Synthesis of 1-Substituted Ellipticines by a New Route to Pyrido[4,3-*b*]-carbazoles

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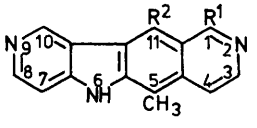
A new approach to pyrido[4,3-*b*]carbazole leading to 1-substituted ellipticines derivatives is described. A five-step synthesis starting from arenediazonium chlorides and 1-morpholinocyclohexenes gave 2-formyl-1-methyl-3,4-dihydrocarbazoles which were then aromatized by manganese dioxide to 2-formyl-1-methylcarbazoles. Knoevenagel malonic acid condensation afforded the corresponding *trans*-acrylic acids, the azides of which were cyclized in boiling diphenyl ether giving pyrido[4,3-*b*]carbazol-1(2*H*)ones. These compounds were transformed into 1-chloroellipticines in boiling phosphorus oxychloride. Finally, the nucleophilic displacement of the chlorine atom by γ-diethylaminopropylamine provided the previously unknown 1-substituted pyrido[4,3-*b*]carbazoles.

We recently described[1] the synthesis of the new ellipticine analogue 5,11-dimethyldipyrido[4,3-*b*][3,4-*f*]-indole (1) which has a structure and biological properties closely related to those of ellipticines.[2] Derivatives of this new heterocyclic ring system with a dialkylamino-alkylamino-side-chain at the 1-position, such as (2),[3] have a still higher antitumour activity on L1210 leukaemia in mice. We decided therefore to examine whether a dialkylaminoalkylamino-side-chain could also increase the antitumour activity in the ellipticine series.



(1) $R^1 = H, R^2 = CH_3$

(2) $R^1 = NHCH_2CH_2CH_2NEt_2, R^2 = H$

From a chemical standpoint, at least fifteen different synthetic routes to pyrido[4,3-*b*]carbazoles have been reviewed.[4] More recently, two new approaches have been reported.[5,6] However, despite the number and diversity of these methods, none of them refers to the preparation of the 1-chlorinated pyrido[4,3-*b*]carbazoles required for the preparation of ellipticine derivatives analogous to (2). We have now worked out a new route to this heterocyclic ring system, following in part the olivacine synthesis described by Wenkert and Dave.[7]

4-Methoxy- and 4-benzyloxy-benzenediazonium chlorides reacted at 0 °C with 1-morpholinocyclohexene and 4-methyl-1-morpholinocyclohexene in dioxan giving the corresponding cyclohexane-1,2-dione and 4-methylcyclohexane-1,2-dione monoarylhydrazones (3a—d).

Among these compounds, only (3a) has already been described [8a] and it is worth pointing out that their formation from enamines in the given conditions took place in better yields than those obtained using the Japp–Klingeman reaction between arenediazonium chlorides and potassium 2-oxocyclohexane-1-carboxylate.[9a,b]

