Tetrahedron Vol 47, No 9, pp 1737-1744, 1991
Printed in Great Britain

0040-4020/91 $3 00+ 00

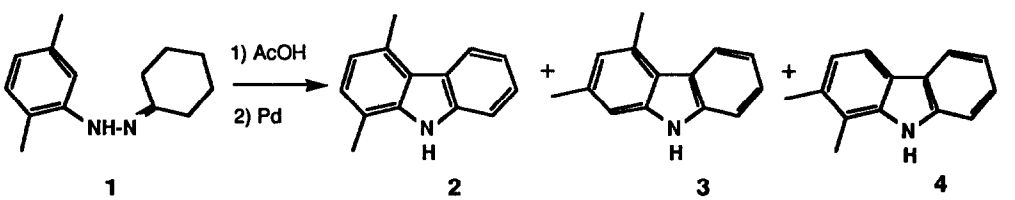
THE FISCHER INDOLE SYNTHESIS OF 8-METHYL-5-SUBSTITUTED-1-OXO-ß-CARBOLINES: A REMARKABLE HIGH YIELD OF A [1,2]-METHYL MIGRATION.

SANTIAGO V. LUIS*, M ISABEL BURGUETE
Departamento de Química Orgánica, Colegio Universitario de Castellón,
Universitat de València, Apdo 224, E-12080 Castellón, SPAIN

(*Received in UK* 12 *November* 1990)

Abstract - A very unusual high yield of rearranged products (*via* methyl migration) has been obtained in the Fischer indole cyclization of the 3-(2,5-dimethyl phenylhydrazone) of 2,3-piperidine dione (**6b**) When a less activated aromatic ring is present in the phenylhydrazone **6**, such a behaviour is not observed and cyclization occurs essentially without rearrangement.

The formation of indole derivatives from 2,6-dialkylsubstituted phenylhydrazones is known to occur by migration, elimination or substitution of an alkyl group [1,2], [1,3], [1,4] and [1,5] alkyl group shifts have been observed during indolization of these compounds[1-4] A few examples of alkyl group migration in the Fischer indole cyclization of 2-alkyl-6-unsubstituted phenylhydrazones have been reported Thus, for instance, cyclization of the 2,5-dimethyl phenylhydrazone of cyclohexanone (**1**) yielded, besides the expected 1,4-dimethyl tetrahydrocarbazole (**2**), 2,4- and 1,2-dimethyl tetrahydrocarbazole (**3** and **4**) as the result of [1,2] and [1,5]-methyl migrations[3c]

