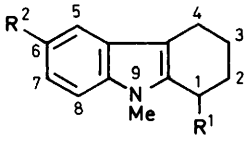
Synthetic Studies of Indoles and Related Compounds, Part 22.[1] The Vilsmeier–Haack Reaction of *N*-Benzyl-1,2,3,4-tetrahydrocarbazoles and its Synthetic Application to Olivacine and Ellipticine[2]

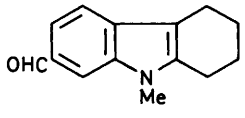
Yuusaku Yokoyama, Naomi Okuyama, Shinji Iwadate, Tokuko Momoi, and Yasuoki Murakami *
School of Pharmaceutical Sciences, Toho University, 2-2-1, Miyama, Funabashi, Chiba 274, Japan

Vilsmeier–Haack reaction of 9-benzyl-1,2,3,4-tetrahydrocarbazole (**18a**) at 120 °C gave 9-benzyl-1-methylcarbazole-3-carbaldehyde (**19a**) and 9-benzyl-1-[*N,N*-(dimethylamino)methyl]carbazole-3-carbaldehyde (**22a**) in moderate yields, whereas, the same reaction at 0 °C gave 9-benzyl-1,2,3,4-tetrahydrocarbazole-1-carbaldehyde (**20a**) in very good yield. The aldehyde (**20a**) was converted into 9-benzyl-1-methylcarbazole (**21a**) by another Vilsmeier–Haack reaction. This carbazole (**21a**) unexpectedly underwent non-regioselective formylation under similar reaction conditions to give a mixture of compound (**19a**) and 9-benzyl-8-methylcarbazole-3-carbaldehyde (**23a**). On the basis of the above results, a mechanism of the formation of the aromatic aldehyde (**19a**) was proposed, which involves 1,5-sigmatropic rearrangement of an *N*-methylidene dimethylammonium cation from the 4a-position to the 3-position as a key step. Vilsmeier–Haack reaction of 9-benzyl-1,2,3,4-tetrahydro-4-methylcarbazole (**18b**) at 100 °C also gave 9-benzyl-1,4-dimethylcarbazole-3-carbaldehyde (**19b**) in moderate yield. The total syntheses of two antitumour alkaloids, olivacine (**10**) and ellipticine (**11**), were achieved by utilizing compounds (**19a**) and (**19b**) as key intermediates.

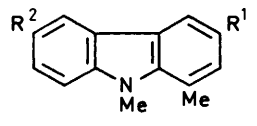
Kucherova has reported[3] that Vilsmeier–Haack (V–H) reaction [$POCl_3$ in diethylformamide (DEF)] of 9-methyl-1,2,3,4-tetrahydrocarbazole (1,2,3,4-tetrahydrocarbazole is abbreviated as THC) (**1**) at 100 °C gave 7-formyl-THC (**5**), whereas Bruck has described[4] that the same compound (**1**) gave a quite abnormal product, 1,9-dimethylcarbazole-3-carbaldehyde (**6**), as the sole product under similar conditions [$POCl_3$ in dimethylformamide (DMF)]. Later, Murakami and Ishii reinvestigated[5] this reaction in some detail to clarify these confused results. They obtained Bruck's product (**6**) as a main product accompanied by several minor components which were Kucherova's product (**5**), unstable 1,2,3,4-tetrahydro-9-methylcarbazole-1-carbaldehyde (**2**), and 1,9-dimethylcarbazole (**7**). Furthermore they carried out stepwise conversion of 6-chloro-9-methyl-THC (**3**) to fully aromatized aldehyde (**8**). Namely, 6-chloro-1-formyl-9-methyl-THC (**4**), obtained by V–H reaction of (**3**), was aromatized under V–H conditions to give 6-chloro-1,9-dimethylcarbazole (**9**), which was then formylated at C-3 by a third V–H reaction. On the basis of the above results, they suggested[5] the plausible mechanism for the formation of the 3-aldehyde (**6**) as shown in Scheme 1. Iminium salt[6] (**12**) formed from DMF and $POCl_3$ attacked the C-1 position of the enamine tautomer (**13**) to give 1-substituted intermediate (**14**). This intermediate was converted into fully aromatized compound



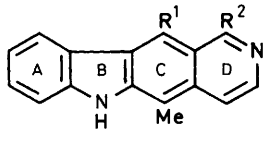
(**1**) $R^1 = R^2 = H$
(**2**) $R^1 = CHO$, $R^2 = H$
(**3**) $R^1 = H$, $R^2 = Cl$
(**4**) $R^1 = CHO$, $R^2 = Cl$



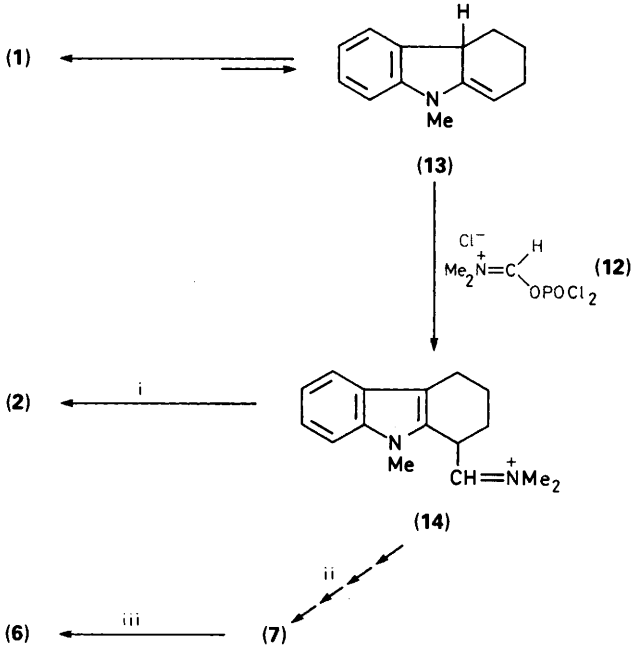
(**5**)



(**6**) $R^1 = CHO$, $R^2 = H$
(**7**) $R^1 = R^2 = H$
(**8**) $R^1 = CHO$, $R^2 = Cl$
(**9**) $R^1 = H$, $R^2 = Cl$



(**10**) $R^1 = H$, $R^2 = Me$ Olivacine
(**11**) $R^1 = Me$, $R^2 = H$ Ellipticine



Scheme 1. *Reagents and conditions:* i, water; ii, prototropy, $-Me_2NH$; iii, (**12**).

Table. Vilsmeier–Haack reaction of 9-benzyl-1,2,3,4-tetrahydrocarbazole (**18a**) and 9-benzyl-1,2,3,4-tetrahydro-4-methylcarbazole (**18b**) under various conditions.

Run	Starting materials	Reaction condition[a]			Yield (%)[b]				
		$POCl_3$ (mol equiv.)	Temp. (°C)	Time (h)	(17)	(19)	(20)	(21)	(22)
1	(18a)[c]	1.0	120	2.0	5	18	3		8
2	(18a)	2.0	120	2.0	trace	45[d]			18
3	(18a)	3.0	120	2.0		38		1	26
4	(18a)	3.0[e]	120	1.0	16	22	8		4[f]
5	(18a)	3.0	140	2.0		20		4	13
6	(18a)	3.0	100	2.0		28	11	1	20
7	(18a)	3.0	0	2.5			90		
8	(18a)	2.0	0	2.5			90		
9	(18a)[g]	1.0	0	2.5			46		
10	(18b)	2.6	100	6.0		38	9		15
11	(18b)	2.6	120	6.0		14			
12	(18b)	2.6	0	6.0			88		
13	(1a)[h]	1.2	100	8.0	34[j]				
14	(1a)[i]	1.3	?	?		55[k]			

[a] Concentration of $POCl_3$ was adjusted to 20% (w/w) by changing the amount of DMF. [b] All yields were isolated ones unless otherwise noted. [c] 21% of starting material was recovered. [d] Contaminated by trace amount of (**17**). [e] DEF was used instead of DMF. [f] Diethylaminomethyl group was substituted instead of dimethylaminomethyl group at 1-position of (**22a**). [g] 48% of starting material was recovered. [h] Kucherova's data.[3] [i] Bruck's data.[4] [j] Product was (**5**). [k] Product was (**6**).

(**7**) by the sequence of prototropy and elimination of dimethylamine. Then, the carbazole (**7**) underwent a second formylation to give final product (**6**). In this mechanism, the intermediates (**14**) [or its hydrolysed product (**2**)] and (**7**) were considered to be key intermediates. This reaction is not only mechanistically interesting, but also synthetically useful for the total syntheses of antitumour alkaloids, such as olivacine[7] (**10**) and ellipticine[8] (**11**), because the 3-formyl group of the aromatic aldehyde (**6**) would be useful for the construction of the pyridine nucleus (ring D) of compounds (**10**) and (**11**). Here we report some new results which lead us to a more reasonable mechanism for this abnormal V–H reaction, and to short-step syntheses of olivacine (**10**) and ellipticine (**11**).

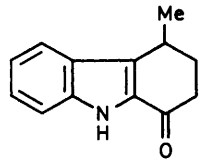
Results and Discussion

Preparation of Starting Materials.—As substrates for the V–H reaction, 9-benzyl-THC (**18a**) and its 4-methyl derivative (**18b**) were selected, because the benzyl group could be removed by Birch reduction at the appropriate stage during the synthesis of olivacine (**10**) and ellipticine (**11**). 9-Benzyl-THC (**18a**) was prepared by benzylation of the corresponding NH-compound according to the reported method.[9] The known indolic ketone (**15**),[10] which was an intermediate in the synthesis of compound (**18b**), was obtained in very low yield (25%) by the reported Fischer indolization[10] of the hydrazone (**16**) (reflux in acetic acid). However, the yield was improved (72–75% yield) by employing our modified Fischer indolization conditions[11] [toluene-*p*-sulphonic acid (PTSA) or ion-exchange resin, Amberlist 15A, in aprotic media (benzene or toluene)].

Vilsmeier–Haack Reaction of 9-*Benzyl-* (**18a**) *and* 9-*Benzyl-*4-*methyl-THC* (**18b**).—The V–H reaction of compound (**18a**) was studied in detail first. The V–H reaction was carried out under various molar ratios of $POCl_3$ in DMF and reaction temperatures, and the results are summarized in the Table.