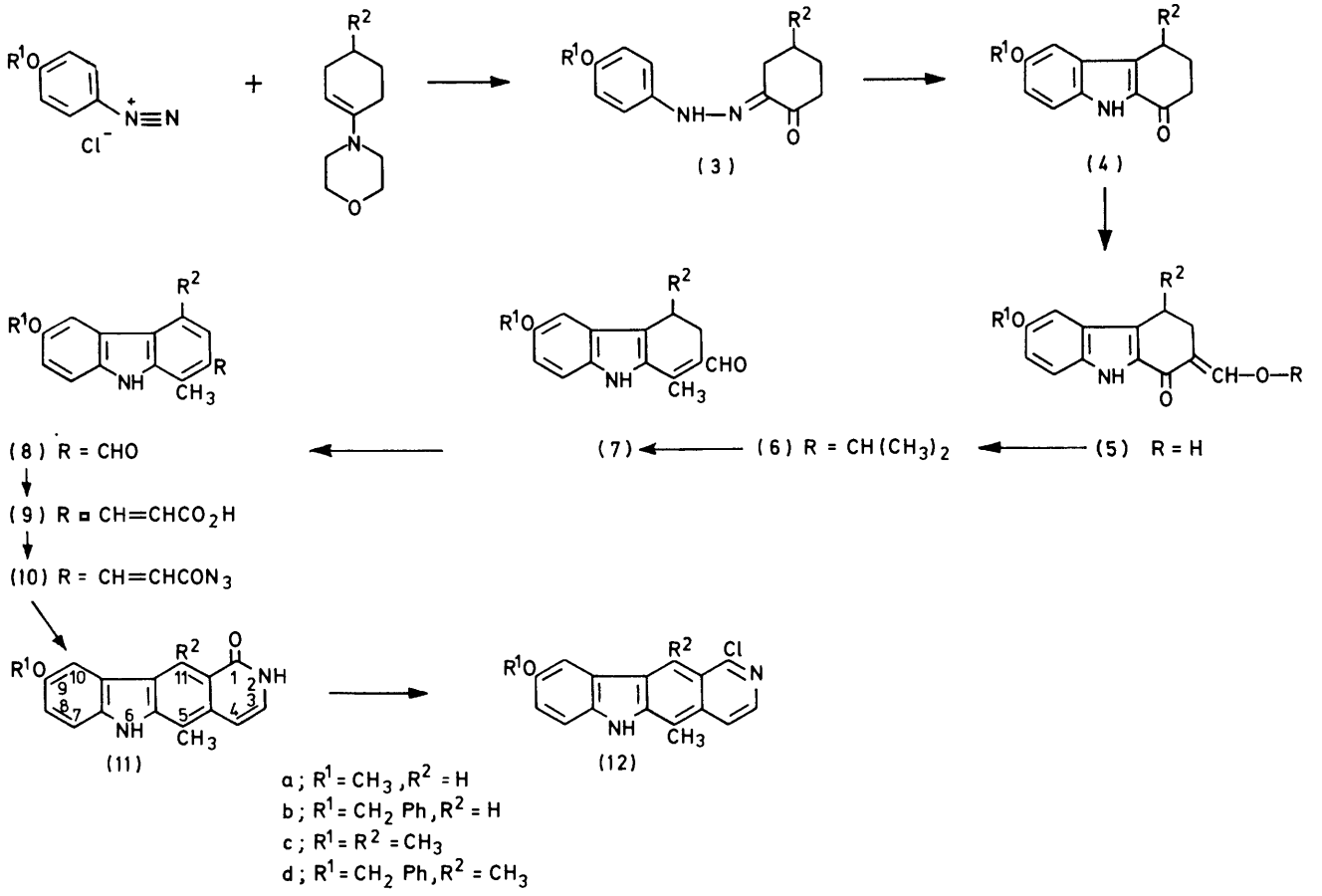
Starting from the arylhydrazones (3a—d) we have prepared successively (Scheme 1): (a) 6-alkoxy-3,4-dihydrocarbazol-1(2*H*)-ones using indolization of (3a—d) by the classical Fisher method under conditions previously described for similar cases; [8b,9a,b] (b) 6-alkoxy-2-hydroxymethylene-3,4-dihydrocarbazol-1(2*H*)-ones (5a—d) by acylation of (4a—d) with ethyl formate and sodium hydride; (c) 6-alkoxy-2-isopropyloxymethylene-3,4-dihydrocarbazol-1(2*H*)-ones (6a—d) formed by etherification of (5a—d) with isopropyl iodide in dimethylformamide solution and in the presence of anhydrous potassium carbonate; (d) 6-alkoxy-2-formyl-1-methyl-3,4-dihydrocarbazoles (7a—d) obtained by transformation of (6a—d) with 4 mol. equiv. of methyllithium and subsequent hydrolysis; (e) 6-alkoxy-2-formyl-1-methylcarbazoles (8a—d) using the aromatization of (7a—d) by manganese dioxide in boiling benzene.

Up to this point, our approach is similar to Wenkert and Dave's olivacine synthesis.[7] However, in order to increase the yields, some technical modifications have been introduced, the most important being the aromatization process (7) ⟶ (8), in which palladium–charcoal is replaced by manganese dioxide. In fact, Pd–C enabled us to obtain only small quantities of aromatized aldehydes which were produced with other compounds and were therefore difficult to purify. On the other hand, the manganese dioxide method gave the expected aromatized aldehydes in high yields and the process could be performed on a large scale.

To our knowledge, this transformation of a cyclic aldehyde to the corresponding aromatic compound by manganese dioxide was reported previously only for formylcyclohexenes.[10] It can be assumed that the reaction is a general one and it could be particularly useful in polynuclear aromatic compound syntheses.

Starting from the carbazolecarbaldehydes (8a—d), the elaboration of the D ring of pyrido[4,3-*b*]carbazole was performed in three steps, by Eloy and Deryckere's reaction scheme [11] involving condensation of malonic acid with the aldehyde (8a—d) to give the *trans*-acrylic acids (9a—d), transformation to the corresponding azides (10a—d) by the mixed anhydride method,[12] and final thermal cyclization to the 9-alkoxy-5-methylpyrido-[4,3-*b*]carbazol-1(2*H*)-ones (11a—d). The last compounds were easily chlorinated to the corresponding 1-chloropyrido[4,3-*b*]carbazoles (12a—d) in boiling phosphorus oxychloride.

All the steps of this synthesis had yields of 60—90%, except for the reaction (10) ⟶ (11) which, in some in-

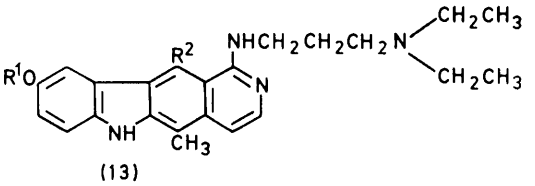


SCHEME 1

stances, had a yield <50%. However, there are nine different steps for the whole transformation (3) ⟶ (12) and, for example, the overall yield of the (3a) ⟶ (12a) synthesis, did not exceed 6.4%.

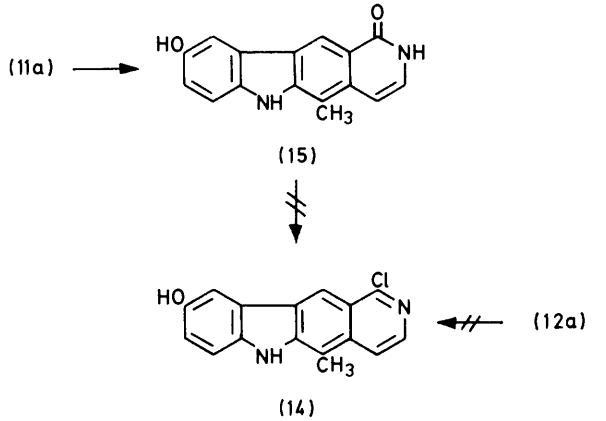
Treatment of the 1-chloropyrido[4,3-*b*]carbazole derivatives (12a—d) with boiling γ-diethylaminopropylamine provided the normal 1-substituted pyrido[4,3-*b*]carbazole analogues of (2).

