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Fischer Indolization and Its Related Compounds. XVI.[1] Vilsmeier-Haack Reaction of N-Methyl-1,2,3,4-tetrahydrocarbazole Derivatives

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Vilsmeier-Haack reaction of 6-chloro-1,2,3,4-tetrahydro-9-methylcarbazole (**1b**) with 3 mol eq. $POCl_3$ at 70° gave three compounds, 6-chloro-1,2,3,4-tetrahydro-9-methylcarbazole-1,1-dicarboxaldehyde (**4**), 6-chloro-3,4-dihydro-9-methylcarbazole-1(2H)-one (**5b**), and 6-chloro-1,2,3,4-tetrahydro-1-hydroxy-9-methylcarbazole-1-carboxaldehyde (**6**), while no 4a-formylated product[1] was obtained. On the other hand, the reaction of the same compound (**1b**) with 1.3 mol eq. $POCl_3$ at 100° gave 6-chloro-1,2,3,4-tetrahydro-9-methylcarbazole-1-carboxaldehyde (**20**), **5b**, 6-chloro-1,2,3,4-tetrahydro-9-methylcarbazole-7-carboxaldehyde (**3b**), and an aromatized compound, 6-chloro-1,9-dimethylcarbazole-3-carboxaldehyde (**2b**). The formation mechanism of the aromatized compound (**2b**) is considered to involve elimination of a dimethylamino group and formation of 6-chloro-1,9-dimethylcarbazole (**21**) as an intermediate.

Keywords——Vilsmeier–Haack reaction; formylation; 1,2,3,4-tetrahydro-9-methylcarbazole; aromatization; reactivity; mechanism; structure

In the preceding paper,[1] we have reported on the Vilsmeier–Haack (V.-H.) reaction of NH-1,2,3,4-tetrahydrocarbazole (NH–THC) derivatives. In this paper we describe the anomalous behavior of their N-methyl congeners on similar treatment with V.-H. reagent.

There are two reports[3,4] on the V.-H. reaction of N-methyl-1,2,3,4-tetrahydrocarbazole (NMe–THC) (**1a**) and its derivative (**1b**), but these claimed quite different results. In 1970, Bruck[3] reported the formation of a fully aromatized aldehyde (**2**) as a sole product on treatment of several NMe–THC derivatives (**1**) with dimethylformamide (DMF) and phosphorus oxychloride ($POCl_3$) as a V.-H. reagent, while in 1957, Kucherova *et al.*[4] described the formation of the 7-formylated product (**3a**) on treatment of NMe–THC (**1a**) itself with diethylformamide (DEF) and $POCl_3$. We, therefore, began our study with a re-investigation of the V.-H. reaction of 6-chloro-NMe–THC (**1b**) under the conditions used in the preceding paper[1] on NH–THC; surprisingly, we obtained results that are entirely different from those of both former researchers, as follows.

Treatment of 6-chloro-NMe–THC (**1b**) with three equivalents of $POCl_3$ at 15% concentration in DMF at 70° gave a mixture of three products.

The first product (**4**) gave an elemental analysis in agreement with the molecular formula $C_{15}H_{14}ClNO_2$, and in the infrared (IR) spectrum it shows a carbonyl band at 1720 cm^{-1}. In the nuclear magnetic resonance (NMR) spectrum, it shows three aromatic protons and two formyl protons. These spectral features reduced the possible structures of the product to two (**4** and **7**). Formula (**4**) was preferred because its ultraviolet (UV) spectrum is similar to that of the mono-aldehyde (**20**) but different from that of the enamide derivative (**8**), which was independently prepared from carbazolenine[1] (**9**) (Chart 2 and Fig. 1). Later, conclusive proof was obtained chemically (*vide infra*).

Treatment of the product (**4**) with 1,2-ethanedithiol and boron trifluoride in acetic acid gave two compounds in 47.8% (**12**) and 31.5% (**13**) yields, respectively. Elemental analysis and mass spectral data indicated that they have the molecular formula $C_{16}H_{18}ClNS_2$ (**12**) and $C_{19}H_{22}ClNS_4$ (**13**). When treated with Raney nickel separately, both compounds provided the corresponding desulfurized products, which were identical with authentic samples of