In the reaction using 1 mol equiv. of $POCl_3$ at 120 °C, the desired aromatic aldehyde (**19a**) was isolated in only 18% yield from a complex mixture (run 1). The use of 2 mol equiv. of $POCl_3$ gave the highest yield of aldehyde (**19a**) (45%, run 2). However, this compound was contaminated by traces of the 7-formyl-THC (**17**). This compound was very difficult to remove from (**19a**) by column chromatography or recrystallization. The use of a greater excess of $POCl_3$ (3.0 mol equiv., run 3) gave a slightly lower yield (38%) of the desired aldehyde (**19a**) than in run 2, but the contaminant (**17**) was not detected in the reaction mixture. Interestingly, the yield of the 7-formyl-THC (**17**) increased when DEF was used instead of DMF (run 4). DEF was used by Kucherova who isolated[3] the 7-formyl-THC (**5**), corresponding to the analogue (**17**), as the sole product (run 13). On the basis of this result, we have reported[12] the effect of formamides on the V–H reaction; the regioselectivity on V–H reaction of compound (**18a**) has been changed dramatically by the choice of various formamides.

The effect of temperature was also important. Higher temperature than 120 °C gave a worse yield of the desired aldehyde (**19a**) due to decomposition of products (run 5), whereas a lower temperature than 120 °C was insufficient to complete the reaction, for the 1-formyl-THC (**20a**) was isolated in appreciable amounts (run 6). The reactions at 0 °C gave quite different results. The 1-formyl-THC (**20a**) was obtained in almost quantitative yield at 0 °C when we used 2 or 3 mol equiv. of $POCl_3$ (runs 7 and 8), while the use of 1 mol equiv. of $POCl_3$ (run 9) gave compound (**20a**) in 46% yield, accompanied by starting material (**18a**) (48% recovery). It is noteworthy that 1 mol equiv. of $POCl_3$ was not enough to complete the reaction in spite of the introduction of only one formyl group into starting compound (**18a**). It is also surprising that the C-1 position, which seemed to be unreactive toward electrophiles, was easily formylated under the very mild conditions used. Similar results have been reported by serveral groups.[13] For example, 1,2,3-trimethylindole (**24**) was formylated at the C-2 methyl group[13a] under V–H reaction conditions to give the aldehyde (**25**), and



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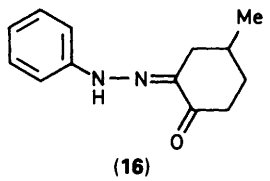

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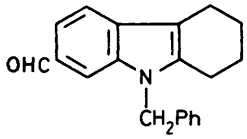

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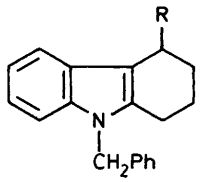
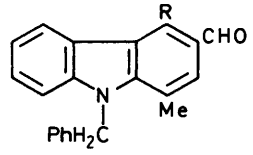
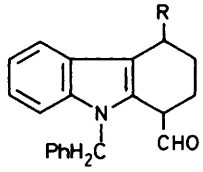


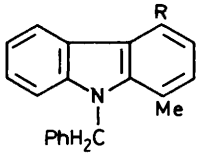
(18a,b)



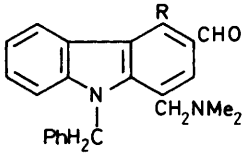
(19a,b)



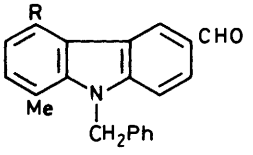
(20a,b)



(21a,b)



(22a,b)



(23a,b)

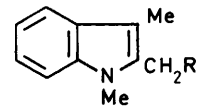
a; R = H, b; R = Me

reaction of 9-methyl-THC (1) with trifluoroacetic anhydride (TFAA) gave 1-trifluoroacetyl derivative (26).[13b]

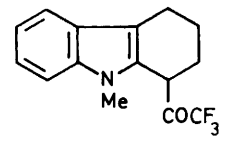
Next, we tried the V–H reaction of the 4-methyl-THC (18b). The yield of the aromatic aldehyde (19b) was comparable with that of (19a) at slightly lower temperature (100 °C) (run 10 *vs.* run 3). The reaction at 0 °C gave the 1-aldehyde (20b) in almost the same yield as that of (20a) (run 12 *vs.* run 4). These results show that the presence of a C-4 methyl group had little effect on the reactivity of the V–H reaction.

The structure of the products (17), (19), and (20) was determined by ^{1}H NMR and other spectral data in comparison with those of the corresponding *N*-methyl derivatives (5), (6), and (2).[5]

Appreciable amounts of 9-benzyl-1-[(*N*,*N*-dimethylamino)-methyl]carbazole-3-carbaldehyde (22a) and its 4-methyl derivative (22b) were isolated as by-products (runs 1, 2, 3, 5, 6, and 10). The yield of the amine (22a) was increased on increasing the molar ratio of $POCl_3$ (runs 1, 2, and 3). The



(24) R = H
(25) R = CHO



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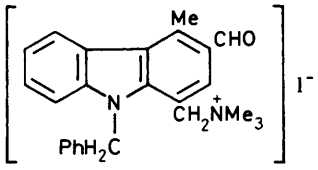

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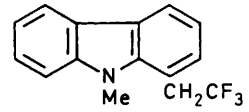


(28)

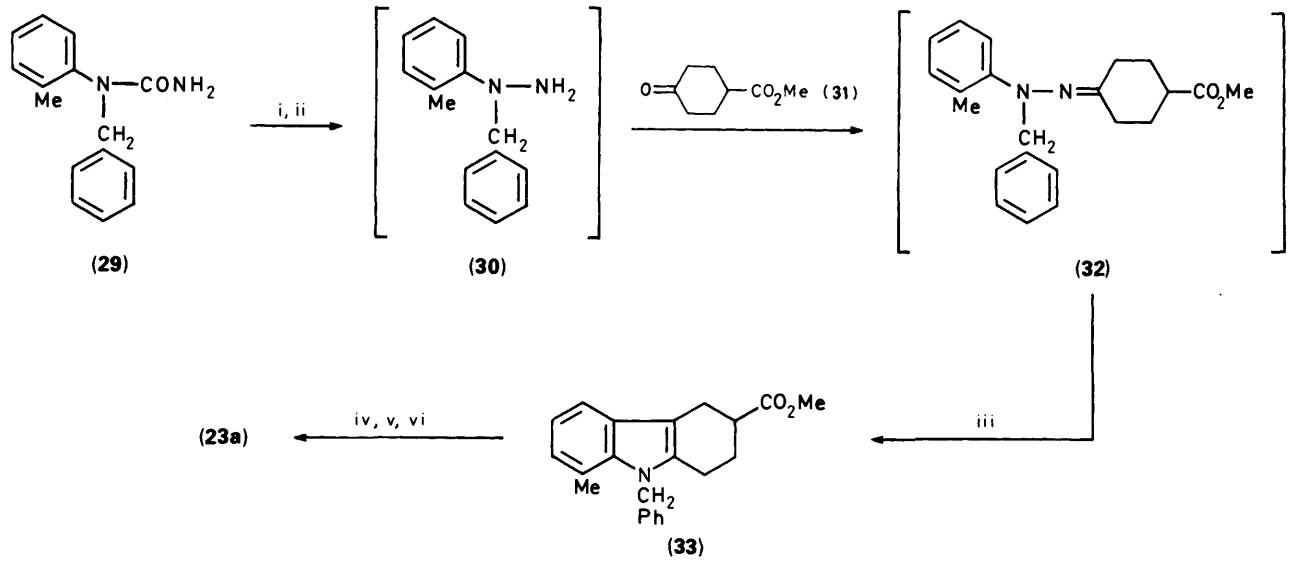
structure of those by-products (22) was closely related to that of 3-formyl-1-methylcarbazoles (19); the dimethylaminomethyl group was attached at C-1 in place of the methyl group of compound (19). The dimethylamino group of compound (22) should arise from DMF. The formation of those amines (22) could not be explained by the previously suggested mechanism[5] (*vide infra*). The structure of the amines (22), especially the position of the dimethylamino and formyl groups, was elucidated by ^{1}H NMR spectra in comparison with those of the aromatic aldehyde (19), and also confirmed by the conversion of amines (22b) into (19b) through hydrogenolysis of the quaternary salt (27) of (22b).

Although the aromatic aldehydes (19) were obtained in only moderate yields, it should be emphasized that a sequence of aromatization, methylation, and regioselective formylation occurred in one pot and that the products could be isolated by very simple chromatographic purification in reproducible yields. As a result, this reaction could be used for synthetic purposes. Bruck had reported[4] that the aromatic aldehyde (6) was obtained in 55% yield without describing the experimental details (run 14), but such a high yield could not be reproduced in the present investigation.

Stepwise conversion of the 9-Benzyl-THC (18) *into the Aromatic Aldehydes* (19).—In order to obtain further information on the reaction pathway to the aromatic aldehydes (19), we carried out stepwise conversion of compounds (18) into aldehydes (19) *via* the 1-formyl-THCs (20) and 1-methylcarbazoles (21). Compounds (20a) and (20b) were allowed to react under the V–H reaction conditions [1.2 mol equiv. $POCl_3$; 120 °C; 45 min for (20a); and 60 °C; 2 h for (20b)]. This reaction gave the expected[5] 1-methylcarbazoles (21a) (60%) and (21b) (44%). Bailey and co-workers also obtained[13b] similar results in that heating of 9-methyl-1-trifluoroacetyl-THC (26) with TFAA gave 9-methyl-1-trifluoroethylcarbazole (28). Consequently, a 1-acyl-THC generally undergoes dehydration and aromatization by the dehydrating (acylating) agent to give a 1-alkylcarbazole.

Surprisingly, the 1-methylcarbazoles (21) were formylated *non-regioselectively* at C-3 and C-6 by V–H reaction conditions to give a mixture of isomers (19a) + (23a) 70%, (19b) + (23b) 80% which had very close R_f-values on TLC, and thus the ratios of products were determined by high-pressure liquid chromatography (HPLC) analysis [(19a):(23a) 3:2, (19b):(23b) 4.5:1]. These results are in sharp contrast to the one-step regioselective conversion of (18) into (19), in which reaction only trace amounts of isomers (23) could be detected by HPLC analysis.

Although the structure of compounds (23) could be estimated by their ^{1}H NMR signals, an alternative synthesis of the isomer



Scheme 2. *Reagents and conditions:* i, NaOCl–NaOH; ii, H^+; iii, AcOH, reflux; iv, Pd–C; v, $LiAlH_4$; vi, pyridinium chlorochromate.