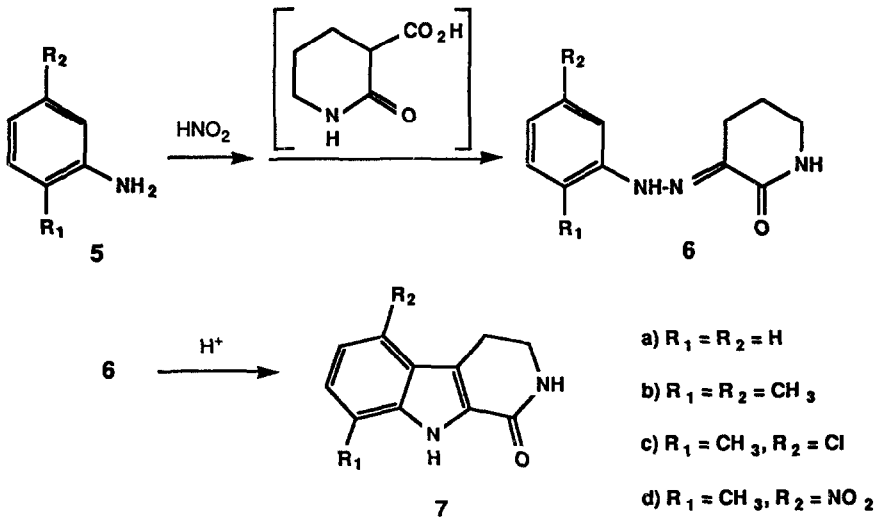


1 **2** **3** **4**

SCHEME I

But for the cases up to now considered, compounds resulting from the attack to the *ortho* unsubstituted position are by far the predominant products and rearranged compounds are only very minor products. As a matter of fact, 2-substituted phenylhydrazones like **1** are frequently used for directed indolizations in the synthesis of 4-substituted indoles[1a,5] Here we report the first example of a Fischer indole cyclization of an 2-alkyl 6-unsubstituted phenylhydrazone where the attack to the *ortho* position carrying a methyl group is almost as important as the attack to the normal unoccupied *ortho* position.

Natural and synthetic heterocycles with the 1H-pyrido [3,4-b] indole skeleton possess interesting properties as pharmacodynamic active compounds[6] Studies with simple ß-carboline alkaloids have shown their interaction with different neurotransmitter systems and how minor changes in the structure and substituents substantially affect the affinity for the receptors considered[7,8]. Fischer indole cyclization of 3-arylhydrazones of 2,3-piperidine diones is one of the most direct routes to these systems[5,9-11]. In an attempt to prepare some 5-substituted-ß-carbolines and to study the effect of substituents in this position on the inhibitory activity of monoamine oxidase[8], we tested the sequence outlined in the scheme II.



SCHEME II

The presence of an alkyl substituent in the 2-position of the aryl group (R_1) was considered essential to avoid the formation of the undesired 7-substituted-ß-carboline which is the predominant product when R = H[11] Hydrazones **6** were obtained in good yields (39-93%) by the Japp-Klingemann reaction of the diazotized anilines **5** with 3-carboxy-2-piperidone prepared *in situ* by saponification of its ethyl ester[13] The stability of the diazonium salts initially formed is the main factor determining the final yield of **6** (Table 1) In some cases, mixtures of the possible *E* and *Z* forms of arylhydrazones **6** can be obtained The *E*/*Z* ratio depends on reaction and crystallization conditions However, no differences have been observed in the Fischer indolization of both isomers, as can be expected according to their easy equilibration in acidic media[5] and specially because an acid-catalysed conversion of the hydrazones into the vinylhydrazines occurs prior to the cyclization Thus, no attempt was made to isolate the pure isomers when a mixture was formed, being used as obtained for the next step.

Cyclization of **6** to give products with the 1,2,3,4-tetrahydro-1-oxo-ß-carboline skeleton was accomplished in fair yields in acidic media (Table1) Indolization is clearly shown in the spectral analysis of the purified products In CDCl3, the ^{1}H NMR shows the presence of two exchangeable signals at ca. 6 and 9-

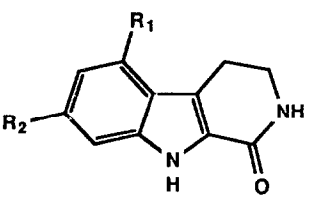
10 ppm corresponding to the amide and indolic protons respectively[14]. The two methylene groups at C-3 and C-4 appear at 3 7 and 3.1-3.4 ppm, the first as a double triplet[15] (J = 2 5, 7 Hz) and the second as a triplet whose chemical shift is sensitive to the nature of substituents in the aromatic ring In the ^{13}C NMR spectra, the *C*=O signal is observed at 163 ppm, as well as eight aromatic carbons in the 110-140 ppm region The aliphatic signals appear at 42 ppm (C-3), 20-23 ppm (C-2) and 16-22 ppm (methyl signals). The mass spectra of the 1,2,3,4-tetrahydro-1-oxo-ß-carboline compounds show the expected fragmentation pattern for an indole system with a fused lactame ring The molecular ions [M^+] are always large and readily undergo the loss of a $NHCH_2$ fragment to give a peak at [M^+-29] which evolves by CO loss to yield the base peak at [M^+-57], a methylene-indole fragment whose stability has been related with the possible rearrangement to give a quinolinium ion From this [M^+-57] ion the fragmentation sequence is the usual for alkylindoles, with an initial loss of HCN[16] For the nitroderivate, fragmentations due to the nitro group are important and the base peak appears at [M^+-17]

Table 1.- Results obtained in the preparation of 1,2,3,4-tetrahydro-1-oxo-ß-carbolines.