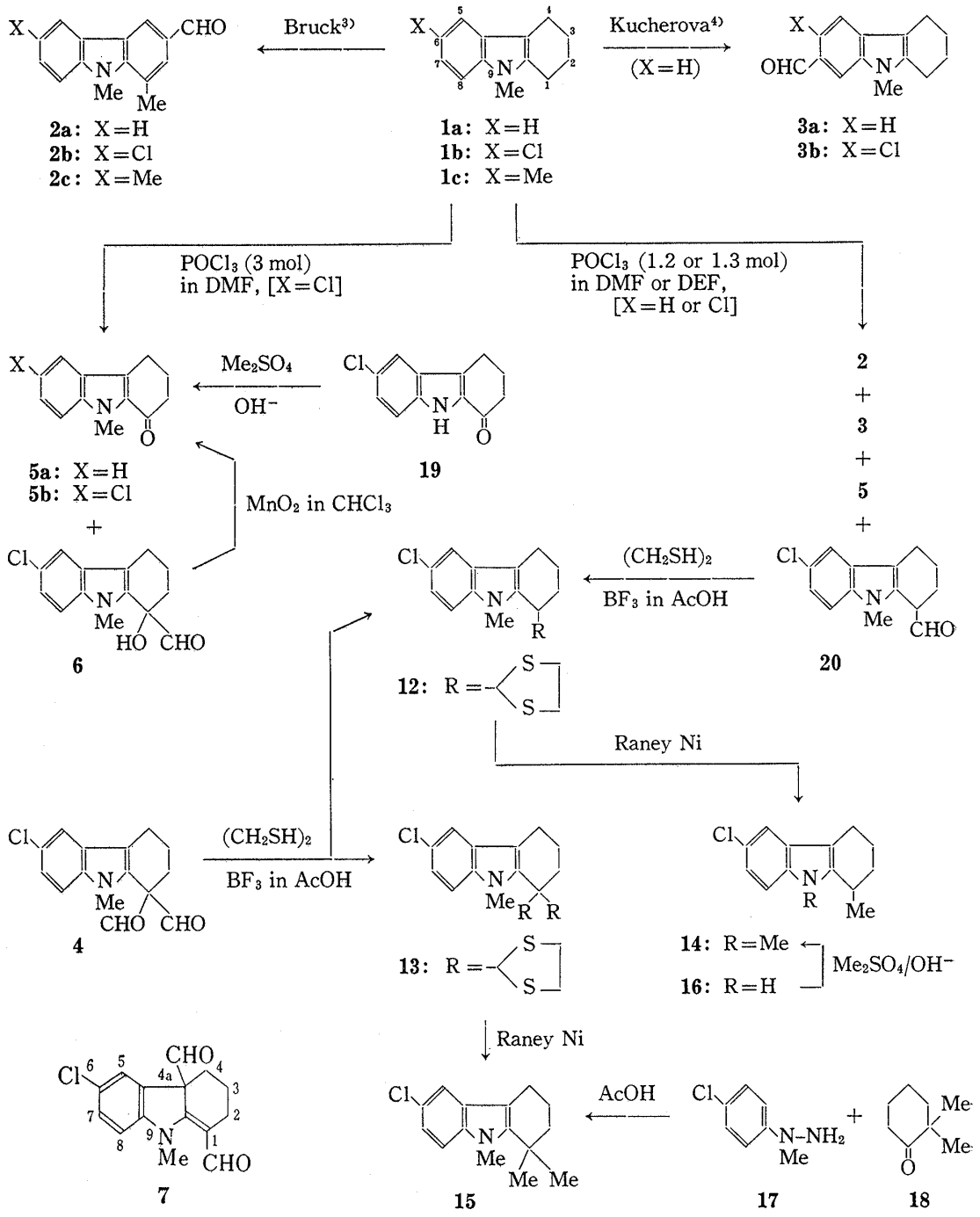


Chart 1

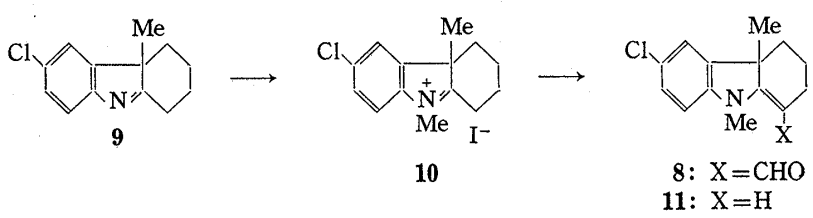


Chart 2

1-methyl-6-chloro-NMe–THC (**14**) and 1,1-dimethyl-6-chloro-NMe–THC (**15**), respectively. These authentic samples were prepared by N-methylation of 1-methyl-6-chloro-NH–THC[1] (**16**) and by treatment of N_1-(*p*-chlorophenyl)-N_1-methylhydrazine[5] (**17**) with 2,2-dimethylcyclohexanone[6] (**18**) in acetic acid. These results indicate that the first product is the dialdehyde (6-chloro-1,2,3,4-tetrahydro-9-methylcarbazole-1,1-dicarboxaldehyde) (**4**).