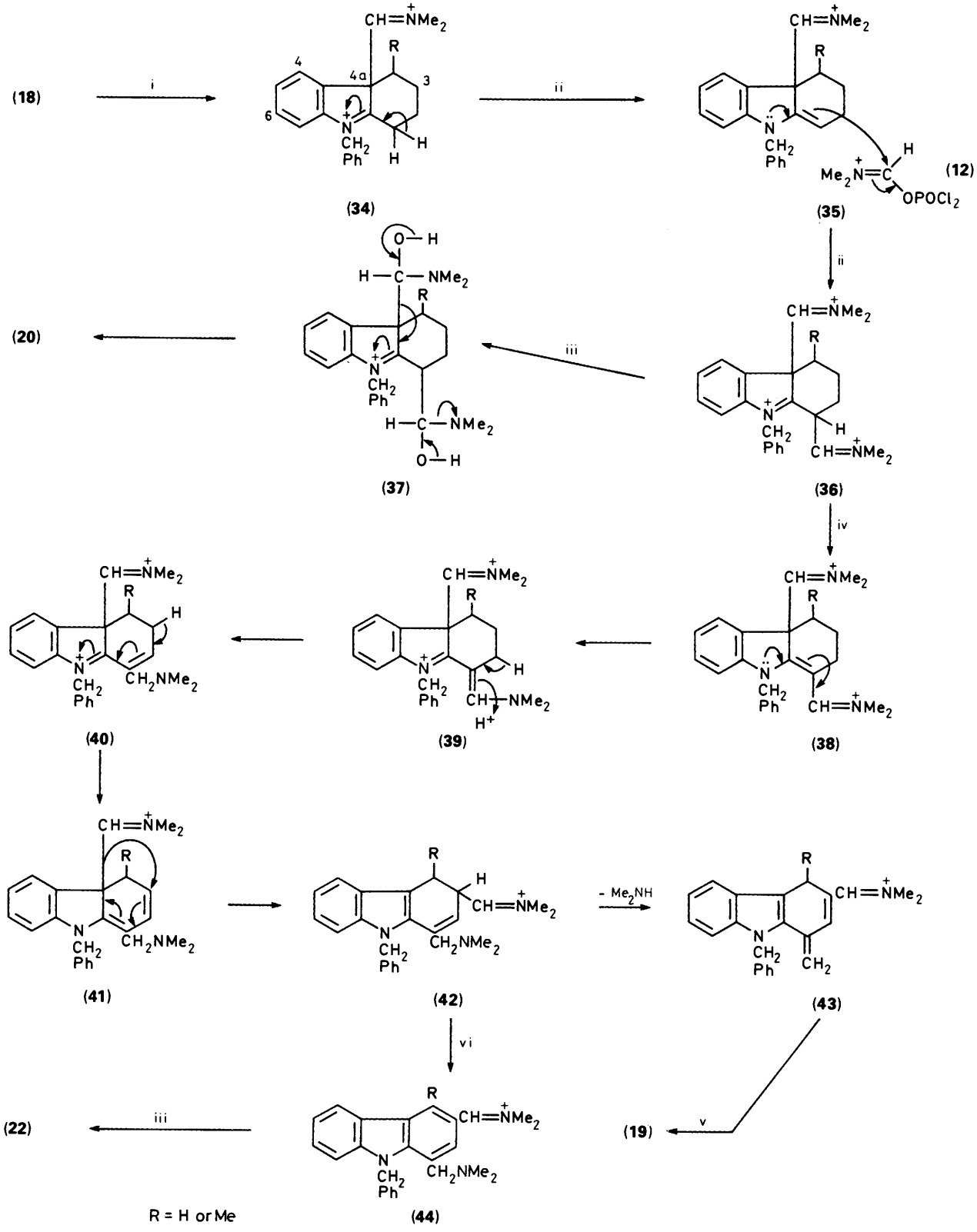
(**23a**) was carried out in order to confirm the structure more definitely, since the new position of the formyl group was very important in considering the reaction pathway of the V–H reaction of compounds (**18**). The synthetic route to compound (**23a**) is shown in Scheme 2. 1-Benzyl-1-(*o*-tolyl)urea (**29**) was treated with NaOCl to give the hydrazine (**30**) as an unstable oil. The above transformation is an application of Hofmann rearrangement of 1,1-disubstituted ureas developed[14] by us as a new synthetic method for the 1,1-disubstituted hydrazines. The crude hydrazine (**30**) was treated with the ketone (**31**) to give the tetrahydrocarbazole (**33**) in one pot without isolation of the intermediate hydrazone (**32**). Compound (**33**) was converted into compound (**23a**) straightforwardly by a three-step sequence; aromatization of the C-ring, reduction of the ester, and oxidation of the alcohol. This synthetic aldehyde (**23a**) was identical with the product of the V–H reaction of the 1- methylcarbazole (**21a**) by the comparison with spectral data and m.p.s.

Mechanism.—The previously suggested mechanism[5] could not explain the following results; (i) regioselective formylation in the one-step conversion of (**18**) into (**19**), (ii) requirement of 2 mol equivalents of $POCl_3$ for the quantitative formation of the aldehydes (**20**), (iii) formation of the amine (**22**). Thus we propose a new mechanism in order to explain all of the above results reasonably as shown in Scheme 3.

The first V–H reagent (**12**) attacked the C-4a position of the THC (**18**) [formation of dionium salt (**34**)], followed by isomerization of the double bond to form the reactive enamine (**35**). This molecule (**35**) was attacked by the second V–H reagent (**12**) to produce the key intermediate (**36**). The reaction should stop here at 0 °C. At this point the addition of water would easily cause the elimination of DMF from C-4a, followed by hydrolysis of the iminium group in the C-1 substituent to form the 1-aldehyde (**20**) [(**36**) ⟶ (**37**) ⟶ (**20**)]. A similar mechanism has also been suggested by other groups[13,15] in order to explain the abnormally high reactivity of the C-2 sidechain of 1,2,3-trialkylindoles toward electrophiles. At high temperature (100 or 120 °C), the intermediate (**36**) would be isomerized to diene (**41**) *via* intermediates (**38**), (**39**), and (**40**) by prototropy under anhydrous conditions. Then the iminium cation at C-4a of compound (**41**) would rearrange to the 3-position by a 1,5-sigmatropic process. The resulting intermediate (**42**) would be changed into the aromatic aldehyde (**19**) *via* intermediate (**43**) by successive proton transfer, followed by hydrolysis. It should be noted that the dehydrogenation (oxidation) does not occur in the transformation of tri-iminium salt (**36**) to aldehyde (**19**). On the other hand, the aromatic amine (**22**) should be produced from the intermediate (**42**) by dehydrogenation and subsequent hydrolysis of intermediate (**44**), although it is not clear at the present time what oxidant is responsible for the formation of the amine (**22**). The isolation of the amine (**22**) strongly supports the formation of the intermediate (**42**). It is the key point in the above mechanism that the 1-methylcarbazoles (**21**) should not be produced during the reaction, since compounds (**21**) were non-regioselectively formylated by the V–H reagent to give a mixture of 3- (**19**) and 6-formylated products (**23**). Although we lack further experimental evidence for this unique sigmatropic rearrangement, the above mechanism can clearly explain the regioselective formylation at the 3-position.

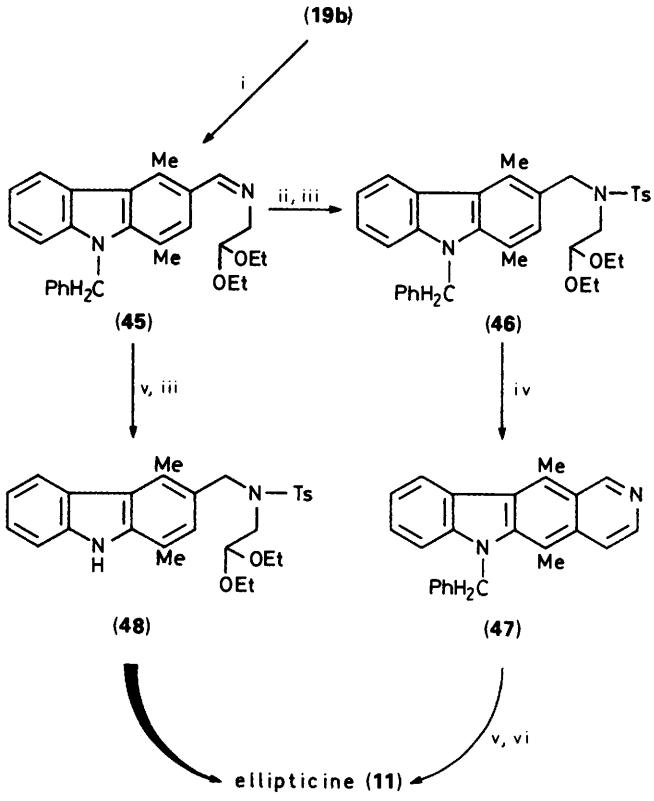
Total Synthesis of Olivacine (**10**) *and Ellipticine* (**11**).—There have been many reports[16] on the total syntheses of olivacine (**10**) and ellipticine (**11**) by various routes. Among them, the efficient synthesis of ellipticine (**11**) using 1,4-dimethylcarbazole-3-carbaldehyde (**50**) has been reported by Jackson *et al.*[17] However, compound (**50**) had been obtained[18] in low yield (35%) by V–H reaction of 1,4-dimethylcarbazole (**49**) because of non-regioselective formation of aldehyde (**50**) and the 6-formyl isomer (**51**). On the other hand, we obtained regioselectively the aromatic aldehyde (**19b**) in only one step from the tetrahydrocarbazole (**18b**). Thus, we applied Jackson's route to compound (**19b**). Scheme 4 shows the synthetic route for ellipticine (**11**).