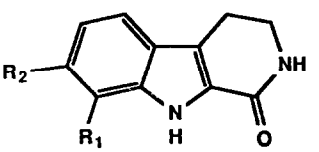
starting amine	R1	R2	Hydrazone (yield)		oxocarboline (yield)	
5a	H	H	**6a**	(77)	**7a**	(85)[a]
5b	CH_3	CH_3	**6b**	(39)	**7b+8b**	(91)[a,b]
5c	CH_3	Cl	**6c**	(70)	**7c**	(72)[a]
5d	CH_3	NO_2	**6d**	(93)	**7d**	(54)[c]

a) 98 % formic acid used for indolization b) ratio **7b/8b**. 1 1-1.35, some **9b** seems to be also formed c) PPA used instead of formic acid

Surprisingly, when the 3-(2,5-dimethylphenylhydrazone) of 2,3-piperidinedione (**6b**) was submitted to the general treatment (98% formic acid, 1h, reflux) a simple ^1H NMR analysis of the crude product revealed the presence of several compounds with the 1,2,3,4-tetrahydro-1-oxo-ß-carboline structure Separation of the isomers was difficult, but after careful chromatography and fractional crystallization, pure samples of the expected 1,2,3,4-tetrahydro-5,8-dimethyl-1-oxo-ß-carboline (**7b**) as well as of the rearranged product 1,2,3,4-tetrahydro-5,7-dimethyl-1-oxo-ß-carboline (**8b**) could be obtained



8



9

Differences between **7b** and **8b** are obvious in the ^{1}H and ^{13}C NMR spectra. For **8b** the two aromatic protons appear as singlets at 6 73 and 7 06 ppm, and an aromatic non-quaternary carbon is observed at 109.8 ppm according with the highfield shift expected for the unsubstituted C-8[12] In the same way, the ^{13}C signal for the methyl group in position 5 is present at 19 3 and 19 5 ppm in both, **7b** and **8b**, but for **8b** the *C*H3-8 peak which appears at 16-17 ppm is absent showing instead a signal at 21 6 ppm for *C*H3-7 The presence in the ^{1}H NMR of the crude product of minor signals at 2 42 (s) , 2 47 (s) and additional doublets centered at about 6.76 and 7.00 ppm would suggest the formation of 1,2,3,4-tetrahydro-7,8-dimethyl-1-oxo-ß-carboline (**9b**, $R_1 = R_2 = CH_3$) but in much lower yields However, pure **9b** could not be isolated. Compounds **8b** and **9b** should be formed from the [3,3]-sigmatropic shift of the monoprotonated enehydrazine involving the substituted *ortho* position, according to the general mechanism of the Fischer indolization[1], 1-oxo-ß-carboline **8b** resulting from the [1,2]-shift of the methyl group and **9b** arising from a double [1,2]-shift or a [1,5]-sigmatropic shift of the methyl group[3,4]

The rearrangements observed for hydrazone **6b** are comparable to the ones described by Fusco in the cyclization of the 2,5-dimethyl phenylhydrazone of cyclohexanone (**1**)[3c], but the yields of rearranged products are much higher in our case From different experiments, the ratio of *"normal"* (**7b**) to *"rearranged"* (**8b**) products ranged from 1.1 to 1 35 This is remarkable because it represents that more than 40% of the indolic products obtained corresponds to **8b**, i e , C-C formation during this indolization occurs almost unselectively on both *ortho* positions, although one of them is occupied by a methyl group

