required propionitrile derivative.

3.2. Condensation of propionitriles with ethyl bromoacetate

The propionitriles (0·1 mole) were refluxed with ethyl bromoacetate (22·5 ml, 0·2 mole) dissolved in ethyl alcohol (10 ml, 95%) for 48 hr. The reaction mixture was then cooled and poured over crushed ice and basified with aqueous sodium hydroxide (40%) below 0°, with constant stirring until the odour of ethyl bromoacetate disappeared. The whole was extracted twice with chloroform. The combined chloroform extracts were washed with water, saturated sodium chloride solution and again with water. The extract was then dried over anhydrous sodium sulphate and evaporated to give an oil in all cases which were used as such for further reactions.

3.3. Dieckmann cyclization of glycine ethyl esters with sodium ethoxide and subsequent reaction with ammonium formate

Sodium ethoxide (prepared from 2·5 g of sodium in 125 ml of absolute ethanol) was added to the glycine ethyl esters in absolute ethyl alcohol (25-30 ml). The resulting mixture was refluxed for 3 hr. Excess of ammonium formate (20 g) was then added in two portions over a 48 hr period of refluxing on a steam bath. The solvent was removed by distillation under reduced pressure when a thick paste was obtained. Water was added to it. The water soluble product was decanted and a small quantity of ethyl alcohol was added to the residue when a crystalline solid separated. It was filtered and crystallized from appropriate solvent.

3.3.1. 3-Amino-1-(3-methylphenyl)-4-cyano-3-pyrroline (4·5 g) m.p. 223-226°. IR (KBr): v_max 3350 (—NH), 2200 (—CN—), 1650 (> C = C <), 1600, 1500 (Ar.) cm⁻¹. (Found C, 72·8; H, 6·9; N, 21·5. C₁₂H₁₃N₃ requires C, 72·4; H, 6·5; N, 21·1%).

3.3.2. 3-Amino-1-(4-methylphenyl)-4-cyano-3-pyrroline (4·6 g), m.p. 243-45°. IR (Nujol) v_max: 3350 (—NH—), 2200 (—CN), 1650 (> C = C <), 1600, 1550, 1500 (Ar.) cm⁻¹. NMR (CF₃CO₂H) 2·2 (3H, s, —CH₃), 4·6 (4H, s, N(CH₃)₂), 7·3 (4H, s, ar.). (Found C, 72·4; H, 6·8; N, 21·1. C₁₃H₁₄N₃ requires C, 72·4; H, 6·5; N, 21·1%).

3.3.3. 3-Amino-1-(4-ethoxyphenyl)-4-cyano-3-pyrroline (3·7 g) m.p. 254-56° (dimethylformamide-ethanol). IR (Nujol) v_max: 3400 (—NH), 2200 (—CN), 1660 (> C = C <), 1600, 1545, 1500 (Ar.) cm⁻¹. NMR (CF₃CO₂H) 1·5 (3H, t, —O—CH₂—CH₃), 4·2 (2H, m, —O—CH₂—CH₃), 4·85 (4H, s, —N(CH₃)) 7·0—7·6 (4H, m, ar.). (Found C, 67·7; H, 6·8; N, 18·7. C₁₃H₁₅ON₃ requires C, 68·1; H, 6·6; N, 18·4%).
3.3.4. 3-Amino-1-(3, 4-dimethylphenyl)-4-cyano-3-pyrroline (3·4 g), m.p. 246-48° (dimethylformamide-alcohol) (Found C, 73·4; H, 6·8; N, 19·4. C_{19}H_{18}N_{3} requires C, 73·2; H, 7·0; N, 19·7%).

3.4. Reaction of guanidine carbonate with 3-amino-4-cyano-3-pyrroline

The foregoing pyrrolines (0·01 mole) were heated with guanidine carbonate (0·01 mole) in 2-ethoxyethanol (10 ml) at the reflux temperature for 6-7 hr. The mixture was poured in cold water, when a crystalline 2, 4-diamino-6, 7-dihydro-5H-pyrrolo (3, 4-d)pyrimidines were separated.

3.4.1. 2, 4-Diamino-6-(3-methylphenyl)-6, 7-dihydro-5H-pyrrolo -(3, 4-d)-pyrimidine (900 mg) m.p. 269-72° (dimethylformamide-water). IR (Nujol) v_{max} : 3460 (-NH), 1600, 1500 (ar.) cm^{-1}. NMR (CF_{3}CO_{2}H) 2·5 (3H, s, CH_{3}), 5·33 (4H, s, N<CH_{3}>, 7·5 (4H, broad s, ar.), 8·3 (4H, s, 2 (NH_{2})). m/e 241 (M^{+}). (Found C, 65·1; H, 6·2; N, 29·4. C_{18}H_{15}N_{3} requires C, 64·7; H, 6·2; N, 29·1%).

