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REARRANGEMENT UNDER ALKALINE CONDITIONS OF COMPOUNDS RELATED TO TETRACYCLIC *STRYCHNOS* INDOLE ALKALOIDS

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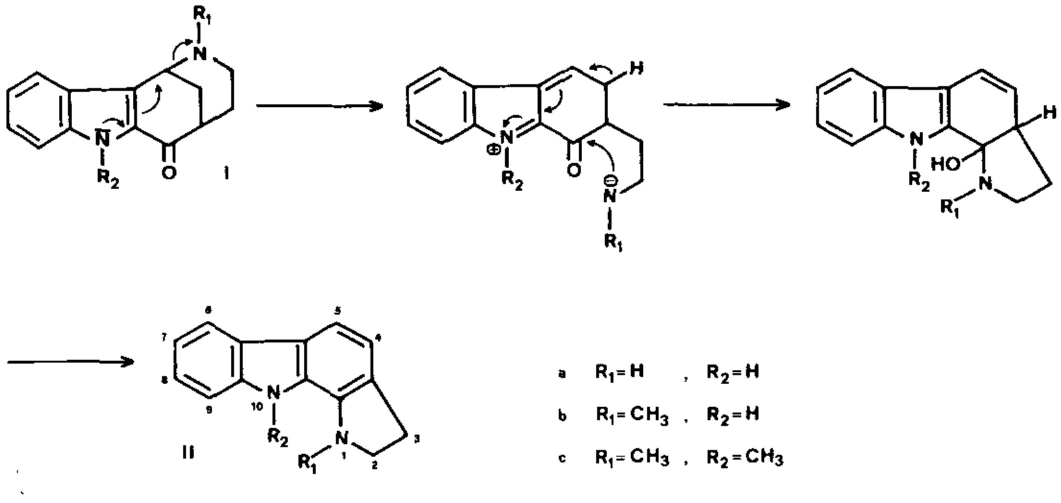
Abstract - Treatment of 6-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indoles under Wolff-Kishner conditions gave 2,3-dihydro-1*H*-pyrrolo[2,3-*a*]carbazoles.

Cleavage of the C-N_b bond in 3-aminomethylindoles is a well known reaction which was initially studied in gramine and related compounds.[1] Afterwards, this property has been applied to the structural elucidation of the indole alkaloids uleine[2] and vallesamine,[3] to establish a correlation between ervitsine and methuenine,[4] as well as to the synthesis of alkaloids bearing a pyrido[4,3-*b*]carbazole system such as olivacine, ellipticine and guatambuine.[5-7] In this context, a gramine type fragmentation from tetracyclic systems related to *Strychnos* or *Aspidosperma* indole alkaloids generally occurs when the piperidine nitrogen atom bears a positive charge. This can be achieved by treating the tetracyclic tertiary amine with acid[4-6] or in the presence of an acylating agent.[2,6,8] Fragmentation also occurs from the corresponding quaternary salts[2,3] and by acid treatment of appropriate N-acylpiperidine derivatives.[7,9]

We have observed a fragmentation of this type in alkaline medium in the attempts to reduce under Wolff-Kishner conditions the ketone Ia, a potential intermediate for the synthesis of the pentacyclic ring skeleton of some *Strychnos* indole alkaloids.[10] Thus, when compound Ia was heated with hydrazine hydrate and potassium hydroxide in refluxing ethylene glycol the carbazole IIa was obtained. A similar treatment from deethyldasycarpidone (Ib)[10] afforded the carbazole IIb. Carbazole IIa was also formed in the attempts to prepare the hydrazone of Ia with hydrazine hydrate and ethylene glycol.

In a previous work[11] we succeeded in effecting the Wolff-Kishner reduction of the ketone group present in the pyrrole analogous to Ic, in which the pyrrole nitrogen is methylated. In order to verify if the acidity of the indole N_a-H favoured the observed cleavage of the C-N_b bond under alkaline conditions we tried the reaction with



a R_1=H , R_2=H
b R_1=CH_3 , R_2=H
c R_1=CH_3 , R_2=CH_3

the N_α-methyl derivative Ic. This compound was prepared from Ib by treatment with dimethyl carbonate and sodium hydride in refluxing tetrahydrofuran. When compound Ic was treated under Wolff-Kishner conditions carbazole IIc was isolated in 70% yield as the only product.

The formation of carbazoles II can be accounted for by considering that after the initial cleavage of the C-N_b bond an intramolecular attack of the resulting amide anion upon the carbonyl group occurs. Further irreversible dehydration leads to the dihydropyrrolocarbazoles II.

Since the described reactions proceeded in good yields they establish an alternative synthetic method for the preparation of the pyrrolo[2,3-*a*]carbazole system.[12]

EXPERIMENTAL

Nmr spectra were determined with a Perkin-Elmer R-24B (60 MHz) instrument using internal TMS (δ0) as a reference. Ir spectra were taken with a Perkin-Elmer 577 spectrophotometer, and only noteworthy absorptions (reciprocal centimeters) are listed. Mass spectra were obtained with a Hewlett-Packard 5930A spectrometer. Melting points were determined with a Büchi capillary melting point apparatus and are uncorrected. Microanalyses were performed by the Instituto de Química Bio-Orgánica, Barcelona.