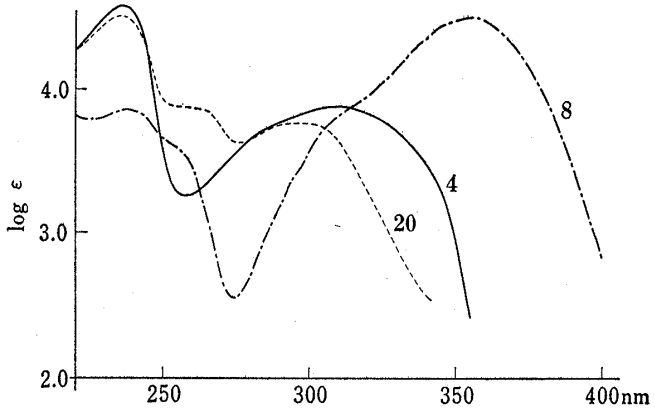


Fig. I. UV Spectra of the Dialdehyde[6-Chloro-1,2,3,4-tetrahydro-9-methylcarbazole-1,1-dicarboxaldehyde] (**4**), the Enamide Derivative[6-Chloro-2,3,4,4a-tetrahydro-4a,9-dicarboxaldehyde] (**8**), and the Mono-aldehyde[6-Chloro-1,2,3,4-tetrahydro-9-methylcarbazole-1-carboxaldehyde] (**20**)

The second product (**5b**) in the V.-H. reaction of 6-chloro-NMe–THC (**1b**) shows no formyl proton in the NMR spectrum but exhibits a carbonyl band at 1650 cm^{-1} in the IR spectrum. Its elemental analysis and mass spectral data are consistent with the molecular formula $C_{13}H_{12}ClNO$, and the UV spectrum is characteristic of a 2-acylindole chromophore. These results suggested that the product could be 6-chloro-NMe–THC-1-one (**5b**) and this was confirmed by N-methylation of 6-chloro-NH–THC-1-one[1] (**19**).

The third product (**6**) was obtained as an oily substance. In the mass spectrum, it shows a parent peak at *m/e* 263 corresponding to the molecular formula $C_{14}H_{14}ClNO_2$. In the IR spectrum, a hydroxy and a carbonyl band appear at 3425 and 1720 cm^{-1}, respectively. In the NMR spectrum, it shows a 1H formyl proton at 9.62 δ as a singlet with 6H aliphatic and 3H aromatic signals. Oxidation of this product (**6**) with manganese dioxide in chloroform gave the ketonic compound (**5b**) which was identical with the second product (**5b**). These results establish the structure of the third product as 6-chloro-1,2,3,4-tetrahydro-1-hydroxy-9-methylcarbazole-1-carboxaldehyde (**6**).

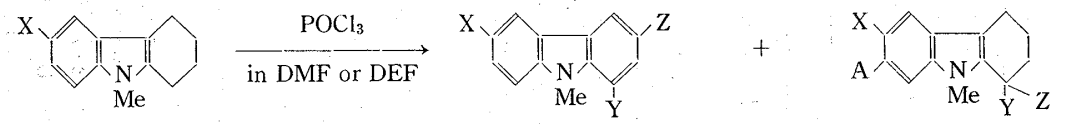
As described above, our experimental results differed completely from those of the previous workers.[3,4] These results led us to conclude that V.-H. reaction of an NMe–THC derivative is greatly affected by the experimental conditions used. In order to find a predominant factor in the reaction pattern, we[7] tried to follow rigidly the reaction conditions used by the Russian group.[4]

Treatment of NMe–THC (**1a**) with $POCl_3$ at *ca.* 15% concentration in DEF gave a mixture of three reported products, the fully aromatized product[3] (**2a**), the ketonic derivative[8] (**5a**), and the 7-formylated product[4] (**3a**). Their identities were confirmed by determination of their physical and spectral properties and by comparison of the melting points with the reported values. These results indicate clearly that the V.-H. reaction of an NMe–THC derivative can provide both types of products, *i.e.*, those reported by Kucherova[4] and by Bruck.[3] Next, we tried to find better conditions for the preferential synthesis of Kucherova's and/or Bruck's type of product. These results are listed in Table I (Exp. 3—5). During these trials, we obtained two new compounds, a mono-aldehyde (**20**) and an aromatic aldehyde (**3b**), and a known one, a fully aromatized aldehyde[3] (**2b**).