These unusual results cannot be explained in a simple way Clearly, steric factors will always favour the attack involving the unsubstituted *ortho* position The nature of substituents and in particular the presence of alkyl groups in the arylhdrazone moiety has been shown to play a significant role in some rearrangments of arylhydrazones[2-4,17] However, electronic factors related to the structure of the aromatic ring in **6** cannot be the only responsible for the very high yields of rearranged products because such factors are quite equivalent in **1** for which rearranged compounds are minor products In consequence, electronic factors related to the structure of the 2,3-piperidinedione moiety have to be considered essential for such a behaviour In this sense, the presence of the amide group in **6** would make more reactive the monoprotonated enehydrazine The conjunction of both activating factors in **6b** would be responsible for making much less selective the subsequent step in which the new C-C bond is formed This is supported by the fact that when the aromatic ring in **6** is not so activated, rearrangements are much less important This is the case for **6c** for which one of the methyl groups has been substituted by a chlorine atom The *normal* 5-chloro-1,2,3,4-tetrahydro-8-methyl-1-oxo-ß-carboline **7c** was the only important indolic product obtained from **6c** When an even less activated phenylhydrazone was used (**6d**, $R_1 = CH_3$, $R_2 = NO_2$), indolization could not be accomplished with formic acid Cyclication was possible with the use of PPA, but also in this case the formation of **8d** or **9d** could not be detected

EXPERIMENTAL SECTION

General Procedure for the Preparation of arylhydrazones: 3-(2-Methyl-5-nitrophenylhydrazone) of 2,3-piperidinedione (6d). 2-Methyl-5-nitroaniline (2 51g, 16.5 mmol) was dissolved in concentrated HCl (5.5 ml) and, after cooling, ice (7 g) was added to the solution. Sodium nitrite (1 2 g, 17 mmol) in water (6 ml) was then added dropwise to the stirred cold suspension and after addition was complete (half an hour) stirring was continued for 20 minutes. Temperature was kept below 4 °C during diazotization process. The solution was filtered and added to a solution of ethyl 2-oxopiperidine-3-carboxylate (3 g, 17.5 mmol) in water (20 ml) containing potassium hydroxide (0 98 g, 20 mmol) which had been kept at room temperature overnight and previously cooled by addition of ice (20 g) The mixture was adjusted to pH 4-5 by the addition of cold saturated aqueous sodium acetate Stirring was continued in an ice bath for 5 hours, after which time the yellowish solid was filtered, washed with very small amounts of water and ethanol and dried to give the phenylhydrazone **6d** (4 0 g, 93%) Recrystallization from ethanol gave an analytical sample of the Z-form. m p 228-232 °C Anal. Calc for $C_{12}H_{14}N_4O_3$ C, 54 96, H, 5 34, N, 21 37. Found. C, 55 11; H, 5 08; N, 21 61 IR (KBr)(cm^{-1}) 3299, 3159, 2948, 1649, 1547, 1416, 1351, 1334, 1271, 1224, 796, 723, 641. ^1H NMR (200 MHz, $CDCl_3$) 2 04 (2H, m, H-5'), 2 30 (3H, s, C*H*3-2), 2 79 (2H, t, J = 6 Hz; H-4'); 3.43 (2H, dt,J = 2 5, 6 Hz, H-6'), 6 03 (1H, br, CON-*H*), 7 20 (1H, d, J =8 Hz, H-3), 7 66 (1H, dd, J = 8, 2.5 Hz, H-4), 8 35 (1H, d, J = 2.5 Hz, H-6), 10 31 (1H, br; =N-N-*H*) ^{13}C NMR (50 3 MHz, $CDCl_3$) 17 2 (*C*H3-2), 22.4 (C-5'), 30 9 (C-4'), 42 0 (C-6'), 106 6 (C-6), 115 0 (C-4), 128 8, 129.4 (C-1,C-2); 130 9 (C-3); 143 1 (C-5), 148 0 (C-3'), 164 3 (C-2') MS (m/e (%)) 262 (100), 152 (17), 113 (31), 104 (22)· 77 (23), 41 (49)

