The Synthetic Study of 2,3-Dihydro-1H-pyrrolo [1,2-a] indole Ring System

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The 2,3-Dihydro-1H-pyrrolo[1,2-a]indole ring system was synthesised by the condensation reaction of toluquinone and 2-cyanomethylenepyrrolidine.

The mitomycin antibiotics have a novel ring system (I, mitomycin B), which was converted to aziridinopyrrolo [1,2-a] indoloquinone (II) by J. S. Webb *et al.*¹⁾ In the synthetic studies of mitomycin analogues, substituted 2,3-dihydro-1H-pyrrolo[1,2-a]indoles (III) are useful intermediates for the preparation of the 2,3-dihydro-1H-pyrrolo[1,2-a]indoloquinone ring system.²⁾ Substituted 2,3-dihydro-1H-pyrrolo [1,2-a]indoles have already been synthesised from substituted 2-carbethoxyindoles by the Lederle group³⁾ and by us.⁴⁾

In the present communication we wish to describe the condensation products of toluqui-

none (IX) and 2-cyanomethylenepyrrolidine (VIII) which was prepared from the iminoether of 2-pyrrolidone (IV) and benzyl cyanoacetate (V) by the condensation reaction, hydrogenolysis of the condensed benzyl ester (VI) and decarboxylation.⁵⁾

At first we expected that the condensation reaction would proceed, like the Nenitzescu indole synthesis (Fig. 2),⁶⁾ to produce 6-methyl-7-hydroxy-9-cyano-2,3-dihydro-1H-pyrrolo[1,2-a]indole (XIa) by one step. However reactions of quinone (IX) and nitrile (VIII) in methanol or acetone are not promising and when nitrile (VIII) reacts with two equivalent

(I)

(II)

(III)

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3) a) G. R. Allen, Jr. and M. J. Weiss, *ibid.*, **30**, 2904 (1965), b) W. A. Remers, R. H. Roth and M. J. Weiss, *ibid.*, **30**, 2910 (1965).

4) T. Hirata, Y. Yamada and M. Matsui, *Tetrahedron Letters*, 1969, 19; Y. Yamada, T. Hirata and M. Matsui, *ibid.*, 1969, 101.

of quinone (IX) in the presence of acetic acid, two quinone isomers (Xa and Xb) are produced in fairly good yield. The two isomeric quinones are separated by column chromatography on silica gel. The structure of quinones Xa and Xb were determined from NMR

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6) C. D. Nenitzescu, *C. A.*, **24**, 110 (1930).

FIG. 1.

FIG. 2.

at C 6' in Xb shows the coupling constant (3 cps) of meta coupling,⁷⁾ whereas that in Xa is almost singlet. The signal of C 3'-H in Xa is quartet (J 1.5 cps) coupling with methyl protons and that of C 4'-H in Xb splits into

FIG. 3.

data. The signals of N-H at lower field (Xa δ 8.75, Xb δ 8.55 in DMSO) show that the proton associates with the carbonyl group of the quinone system. The signal of the proton

7) G. R. Allen Jr., C. Pidacks and M. J. Weiss, *J. Am. Chem. Soc.*, **88**, 2536 (1966).

a apparent quartet coupling with C 6'-H (J 3 cps) and methyl protons (J 1.5 cps).⁷⁾

The mechanism of this reaction is supposed as Fig. 3. The disproportionation reaction of toluquinone and condensed hydroquinone (XII) is proved by the fact that much amount of toluhydroquinone was isolated from the reaction mixture and the increase of the yield of quinone adducts (Xa, b) by adding two equivalents of toluquinone.

The instability of hydroquinones (XII) in the neutral or alkaline state gives a reason for the low yield of quinone adducts when the reaction was carried out in the absence of acetic acid.

Condensed quinones, Xa and Xb, are converted to 6-methyl-7-hydroxy-9-cyano-2,3-dihydro-1H-pyrrolo[1,2-a]indole (XIa) and 5-methyl-7-hydroxy-9-cyano-2,3-dihydro-1H-pyrrolo[1,2-a]indole (XIb) respectively by treating with aluminium amalgam in the presence of water in tetrahydrofuran in very poor yield. Treating quinones Xa, b or hydroquinone (XII) with sodium borohydride in absolute alcohol or with metal lithium in liquid ammonia also afforded substituted 7-hydroxy-2,3-dihydro-1H-pyrrolo[1,2-a]indoles XI in low yield (ca. 10%).

The NMR spectrum of XIa shows that the signals of C 8-H and C 5-H of XIa are singlet (para coupling) and those of C 8-H and C 6-H of XIb are doublet (2 cps meta coupling).

