Communications to the Editor

[Chem. Pharm. Bull. 35(1) 425—428 (1987)]

EFFICIENT SYNTHESIS OF 6H-PYRIDO [3,2-b] CARBAZOLE DERIVATIVES FROM 3-AMINO-1,4-DIMETHYL CARBAZOLE

Jean-Charles Lancelot,[a] Sylvain Rault,[a] Max Robba,[a] and Nguyen Huy Dung,[b]

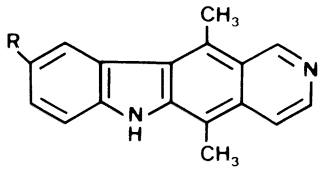
Laboratoire de Chimie Thérapeutique, U.E.R. des Sciences Pharmaceutiques,[a] 1, rue Vaubénard, 14032 Caen Cédex, France, Laboratoire de Chimie Minérale et Structurale,[b] 1, rue Vaubénard, 14032 Caen Cédex, France.

The synthesis of 3-amino-1,4-dimethylcarbazole is described and its reaction with β-ketoesters gives new 6H-pyrido [3,2-b] carbazole derivatives.

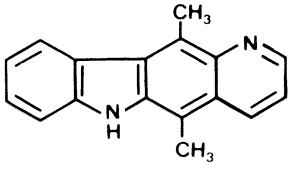
KEYWORDS —— 3-Amino-1,4-dimethylcarbazole ; 6H-pyrido [3,2-b] carbazole ; Conrad-Limpach reaction ; lactam-lactim tautomerism

Since the isolation of ellipticine 1 and methoxyellipticine 1a and the discovery of their potent anticancer activity, [1] numerous syntheses of pyridocarbazoles have been reported. However in contrast with the intense activity directed toward the synthesis of pyrido [4,3-b] [2], [3,4-b] [3], [3,2-c], [4,3-c], [3,4-c], and [2,3-c] [4] carbazoles, very little attention has been focused on the isomeric pyrido [3,2-b] carbazoles 2. Surveying the literature, we have only found papers about 2,4-disubstituted derivatives. [5]

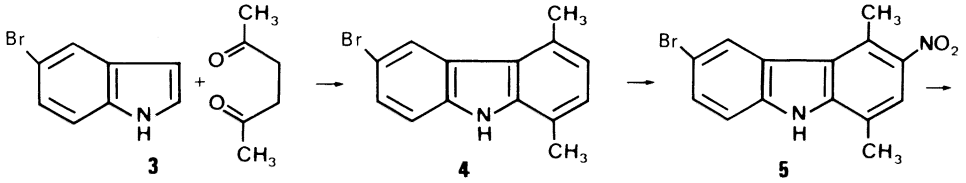
We describe now a convenient approach for the construction of 5,11-dimethyl-6H pyrido [3,2-b] carbazole derivatives making use of 3-amino-1,4-dimethylcarbazole 6. We have adjusted the conditions for the synthesis of this latter, yet unknown key intermediate 6 during the course of our work in the preparation of nitrocarbazoles. [6] This compound 6 was obtained in three steps starting from 5-bromoindole 3 via 6-bromo-1,4 dimethylcarbazole, [7] 4 first by nitration in acetic anhydride, followed by reduction with hydrogen under pressure over palladium charcoal. This latter reaction resulted in the reduction of the nitro group and the debromination at the 6 position (the presence of the bromine atom is necessary for the reaction to permit a selective mononitration at the 3 position). Condensation of ethyl acetoacetate with the amine 6 led to a non-isolable intermediate which was then cyclized by heating at 230°C in diphenylether to give the pyridocarbazolone 7 in 65% yield. This compound exhibits the lactam-lactim tautomerism. In the solid state CO and NH absorption in the IR spectrum, and an X-ray crystallographic study [8] clearly established the existence of the lactam form 7. However in solution, the OH absorption in the IR spectrum (CH_3CN) and the formation of acetoxy compound 8 during the reaction of 7 with acetic anhydride indicate the