The structure of the mono-aldehyde (**20**) was established by transformation of it into the mono-dithioacetal (**12**) described above on treatment with 1,2-ethanedithiol and boron trifluoride in acetic acid.

On the other hand, the structure of the aromatic aldehyde (**3b**) was deduced from the spectral evidence. In the NMR spectrum, it shows two 1H singlets due to aromatic protons at 7.24 and 7.62 δ, 8H signals in the aliphatic proton region, and a formyl proton at 10.33 δ

TABLE I.



1a : X=H
1b : X=Cl

2a : X=H, Y=Me, Z=CHO
2b : X=Cl, Y=Me, Z=CHO

3a : X=H, Y=Z=H, A=CHO
3b : X=Cl, Y=Z=H, A=CHO
4 : X=Cl, Y=Z=CHO, A=H
5a : X=H, Y+Z=O, A=H
5b : X=Cl, Y+Z=O, A=H
6 : X=Cl, Y=OH, Z=CHO, A=H
20 : X=Cl, Y=CHO, Z=A=H

No. of experiment	Starting material	Solvent (reagent)	$POCl_3$ mol eq.[a]	$POCl_3$ conc.(%)	Temp.	Recovery of the starting material(%)	Yields of products(%) 2 (a or b)	3 (a or b)	4	5	6	20
Exp. 1	**1b**	DMF	3.0	15.0	70°[b]	0	0	0	66.0	9.9(**b**)	12.0	0
Exp. 2	**1a**	DEF	1.2	16.1	100°[c]	14.8	27.5(**a**)	6.1(**a**)		2.3(**a**)	0	0
(Comparative data)												
Kucherova[4]	**1a**	DEF	1.2	14.8	100°[d]			34.0(**a**)				
Exp. 3	**1b**	DMF	1.3	20.6	100°[b]	10.0[e]	22.6(**b**)	1.6(**b**)	0	6.3(**b**)	0	1.8
Exp. 4	**1b**	DMF	1.3	6.1	100°[b]	31.8	1.5(**b**)	1.1(**b**)	0	2.4(**b**)	0	32.2
Exp. 5	**1b**	DMF	1.3	6.1	70°[b]	28.5	trace(**b**)	0	0	8.7(**b**)	0	30.9
(Comparative data)												
Bruck[3]	**1a**	DMF	1.3	?	?		55.0(**a**)					
Bruck[3]	**1b**	DMF	1.3	?	?		+					

a) Molar equivalent with respect to the starting material (1).
b) Reaction time: 45 min.
c) Reaction time: 2.5 hr.
d) Reaction time: 8 hr.
e) A trace amount of 6-chloro-1,9-dimethylcarbazole (**21**) was detected in the mother liquor of recrystallization by gas chromatography.

as a singlet.

The identification of the fully aromatized aldehyde (**2b**) as the reported compound 6-chloro-1,9-dimethylcarbazole-3-carboxaldehyde[3] was based on its spectral data and its melting point, mp 171—173° (reported mp 168—169°[3]).

Our results clearly indicate that the work of both Bruck[3] and Kucherova[4] could be essentially correct, but minor differences between their experimental conditions caused major differences between their results. Formation of the 7-formylated derivative (**3**) is easy to understand, since it is well known in the chemistry of indoles that electrophilic attack on the aromatic ring of the indole nucleus takes place at the C_6 position[9] if the indolic nitrogen atom can not be converted into a quaternary amine under the conditions used. However, it is of interest that fully aromatized aldehydes (**2**) were formed in this reaction. We assume that the reaction proceeded according to the process shown by Chart 3. In this process, it should be pointed out that the fully aromatized NMe-carbazole (**27**) was produced first, and was then formylated at the C_3(or C_6) position of the carbazole nucleus by the V.-H. reagent,[10] whereas in direct formylation on the benzene ring of NMe–THC (**1**) itself by the same reagent, formylation takes place at the C_7 position of an NMe–THC skeleton. The stepwise mechanism is, moreover, supported by the fact that when treated with the V.-H. reagent at 100° for 45 min, the mono-aldehyde (**20**) gave the fully aromatized aldehyde (**2b**) and 6-chloro-1,9-dimethylcarbazole (**21**) in 33.2% and 28.8% yields, respectively (Chart 4). The former (**2b**) could also be formed by formylation of the latter (**21**). In a precise examination of the mixture