It has been stated, however, that demethylation of 9-methoxyellipticine to the 9-hydroxylated derivative increases the antitumour activity.[13] We first tried to prepare the 9-hydroxy-derivatives (13e and f) by demethylation of (13a and b) in boiling pyridine hydrochloride or acetic acid–hydrobromic acid, but the reaction was accompanied by rapid cleavage of the side-chain. Then we tried to prepare the hydroxylated compound (13e) using 1-chloro-9-hydroxy-5-methylpyrido[4,3-*b*]carbazole (14) as an intermediate. Neither the demethylation of the 1-chloromethoxylated compound (12a) nor the chlorination of 9-hydroxy-5-methylpyrido[4,3-*b*]-carbazol-1(2*H*)-one (15) formed by de-



(13)

a; $R^1 = CH_3$, $R^2 = H$
b; $R^1 = CH_2Ph$, $R^2 = H$
c; $R^1 = R^2 = CH_3$
d; $R^1 = CH_2Ph$, $R^2 = CH_3$
e; $R^1 = R^2 = H$
f; $R^1 = H$, $R^2 = CH_3$



SCHEME 2

methylation of compound (11a) could provide the derived intermediate (Scheme 2). Finally, the synthesis of the 9-hydroxy-derivatives (13e and f) could be achieved from benzylated compounds (13b and d) using catalytic hydrogenation with palladium–charcoal.

Considering the synthetic pathways, the structure of the various intermediates and final products should be unambiguous. All substances could be purified by crystallization and were checked to give single spots on t.l.c. There were occasional difficulties in the elemental analysis of the final substituted pyridocarbazoles, due to hydration or co-crystallization with solvent molecules. High-resolution 100-MHz ^{1}H n.m.r. carried out in the Fourier-transform mode using extensive homonuclear decoupling definitely established the structure of all the pyrido[4,3-*b*]carbazoles (Tables 1 and 2).

The biological properties of the substituted ellipticine derivatives (13a—f) and those of the corresponding dipyrido[4,3-*b*][3,4-*f*]indole (2) [14] have been investigated, compared with unsubstituted ellipticine and compound (1), on transformed cells cultured *in vitro* and on mice L1210 leukaemia. The biological results will be reported elsewhere.[15] They clearly indicate that substitution at the 1-position by the γ-diethylaminopropylamino side-chain noticeably increases antitumour activity in both series, at least for L1210 leukaemia.

This may be a general property useful for research development and for analysis in terms of structure–activity relationships of the effect of substitution of polycyclic DNA intercalating drugs. At all events, our synthesis can provide new substituted ellipticines in reasonable yield from readily available materials.

TABLE 1

^{1}H N.m.r. characteristics [chemical shift relative to Me_4Si; coupling constants in Hz; *ca.* 10^{-2} M in $(CD_3)_2SO$; 34 °C; 100 MHz] of pyrido[4,3-*b*]carbazoles

Compound	2-NH	3-H	4-H	11-H	5-CH_3	11-CH_3	6-NH	7-H	8-H	10-H	OCH_3	OCH_2Ph
(11a)	10.87	7.12	6.71	8.91	2.66		11.17	7.44	7.07	7.85	3.87	
	($J_{2,3}$ 5.5, $J_{3,4}$ 7.4)							($J_{7,8}$ 8.7, $J_{8,10}$ 2.5)				
(11b)	10.89	7.13	6.71	8.90	2.66		11.20	7.45	7.15	7.96		5.22,
	($J_{2,3}$ 5, $J_{3,4}$ 7.5, $J_{2,4}$ 0.5)				($J_{11,5\alpha}$ 0.5)			($J_{7,8}$ 8.8, $J_{8,10}$ 2.5)				7.35—7.55
(11c)	10.64	7.06	6.63		2.60	3.45	11.15	7.47	7.12	7.78	3.87	
	($J_{2,3}$ 6.0, $J_{3,4}$ 7.4, $J_{2,4}$ 1.5)							($J_{7,8}$ 8.7, $J_{8,10}$ 2.4)				
(11d)	10.65	7.06	6.63		2.58	3.41	11.16	7.46	7.18	7.86		5.22,
	($J_{2,3}$ 5.5, $J_{3,4}$ 7.5, $J_{2,4}$ 1.3)							($J_{7,8}$ 8.8, $J_{8,10}$ 2.4)				7.35—7.55
(12a)		8.18	7.97	9.04	2.35		11.38	7.50	7.19	8.07	3.92	
		($J_{3,4}$ 6.1, $J_{4,11}$ 0.9)		($J_{10,11}$ 0.3, $J_{11,5\alpha}$ 0.6)				($J_{7,8}$ 8.7, $J_{8,10}$ 2.5, $J_{7,10}$ 0.6)				
(12b)		8.17	7.99	9.02	2.84		11.39	7.51	7.27	8.19		5.25,
		($J_{3,4}$ 6.1, $J_{4,11}$ 1.0)			($J_{11,5\alpha}$ 0.4)			($J_{7,8}$ 8.7, $J_{8,10}$ 2.5)				7.35—7.55
(12c)		8.09	7.87		2.74	3.42	11.29	7.50	7.21	7.83	3.89	
		($J_{3,4}$ 6.0)						($J_{7,8}$ 8.7, $J_{8,10}$ 2.5)				
(12d)		8.11	7.89		2.76	3.40	11.35	7.52	7.29	7.94		5.25,
		($J_{3,4}$ 5.9)						($J_{7,8}$ 8.8, $J_{8,10}$ 2.3)				7.35—7.55
(15)	10.88	7.11	6.70	8.75	2.64		11.05	7.35	6.96	7.53	9.04	
	($J_{2,3}$ 5.5, $J_{3,4}$ 7.5)							($J_{7,8}$ 8.6, $J_{8,10}$ 2.5)				(9-OH)