The mechanism of this cyclization is ambiguous except that the intermediates are hydroquinones (XII) because by treating XII with aluminium amalgam, sodium borohydride and metal lithium cyclized XI are also obtained. Thus the Bucherer type reaction perhaps occurred through the path in Fig. 4. The attempts to convert the quinone adducts

FIG. 4.

FIG. 5.

(Xa, b) to XI by the path in Fig. 5 by the treatment with acid followed by reduction⁷⁾ were unsuccessful. In this case the expected cyclization of quinone adducts to form quinoniminonium derivative (XIII) did not occur.

EXPERIMENTAL

1) *2-Cyanocarbobenzylloxymethylenepyrrolidine* (VI). Ethyl iminoether of 2-pyrrolidone (IV 24 g) and benzyl cyanoacetate (V, 44 g) were mixed in a round-bottomed flask and triethylamine (1 ml) was added. The reaction mixture was kept at room temperature for 3 hr. Ether was added to the solidified reaction mixture and the crystalline mass was filtered and washed with ether.

Yield 29 g. Mp 147~8°C. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 2240 (CN), 3320 (N-H), 1655 (C=O). Found: C, 69.28; H, 5.81; N, 11.70. Calcd. for C₁₄H₁₄O₂N₂: C, 69.40; H, 5.81; N, 11.56%.

2) *2-Cyanomethylenepyrrolidone* (VIII). 2-Cyanocarbobenzylloxymethylenepyrrolidine (VI 22 g) was dissolved in 200 ml of hot ethyl acetate and hydrogenated under atmospheric pressure over 5 g of palladium charcoal (10%). After absorption of 2.2 liters of hydrogen, ethyl acetate was evaporated and the residue was extracted with hot sodium carbonate solution. The extract was filtered to remove catalyst and acidified with dilute hydrochloric acid. The separated crystals of acid (VII) was soon decarboxylated to give 2-cyanomethylenepyrrolidine hydrochloride. The reaction mixture was made alkaline with sodium carbonate and extracted with methylene dichloride. The extract was dried over anhydrous sodium sulfate and the solvent was evaporated. The residue was crystallized by cooling. Yield 8.5 g (87%). Mp 68~71°C. (Recrystallized from *n*-hexane). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3260 (N-H), 2220 (CN), 1615 (C=C). NMR (in DCl₃) δ :

3.66 (singlet, $\text{N}-\text{C}=\text{C} \begin{smallmatrix} \text{H} \\ \text{CN} \end{smallmatrix}$), 3.95 (singlet, $\text{N}-\text{C}=\text{C} \begin{smallmatrix} \text{CN} \\ \text{H} \end{smallmatrix}$)⁸, 5.42 (1H, broad, N-H). Found: C, 66.29; H, 7.39; N, 25.10. Calcd. for $\text{C}_6\text{H}_8\text{N}_2$: C, 66.64; H, 7.46; N, 25.91%.

3) 2-Cyano(4'-methylbenzoquinonyl)methylenepyrrolidine (Xa) and 2-cyano(3'-methylbenzoquinonyl)methylenepyrrolidine

a) Reaction of toluquinone (IX) with 2-cyanomethylenepyrrolidine (VI). 2-Cyanomethylenepyrrolidine (13 g) was dissolved in methanol (150 ml) and acetic acid (8.6 ml) and toluquinone (29.5 g, 2 equiv. of nitrile) in 150 ml of methanol was added dropwise with stirring at room temperature. The color of the reaction mixture became purple and the crystals of Xa and Xb precipitated. Three hours later the purple crystals were filtered. Yield 19 g (70%). The crystals show two spots in thin-layer chromatography of silica gel by using methylene chloride.

b) Separation of two isomers Xa and Xb. Quinones (X, 3.3 g) absorbed on silica gel (10 g) was placed on a column of silica gel (260 g) and eluted with methylene dichloride. The purple colored fractions were divided into two parts by checking on TLC. The first fractions were concentrated to give 1.35 g of quinone (Xa) and the second fractions gave 0.85 g of quinone (Xb). Xa: Mp 160~165°C (Decomposed). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3660, 3280 (N-H), 2220 (CN), 1660, 1640 (C=O), 1590. 1560 UV $\lambda_{\text{max}}^{\text{EtOH}}$ $\text{m}\mu$ (ϵ) 232 (14,900), 278 (14,400). NMR (in DMSO- d_6) δ : 8.75 (N-H), 6.52 (singlet, C 6'-H), 6.74 (quartet, C 3'-H), 3.57 (triplet, C 5-H₂), 2.91 (triplet, C 3-H₂), 2.04 (multiplet, C 4-H₂), 1.99 (singlet, CH₃). Found: C, 68.11; H, 5.31; N, 12.33. Calcd. for $\text{C}_{13}\text{H}_{12}\text{O}_2\text{N}_2$: C, 68.41; H, 5.30; N, 12.27. Xb: Mp 145~150°C (Decomposed). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3260 (N-H), 2220 (CN), 1640, 1590 (C=O). UV $\lambda_{\text{max}}^{\text{EtOH}}$ $\text{m}\mu$ (ϵ), 232 (15,500), 278 (13,700). NMR (in DMSO- d_6) δ : 8.56 (N-H), 6.45 (doublet, C 6'-H), 6.64 (quartet, C 4'-H), 3.52 (triplet, C 5-H₂), 2.89 (triplet, C 3-H₂), 1.92-2.03 (multiplet, C 4-H₂), 2.01 (singlet, CH₃). Found: C, 68.33; H, 5.36; N, 12.42. Calcd. for $\text{C}_{13}\text{H}_{12}\text{O}_2\text{N}_2$: C, 68.41; H, 5.30; N, 12.27%.