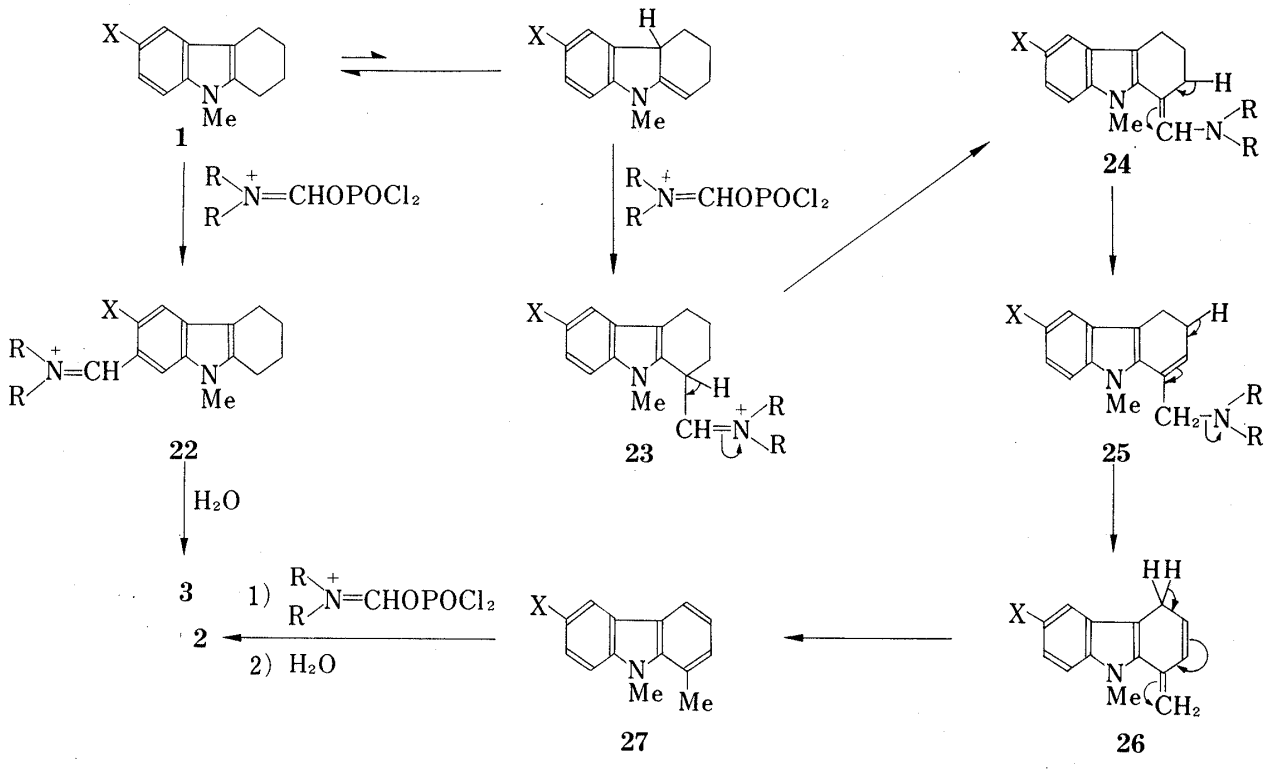


Chart 3

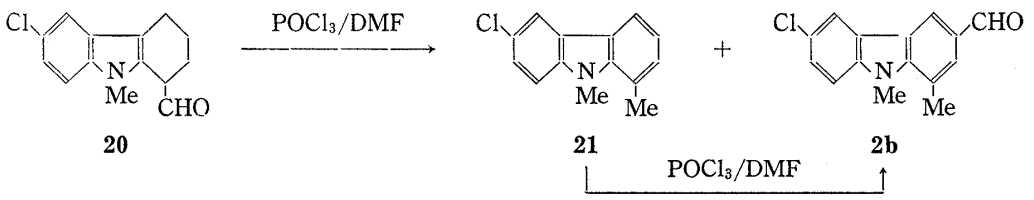


Chart 4

in Exp. 3 (Table I), a trace amount of the latter (**21**) was also detected by gas chromatography. These results account for the formation of a fully aromatized product from an N–Me THC derivative upon treatment with the V.-H. reagent.