Precision (on last digit): 0.002 p.p.m.; (on *J* values) 0.2 Hz.

TABLE 2

^{1}H N.m.r. characteristics [a] of pyrido[4,3-*b*]carbazoles (13 a—f) ($NH\text{–}\overset{\alpha}{C}H_2\text{–}\overset{\beta}{C}H_2\overset{\gamma}{C}H_2\text{–}NEt_2$)

Compound	3-H	4-H	11-H	5-CH_3	11-CH_3	6-NH	7-H	8-H	10-H	OH	OCH_3	OCH_2Ph	1-NH	α-CH_2	β-CH_2	γ-CH_2	CH_2–CH_3
(13a)	7.81	7.02	8.82	2.69		10.96	7.43	7.10	7.64		3.89		7.51	3.56	1.84	2.45	2.53 1.01
	($J_{3,4}$ 6.3)							($J_{7,8}$ 8.7, $J_{8,10}$ 2.5)						($J_{NH,\alpha\text{-}CH_2}$ 5, J_{CH_2,CH_2} 7)			(J 7.0)
(13b)	7.81	7.02	8.81	2.69		11.00	7.44	7.18	7.74			5.22, 7.35—7.55	Exch.	3.57	1.84	2.45	2.53 1.00
	($J_{3,4}$ 6.2)							($J_{7,8}$ 8.6, $J_{8,10}$ 2.5)						(J_{CH_2,CH_2} 6.9)			(J 7.0)
(13c)	7.75	6.97 *		2.63	3.33	10.92	7.43	7.11	7.74 *		3.88		6.44	3.50	1.81	2.55	2.50 0.95
	($J_{3,4}$ 6.1)							($J_{7,8}$ 8.6, $J_{8,10}$ 2.4, $J_{7,10}$ 0.3)						($J_{NH,\alpha\text{-}CH_2}$ 5, J_{CH_2,CH_2} 6.9)			(J 7.0)
(13d)	7.75	6.97		2.62	3.28	10.94	7.43	7.18	7.81			5.23, 7.35—7.55		3.49	1.81	2.55	2.50 0.95
	($J_{3,4}$ 6.2)							($J_{7,8}$ 8.7, $J_{8,10}$ 2.4)						($J_{NH,\alpha\text{-}CH_2}$ 5, J_{CH_2,CH_2} 6.8)			(J 7.1)
(13e)	7.79	7.00	8.71	2.66		10.82	7.32	6.95	7.49	9.03			7.61	3.56	1.83	2.45	2.54 1.01
	($J_{3,4}$ 6.2)							($J_{7,8}$ 8.7, $J_{8,10}$ 2.3)						($J_{NH,\alpha\text{-}CH_2}$ 5, J_{CH_2,CH_2} 6.9)			(J 7.0)
(13f)	7.74	6.96		2.62	3.28	10.77	7.32	6.94	7.65	8.93			6.45	3.51	1.81	2.50	2.51 0.96
	($J_{3,4}$ 6.2)							($J_{7,8}$ 8.6, $J_{8,10}$ 2.4)						($J_{NH,\alpha\text{-}CH_2}$ 5, J_{CH_2,CH_2} 6.9)			(J 7.1)

* Nuclear Overhauser 4-H enhancement: {5α-CH_3} 20%; 10-H {11α-CH_3} 40%. Precision, on last digit, 0.002 p.p.m.; on *J* values, 0.2 Hz.

[a] For conditions see Table 1.

EXPERIMENTAL

M.p.s were determined with a Reichert hot stage microscope. I.r. spectra were obtained in KBr pellets with a Perkin-Elmer double beam spectrometer model 21. Unless otherwise stated, n.m.r. spectra were recorded with an Hitachi–Perkin-Elmer 60-MHz apparatus [solvent $(CD_3)_2SO$; Me_4Si as internal standard].