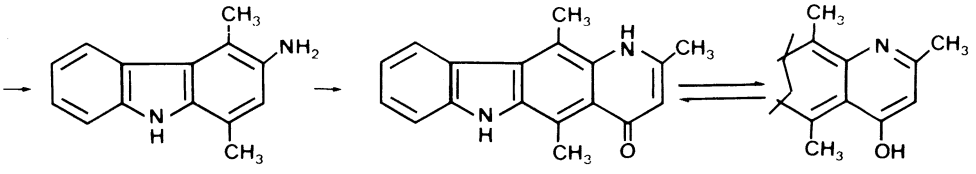
1 R = H
1a R = OCH_3



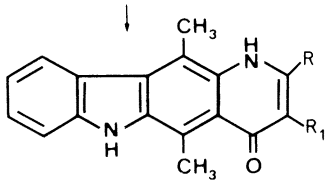
2



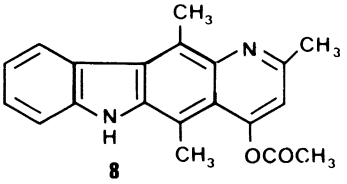
3 **4** **5**



6 **7** **7a**

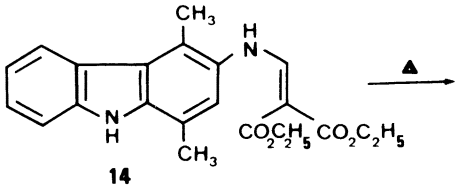


9 R = CF_3 - R_1 = H
10 R = $(CH_2)_2CH_3$ - R_1 = H
11 R = $CH(CH_3)_2$ - R_1 = H

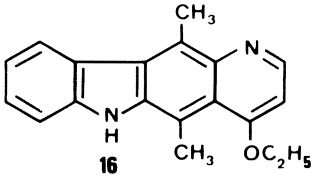


8

12 R = R_1 = CH_3
13 R = CH_3 - R_1 = $CH_2C_6H_5$
15 R = H - R_1 = $CO_2C_2H_5$



14



16

TABLE 1 : M.P., IR ^{1}HNMR SPECTROSCOPIC DATA OF CARBAZOLES

Compd N°	m.p(°C)	IR(KBr) (ν C=O and NH cm^{-1})	HNMR(DMSO-d6/δppm)					
			H2	H5	H6	H7	H8	Others
5	228	3310 (NH) 1310 (NO_2)	7.66	8.03	-	7.77	7.33	NH : 11.69 CH_3(1) : 2.43 CH_3(4) : 2.71
6	198	3140 (NH) 3380,3320,1600 (NH_2)	6.66	8.13	7.06	7.36	7.36	NH : 10.63 NH_2: 4.45 CH_3(1) : 2.43 CH_3(4) : 2.50
14	230	3280 (NH) 1675,1650 (C=O)	7.13	8.13	7.13	7.40	7.40	NH : 11.22, 11.09 CH3(1) : 2.51 CH3(4) : 2.71 CH : 8.38 CH_2CH_3: 4.13, 1.23

TABLE 2 : M.P., IR ^{1}HNMR SPECTROSCOPIC DATA OF PYRIDO[3.2-b] CARBAZOLES

Compd N°	m.p(°C)	IR(KBr) (ν C=O and NH cm^{-1})	HNMR(DMSO-d6/δppm)						
			H2	H3	H7	H8	H9	H10	Others
7*	265	3420,3240 (NH) 1620 (C=O)	-	5.73	7.41	7.41	7.06	8.25	NH : 9.95, 11.01 CH_3 : 3.11, 2.98, 2.38
8	170	3240 (NH) 1720 (C=O)	-	7.03	7.43	7.43	7.19	8.23	NH : 11.03 CH_3 : 2.86, 2.66, 2.46 $CHOCH_3$: 2.46
9	250 (sublim)	3400,3300 (NH) 1625 (C=O)	-	7.16	7.33	7.33	7.06	8.03	NH : 7.83, 10.93 CH_3 : 2.76, 2.59
10	251	3420,3260 (NH) 1610 (C=O)	-	5.76	7.43	7.43	7.10	8.26	NH : 9.83, 10.99 CH_3 : 3.10, 2.96 $(CH_2)_2CH_3$: 2.60, 1.70, 0.96
11	240	3420,3200 (NH) 1610 (C=O)	-	5.80	7.43	7.43	7.06	8.26	NH : 9.70, 11.00 CH_3 :3.10,3.00 $CH(CH_3)_2$: 3.23, 1.30
12	265 (sublim)	3425,3160 (NH) 1610 (C=O)	-	-	7.43	7.43	7.06	8.26	NH : 9.66, 10.89 CH_3 :3.10, 2.96, 2.43, 1.96
13	280	3420,3200 (NH) 1610 (C=O)	-	-	7.40	7.40	7.06	8.20	NH : 9.70, 10.90 CH_3 :3.06, 2.93, 2.33 CH_2 :3.86 C_6H_5 : 7.09
15	275	3340,3250 (NH) 1685,1620 (C=O)	8.26	-	7.43	7.43	7.10	8.26	NH : 11.19 CH_3 :3.03, 2.90 CH_2CH_3 : 4.16, 1.25
16	264	3200 (NH)	8.50	6.75	7.43	7.43	7.13	8.23	NH : 10.93 CH_3 : 3.20, 3.00 CH_2CH_3 : 4.16, 1.48