The aromatic 3-aldehyde (**19b**) was converted into the tosyl amide (**46**) through the Schiff's base (**45**), and *N*-benzylellipticine (**47**) was smoothly obtained by a sequence involving modified Pomeranz–Fritsch cyclization,[19] followed by spontaneous detosylation and aromatization. However, the next debenzylation step gave unsatisfactory results. Because Birch reduction which is the only effective method to remove the benzyl group in this situation,[20] also reduced the pyridine nucleus, a re-aromatization step by Pd/C was thus required. So we next planned an alternative route which involved deprotection of the benzyl group before formation of the pyridine nucleus; *i.e.* Birch reduction of the Schiff's base (**45**) was carried out to remove the benzyl group with simultaneous reduction of the carbon–nitrogen double bond. The resulting unstable amine was

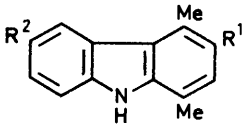


Scheme 3. *Reagents and conditions:* i, (**12**); ii, 0 °C; iii, water; iv, 100 or 120 °C; v, prototropy, then water; vi, dehydrogenation.

tosylated directly without purification to give the acetal (**48**) in 81% yield from the imine (**45**). This compound (**48**) had already been converted into ellipticine (**11**) in high yield (84%) by Jackson.[17] Thus, the very efficient formal total synthesis of compound (**11**) was accomplished in only five steps from compound (**18b**) (overall yield 22.4%). All physical and spectral data of the acetal (**48**) and the synthetic ellipticine (**11**) were in accord with the reported values.[17]



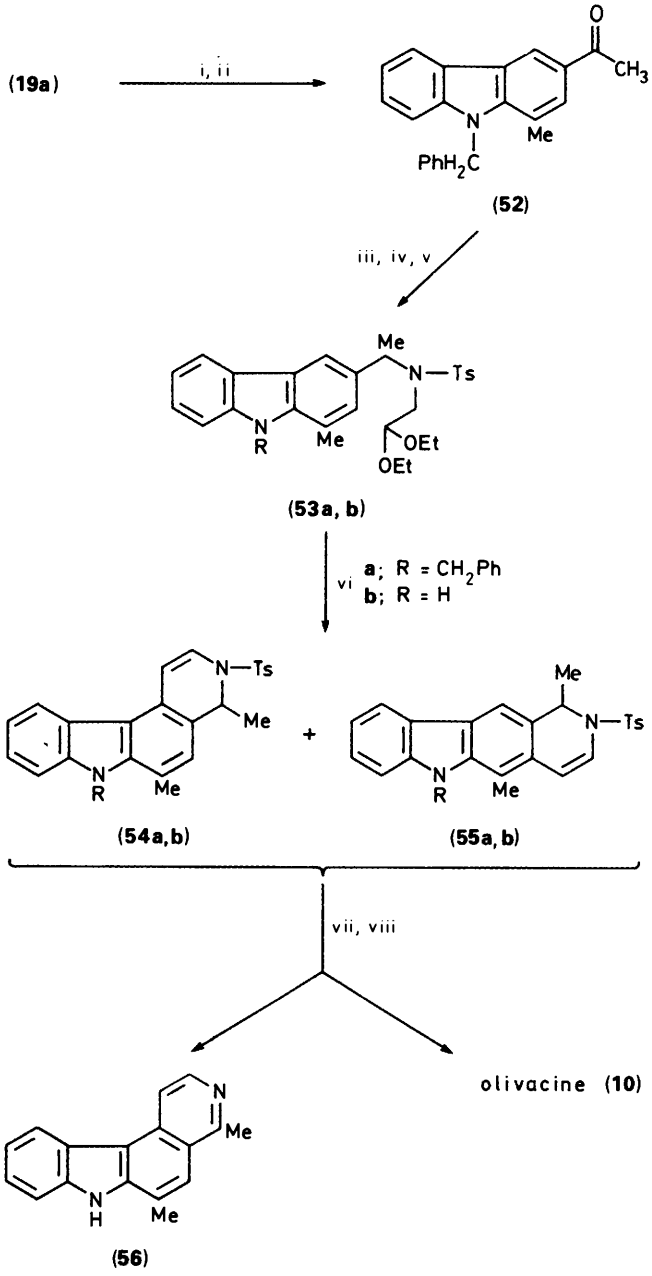
Scheme 4. *Reagents and conditions:* i, $H_2NCH_2CH(OEt)_2$; ii, $NaBH_4$; iii, TsCl–Na_2CO_3; iv, 6M-HCl–dioxane; v, Li/liq. NH_3; vi, 10% Pd–C/decalin.



(**49**) $R^1 = R^2 = H$
(**50**) $R^1 = CHO, R^2 = H$
(**51**) $R^1 = H, R^2 = CHO$

The synthesis of olivacine (**10**) using Pomeranz–Fritsch cyclization is not such an attractive route as is the synthesis of ellipticine (**11**), because there are two possible positions for the cyclization in the acetal (**53**). In spite of the above situation, we carried out the synthesis of olivacine (**10**) by this route to clarify the regioselectivity of the cyclization. The synthetic route is shown in Scheme 5.

The aromatic aldehyde (**19a**) was converted into the methyl ketone (**52**) by treatment with methyl-lithium and subsequent Jones oxidation. This ketone (**52**) was treated by the same manner as in ellipticine synthesis to give the acetal (**53a**). Treatment of acetal (**53a**) with 6M-hydrochloric acid–dioxane gave an inseparable mixture of two products (**54a**) and (**55a**) whose structures were estimated as cyclized products based on the ^1H NMR spectrum of the mixture. These compounds, however, did not undergo spontaneous detosylation and aromatization, in contrast to the cyclization of the acetals (**46**) and (**48**). This mixture was directly subjected to Birch reduction to remove both the benzyl and tosyl groups. After aromatization of the crude amines by Pd/C, the final products were separated by repeated chromatography and recrystallization to give olivacine (**10**) and the isomer (**56**) in 12 and 10% yield from the ketone (**52**), respectively. Recently, a similar cyclization using



Scheme 5. *Reagents and conditions:* i, MeLi, −78 °C; ii, $HCrO_4$–acetone (Jones reagent); iii, $H_2NCH_2CH(OEt)_2$; iv, $NaBH_4$; v, TsCl–pyridine; vi, 6M-HCl–dioxane; vii, Na/liq. NH_3; viii, 10% Pd–C/decalin.

the N^9-unprotected acetal (**53b**) was reported[21,22] by other groups. In contrast to our results, cyclization of compound (**53b**) proceeded regioselectively to afford the desired dihydrocarbazole (**55b**), and only trace amounts of the isomer (**54b**) could be detected. It is interesting that protection of the indole nitrogen by a benzyl group had such a drastic effect on the direction of cyclization. All the physical and spectral data of the synthetic olivacine (**10**) were in accord with previously reported values.[7,23]

Experimental

M.p.s were determined on a Yanagimoto micro-melting hot-stage apparatus and are uncorrected. IR spectra were recorded in Nujol mulls on a Shimadzu IR-400 spectrometer. UV spectra were measured with a Hitachi 340 spectrophotometer. ^1H

NMR spectra were recorded on Hitachi R-24B (60 MHz) (unless otherwise stated) or JEOL GX-400 (400 MHz) spectrometers with tetramethylsilane as internal reference. Mass spectra were measured with a JEOL JMS-01-SG-2 spectrometer using a direct inlet system. Analytical HPLC was performed on a Hitachi 635A liquid chromatograph equipped with variable-wavelength UV–visible detector and Waters Radial Compression System RCM-100. For column chromatography, Merck Kieselgel 60 was used.

9-*Benzyl*-1,2,3,4-*tetrahydrocarbazole* (**18a**).—A suspension of KOH (101.6 g, 1.80 mol) and 1,2,3,4-tetrahydrocarbazole (74.7 g, 0.44 mol) in dimethyl sulphoxide (DMSO) (900 ml) was stirred for 1.5 h at room temperature. Then benzyl bromide (107.7 ml, 0.91 mol) was added to the mixture at room temperature. After 2.5 h, the reaction mixture was diluted with ice–water (900 ml) and extracted with ether. The organic layer was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave a pale yellow oil. This oil was distilled under reduced pressure to give the title compound (**18a**) (96.4 g, 84%), b.p. 184 °C (1 mmHg) [lit.,[9] 195 °C (2 mmHg)] as a pale yellow oil, which solidified immediately. Recrystallization from aqueous ethanol gave prisms, m.p. 51–52 °C (lit.,[9] 49–50 °C).

2-*Hydroxymethylene*-4-*methylcyclohexanone*.—By analogy to the reported method for 2-hydroxymethylenecyclohexanone,[24] 4-methylcyclohexanone was treated with ethyl formate in the presence of sodium ethoxide to give the title compound as an oil, b.p. 72–74 °C (5 mmHg) [lit.,[25] 108–109 °C (26 mmHg)].

(Z)-4-*Methylcyclohexane*-1,2-*dione* 2-*Phenylhydrazone* (**16**).—Sodium nitrite (12.6 g, 183 mmol) was added portionwise to an ice-cooled solution of aniline (15.0 g, 161 mmol) in 2.5M-aqueous HCl (155 ml). The resulting diazonium solution was added to a solution of 2-hydroxymethylene-4-methylcyclohexanone (24.3 g, 173 mmol) in 50% aqueous KOH (38.8 ml)–ethanol (135 ml) below 7 °C and the mixture was stirred for 30 min at this temperature. The reaction mixture was poured into ice–water (1:1) and the resulting precipitate was collected by filtration. Recrystallization from aqueous ethanol gave the *title compound* (**16**) (25.0 g, 72%) as orange plates, and which was further recrystallized from benzene–ethanol to give yellow plates, m.p. 146–149 °C (lit.,[10] 137–140 °C).

3,4-*Dihydro*-4-*methylcarbazol*-1(2H)-*one* (**15**).—(*a*) *Fischer indolization with PTSA*. PTSA monohydrate (10.7 g, 56 mmol) was dehydrated in benzene (120 ml) using Dean–Stark apparatus and a solution of the hydrazone (**16**) (6.0 g, 27.8 mmol) in benzene (60 ml) was added to the above solution. The mixture was stirred for 2.5 h at room temperature and the solvent was evaporated off. Water (250 ml) was added to the residue and the mixture was extracted with chloroform. The organic layer was washed successively with 5% aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$, and the solvent was evaporated off. The residue was chromatographed on silica gel with benzene–ethyl acetate (20:1) to give the title compound (**15**) as a yellow solid (4.69 g, 85%), which was recrystallized from chloroform–hexane to give prisms, m.p. 139–140 °C (lit.,[10] 145–146 °C).

(*b*) *Fischer indolization with cation-exchange resin Amberlist* 15. A mixture of the hydrazone (**16**) (25.75 g, 119 mmol) and Amberlist 15 (Rohm and Haas; 61 g, 299 mmol equiv.) in dry toluene (250 ml) was heated at 115 °C for 3.5 h. The resin was filtered off and washed with chloroform. After evaporation of the combined organic layer, the obtained orange solid (19.44 g) was recrystallized from chloroform–hexane to give the title compound (**15**) (16.96 g, 72%) as pale yellow prisms, m.p. 130–139 °C.

9-*Benzyl*-1,2,3,4-*tetrahydro*-4-*methylcarbazole* (**18b**).—A mixture of the ketone (**15**) (16.9 g, 85 mmol), KOH (10.0 g, 179 mmol), and hydrazine hydrate (7.4 ml, 153 mmol) in triethylene glycol (70 ml) was heated at 150 °C for 2 h with continuous removal of water. Then the temperature was raised to 200 °C and kept there for 2.5 h. The reaction mixture was diluted with water (700 ml) and extracted with ether. The organic layer was washed with saturated aqueous NaCl and dried over $MgSO_4$. The solvent was evaporated off to give a dark brown oil (17.95 g).