3.4.2. 2, 4-Diamino-6-(4-methylphenyl)-6, 7-dihydro-5H-pyrrolo-(3, 4-d)pyrimidine (1·3 g) m.p. 274-75° (dimethylformamide-ethanol). IR (Nujol) v_{max} : 3350 (-NH), 1650 (>C=C<), 1600, 1550, 1500 (ar.) cm^{-1}. NMR (CF_{3}CO_{2}H), 2·2 (3H, s, -CH_{3}), 5·0 (4H, s, N<CH_{3}>, 7·2 (4H, s, ar.). (Found C, 65·0; H, 6·2; N, 29·4. C_{18}H_{15}N_{3} requires C, 64·7; H, 6·2; N, 29·1%).

3.4.3. 2, 4-Diamino-6-(4-ethoxyphenyl)-6, 7-dihydro-5H-pyrrolo (3, 4-d)-pyrimidine (1·8 g), m.p. 263-64° (dimethylformamide-water). IR (Nujol) v_{max} : 3400 (-NH), 1650 (>C=O), 1600, 1550, 1500 (ar.) cm^{-1}. NMR (CF_{3}CO_{2}H) 1·5 (3H, t, -CH_{2}--CH_{2}), 4·2 (2H, m, O--CH_{2}--CH_{2}, 5·3 (4H, s, N<CH_{3}>, 7·0-7·6 (4H, m, ar.). (Found C, 61·7; H, 6·5; N, 25·8. C_{18}H_{17}ON_{3} requires C, 62·0; N, 6·3; N, 25·8%).

3.4.4. 2, 4-Diamino-6 (3, 4-dimethylphenyl)-6, 7-dihydro-5H-pyrrolo (3, 4-d)pyrimidine (850 mg), m.p. 267-68° (dimethylformamide-water). IR (Nujol) v_{max} : 3350 (-NH-), 1660 (>C=C<), 1600, 1550, 1500 (ar.) cm^{-1}. NMR (CF_{3}CO_{2}H), 2·4 (6H, s, 2-CH_{3}), 5·6 (4H, broad s, N<CH_{3}>, 7·5 (4H, m, ar.). (Found C, 65·5; H, 6·8; N, 27·5. C_{14}H_{17}N_{3} requires C, 65·9; H, 6·5; N, 27·5%).

3.5. Reaction of 3-amino-1-(3,4-dimethylphenyl)-4-cyano-3-pyrroline with triethyl orthoformate

A solution containing acetic anhydride (10 ml), triethyl orthoformate (10 ml) and the above pyrroline (2·2 g) was heated at reflux for 2 hr and evaporated under reduced pressure. The yellow crystalline solid which separated was crystallised from ethyl acetate-petrol ether (40-60°).
3.5.1. 3-Ethoxymethyleneimino-(3, 4-dimethylphenyl)-4-cyano-3-pyrroline (1.8 g), m.p. 160-62°, IR (Nujol) ν max: -2210 (-CN), 1610, 1500 (ar.). cm⁻¹. NMR (CDCl₃) 1.4 (3H, t, -CH₂-CH₃), 2.25 (6H, s, 2-CH₃), 4.25-4.7 (4H, m, N<CH), 6.45 (2H, d, ar.). 7.2 (1H, d, J=8Hz, ar.). 8.0 (1H, s, N=CH-O), m/e 269 (M⁺).
(Found C, 71.1; H, 7.1; N, 15.3). C₁₆H₁₆N₄O requires C, 71.4; H, 7.1; N, 15.6%)

3.6. Reaction of 3-ethoxymethyleneimino-1-(3,4-dimethylphenyl)-4-cyano-3-pyrroline with hydroxylamine hydrochloride

To a solution of anhydrous pyridine and absolute ethanol (10 ml, 1:1) were added (1.4 g, 0.5 mole) of the above ethoxymethyleneimino-pyrroline and hydroxylamine hydrochloride (0.25 g). The mixture was heated at reflux temperature for 4 hr and then cooled in an ice-bath when a fine solid separated. It was filtered and crystallised from dilute acetic acid in pale yellow prisms.

3.6.1. 4-Amino-6-(3, 4-dimethylphenyl)-6, 7-dihydro-5H-pyrrolo-(3, 4-d)-pyrimidine-3-oxide (890 mg), m.p. 263-64°. IR (Nujol) ν max: 3350 (-NH), 1660 (>C=C<), 1600, 1550, 1500 (ar.) cm⁻¹. NMR (CF₃CO₂H) 2.41 (6H, s, 2-CH₃), 5.6 (4H, broad d, N<CH), 7.5 (3H, s, ar.), 8.33 (2H, broad s, -NH₂), 9.13 (1H, s, N=CH=N), m/e 256 (M⁺).
(Found C, 63.4; H, 6.1; N, 21.2. C₁₄H₁₃N₄O requires C, 63.2; H, 6.0; N, 21.1%).

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