3-(Phenylhydrazone) of 2,3-piperidinedione (6a): Obtained as a brown solid (77%). m p · 243-244 °C (EtOH) (lit.[13] m.p 244-245 °C)

3-(2,5-Dimethylphenylhydrazone) of 2,3-piperidinedione (6b): Obtained as a light yellow solid (39%) m p 160-164 ºC (MeOH) (Z-form) Anal Calc for $C_{13}H_{17}N_3O$ C, 67 53, H, 7.36, N, 18.18. Found. C, 67 25, H, 7 17, N, 18 16 IR (KBr)(cm^{-1}) 3299, 3169, 2941, 1653, 1547, 1420, 1329, 1259, 1170, 792, 733, 661 ^1H NMR (200 MHz, $CDCl_3$) 2 00 (2H, m, H-5'), 2 21 and 2 33 (3H each, 2s; C*H*3-2 and C*H*3-5); 2 75 (2H, t, J = 6 Hz, H-4'), 3.39 (2H, dt, J = 2 5, 6 Hz, H-6'), 5 81 (1H, br, CON-*H*); 6 66 (1H; d, J = 8 Hz; H-4), 6 98 (1H, d, J = 8 Hz, H-3), 7 37 (1H, s, H-6), 10 30 (1H, br , =N-N-*H*) MS (m/e (%)). 231 (100), 160 (18), 120 (38), 91 (15), 77 (13)

3-(5-Chloro-2-methylphenylhydrazone) of 2,3-piperidinedione (6c): Obtained as a light yellow solid (70%) m p · 149-151 °C (MeOH) (Z-form) Anal Calc for $C_{12}H_{14}N_3ClO$ C, 57 26, H, 5 57, N, 16 70 Found C, 56 98, H, 5 69, N, 16 83 IR (KBr)(cm^{-1}) 3299, 3159, 2964, 1653, 1555, 1415, 1339, 1259, 1150, 800, 725, 669 ^1H NMR (200 MHz, $CDCl_3$) 2 01 (2H, m, H-5'), 2 18 (3H, s, C*H*3-); 2 74 (2H; t, J = 6Hz, H-4'), 3 43 (2H, dt, J = 6, 2 5 Hz, H-6'), 5 89 (1H, br; CON-*H*), 6 80 (1H, dd, J = 8, 2 Hz, H-4), 7.14 (1H, d, J = 8 Hz, H-3); 7 51 (1H, d,J = 2 Hz, H-6), 10 29 (1H, br; =N-N-*H*) MS (m/e (%)) 253 (39); 251 (100); 182 (6), 180 (19), 142 (21), 140 (36), 139 (19)

General Procedure for cyclization of hydrazones 6 in Formic acid: 1,2,3,4-Tetrahydro-5,8-dimethyl-1-oxo-ß-carboline (7b) and 1,2,3,4-tetrahydro-5,7-dimethyl-1-oxo-ß-carboline (8b): The phenylhydrazone **6b** (0.83 g, 3 6 mmol) was refluxed in 98% formic acid (5 ml) for 1 hour The solution was carefully neutrallized by the addition of an aqueous solution of Na_2CO_3 and then partially concentrated. The product which separated was just brought into solution by the dropwise addition of hot dioxane. On cooling the crude oxocarboline (**7b** + **8b**) precipated and was filtered off (0 7 g, 91%) This crude product was chromatographed on silica using as eluents CH_2Cl_2, then mixtures CH_2Cl_2/EtOAc, then EtOAc and finally mixtures EtOAc/MeOH, **7b** being eluted first. Analytical samples of **7b** and **8b** were prepared by recrystallization of selected fractions in benzene or ethyl acetate