A mixture of this oil and powdered KOH (18.5 g, 330 mmol) in DMSO (40 ml) was stirred for 1 h. Benzyl bromide (23 ml, 194 mmol) was then added to the mixture and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water (400 ml) and extracted with ether. The organic layer was washed successively with 10% aqueous HCl and saturated aqueous NaCl and dried over $MgSO_4$. After evaporation of the solvent, the resulting dark brown oil was distilled under reduced pressure to give the *title compound* (**18b**) (18.11 g, 77%), b.p. 190–198 °C (0.1 mmHg), which solidified immediately to give an orange solid. This solid was recrystallized from hexane to give pale yellow prisms, m.p. 92–94 °C (lit.,[26] 54.5–55.5 °C) (Found: C, 87.2; H, 7.65; N, 5.0. $C_{20}H_{21}N$ requires C, 87.25; H, 7.7; N, 5.1%); ν_{max} 1 600 cm^{-1} (ArH); $\delta_H(CDCl_3)$1.35 (3 H, d, *J* 8 Hz, CMe), 1.6–2.1 (4 H, m, 2- and 3-H_2), 2.4–2.7 (2 H, m, 1-H_2), 2.9–3.4 (1 H, m, 4-H), 5.13 (2 H, s, PhCH_2), 6.8–7.3 (8 H, m, ArH), and 7.5–7.7 (1 H, m, 5-H); *m/z* 275 (M^+, 58%) and 260 (100).

General Procedure for V–H Reaction of the Tetrahydrocarbazoles (**18a**) *and* (**18b**).—A mixture of the THC (**18a**) or (**18b**) (2.0 mmol), $POCl_3$, and DMF was stirred under the conditions indicated in the Table. The reaction mixture was poured into ice–water and stirred for 30 min. The solution was basified to pH 14 by addition of K_2CO_3 and extracted with benzene (×3). The combined organic layer was washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the resulting dark brown oil was chromatographed on silica gel with benzene–ethyl acetate (10:1) and separated into five products. The products of the V–H reaction of compound (**18a**) (in the order of elution) were: 9-*Benzyl*-1-*methylcarbazole* (**21a**). Needles (from benzene–hexane), m.p. 136–139 °C (Found: C, 88.7; H, 6.45; N, 5.05. $C_{20}H_{17}N$ requires C, 88.55; H, 6.25; N, 5.15%); ν_{max} 1 585 cm^{-1} (arom); $\delta_H(CDCl_3)$ 2.58 (3 H, s, CMe), 5.66 (2 H, s, PhCH_2), 6.7–7.5 (10 H, m, ArH), and 7.7–8.2 (2 H, m, 4- and 5-H); *m/z* 271 (M^+, 100%).

9-*Benzyl*-1,2,3,4-*tetrahydrocarbazole*-1-*carbaldehyde* (**20a**). Unstable oil (Found: C, 82.65; H, 6.65; N, 4.9. $C_{20}H_{19}NO$ requires C, 83.0; H, 6.6; N, 4.85%); ν_{max}(neat) 1 720 cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.6–2.6 (4 H, m, 2- and 3-H_2), 2.7–3.1 (2 H, m, 4-H_2), 3.4–3.7 (1 H, m, 1-H), 5.22 (2 H, s, PhCH_2), 6.7–7.4 (8 H, m, ArH), 7.4–7.7 (1 H, m, 5-H), and 9.52 (1 H, d, *J* 3 Hz, CHO); *m/z* 289 (M^+, 40%) and 260 (100).

9-*Benzyl*-1-*methylcarbazole*-3-*carbaldehyde* (**19a**). Needles (from benzene–hexane), m.p. 116–118 °C (Found: C, 84.0; H, 5.7; N, 4.65. $C_{21}H_{17}NO$ requires C, 84.25; H, 5.7; N, 4.7%); ν_{max} 1 690 (CO) and 1 595 cm^{-1} (arom); $\delta_H(CDCl_3)$ 2.65 (3 H, s, 1-Me), 5.72 (2 H, s, PhCH_2), 6.7–7.5 (8 H, m, ArH), 7.64 (1 H, s, 2-H), 8.0–8.25 (1 H, m, 5-H), 8.42 (1 H, s, 4-H), and 9.95 (1 H, s, CHO); *m/z* 299 (M^+, 37%) and 91 (100).

9-*Benzyl*-1,2,3,4-*tetrahydrocarbazole*-7-*carbaldehyde* (**17**). Yellow prisms (from hexane–ethyl acetate), m.p. 91–101 °C (Found: C, 82.85; H, 6.65; N, 4.8. $C_{20}H_{19}NO$ requires C, 83.0; H, 6.6; N, 4.85%); ν_{max} 1 665 cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.6–2.2

(4 H, m, 2- and 3-H_2), 2.4–3.0 (4 H, m, 1- and 4-H_2), 5.31 (2 H, s, PhCH_2), 6.9–7.5 (5 H, m, ArH), 7.5–7.9 (3 H, m, 5-, 6-, and 8-H), and 9.95 (1 H, s, CHO); *m/z* 289 (M^+, 100%).

9-Benzyl-1-[(N,N-dimethylamino)methyl]carbazole-3-carbaldehyde (**22a**). Needles (from benzene–hexane), m.p. 122–125 °C (Found: C, 80.6; H, 6.7; N, 8.05. $C_{23}H_{22}N_2O$ requires C, 80.65; H, 6.5; N, 8.2%); ν_{max} 1 690 cm^{-1} (CO); $\delta_H(CDCl_3)$ 2.20 (6 H, s, NMe_2), 3.50 (2 H, s, CH_2N), 6.15 (2 H, s, PhCH_2), 6.8–7.5 (8 H, m, ArH), 7.70 (1 H, d, *J* 2 Hz, 2-H), 8.0–8.3 (1 H, m, 5-H), 8.55 (1 H, d, *J* 2 Hz, 4-H), and 10.0 (1 H, s, CHO); *m/z* 342 (M^+, 45%) and 297 (100).

The V–H reaction products of compound (**18b**) (in the order of elution) were: *9-Benzyl-1,4-dimethylcarbazole* (**21b**). Needles (from benzene–hexane), m.p. 146–148 °C (Found: C, 88.45; H, 6.8; N, 4.8. $C_{21}H_{19}N$ requires C, 88.4; H, 6.7; N, 4.9%); ν_{max} 1 610 cm^{-1} (arom); $\delta_H(CDCl_3)$ 2.57 (3 H, s, 1-Me), 2.58 (3 H, s, 4-Me), 5.67 (2 H, s, PhCH_2), 6.7–7.4 (10 H, m, ArH), and 8.0–8.4 (1 H, m, 5-H); *m/z* 285 (M^+, 100%).

9-Benzyl-1,2,3,4-tetrahydro-4-methylcarbazole-1-carbaldehyde (**20b**). Unstable oil (a mixture of diastereoisomers) (Found: C, 82.9; H, 7.0; N, 4.6. $C_{21}H_{21}NO$ requires C, 83.15; H, 7.0; N, 4.6%); ν_{max}(neat) 1 720 cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.32 and 1.43 (total 3 H, each d, *J* 7 Hz, 4-Me), 1.6–2.4 and 2.8–3.6 (total 6 H, m, 1- and 4-H and 2- and 3-H_2), 5.19 (2 H, s, PhCH_2), 6.7–7.4 (8 H, m, ArH), 7.4–7.8 (1 H, m, 5-H), 9.48 and 9.52 (total 1 H, each d, *J* 3 Hz, CHO); *m/z* 303 (M^+, 39%) and 274 (100).

9-Benzyl-1,4-dimethylcarbazole-3-carbaldehyde (**19b**). Pale yellow needles (from benzene–hexane), m.p. 169–171 °C (Found: C, 84.35; H, 6.2; N, 4.4. $C_{22}H_{19}NO$ requires C, 84.3; H, 6.1; N, 4.45%); ν_{max} 1 665 cm^{-1} (CO); $\delta_H(CDCl_3)$ 2.59 (3 H, s, 1-Me), 3.14 (3 H, s, 4-Me), 5.71 (2 H, s, PhCH_2), 6.8–7.5 (8 H, m, ArH), 7.62 (1 H, s, 2-H), 8.2–8.5 (1 H, m, 5-H), and 10.27 (1 H, s, CHO); *m/z* 313 (M^+, 66%) and 91 (100).

9-Benzyl-1-[(N,N-dimethylamino)methyl]-4-methylcarbazole-3-carbaldehyde (**22b**). Pale yellow needles (from benzene–hexane), m.p. 154–155 °C (Found: C, 80.65; H, 6.9; N, 7.75. $C_{24}H_{24}N_2O$ requires C, 80.85; H, 6.8; N, 7.85%); ν_{max} 1 670 cm^{-1} (CO); $\delta_H(CDCl_3)$ 2.21 (6 H, s, NMe_2), 3.28 (3 H, s, 4-Me), 3.48 (2 H, s, CH_2N), 6.21 (2 H, s, PhCH_2), 6.8–7.5 (8 H, m, ArH), 7.72 (1 H, s, 2-H), 8.2–8.5 (1 H, m, 5-H), and 10.35 (1 H, s, CHO); *m/z* 356 (M^+, 41%) and 311 (100).

Conversion of the Dimethylamine (**22b**) *into the 1-Methyl-3-aldehyde* (**19b**).—A mixture of the amine (**22b**) (105 mg, 0.29 mmol) and methyl iodide (3 ml) was refluxed under argon. After 3 h, excess of methyl iodide was evaporated off and the resulting solid was washed with hot ethanol to give the crude quaternary salt (**27**) as a pale yellow solid.

A mixture of this salt (113 mg) and 10% Pd–C (113 mg) in ethanol (20 ml) was heated at 80 °C for 9.5 h under hydrogen. The Pd–C was filtered off and washed excessively with hot ethanol. After the combined mother liquor and washings had been evaporated, the resulting residue (100 mg) was chromatographed on silica gel with benzene to give a pale yellow solid [43 mg, 47% from (**22b**)], which was recrystallized from benzene–hexane to afford pale yellow needles, m.p. 165–170 °C. This sample was identical with the 1-methyl-3-aldehyde (**19b**) obtained from the V–H reaction of compound (**18b**).

V–H Reaction of 9-Benzyl-1,2,3,4-tetrahydrocarbazole-1-carbaldehyde (**20a**).—A solution of compound (**20a**)(1.36 g, 4.7 mmol) in DMF (6 ml) was added to a solution of $POCl_3$ (0.52 ml, 5.6 mmol) in DMF (5 ml) under argon and the mixture was heated at 100 °C. After 2 h, the mixture was poured into water (100 ml) and extracted with benzene. The combined organic layer was washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue (1.16 g) was chromatographed on silica gel with hexane–benzene (10:1) to give the 1-methylcarbazole (**21a**) as needles (0.72 g, 56%).