4-Alkoxyphenylhydrazone of Cyclohexane-1,2-diones (3a—d).—*p*-Anisidine (123 g, 1 mol) in ice-cooled 4N-hydrochloric acid (500 ml) or *p*-benzyloxyaniline hydrochloride (235.5 g, 1 mol) in ice-cooled 2N-hydrochloric acid (500 ml) was stirred at 0 °C and the mixture was treated dropwise with aqueous sodium nitrite (69 g) below 5 °C. To the resulting solution, the required enamine [16] (1 mol) in dry dioxan (400 ml) was added over 15 min with vigorous stirring and the mixture was left at room temperature for 1 h. The red precipitate was then collected and purified in boiling alcohol, giving the expected arylhydrazone which was sufficiently pure for the next reaction. However, analytical samples were recrystallized from alcohol. All compounds gave $\nu_{max.}$ 3 220—3 240 (NH), 1 660—1 665 (C=O), and 1 490—1 495 (C=N) cm^{-1}. Compound (3a) (85%) had m.p. 204—205 °C (lit.,[8a] 233—235 °C) (Found: C, 67.2; H, 6.8; N, 12.0. Calc. for $C_{13}H_{16}N_2O_2$: C, 67.2; H, 6.9; N, 12.0%); (3b) (76%), m.p. 161—162 °C (Found: C, 73.7; H, 6.3; N, 9.2. $C_{19}H_{20}N_2O_2$ requires C, 74.0; H, 6.5; N, 9.0%); (3c) (77%), m.p. 159—160 °C (decomp.) (Found: C, 68.5; H, 7.2; N, 11.5. $C_{14}H_{18}N_2O_2$ requires C, 68.2; H, 7.3; N, 11.3%); and (3d) (82%), m.p. 165 °C (Found: C, 74.3; H, 6.6; N, 8.7. $C_{20}H_{22}N_2O_2$ requires C, 74.5; H, 6.8; N, 8.6%).

6-Alkoxy-3,4-dihydrocarbazol-1(2H)-ones (4a—d).—The hydrazone (3) (1 mol) was added to a solution of sulphuric acid (*d* 1.84; 196 g) in dry alcohol (2.5 l). The mixture was stirred and heated under reflux until the starting material disappeared on t.l.c. (silica; benzene–alcohol 4 : 1) (2—4 h). The cooled mixture was filtered, the crystallized solid was collected, and the mother liquor was concentrated to 800 ml. After addition of water (1 200 ml), it was stirred overnight at room temperature and filtered, giving another fraction of the expected product. The whole solid was then washed with water and recrystallized in the given solvent. All products have $\nu_{max.}$ 3 220—3 260 (NH) and 1 630—1 640 (C=O) cm^{-1}. Compound (4a) (60%) had m.p. 216—219 °C (from alcohol) (lit.,[9b] 215—217 °C) (Found: C, 72.3; H, 6.2; N, 6.5. Calc. for $C_{13}H_{13}NO_2$: C, 72.5; H, 6.0; N, 6.5%); (4b) (40%), m.p. 211 °C (from dimethylformamide) (Found: C, 78.0; H, 5.9; N, 4.7. $C_{19}H_{17}NO_2$ requires C, 78.3; H, 5.8; N, 4.8%); (4c) (30%), b.p. 214—240 °C at 0.15 Torr, m.p. 133—134 °C (from alcohol) (Found: C, 73.4; H, 6.5; N, 6.2. $C_{14}H_{15}NO_2$ requires C, 73.3; H, 6.6; N, 6.1%); (4d) (50%), m.p. 193 °C (from xylene) (Found: C, 78.8; H, 6.2; N, 4.3. $C_{20}H_{19}NO_2$ requires C, 78.6; H, 6.2; N, 4.5%).

6-Alkoxy-2-hydroxymethylene-3,4-dihydrocarbazol-1(2H)-ones (5a—d).—To a 3,4-dihydrocarbazol-1(2*H*)-one (4) (1 mol) in ethyl formate (1.3 l) was added portionwise sodium hydride (2 mol; 50% in mineral oil). An exothermic reaction was observed. After 30 min with stirring, a second portion of sodium hydride (2 mol) was added and the reaction was left for a further 30 min. The cooled mixture was then poured into cold water (2.5 l), acidified by hydrochloric acid, and the product was filtered off and recrystallized giving yellow crystals, $\nu_{max.}$ 3 200—3 280 (OH) and 1 625—1 635 (C=O) cm^{-1}. Compound (5a) (85%) had m.p. 165—170 °C (from CH_3OH–H_2O, 3 : 2) (Found: C, 69.3; H, 5.4; N, 5.4. $C_{14}H_{13}NO_3$ requires C, 69.1; H, 5.3; N, 5.7%); (5b) (95%), m.p. 190 °C (from acetic acid) (Found: C, 75.5; H, 5.5; N, 4.1. $C_{20}H_{17}NO_3$ requires C, 75.2; H, 5.3; N, 4.3%); (5c) (86%), m.p. 175—177 °C (from benzene) (Found: C, 70.1; H, 5.7; N, 5.2. $C_{15}H_{15}NO_3$ requires C, 70.0; H, 5.8; N, 5.4%); (5d) (77.5%), m.p. 178—182 °C (decomp.) (from xylene) (Found: C, 75.8; H, 5.9; N, 3.9. $C_{21}H_{19}NO_3$ requires C, 75.6; H, 5.7; N, 4.2%).