1,2,3,4-Tetrahydro-5,8-dimethyl-1-oxo-ß-carboline (7b): Obtained as transparent prisms m p.. 220-221 °C (benzene). Anal. Calc. for $C_{13}H_{14}N_2O$: C, 72 90, H, 6 54, N, 13 08. Found. C, 72 95; H, 6.43, N, 13.12 IR (KBr)(cm^{-1}): 3387, 3336, 1649, 1548, 1496, 1434, 1377, 1329, 1029, 816, 772 ^1H NMR (200 MHz, $CDCl_3$)· 2 45 (3H, s; C*H*3-8), 2 62 (3H, s, C*H*3-5), 3 29 (2H, t, J = 7 Hz, H-4), 3 72 (2H, dt, J = 2.5, 7 Hz, H-3); 5 63 (1H; br; H-2); 6.80 (1H, d, J = 7 Hz, H-6), 6 99 (1H, d, J = 7 Hz, H-7), 8 94 (1H, br; H-9). ^{13}C NMR (50.3 MHz, $CDCl_3$): 16 2(*C*H3-8), 19 3 (*C*H3-5), 22 9 (C-4), 42 2 (C-3), 119.3 (C-8), 120 9 (C-4a), 121.6 (C-6); 124 4 (C-4b), 125 7 (C-7), 125 9 (C-5), 130 0 (C-9a); 137 1 (C-8a); 163 3 (C-1) MS (m/e (%)). 215 (12); 214 (78), 185 (22), 158 (33), 157 (100), 156 (23), 128 (12), 115 (10)

1,2,3,4-Tetrahydro-5-7-dimethyl-1-oxo-ß-carboline (8b): Obtained as white prisms. m p. 225-227 °C (EtOAc) Anal. Calc for $C_{13}H_{14}N_2O$ C, 72 90, H, 6 54, N, 13 08 Found· C, 72 66; H, 6.48; N, 13 19 IR (KBr)(cm^{-1}): 3275, 3223, 1663, 1546, 1496, 1438, 1392, 1328, 1286, 837, 802. ^1H NMR (200 MHz, $CDCl_3$). 2.42 (3H; s, C*H*3-7), 2 61 (3H, s, C*H*3-5), 3 26 (2H, t, J = 7 Hz, H-4), 3 71 (2H, dt, J = 2 5, 7 Hz, H-3), 5 67 (1H, br; H-2) 6 73 (1H, s, H-6), 7 06 (1H, s, H-8), 9 06 (1H, br; H-9). ^{13}C NMR (50 3 MHz,$CDCl_3$) 19 5 (*C*H3-5), 21 6 (*C*H3-7), 22 9 (C-4), 42 1 (C-3), 109 8 (C-8), 120 4 (C-4a), 122.8 (C-4b), 123 6 (C-6), 125 5 (C-9a); 132 1 (C-5), 135 8 (C-7), 138 0 (C-8a), 163.3 (C-1) MS (m/e (%)): 214 (85), 185 (15), 157 (100), 128(14)

1,2,3,4-Tetrahydro-1-oxo-ß-carboline (7a): Obtained as a colourless solid (85%). m p · 183-184 °C (lit [9a] m.p 183-185 °C). IR (KBr)(cm^{-1}) 3408, 3229, 1655, 1540, 1500, 746 ^1H NMR (200 MHz, $CDCl_3$) 3.08 (2H, t; J = 7 Hz, H-4), 3 74 (2H, dt, J = 2 5, 7 Hz, H-3), 6 59 (1H, br, H-2), 7 15 (1H, t; J = 8 Hz,H-6), 7 30 (1H, dt, J = 1.5, 8 Hz, H-7), 7 51 (1H, d, J = 8 Hz, H-8), 7 61 (1H, d, J = 8 Hz, H-5), 10 34 (1H, br; H-9) ^{13}C NMR (50 3 MHz, $CDCl_3$) 20 6 (C-4), 42 0 (C-3), 112 8 (C-8), 120.1 (C-4a), 120.3 and 120 4 (C-5 and C-6), 125 3 (C-4b), 125 3 (C-7), 126 4 (C-9a), 137 7 (C-8a), 163 9 (C-1) MS (m/e (%)): 186 (82), 157 (39), 129 (100), 128 (20), 102 (14)