2,7-Dimethyl-6-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (Ic). To a suspension of 1 g (4.16 mmol) of Ib[10] and 1.25 g (29.2 mmol) of 56-60% sodium hydride dispersion in mineral oil in 50 ml of tetrahydrofuran, a solution of 17.5 ml (208 mmol) of dimethyl carbonate in 30 ml of tetrahydrofuran was added under nitrogen atmosphere. The mixture was refluxed with stirring for 72 h. The reaction mixture was poured into 300 ml of cold water, acidified with 10% hydrochloric acid solution, and washed with methylene chloride. The aqueous layer was basified with 2N sodium hydroxide and extracted several times with methylene chloride. The extracts were washed with water, dried over sodium sulfate and the solvent removed to give an oil. Chromatographic purification (silica gel, 99/1 chloroform/methanol) afforded 591 mg (56% yield) of pure Ic; ^{1}H nmr ($CDCl_3$): δ1.7-2.8 (complex signal, 7H, alicyclic), 2.2 (s, 3H, N_b-CH_3), 4.05 (s, 3H, N_a-CH_3), 4.25 (t, 1H, NCH), 6.8-7.7 (m, 4H, Ar-H); ir ($CHCl_3$): 1650 cm^{-1} (ketone). The picrate recrystallized from ethanol melted at 216-218°C. Anal. Calcd for $C_{22}H_{21}N_5O_8$: C, 54.66; H, 4.38; N, 14.48. Found: C, 54.56; H, 4.40; N, 14.37.

2,3-Dihydro-1*H*-pyrrolo[2,3-*a*]carbazole (IIa). To a solution of 200 mg (0.88 mmol) of Ia[10] in 5 ml of ethylene glycol, 0.3 ml (6.2 mmol) of 80% hydrazine hydrate were added. The resulting mixture was refluxed for 2 h, and then enough water and excess of hydrazine hydrate was distilled to raise the temperature of 185°C. After cooling, 0.3 g (5.4 mmol) of potassium hydroxide in 3 ml of ethylene glycol were added and the resulting solution was refluxed for 6 h. The reaction mixture was poured into ice-water and extracted several times with ethyl acetate (halogenated solvents cause darkening of the product). The organic extracts were washed with water, dried, and the solvent removed under reduced pressure to give a solid which was chromatographed on silica gel. On elution with chloroform, 145 mg (79% yield) of IIa were obtained (mp 173-174°C); ^{1}H nmr (DMSO-d_6): δ2.7-3.5 (m, 2H, Ar-CH_2), 3.35-3.9 (m, 2H, N-CH_2), 5.0 (s, 1H, N_b-H), 6.8-7.6 (m, 5H, Ar-H), 7.9 (d, J=7 Hz, 1H, C_6-H), 11.0 (s, 1H, N_a-H) ; ir (KBr): 3290 (N_a-H) and 3300-2500 cm^{-1} (N_b-H); mass spectrum, m/e (relative intensity): 208(M^+, 100), 207(91), 206(37), 180(32), 152(30), 104(30), 103(41), 90(36), 77(31), 76(32). The picrate recrystallized from ethanol melted at 183-186°C. Anal Calcd for $C_{20}H_{15}N_5O_7.C_2H_5OH$: C, 54.65; H, 4.37; N, 14.48. Found: C, 54.74, H, 4.18; N, 14.36.

1-Methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*a*]carbazole (IIb). Operating from Ib as above, crude IIb was obtained in 74% yield (mp 130-132°C); ^{1}H nmr (DMSO-d_6): δ2.9 (s, 3H, N-CH_3), 2.8-3.5 (m, 4H, $(CH_2)_2$), 6.9 (d, J=7 Hz, 1H, C_4-H), 7.0-7.3 (m, 3H, Ar-H), 7.4 (d, J=7 Hz, 1H, C_5-H), 7.7-8.1 (m, 2H, C_6-H and N_a-H); ir (KBr): 3320 cm^{-1} (N_a-H); mass spectrum, m/e (relative intensity): 222(M^+, 98), 221(57), 207(29), 206(39), 180 (23), 111(21), 103(24), 78(100), 77(37). The picrate recrystallized from acetone melted at 190-192°C. Anal. Calcd for $C_{21}H_{17}N_5O_7$: C, 55.88; H, 3.80; N, 15.51. Found:

C, 55.81; H, 3.86; N, 15.06.

1,10-Dimethyl-2,3-dihydro-1*H*-pyrrolo[2,3-*a*]carbazole (IIc). Operating from Ic as above, compound IIc was obtained in 70% yield after purification on a silica gel column (ethyl acetate); ^{1}H nmr ($CDCl_3$): δ2.7 (s; 3H, N_b-CH_3), 2.85-3.2 (m, 2H, Ar-CH_2), 3.25-3.6 (m, 2H, N-CH_2), 3.9 (s, 3H, N_a-CH_3), 6.85 (d, J=7 Hz, 1H, C_4-H), 6.95-7.4 (m, 3H, Ar-H), 7.45 (d, J=7 Hz, 1H, C_5-H), 7.8 (d, J=7 Hz, 1H, C_6-H). The picrate recrystallized from ethanol melted at 194-196°C. Anal. Calcd for $C_{22}H_{19}N_5O_7$: C, 56.77; H, 4.11; N, 15.05. Found: C, 56.66; H, 3.99; N, 15.37.

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