6-Alkoxy-2-isopropoxymethylene-3,4-dihydrocarbazol-1(2H)-ones (6a—d).—Compound (5) (1 mol), freshly distilled dimethylformamide (960 ml), and anhydrous potassium carbonate (498 g, 3.5 mol) were mixed and cooled below 5 °C. To this stirred mixture, immersed in an ice-cold bath, isopropyl iodide (840 g, 5 mol) was added over 1 h and stirring at 0.5 °C was continued for a further 6 h. Finally, the mixture was left for 1 h to reach room temperature, filtered, and the solid was washed with acetone. The filtered solid and the residue from solvent evaporation were taken up in water. The solids were collected and then recrystallized giving yellow needles, $\nu_{max.}$ 1 650—1 655 cm^{-1} (C=O); δ 1.25—1.4 (CH_3CH, *J* 6 Hz), 2.1—2.4 (CH), and 4.3—4.45 (=CH). Compound (6a) (84%) had m.p. 187—195 °C (from alcohol) (Found: C, 71.7; H, 6.9; N, 4.7. $C_{17}H_{19}NO_3$ requires C, 71.5; H, 6.7; N, 4.9%); (6b) (60%), m.p. 198 °C (from xylene) (Found: C, 76.1; H, 6.6; N, 3.9. $C_{23}H_{23}NO_3$ requires C, 76.4; H, 6.4; N, 3.8%); (6c) (67%), m.p. 167 °C (from methanol or cyclohexane) (Found: C, 71.9; H, 6.8; N, 4.6. $C_{18}H_{21}NO_3$ requires C, 72.2; H, 7.0; N, 4.6%); (6d) (60%), m.p. 146—155 °C (from cyclohexane) (Found: C, 76.9; H, 6.7; N, 3.4. $C_{24}H_{25}NO_3$ requires C, 76.7; H, 6.7; N, 3.7%).

6-Alkoxy-2-formyl-1-methyl-3,4-dihydrocarbazoles (7a—d).—Isopropyl ether (6) (0.175 mol) was dissolved in dry diethyl ether (600 ml) and to the stirred, ice-cooled mixture, protected by a calcium chloride tube, an ether solution of methyl-lithium (1.3N; 538 ml, 0.7 mol) was added dropwise. A red-brown colour appeared, stirring was continued for 30 min, and the mixture was poured into a saturated ammonium chloride solution (2 l). The resulting mixture was extracted with diethyl ether (4 × 500 ml) and the combined extracts were stirred for 15 min with 6N-hydrochloric acid (200 ml) giving a brown precipitate. The mixture was then adjusted to pH 9—10 by dropwise addition of 1N-sodium hydroxide solution at room temperature, extracted with chloroform, and the combined extracts were washed with water. After drying (Na_2SO_4), the solvent was evaporated, giving a solid residue. For compounds (7a—c), the solid was taken up in benzene (100 ml), filtered, and recrystallized. In the case of compound (7d), it was chromatographed on silica (700 g) with methylene chloride as eluant. Compounds (7) formed yellow crystals, $\nu_{max.}$ 1 605—1 620 cm^{-1} (C=O); δ 2.45—2.55 (1-CH_3), 10.1—10.6 (CHO), and 1.2 [4-CH_3 (7c and d)]. Compound (7a) (80%) had m.p. 194 °C (from xylene) (Found: C, 74.7; H, 6.1; N, 5.8. $C_{15}H_{15}NO_2$ requires C, 74.6; H, 6.2; N, 5.8%); (7b) (76%), m.p. 158 °C (from benzene) (Found: C, 80.8; H, 6.4; N, 3.9. $C_{21}H_{19}NO_2$ requires C, 80.8; H, 6.1; N, 3.9%); (7c) (86%), m.p. 208 °C (from xylene) (Found: C, 75.5; H, 6.7; N, 5.2. $C_{16}H_{17}NO_2$ requires C, 75.2; H, 6.7; N, 5.4%); (7d) (96.5%), m.p. 78—80 °C (from benzene) (Found: C, 80.9; H, 6.3; N, 3.5. $C_{22}H_{21}NO_2,0.5C_6H_6$ requires C, 81.0; H, 6.4; N, 3.7%).

6-Alkoxy-2-formyl-1-methylcarbazoles (8a—d).—In a 4-l

round-bottomed flask equipped with a mechanical stirrer and a Dean–Stark apparatus fitted on a reflux condenser were placed dihydrocarbazole (7) (0.1 mol) and dry benzene (2 l). The mixture was heated at reflux and after dissolution of starting material, active manganese dioxide [17] (110 g, 1.26 mol) was added. Reflux under vigorous stirring was continued for 30 min, and using a well ventilated hood, manganese dioxide was filtered off and washed well with acetone or hot chloroform, till complete extraction of the expected product. After evaporation of the solvent to dryness, the solid residue was recrystallized giving yellow crystals, $\nu_{max.}$ 1 650—1 675 (C=O) cm^{-1}; δ 2.8—2.9 (1-CH_3), 10.4—10.8 (CHO), and 2.8 [4-CH_3 (8c and 8d)]. Compound (8a) (70%) had m.p. 174 °C (from benzene or alcohol) (Found: C, 75.3; H, 5.6; N, 5.9. $C_{15}H_{13}NO_2$ requires C, 75.3; H, 5.4; N, 5.8%); (8b) (73%), m.p. 205 °C (from xylene) (Found: C, 79.9; H, 5.3; N, 4.7. $C_{21}H_{17}NO_2$ requires C, 79.8; H, 5.0; N, 4.4%); (8c) (88%), m.p. 158—160 °C (from cyclohexane) (Found: C, 75.7; H, 6.1; N, 5.6. $C_{16}H_{15}NO_2$ requires C, 75.8; H, 5.9; N, 5.5%); (8d) (50%), m.p. 162—164 °C (from xylene) (Found: C, 81.6; H, 6.0; N, 3.5. $C_{22}H_{19}NO_2,0.5C_8H_{10}$ requires C, 81.6; H, 6.2; N, 3.6%).