5-Chloro-1,2,3,4-tetrahydro-2-methyl-1-oxo-ß-carboline (7c): Obtained as a white solid (72%). m p 249-251 °C Anal. Calc. for $C_{12}H_{11}N_2OCl$ C ,61 41, H, 4 69, N, 11 94 Found C, 61 64, H, 4 73, N, 11 70 IR (KBr)(cm^{-1}). 3314, 3252, 1664, 1540, 1489, 1375, 1327, 1281, 1232, 1189, 1028, 942, 793, 765 ^1H NMR (200 MHz, $CDCl_3$) 2 48 (3H, s, C*H*3-8), 3 40 (2H, t, J = 7 Hz, H-4), 3 73 (2H, dt, J = 2 5, 7 Hz, H-3), 5 90 (1H, br; H-2), 6 98 (1H, d, J = 8 Hz) and 7 03 (1H; d, J = 8 Hz) (H-6 and H-7) ^{13}C NMR

(50 3 MHz, $CDCl_3$) 16 2 (CH_3-8), 22 0 (C-4), 42 1 (C-3); 120.2 and 120.7 (C-4a and C-8), 120 9 (C-6); 122 7 (C-5), 125.3 (C-4b); 125.9 (C-7), 126.9 (C-9a), 138 0 (C-8a), 162 9 (C-1). MS (m/e (%))· 236 (26), 234 (79), 207 (11), 205 (35), 179 (33), 177 (100); 165 (7); 163 (23); 142 (20), 141 (18), 140 (19).

1,2,3,4-Tetrahydro-2-methyl-5-nitro-1-oxo-ß-carboline (7d): The hydrazone **6d** (1 g, 3.8 mmol) and polyphosphoric acid (6 ml) were slowly heated in an oil bath with stirring At ca. 100 °C the solid dissolved and heating was continued for 5 minutes The cooled mixture was poured on ice-water (50 g) and the solid formed was filtered, washed with water and dried to give the crude **7d** as a brown solid (0 5 g, 54 %) which was chromatographed on silica (CH_2Cl_2/AcOEt and AcOEt/MeOH mixtures as eluent) to give the pure oxocarboline as a yellow solid m p >250 °C Anal Calc for $C_{12}H_{11}N_3O_3$· C, 58.78, H, 4.49, N, 17.14. Found C, 58.65, H, 4.41, N, 16 98. IR (KBr)(cm^{-1}) 3354, 3234, 3127, 1684, 1666, 1510, 1379, 1337, 1325, 1291, 819, 776. 762 ^1H NMR (200 MHz, $CDCl_3$) 2 61 (3H, s, CH_3-8), 3.41 (2H; t, J = 7 Hz, H-4), 3 72 (2H, dt, J = 2 5, 7 Hz, H-3), 5 74 (1H, br, H-2), 7 17 (1H, d, J = 8 Hz, H-7), 8 00 (1H; d, J = 8 Hz, H-6), 9.57 (1H, br, H-9) ^{13}C NMR (50 3 MHz, $CDCl_3$) 17 0 (CH_3-8), 23 4 (C-4), 42 0 (C-3), 107.4 (C-4a), 118 9 (C-4b), 119 4 (C-6), 124 2 (C-7), 129 7, 130 0 and 131 2(C-5, C-8 and C-9a), 138 3 (C-8a); 162 6 (C-1) MS (m/e (%)) 245 (92), 229 (17), 228 (100), 188 (26), 142 (18)

REFERENCES AND NOTES:

1 - a) Robinson, B. *"The Fischer indole synthesis"*, J Wiley & Sons, New York, **1982**
b) Fusco, R ; Sannicolò, F *Tetrahedron* **1980**, *36*, 161

2 - a) Carlin, R B , Henley Jr , W O , Carlson, D P *J Am Chem Soc* **1957**, *79*, 5712.
b) Carlin, R B , Moores, M S *J Am Chem Soc* **1962**, *84*, 4107

3 - a) Fusco, R , Sannicolò, F *Gazz ChimItal* **1973**, 197
b) Fusco, R , Sannicolò, F *Tetrahedron Lett* **1975**,3351
c) Fusco, R , Sannicolò, F *Tetrahedron Lett* **1978**, 4827.