V–H Reaction of 9-Benzyl-1-methylcarbazole (**21a**).—To a solution of compound (**21a**) (0.271 g, 1 mmol) in DMF (0.77 ml) was added $POCl_3$ (0.11 ml, 1.2 mmol) and the mixture was heated at 120 °C. After 2 h, the mixture was poured into water (100 ml) and extracted with benzene. The organic layer was washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the resulting brown oil (0.281 g) was chromatographed on silica gel with benzene to give a mixture of compound (**19a**) and 9-benzyl-8-methylcarbazole-3-carbaldehyde (**23a**) as a solid (0.218 g, 73%). HPLC analysis of this mixture (Merck Lichrosorb Si-100, 250 mm × 4 mm) with hexane–ethyl acetate (20:1) showed that the ratio of products (**19a**) and (**23a**) was 3:2. Compound (**23a**) was isolated by repeated silica gel chromatography with hexane–ethyl acetate (40:1) and recrystallization from hexane–ethyl acetate to give *prisms*, m.p. 145–147 °C (Found: C, 84.2; H, 5.7; N, 4.55. $C_{21}H_{17}NO$ requires C, 84.25; H, 5.7; N, 4.65%); ν_{max} 1 660 cm^{-1} (CO); $\delta_H(CDCl_3)$ 2.63 (3 H, s, 8-Me), 5.69 (2 H, s, PhCH_2), 6.8–7.5 (8 H, m, ArH), 7.7–8.2 (2 H, m, 2- and 5-H), 8.50 (1 H, d, *J* 2 Hz, 4-H), and 9.97 (1 H, s, CHO); *m/z* 299 (M^+, 52%) and 91 (100).

V–H Reaction of 9-Benzyl-1,2,3,4-tetrahydro-4-methylcarbazole-1-carbaldehyde (**20b**).—To a solution of compound (**20b**) (435 mg, 1.43 mmol) in DMF (3 ml) was added $POCl_3$ (0.16 ml, 1.7 mmol) under argon at 0 °C and the resulting solution was heated at 60 °C. After 2 h, the mixture was poured into water (30 ml), basified to pH 14 with K_2CO_3, and extracted with chloroform. The organic layer was washed with saturated aqueous NaCl and dried over $MgSO_4$. After evaporation of the solvent, the dark red oil was chromatographed on silica gel with hexane–benzene (10:1) to give the 1,4-dimethylcarbazole (**21b**) as a yellow solid (177 mg, 43%).

V–H Reaction of 9-Benzyl-1,4-dimethylcarbazole (**21b**).—To a solution of compound (**21b**) (0.234 g, 0.82 mmol) in DMF (1.1 ml) at 0 °C was added $POCl_3$ (0.20 ml, 2.1 mmol) and the mixture was heated at 100 °C. After 6 h, the mixture was poured into water (20 ml), adjusted at pH 14 with K_2CO_3, and extracted with chloroform. The organic layer was washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the resulting dark red oil (0.327 g) was chromatographed on silica gel with benzene to give a mixture of compound (**19b**) and 9-benzyl-5,8-dimethylcarbazole-3-carboxaldehyde (**23b**) as a solid (0.209 g, 81%). HPLC analysis of this mixture (Waters Radial Pack Silica 5μ, 100 mm × 8 mm) with hexane–ethyl acetate (20:1) showed that the ratio (**19b**):(**23b**) was 4.5:1. Compound (**23b**) was isolated by repeated silica gel chromatography with hexane–ethyl acetate (40:1) and was recrystallized from hexane–benzene to give *prisms*, m.p. 143–144 °C (Found: C, 84.15; H, 6.05; N, 4.4. $C_{22}H_{19}NO$ requires C, 84.3; H, 6.1; N, 4.45%); ν_{max} 1 670 cm^{-1} (CO); $\delta_H(CDCl_3)$ 2.58 and 2.89 (2 × 3 H, 2 × s, 5- and 8-Me), 5.76 (2 H, s, PhCH_2), 6.8–7.4 (8 H, m, ArH), 7.87 (1 H, dd, *J* 8 Hz and 2 Hz, 2-H), 8.64 (1 H, d, *J* 2 Hz, 4-H), and 9.91 (1 H, s, CHO); *m/z* 313 (M^+, 50%) and 91 (100).

Alternative Synthesis of 9-Benzyl-8-methylcarbazole-3-carbaldehyde (**23a**).—N-*Benzyl*-N-(*o-tolyl*)*urea* (**29**). Trifluoroacetic acid (4.0 ml) was added to a vigorously stirred suspension of *N*-benzyl-*o*-toluidine[27] (5.00 g, 25 mmol) and NaOCN (3.30 g, 51 mmol) in benzene (60 ml), and the mixture was stirred at

room temperature for 1.5 h. Then the mixture was poured into ice–water and extracted with ethyl acetate. The organic layer was washed with water and dried over $MgSO_4$. After evaporation of the solvent, the resulting solid (6.13 g) was recrystallized from benzene–hexane to give the *title compound* (5.17 g, 85%), which was further recrystallized from the same solvents to afford rods, m.p. 123–125 °C (Found: C, 75.1; H, 6.75; N, 11.75. $C_{15}H_{16}N_2O$ requires C, 74.95; H, 6.7; N, 11.65%); ν_{max} 3 420 cm^{-1} (NH); $\delta_H(CDCl_3)$ 2.07 (3 H, s, Me), 4.45 (2 H, s, NH_2), 4.31 and 5.10 (each 1 H, each d, *J* 15 Hz, $PhCH_2$), and 6.7–7.3 (9 H, m, ArH); *m/z* 240 (M^+, 100%).

Methyl 9-benzyl-1,2,3,4-tetrahydro-8-methylcarbazole-3-carboxylate (**33**). A mixture of 14% aqueous NaOH (19 ml, 67 mmol) and 10% aqueous NaOCl (11 ml, 14.8 mmol) was added dropwise to a solution of the urea (**29**) (3.00 g, 12.5 mmol) in ethanol (60 ml) below 5 °C. After addition was complete, the temperature was raised to room temperature and kept there for 1 h. The reaction mixture was poured into water and extracted with ether to remove *N*-benzyl-*o*-toluidine formed as a by-product and the unchanged urea (**29**). The aqueous layer was acidified with 5% aqueous HCl and kept for 30 min at room temperature. Then the solution was made alkaline by addition of 20% aqueous NaOH and was extracted with ether. The organic layer was dried over K_2CO_3. After evaporation of the solvent, crude 1-benzyl-1-(*o*-tolyl)hydrazine (**30**) was obtained as a yellow oil.

This oil (2.27 g) was mixed with methyl 4-oxocyclohexanecarboxylate (**31**)[28] (1.17 g, 7.5 mmol) and AcOH (20 ml). After being refluxed for 10 min, the mixture was poured into water and extracted with ether. The organic layer was washed successively with 5% aqueous K_2CO_3 and water, and dried over $MgSO_4$. After evaporation of the solvent, the obtained brown solid (3.51 g) was chromatographed on silica gel with benzene to give the *title compound* (**33**) [1.25 g, 30% from (**29**)] as a yellow solid, which was recrystallized from benzene–hexane to afford prisms, m.p. 133.5–136 °C (Found: C, 79.45; H, 7.0; N, 4.0. $C_{22}H_{23}NO_2$ requires C, 79.25; H, 6.95; N, 4.2%); ν_{max} 1 718 cm^{-1} (CO); $\delta_H(CDCl_3)$ 2.0–3.2 (7 H, m, aliphatic H), 2.49 (3 H, s, 8-Me), 3.71 (3 H, s, OMe), 5.46 (2 H, s, NCH_2Ph), and 6.7–7.5 (8 H, m, ArH); *m/z* 333 (M^+, 100%).

Methyl 9-benzyl-8-methylcarbazole-3-carboxylate. A mixture of the tetrahydrocarbazole (**33**) (807 mg, 2.42 mmol) and 10% Pd–C (600 mg) in *p*-cymene (8 ml) was refluxed for 2.5 h. Then the catalyst was filtered off and washed thoroughly with ethyl acetate. After evaporation of the organic solvents, the resulting residue was chromatographed on silica gel with benzene to give the *title compound* (500 mg, 63%) as a solid, which was recrystallized from benzene–hexane to afford fine needles, m.p. 171.5–174 °C (Found: C, 80.15; H, 5.85; N, 4.25. $C_{22}H_{19}NO_2$ requires C, 80.2; H, 5.8; N, 4.25%); ν_{max} 1 705 cm^{-1} (CO); $\delta_H(CDCl_3)$ 2.59 (3 H, s, 8-Me), 3.95 (3 H, s, OMe), 5.70 (2 H, s, NCH_2Ph), 6.8–7.4 (8 H, m, ArH), 8.08 (2 H, m, 2- and 5-H), and 8.80 (1 H, br s, 4-H); *m/z* 329 (M^+, 55%) and 91 (100).

(9-Benzyl-8-methylcarbazol-3-yl)methanol. A mixture of methyl 9-benzyl-8-methylcarbazole-3-carboxylate (400 mg, 1.22 mmol) and $LiAlH_4$ (231 mg, 6.0 mmol) in dry THF (30 ml) was refluxed for 40 min. The reaction was quenched with 5% NaOH (1.5 ml), and the precipitate was filtered off and washed thoroughly with ethyl acetate. The combined organic layer was evaporated to give the *title compound* (347 mg, 95%) as a solid, which was recrystallized from benzene–hexane to afford needles, m.p. 149–150.5 °C (Found: C, 83.55; H, 6.3; N, 4.3. $C_{21}H_{19}NO$ requires C, 83.7; H, 6.35; N, 4.65%); ν_{max} 3 350 cm^{-1} (OH); $\delta_H(CDCl_3)$ 2.60 (3 H, s, 8-Me), 4.79 (2 H, s, OCH_2), 5.70 (2 H, s, NCH_2Ph), 6.8–7.5 (9 H, m, ArH), and 8.00 (2 H, m, 4- and 5-H); *m/z* 301 (M^+, 95%) and 91 (100).

9-Benzyl-8-methylcarbazole-3-carbaldehyde (**23a**). A solution of the above alcohol (200 mg, 0.66 mmol) in dry methylene dichloride (2 ml) was added to a suspension of pyridinium chlorochromate (215 mg, 1.0 mmol) in dry methylene dichloride (3 ml) in one portion at room temperature and the whole was stirred for 1 h. Then the reaction mixture was diluted with ethyl acetate. The resulting precipitate was filtered off and washed thoroughly with ethyl acetate. The combined organic layer was washed with water and dried over $MgSO_4$. After evaporation of the solvent, the residue (177 mg) was chromatographed on silica gel with benzene to give the 3-formylcarbazole (**23a**) (147 mg, 74%), which was recrystallized from benzene–hexane to afford needles, m.p. 146–147 °C (Found: C, 84.55; H, 5.65; N, 4.45. Calc for $C_{21}H_{17}NO$: C, 84.25; H, 5.7; N, 4.7%). This sample was identical with the compound obtained from V–H reaction of compound (**18a**).