trans-β-(6-*Alkoxy*-1-*methylcarbazol*-2-*yl*)*acrylic Acids* (9a—d).—Formylcarbazole (8) (0.2 mol) was dissolved in dry pyridine (800 ml) containing piperidine (3 ml) and the mixture was heated under reflux. Malonic acid (22.9 g, 0.22 mol) was added at once and reflux was continued for 15 min. This treatment with malonic acid (0.22 mol) was repeated twice, then pyridine was evaporated under reduced pressure. The solid residue was taken up in water, filtered, washed with water and acetone, then purified in acetic acid giving yellow crystals, $\nu_{max.}$ 1 660—1 665 (C=O) and 3 400 and 3 200—2 200 (OH) cm^{-1}; δ 6.5—6.6 and 8.1—8.2 (CH=CH, *J* 16 Hz). Compound (9a) (90%) had m.p. 293—295 °C (decomp.) (Found: C, 70.4; H, 5.3; N, 4.8. $C_{17}H_{15}NO_3,0.5H_2O$ requires C, 70.3; H, 5.5; N, 4.8%); (9b) (88.5%), m.p. 265—266 °C (Found: C, 77.2; H, 5.0; N, 3.8. $C_{23}H_{19}NO_3$ requires C, 77.2; H, 5.3; N, 3.9%); (9c) (66%), m.p. 288—298 °C (decomp.) (Found: C, 72.8; H, 5.8; N, 4.4. $C_{18}H_{17}NO_3$ requires C, 73.2; H, 5.8; N, 4.7%); (9d) (75%), m.p. 258—264 °C (decomp.) (Found: C, 77.3; H, 5.5; N, 3.4. $C_{24}H_{21}NO_3$ requires C, 77.6; H, 5.7; N, 3.7%).

trans-β-(6-*Alkoxy*-1-*methylcarbazol*-2-*yl*)*acryloyl Azides* (10a—d).—Acrylic acid (9) (0.1 mol) was added to a solution of triethylamine (11.1 g, 0.11 mol) in acetone (260 ml). Maintaining the temperature at 0 °C, a solution of ethyl chloroformate (14.75 g, 0.136 mol) in acetone (90 ml) was added dropwise. The mixture was then stirred at 0 °C for 1 h and then a solution of sodium azide (9.5 g, 0.15 mol) in water (20 ml) was added progressively. The mixture was stirred in the cold for a further 1 h, left to reach room temperature, and poured into ice–water (1 l). The solid was collected, washed with water and a small quantity of acetone, and dried. The azide was used for the following reaction without further purification.

9-*Alkoxy*-5-*methylpyrido*[4,3-*b*]*carbazol*-1(2H)-*ones* (11a—d).—A mixture of diphenyl ether (180 ml) and tributylamine (14.1 g, 22 mmol) was heated in a three-necked flask to 240 °C. A suspension of azide (10) (20 mmol) in diphenyl ether (50 ml) at 40 °C was added to the preceding solution with vigorous stirring, as quickly as possible, whilst maintaining the temperature at 240 °C. The mixture was kept at 240—245 °C for a further 20 min, diphenyl ether was removed under reduced pressure, and after cooling and addition of benzene (100 ml) and light petroleum ether, the solid obtained was collected. Pyrido[4,3-*b*]carbazoles (11) were then recrystallized, giving yellow crystals. In the case of compound (11a), however, purification was performed after extraction of the solid with aqueous 1N-potassium hydroxide solution, which gave a small quantity of recovered acid (9a), the presence of which was explained by its low solubility and consequently its incomplete transformation into azide (10a), $\nu_{max.}$ 2 800—3 350 (NH) and (OH) and 1 635—1 650 (C=O) cm^{-1}. Compound (11a) (47%) had m.p. 297—302 °C (from acetic acid) (Found: C, 73.5; H, 5.0; N, 9.9. $C_{17}H_{14}N_2O_2$ requires C, 73.3; H, 5.0; N, 10.0%); (11b) (72%), m.p. 258 °C (from dioxan) (Found: C, 74.3; H, 5.5; N, 7.3. $C_{23}H_{18}N_2O_2,H_2O$ requires C, 74.1; H, 5.4; N, 7.5%); (11c) (59%), m.p. 292—298 °C (from dioxan) (Found: C, 73.6; H, 5.5; N, 9.2. $C_{18}H_{20}N_2O_2$ requires C, 73.9; H, 5.5; N, 9.5%); (11d) (30%), m.p. 268—270 °C (from dioxan) (Found: C, 76.6; H, 5.5; N, 7.4. $C_{24}H_{20}N_2O_2,0.5H_2O$ requires C, 76.3; H, 5.6; N, 7.4%).