* IR (CH_3CN) νOH = 3650 and 3550 cm^{-1}

existence of the lactim form 7a. Structure 8 is confirmed by a single CO absorption on the IR spectrum (1720 cm^{-1}) and by the deshielding of H-3 in the ^1H NMR spectrum. In a similar manner in 50-70% yield condensation of various β-ketoesters with the amine 6 led to the corresponding pyridones 9-13.

On the other hand, when diethyl ethoxymethylidenemalonate was used, the reaction yielded the isolable intermediate 14 which gave either the 3-carbethoxypyridone 15 in 60% yield by heating in diphenylether or the 4-ethoxy pyridine 16 in 33% yield by sublimation in vacuo at 260°C. In the light of the in vitro antimitotic activity (Leukemia L 1210 culture cells) of compounds 7, 8 and 16 [9] further studies concerning the chemistry and biological activity of title and related compounds are in progress.

REFERENCES

1) (a) S. Goodwin, A.F. Smith and E.C. Horning, J. Am. Chem. Soc., 81, 1903 (1959)
(b) R.B. Woodward, G.A. Iacobucci and F.A. Hochstein, ibid, 81, 4434 (1959)
(c) G.H. Svoboda, G.A. Poore and M.L. Montfort, J. Pharm. Sci., 57, 1720 (1968)

2) For reviews, see :
(a) M. Sainsbury, Synthesis, 1977, 437.
(b) R. Barone and M. Chanon, Heterocycles, 16, 1357 (1981).

3) G. Saulnier and W. Gribble, J. Org. Chem., 48, 2690 (1983)

4) S. Pelaprat, R. Oberlin, I. Le Guen and B.P. Roques, J. Med. Chem., 23, 1330 (1980)

5) (a) J.C. Perche, G. Saint-Ruf and N.P. Buu-Hoi, J. Chem. Soc., 1972, 260
(b) N.S. Kozlov, V.V. Misenzhnikov, T.P. Shulyateva and L.D. Dryabkina, Katalit. Syntez. Organ. Soedin., 1976, 40, 4 (1976).
(c) N.S. Kozlov, V.V. Misenzhnikov, T.P. Shulyateva, V.M. Adanin and V.G. Sakharovskü, Khim. Geterotsikl. Soedin., 1983, (4), 498.

6) J.C. Lancelot, J.M. Gazengel, S. Rault, Nguyen Huy Dung and M. Robba, Chem. Pharm. Bull., 32, 4447 (1984) (and reference cited therein).

7) (a) P.A. Cranwell and J.E. Saxton, J. Chem. Soc., 1962, 3482
(b) L.K. Dalton, S. Demerac, B.C. Elmes, J.W. Loder, J.M. Swan and T. Teitei, Austr. J. Chem., 20, 2715 (1967).
(c) L.K. Dalton and T. Teitei, ibid, 21, 2053 (1968).

8) Nguyen Huy Dung, B. Viossat, J.C. Lancelot and M. Robba, Chem. Pharm. Bull., 1987 (to be published).

9) J.C. Lancelot, S. Rault, M. Robba, T. Tabka, P. Gauduchon and J.Y. Le Talaer, 22e Rencontres Internationales de Chimie Thérapeutique. Clermont-Ferrand, 3-5 Septembre 1986.

(Received October 13, 1986)