4) Cyclization of quinone adducts

a) 6-Methyl-7-hydroxy-9-cyano-2,3-dihydro-1H-pyrrolo-[1,2-a]indole (XIa). Quinone (Xa 1.1 g) was dissolved

in 50 ml of tetrahydrofuran (freshly distilled with lithium aluminium hydride) and 2 ml of water and stirred at room temperature with aluminium amalgam which was prepared from 2 g of aluminium turning. Stirring was continued at room temperature until the purple color of the reaction mixture disappeared. Then the reaction mixture was heated at 50~60°C for 30 hr and poured on diluted hydrochloric acid. The solution was extracted with ethyl acetate and the extract was washed with water and dried over anhydrous sodium sulfate. After evaporation of the solvent, methanol was added to the residue and separated crystals were filtered. Yield 0.1 g. Mp 263~264°C (Decomposed). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3320 (OH), 2250 (CN), 1630, 1570, 1540 (C=C). NMR (in DMSO- d_6) δ : 9.22 (O-H), 7.16, 6.91 (singlet, C 8-H, C 5-H), 4.03 (triplet, C 3-H₂), 3.06 (triplet, C 1-H₂), 2.44~2.70 (multiplet, C 2-H₂), 2.24 (singlet, CH₃). Found: C, 73.47; H, 5.69; N, 13.31. Calcd. for $\text{C}_{13}\text{H}_{12}\text{ON}_2$: C, 73.56; H, 5.70; N, 13.20%.

b) 5-Methyl-7-hydroxy-9-cyano-2,3-dihydro-1H-pyrrolo-[1,2-a]indole (XIb). Quinone (Xb, 0.8 g) in tetrahydrofuran (50 ml) was treated with aluminium amalgam (2 g) and water 2 ml following the method of 4) a). The reaction mixture was treated by the same procedure as in the case of XIa and 0.05 g of XIb was obtained. Mp 285~290°C. (Decomposed). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3320 (O-H), 2240 (CN), 1620, 1550 (C=C). NMR (in DMSO- d_6) δ : 6.64, 6.47 (doublets, $J=2$ cps, C 8-H, C 6-H), 4.29 (triplet, C 3-H₂), 2.05 (singlet, CH₃). Found: C, 72.99; H, 5.72; N, 13.03. Calcd. for $\text{C}_{13}\text{H}_{12}\text{ON}_2$: C, 73.56; H, 5.70; N, 13.20%.

5) Cyclization of the mixture of two quinones (Xa and Xb) to 2,3-dihydro-1H-pyrrolo[1,2-a]indole system

a) Cyclization with sodium borohydride. Quinone (0.2 g) was suspended in 30 ml of absolute ethanol and hydrogenated over platinum dioxide under atmospheric pressure until the color of quinone disappeared. Then 0.2 g of sodium borohydride was added to the reduced solution and the mixture was stirred at room temperature (15~20°C) for 48 hr. The reaction mixture was poured into cooled 10% sulfuric acid solution and extracted with ethyl acetate. The extract was washed with water and after drying over sodium sulfate ethyl acetate was evaporated. Methanol was added to the residue and the precipitated crystals were filtered. Yield 0.02 g.

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b) Cyclization with metal lithium in liquid ammonia. Metal lithium (0.2 g) was dissolved in 50 ml of liquid ammonia and 0.3 g of quinone in 50 ml of dry tetrahydrofuran was added dropwise with vigorous stirring and stirring was continued for 1 hr after the addition of quinone. Excess lithium was decomposed with

ammonium chloride and after evaporation of liquid ammonia the reaction mixture was poured into cooled 10% sulfuric acid solution. By treating the solution with ethyl acetate as in procedure a) 0.05 g of a mixture of XIa and XIb was obtained.