9-*Alkoxy*-1-*chloro*-5-*methyl*-6H-*pyrido*[4,3-b]*carbazoles* (12a—d).—A suspension of pyrido[4,3-*b*]carbazone (11) (20 mmol) in phosphorus oxychloride (1 l) was warmed to reflux under stirring for 3 (12a), 6 (12b), and 7 h (12c and d), respectively. Dissolution of starting material, precipitation of a solid, and dissolution of the precipitate were observed. The excess of phosphorus oxychloride was removed under reduced pressure. The residue was taken up in water in the presence of chloroform, treated under stirring with aqueous 1N-sodium hydroxide solution to adjust the pH to 8—9, and stirring was continued till the disappearance of the red colour. The solid was collected. Chloroform was evaporated and the combined solids were recrystallized, affording yellow or orange crystals. Compound (12a) (73%) had m.p. 264 °C (from ethyl acetate) (Found: C, 68.5; H, 4.4; N, 9.2; Cl, 11.8. $C_{17}H_{13}ClN_2O$ requires C, 68.8; H, 4.3; N, 9.4; Cl, 11.9%); (12b) (88%), m.p. 248—250 °C (from ethanol and xylene successively) (Found: C, 72.7; H, 4.8; N, 6.9; Cl, 9.11. $C_{23}H_{17}ClN_2O{\cdot}0.5C_2H_5OH$ requires C, 72.8; H, 5.0; N, 7.0; Cl, 8.9%); (12c) (25%) m.p. 241—245 °C (from xylene) (Found: C, 69.8; H, 5.0; N, 9.2; Cl, 11.6. $C_{18}H_{15}ClN_2O$ requires C, 69.5; H, 4.8; N, 9.0; Cl, 11.4%); (12d) (70%), m.p. 221—222 °C (from xylene) (Found: C, 74.6; H, 5.1; N, 7.3.; Cl, 9.0. $C_{24}H_{19}ClN_2O$ requires C, 74.5; H, 4.9; N, 7.2; Cl, 9.1%).

9-*Alkoxy*-1-(γ-*diethylaminopropylamino*)-5-*methyl*-6H-*pyrido*[4,3-b]*carbazoles* (13a—d).—Chloro-derivative (12) (500 mg) was mixed with γ-diethylaminopropylamine (8 ml) under nitrogen and heated to reflux until the disappearance of the starting chloro-derivative on t.l.c. (1.5—2.5 h). The excess of amine was recovered under reduced pressure and the residue, taken up in 1N-sodium hydroxide solution (100 ml), afforded a solid which was then collected, dried, and recrystallized. Compound (13a) (23%) had m.p. 185—187 °C (from acetonitrile) (Found: C, 72.7; N, 7.7.; N, 15.8. $C_{24}H_{30}N_4O{\cdot}CH_3CN$ requires C, 72.3; H, 7.7; N, 16.2%); (13b) (78.4%), m.p. 207—214 °C (from alcohol) (Found: C, 76.9; H, 7.3; N, 11.7. $C_{30}H_{34}N_4O$ requires C, 77.2; H, 7.3; N, 12.0%); (13c) (47%), m.p. 156 °C (from cyclohexane) (Found: C, 73.9; H, 7.9; N, 13.9. $C_{25}H_{32}N_4O$ requires C, 74.2; H, 7.9; N, 13.8%); (13d) (50%), m.p. 175 °C (from xylene) (Found: C, 77.1; H, 7.3; N, 11.6. $C_{31}H_{36}N_4O$ requires C, 77.4; H, 7.5; N, 11.6%).

9-*Hydroxy*-1-(γ-*diethylaminopropylamino*)-5-*methyl*- *and*

5,11-*dimethyl*-6H-*pyrido*[4,3-b]*carbazoles* (13e *and* f).—The benzyloxy-derivative (13c and d) (1 mmol) in absolute alcohol (100 ml) were heated at 50 °C and stirred with palladium–charcoal (30%, 40 mg) under hydrogen. The reaction was complete when t.l.c. indicated the disappearance of the starting material (4 h). Filtration and removal of the alcohol under reduced pressure afforded a solid residue which was then recrystallized from xylene, giving yellow crystals. Compound (13e) (85%) had m.p. 218—224 °C (Found: C, 71.9; H, 7.5; N, 14.2. $C_{23}H_{28}N_4O\cdot 0.5H_2O$ requires C, 71.7; H, 7.5; N, 14.5%); (13f) (62%), m.p. 125 °C (Found: C, 70.8; H, 7.6; N, 13.4. $C_{24}H_{30}N_4O\cdot H_2O$ requires C, 70.5; H, 7.9; N, 13.7%).

9-*Hydroxy*-5-*methyl*-6H-*pyrido*[4,3-b]*carbazol*-1(2H)-*one* (15).—9-Methoxypyrido[4,3-*b*]carbazole (11a) (5 g, 18 mmol) and anhydrous pyridine hydrochloride (50 g) were heated to reflux (220—230 °C) for 30 min. The mixture was poured in ice–water. The solid was filtered off, washed with water, and recrystallized from alcohol (charcoal) giving beige crystals (2.6 g, 55%), m.p. >350 °C (Found: C, 72.5; H, 4.3; N, 10.4. $C_{16}H_{12}N_2O_2$ requires C, 72.7; H, 4.3; N, 10.6%).

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