9-Benzyl-3-[(2,2-diethoxyethyl)iminomethyl]-1,4-dimethylcarbazole (**45**).—A mixture of 9-benzyl-1,4-dimethylcarbazole-3-carbaldehyde (**19b**) (940 mg, 3.0 mmol) and aminoacetaldehyde diethyl acetal (0.48 ml, 3.3 mmol) were heated at 100 °C under argon. After 2 h, benzene was added to the mixture and was evaporated off to remove water (azeotrope). This operation was repeated 3 times. The resulting solid (1.30 g) was recrystallized from hexane–benzene to give the *title compound* (**45**) (1.04 g, 81%) as a yellow solid, m.p. 88–97 °C. Further recrystallization from hexane–benzene gave yellow needles, m.p. 99–101 °C (Found: C, 78.55; H, 7.55; N, 6.4. $C_{28}H_{32}N_2O_2$ requires C, 78.45; H, 7.55; N, 6.55%); ν_{max} 1 635 cm^{-1} (C=N); $\delta_H(CDCl_3)$ 1.20 (6 H, t, *J* 6 Hz, 2 × CH_2Me), 2.61 (3 H, s, 1-Me), 3.00 (3 H, s, 4-Me), 3.5–3.9 (6 H, m, 2 × OCH_2Me and $CHCH_2N$), 4.83 [1 H, t, *J* 5 Hz, $CH(OEt)_2$], 5.75 (2 H, s, CH_2Ph), 6.9–7.5 (8 H, m, ArH), 7.78 (1 H, s, 2-H), 8.2–8.4 (1 H, m, 5-H), and 8.82 (1 H, s, CH=N); *m/z* 428 (M^+, 24%) and 103 (100).

9-Benzyl-3-{[N-(2,2-diethoxyethyl)-N-tosylamino]methyl}-1,4-dimethylcarbazole (**46**).—$NaBH_4$ (386 mg, 10 mmol) was added portionwise to a solution of the Schiff's base (**45**) (439 mg, 1.0 mmol) in MeOH (6 ml) at room temperature and the mixture was stirred for 2 h. After evaporation of the solvent, the resulting colourless residue was acidified with 1% aqueous HCl, and washed with benzene. The aqueous layer was basified with 30% aqueous NaOH, and extracted with benzene. The organic layer was washed with saturated aqueous NaCl and dried over $MgSO_4$. After evaporation of the solvent, the obtained oil (481 mg) was mixed with toluene-*p*-sulphonyl chloride (253 mg, 1.3 mmol) and Na_2CO_3 (96 mg, 0.91 mmol) in tetrahydrofuran (THF)–water (1:2; 9 ml), and the mixture was stirred at room temperature. After 1.5 h, the reaction mixture was diluted with water (30 ml) and extracted with chloroform. The organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$, and evaporated. The pale yellow residue (579 mg) was chromatographed on silica gel with benzene to give the *title compound* (**46**) as a solid [499 mg, 84% from (**45**)], which was recrystallized from methylene dichloride–hexane to give prisms, m.p. 150–152 °C (Found: C, 72.0; H, 7.0; N, 4.8. $C_{35}H_{40}N_2O_4S$ requires C, 71.9; H, 6.9; N, 4.8%); ν_{max} 1 340 and 1 155 cm^{-1} (SO_2); $\delta_H(CDCl_3)$ 1.04 (6 H, t, *J* 7 Hz, 2 × CH_2Me), 2.34 (3 H, s, 1-Me or $SO_2C_6H_4Me$), 2.47 (3 H, s, $SO_2C_6H_4Me$ or 1-Me), 2.83 (3 H, s, 4-Me), 3.1–3.7 (6 H, m, 2 × OCH_2Me and $CHCH_2N$), 4.41 (1 H, t, *J* 6 Hz, $CHOEt_2$), 4.66 (2 H, s, $ArCH_2N$), 5.72 (2 H, s, CH_2Ph), 6.8–7.5 (11 H, m, ArH), 7.72 (2 H, d, *J* 8 Hz, 2 × 2′-H), and 8.1–8.4 (1 H, m, 5-H); *m/z* 584 (M^+, 13%) and 103 (100).

6-Benzyl-5,11-dimethyl-6H-pyrido[4,3-b]carbazole (**47**).—A solution of the tosyl amide (**46**) (551 mg, 0.94 mmol) in a mixture of 6M-aqueous HCl (1.5 ml) and dioxane (5 ml) was refluxed under argon. After 2.5 h, the reaction mixture was poured into 5% aqueous Na_2CO_3 (50 ml) and extracted

with chloroform. The organic layer was washed with saturated aqueous NaCl and dried over $MgSO_4$. After evaporation of the solvent, the resulting brown residue (379 mg) was chromatographed on neutralized silica gel (Mallinckrodt SilicAR CC-7) with benzene to give the title compound (**47**) as a yellow solid (169 mg, 53%), which was recrystallized from benzene to afford yellow needles, m.p. 243–246 °C (lit.,[29] 239–240 °C) (Found: C, 85.45; H, 6.0; N, 8.05. Calc. for $C_{24}H_{20}N_2$: C, 85.7; H, 6.0; N, 8.35%); ν_{max} 1 600 (arom) cm^{-1}; $\delta_H(CDCl_3)$ 2.76 (3 H, s, 5-Me), 3.22 (3 H, s, 11-Me), 5.66 (2 H, s, CH_2Ph), 7.0–7.5 (8 H, m, ArH), 7.79 (1 H, d, *J* 6 Hz, 4-H), 8.35–8.55 (2 H, m, 3- and 10-H), and 9.68 (1 H, s, 1-H); *m/z* 336 (M^+, 95%) and 245 (100).

5,11-*Dimethyl*-6H-*pyrido*[4,3-b]*carbazole* (*Ellipticine*) (**11**).—In a three-necked flask fitted with a solid CO_2 condenser was placed a mixture of *N*-benzylellipticine (**47**) (55 mg, 0.16 mmol) in liquid NH_3 (20 ml)–THF (7 ml). Lithium wire (34 mg, 4.9 mmol) was added to the solution in small pieces. The resulting deep blue colour changed to colourless after 20 min. The reaction mixture was kept for a further 15 min. The reaction was quenched with saturated aqueous NH_4Cl and the mixture was stirred for 15 min. Then the mixture was made alkaline by addition of K_2CO_3 and extracted with chloroform. The organic layer was washed with saturated aqueous NaCl and dried over $MgSO_4$. After evaporation of the solvent, the resulting pale yellow oil (39 mg) and 10% palladium–carbon (54 mg) in tetralin* (3 ml) were heated at 210 °C for 2 h under argon. Palladium–carbon was removed by filtration and washed with hot ethanol. After the ethanol had been evaporated from the combined mother liquor and filtrate, the resulting residue was chromatographed on neutralized silica gel (Mallinckrodt SilicAR CC-7) with benzene to give the title compound (**11**) as a yellow solid (24 mg, 60%), which was recrystallized from ethanol to afford yellow needles, m.p. 308–312 °C (lit.,[8] 311–315 °C) (Found: C, 83.05; H, 5.75; N, 11.3. Calc. for $C_{17}H_{14}N_2$: C, 82.9; H, 5.75; N, 11.35%); ν_{max} 3 140 (NH) and 1 600 (arom) cm^{-1}; $\delta_H[(CD_3)_2SO]$ 2.74 (3 H, s, 5-Me), 3.21 (3 H, s, 11-Me), 7.1–7.6 (3 H, m, 7-, 8-, and 9-H) 7.85 (1 H, d, *J* 6 Hz, 4-H), 8.3–8.5 (2 H, m, 3- and 10-H), 9.66 (1 H, s, 1-H), and 11.22 (1 H, br s, NH); *m/z* 246 (M^+, 100%).

3-{[N-(2,2-*Diethoxyethyl*)-N-*tosylamino*]*methyl*}-1,4-*dimethylcarbazole* (**48**).—In a three-necked flask fitted with a solid CO_2 condenser was placed a mixture of the Schiff's base (**45**) (280 mg, 0.65 mmol) in liquid NH_3 (20 ml)–THF (6 ml). Lithium wire (68 mg, 9.8 mmol) was added to the solution in small pieces. After 1 h, the reaction was quenched with 10% aqueous Na_2CO_3 and the mixture was stirred for 20 min. Then the mixture was extracted with chloroform, and the extract was washed with saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue was mixed with toluene-l-sulphonyl chloride (162 mg, 0.85 mmol) and Na_2CO_3 (96 mg, 0.91 mmol) in THF–water (1:2; 9 ml), and the mixture was vigorously stirred for 2.5 h at room temperature. The mixture was diluted with water (30 ml), extracted with chloroform, and the extract was dried over $MgSO_4$. After evaporation of the solvent, the brown residue was chromatographed on silica gel with benzene to give the title compound (**48**) as a yellow solid (260 mg, 81%), which was recrystallized from methylene dichloride–hexane to afford needles, m.p. 185–186 °C (lit.,[17] 183.5–185 °C) (Found: C, 67.85; H, 6.85; N, 5.6. Calc. for $C_{28}H_{34}N_2O_4S$: C, 68.0; H, 6.95; N, 5.65%); ν_{max} 3 360 (NH), 1 345, and 1 160 cm^{-1} (SO_2); $\delta_H(CDCl_3)$ 1.04 (6 H, t, *J* 7 Hz, 2 × CH_2Me), 2.36 (6 H, s, 1-Me and $SO_2C_6H_4Me$), 2.77 (3 H, s, 4-Me), 3.2–3.7 (6 H, m, 2 × OCH_2Me and $CHCH_2N$), 4.42 (1 H, t, *J* 6 Hz, $CHOEt_2$), 4.65 (2 H, s, 3-CH_2), 6.95 (1 H, s, 2-H), 7.1–7.5 (5 H, m, ArH), 7.71 (2 H, d, *J* 8 Hz, 2 × 2′-H), 8.10 (1 H, br s, NH), and 8.1–8.5 (1 H, m, 5-H); *m/z* 494 (M^+, 7.3%) and 103 (100).