4 - Miller, B , Matjeka, E R *Tetrahedron Lett* **1977**, 131

5 - Nagasaka, T , Yuge, T , Ohki, S *Heterocycles* **1977**, *8*, 371

6 - Allen, J R F , Holmstedt, B R *Phytochemistry* **1980**, *19*, 1573

7 - a) Muller, W E ; Fehske, K J , Borke, H O , Wollert, U , Nanzand,C , Rommelspacher,H *Pharmacol Biochem Behav* **1981**, *14*, 693
b) Cain, M., Weber, R W , Guzman, F , Cook, J M , Barker, S A ; Rice, K C., Crawley, J N , Paul, S M , Skolnick, P *J Med Chem* **1982**, *25* , 1081

8 - a) Ho, B T , McIsaac, W M , Walker, K E , Estevez, V *J Pharm Sci* **1968**, *57*, 269
b) Ho, B T , McIsaac, W M ; Tansey, L W *J Pharm Sci* **1969**, *58* , 998
c) Ho, B T , Gardner, P M , Walker, K E *J Pharm Sci* **1973**, *62* ,36
d) Tomás, F , Aulló, J.M *J Pharm Sci* **1979**, *68*, 772

9 - a) Abramovitch, R A , Shapiro, D *J Chem Soc* **1956**, 4589

b) Abramovitch, R.A. *J Chem Soc* **1956**, 4593

c) Abramovitch, R A , Muchowski, J M *Can J Chem* **1960**, *38*, 554

10 - a) Horner, J.K., DeGraw, J I , Skinner, W A *Can J Chem* **1966**, *44*, 307

b) DeGraw, J I , Skinner, W A *Can J Chem* **1967**, *45*, 63

11 - a) Von Strandtmant, M , Cohen , M.P., Shavel, J *J Med Chem.* **1963**, *6*, 719.

b) Pouilhès, A , Langlois, Y *Heterocycles* **1985**, *23*, 935

12 - Herdeis,C , Dimmerling, A *Heterocycles* **1984**, *22*, 227

13 - Shapiro, D ; Abramovitch, R A. *J Am Chem Soc* **1955**, *77*, 6690.

14 - ^{1}H and ^{13}C NMR assignments are in good agreement with the values reported for strychnocarpine[12] and different indole alkaloids. See for instance Ungemach, F , Soerens, D , Weber, R , DiPierro, M., Campos, O ; Mokry, P , Cook, J M , Silverton, J V *J Am Chem Soc* **1980**, *102*, 6976, Rubiralta, M , Diaz, A , Vila, C *Tetrahedron Lett* **1990**, 3779

15.- In $F_3CCO_2H/CDCl_3$, methylene groups in C-3 appear as a triplet Some other changes are also observed in this solvent. For instance ^{1}H and ^{13}C NMR spectral data for **7d** are as follows ^{1}H NMR (200 MHz): 2 70 (3H· s, C*H*$_3$-8), 3 52 (2H; t, J = 8 Hz, H-4), 3 87 (2H, t, J = 8 Hz, H-3), 7 31 (1H, d; J = 8 Hz; H-7), 8 13 (1H, d, J = 8 Hz, H-6) ^{13}C NMR (50 3 MHz) 16 8 (*C*H$_3$-8), 22 8 (C-4); 42 2 (C-3), 117 4 (C-4a); 121 4 (C-6); 122 9 (C-4b), 126 2(C-7), 126 6 (C-5), 133 0 (C-8), 139 9 (C-9a), 141 1 (C-8a); 165 2 (C-1)

16 - Marx, M ; Djerassi, C *J Am Chem Soc* **1968**, 90, 679

17 - Fusco, R ; Sannicolò, F *Tetrahedron Lett* **1978**, 1233.