9-*Benzyl*-1-*methylcarbazol*-3-*yl Methyl Ketone* (**52**).—To a solution of the 3-formylcarbazole (**19a**) (2.223 g, 7.43 mmol) in THF (40 ml) at −78 °C was slowly added methyl-lithium (1.5M in hexane; 8.96 ml, 13.4 mmol). After 30 min, the reaction was quenched with saturated aqueous NH_4Cl (50 ml), and most of the THF was evaporated off. The aqueous layer was extracted with methylene dichloride, and the organic layer was washed with saturated aqueous NaCl and dried over $MgSO_4$. After evaporation of the solvent, the obtained oil (2.32 g) was dissolved in acetone (30 ml). 2.67M-Jones reagent (2.42 ml, 6.5 mmol) (prepared by dissolving 26.7 g of CrO_3 in 23 ml of conc. H_2SO_4, diluted with water to a volume of 100 ml) was added to the solution and the reaction mixture was stirred for 30 min at room temperature. The mixture was quenched with saturated aqueous NH_4Cl (50 ml) and extracted with benzene. The organic layer was washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel with hexane–ethyl acetate to give the *title compound* (**52**) (1.75 g, 75%) as a pale yellow solid, which was recrystallized from benzene–hexane to afford prisms, m.p. 145–147 °C (Found: C, 84.2; H,'6.0; N, 4.25. $C_{22}H_{19}NO$ requires C, 84.3; H, 6.1; N, 4.45%); ν_{max} 1 665 (CO) and 1 590 cm^{-1} (arom); $\delta_H(CDCl_3)$ 2.57 (2 × 3 H, each s, 1-Me and COMe), 5.70 (2 H, s, $PhCH_2$), 6.7–7.5 (8 H, m, ArH), 7.72 (1 H, br s, 2-H), 8.0–8.3 (1 H, m, 5-H), and 8.55 (1 H, d, *J* 2 Hz, 4-H); *m/z* 313 (M^+, 45%) and 91 (100).

9-*Benzyl*-3-[1-(2,2-*diethoxyethylimino*)*ethyl*]-1-*methylcarbazole*.—A mixture of the ketone (**52**) (626 mg, 2.0 mmol) and aminoacetaldehyde diethyl acetal (1.45 ml, 10 mmol) were heated at 100 °C for 1.5 h under argon. Toluene was added to the mixture and was then evaporated off to remove the excess of aminoacetaldehyde diethyl acetal and water (azeotrope). This operation was repeated 3 times. The solidified residue was recrystallized from pentane–benzene to give the *title compound* (595 mg, 70%) as granules. Further recrystallization from hexane–benzene gave leaflets, m.p. 146–149 °C (Found: C, 78.6; H, 7.6; N, 6.4. $C_{28}H_{32}N_2O_2$ requires C, 78.45; H, 7.55; N, 6.55%); ν_{max} 1 620 cm^{-1} (C=N); $\delta_H(CDCl_3)$ 1.26 (6 H, t, *J* 7 Hz, 2 × CH_2Me), 2.37 and 2.62 (2 × 3 H, 2 × s, 1-Me and N=CMe), 3.5–4.0 (6 H, m, 2 × OCH_2Me and $CHCH_2N$), 4.95 (1 H, t, *J* 6 Hz, $CHOEt_2$), 5.70 (2 H, s, CH_2Ph), 6.8–7.5 (8 H, m, ArH), 7.68 (1 H, br s, 2-H), 8.0–8.2 (1 H, m, 5-H), and 8.35 (1 H, d, *J* 2 Hz, 4-H); *m/z* 428 (M^+, 7%) and 103 (100).

9-*Benzyl*-3-{1-[N-(2,2-*diethoxyethyl*)-N-*tosylamino*]*ethyl*}-1-*methylcarbazole* (**53a**).—$NaBH_4$ (376 mg, 10 mmol) was added portionwise to an ice-cooled solution of the above Schiff's base (642 mg, 1.5 mmol) in ethanol (10 ml) and the mixture was stirred at room temperature for 3 h. Saturated aqueous $NaHCO_3$ (40 ml) was added to the reaction mixture and the mixture was extracted with methylene dichloride. The organic layer was washed with saturated aqueous NaCl and dried over $MgSO_4$. After evaporation of the solvent, a solution of the crude amine (700 mg) and toluene-*p*-sulphonyl chloride (572 mg, 3.0 mmol) in pyridine (1 ml) was stirred for 2 days at room temperature. Saturated aqueous $NaHCO_3$ (30 ml) was added to the reaction mixture, which was then extracted with methylene dichloride, and the extract washed successively with 5% aqueous citric acid and saturated aqueous NaCl, and was dried ($MgSO_4$). After evaporation of the solvent, the resulting oil was chromatographed on silica gel with hexane–ethyl acetate to give the *title compound* (**53a**) as a solid (600 mg, 68%), which was

* 1,2,3,4-Tetrahydronaphthalene.

recrystallized from benzene–hexane to afford prisms, m.p. 144–146 °C (Found: C, 72.2; H, 7.05; N, 4.5. $C_{35}H_{40}N_2O_4S$ requires C, 71.9; H, 6.9; N, 4.8%); ν_{max} 1 345 and 1 170 cm^{-1} (SO_2); $\delta_H(CDCl_3)$ 1.02 and 1.21 (2 × 3 H, 2 × t, *J* 7 Hz, 2 × CH_2Me), 1.70 (3 H, d, *J* 8 Hz, NCH*Me*), 2.42 (6 H, s, 1-Me and $SO_2C_6H_4Me$), 3.0–3.9 (6 H, m, $CHCH_2N$ and 2 × OCH_2Me), 4.4–4.7 [1 H, m, $CH(OEt)_2$], 5.18 (1 H, q, *J* 7 Hz, NC*H*Me), 5.67 (2 H, s, CH_2Ph), 6.65 (1 H, s, 2-H), 6.7–7.6 (10 H, m, ArH), 7.74 (2 H, d, *J* 8 Hz, 2′-H × 2), and 7.6–8.0 (1 H, m, 5-H); *m/z* 584 (M^+, 6%) and 103 (100).

1,5-*Dimethyl*-6H-*pyrido*[4,3-b]*carbazole* (*Olivacine*) (**10**).—(*a*) *Cyclization of the tosylamide* (**53a**). The tosylamide (**53a**) (453 mg, 0.78 mmol) was dissolved in dioxane (7.7 ml) and conc. HCl (1.95 ml), and the solution was heated at 100 °C for 1 h under argon. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (35 ml) and extracted with methylene dichloride. The organic layer was washed with saturated aqueous NaCl and dried over $MgSO_4$. Evaporation of the solvent afforded a yellow powder (186 mg, 48%), whose ^1H NMR spectrum showed a mixture of the cyclized products (**54a**) and (**55a**). All attempts to separate these products failed. $\delta_H(CDCl_3)$ 1.46 (3 H, d, *J* 7 Hz, CH*Me*), 2.25 (3 H, s, $SO_2C_6H_4Me$), 2.48 and 2.53 (total 3 H, each s, 5-Me), 5.1–5.5 (1 H, m, NC*H*Me), 5.62 (2 H, br s, CH_2Ph), 6.23 (1 H, d, *J* 8 Hz, C*H*=CHN), and 6.6–8.2 (15 H, m, ArH); *m/z* 492 (M^+, 19%) and 91 (100).

(*b*) *Birch reduction and aromatization.* In a three-necked flask fitted with a solid CO_2 condenser, sodium (0.40 g, 17 mmol) was dissolved in liquid NH_3 (40 ml) at −78 °C. To this deep blue solution was added dropwise a solution of the cyclized mixture (**54a**) and (**55a**) (510 mg, 1.0 mmol) in THF (20 ml), and then the mixture was allowed to warm to remove ammonia. After ammonia had been removed (which took 2 h), the reaction was quenched with saturated aqueous $NaHCO_3$ (50 ml) at −78 °C and the mixture was allowed to warm to room temperature. The mixture was extracted with ethyl acetate and the extract was dried over $MgSO_4$. After evaporation of the solvent, the resulting pale yellow oil (271 mg) was mixed with 10% palladium–carbon (315 mg) in tetralin (6 ml) and the mixture was refluxed for 18 h under argon. Palladium–carbon was filtered off and washed thoroughly with hot ethanol. After the filtrate and washings had been evaporated, the residue was chromatographed on neutralized silica gel (Mallinckrodt SilicAR CC-7) with hexane–chloroform–ethanol (100:10:1) to give a mixture of olivacine (**10**) and its isomer (**56**) as a yellow powder (125 mg, 50%). This mixture was chromatographed repeatedly on neutralized silica gel (Mallinckrodt SilicAR CC-7) with hexane–methylene dichloride–ethanol (10:10:1) to afford pure olivacine (**10**) as a yellow powder [62 mg, 25% from (**53a**)] and the isomer (**56**) as a fine yellow powder [51 mg, 20% from (**53a**)]. Both compounds were recrystallized from ethanol–ethyl acetate. Physical data of each product were as follows.

Olivacine (**10**); fine yellow needles, m.p. 320–324 °C (decomp.) [lit.,[7] 318–324 °C (decomp.)] (Found: C, 82.95; H, 5.65; N, 11.1. Calc. for $C_{17}H_{14}N_2$; C, 82.9; H, 5.75; N, 11.35%); ν_{max}(KBr) 3 140 (NH) and 1 600 cm^{-1} (arom); λ_{max}(EtOH) 275, 285, 295, and 327 nm (log ε 4.75, 4.93, 4.89, and 3.76); δ_H [400 MHz; $(CD_3)_2SO$] 2.81 and 3.14 (2 × 3 H, s, 1- and 5-Me), 7.31 (1 H, t, *J* 7 Hz, 8-H or 9-H), 7.5–7.6 (2 H, m, 7-H and 9- or 8-H), 7.77 (1 H, d, *J* 7 Hz, 4-H), 8.06 (1 H, br s, NH), 8.24 (1 H, d, *J* 7 Hz, 10-H), 8.37 (1 H, d, *J* 8 Hz, 3-H), and 8.75 (1 H, s, 11-H); *m/z* 246 (M^+, 100%).

4,6-*Dimethyl*-7H-*pyrido*[3,4-c]*carbazole* (**56**); fine, pale yellow needles, m.p. 313–316 °C (decomp.) (Found: C, 82.4; H, 5.75; N, 11.2. $C_{17}H_{14}N_2$ requires C, 82.9; H, 5.75; N, 11.35%); ν_{max} 3 140 (NH) and 1 595 cm^{-1} (arom); λ_{max}(EtOH) 223, 275, 285, and 327 nm (log ε 4.33, 4.81, 4.21, and 4.00); δ_H [400 MHz; $(CD_3)_2SO$] 2.76 and 2.95 (2 × 3 H, s, 4- and 6-Me), 7.34 and 7.47 (each 1 H, each t, *J* 7 Hz, 9- and 10-H), 7.70 (1 H, d, *J* 7 Hz, 8-H), 8.00 (1 H, s, 5-H), 8.4 (2 H, m, 1- and 2-H), 8.57 (1 H, d, *J* 7 Hz, 11-H), and 12.0 (1 H, br s, NH); *m/z* 246 (M^+, 100%) and 204 (6.7).

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