In addition, the mono-aldehyde (**20**) and the di-aldehyde (**4**) may play important roles in the formation of the ketone (**5**), because treatment of them with an ethanolic alkaline solution gave the ketone (**5b**) in good yield.

Experimental

All melting points were measured on a micro melting point hot stage (Yanagimoto) and are uncorrected. IR, NMR and mass spectra were obtained with Hitachi EPI-G3, JEOL JMN-4H-100, and Hitachi RMU-6E spectrometers, respectively. NMR spectra were measured with tetramethylsilane as an internal reference. Mass spectra were measured by the direct inlet system. Gas chromatography was done with a Hitachi 063 gas chromatograph equipped with a stainless steel column (100 cm × 3 mm) packed with 10% SE-30. Conditions: column temperature, 180°; injection temperature, 215°; detection (FID) temperature, 205°; carrier gas, N_2 (40 ml/min). For column chromatography, silicic acid, 100 mesh, Mallinckrodt Chemical Works (SiO_2), and for preparative TLC, Kiesel gel GF_{254}, Merck, were used. Identification of the products was done by IR spectroscopy, mixed melting point determination, and TLC. The abbreviations used are as follows: s, singlet; d, doublet; d.d, double doublet; t, triplet; q, quartet; m, multiplet; dif, diffused; sh, shoulder.

Vilsmeier-Haack Reaction of 6-Chloro-NMe-THC [6-Chloro-1,2,3,4-tetrahydro-9-methylcarbazole] (1b) with 3 Mol Eq. $POCl_3$——6-Chloro-NMe-THC[1] (**1b**) (2.00 g) was added to an ice-cooled solution of $POCl_3$ (4.16 g) in anhyd. DMF (25 ml). The mixture was heated at 70° (bath temperature) for 45 min, poured into cold water, basified with 10% Na_2CO_3 aq., and extracted with Et_2O. The ethereal layer was washed with water, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (2.506 g) was chromatographed on SiO_2 with benzene as a solvent.

i) The Dialdehyde [6-Chloro-1,2,3,4-tetrahydro-9-methylcarbazole-1,1-dicarboxaldehyde] (**4**): The first eluate gave pale yellow leaflets (1.653 g), mp 129—131°, which were recrystallized from EtOH. *Anal.* Calcd for $C_{15}H_{14}ClNO_2$: C, 65.34; H, 5.12; N, 5.08. Found: C, 65.51; H, 5.21; N, 4.98. IR ν_{max}^{Nujol} cm^{-1}: 1720 (C=O). NMR ($CDCl_3$) δ: 1.70—2.85 (6H, m, aliphatic H), 3.47 (3H, s, NMe), 7.17 (2H, dif.s, C_7– and C_8–H), 7.47 (1H, dif.s, C_5–H), 9.78 (2H, s, CHO × 2). UV λ_{max}^{EtOH} nm (log ε): 235 (4.50), 258 sh (3.88), 264 sh (3.86), 310 (3.89). MS *m/e*: 277 (M^++2, 33% of the intensity of M^+), 275 (M^+).

ii) 6-Chloro-NMe-THC-1-one [6-Chloro-3,4-dihydro-9-methylcarbazole-1(2H)-one] (**5b**): The second eluate gave colorless fine prisms (210 mg), mp 130—133°, which were recrystallized from EtOH. *Anal.* Calcd for $C_{13}H_{12}ClNO$: C, 66.81; H, 5.18; N, 5.99. Found: C, 66.77; H, 5.19; N, 5.94. IR ν_{max}^{Nujol} cm^{-1}: 1650 (C=O). NMR ($CDCl_3$) δ: 2.00—3.05 (6H, m, aliphatic H), 4.01 (3H, s, NMe), 7.12—7.37 (2H, m, C_7– and C_8–H), 7.57 (1H, d, J=2.0 Hz, C_5–H). UV λ_{max}^{EtOH} nm (log ε): 241.5 (4.36), 312 (4.34). MS *m/e*: 235 (M^++2, 30% of the intensity of M^+), 233 (M^+). This material was identical with an authentic sample,[11] mp 131—133°, prepared from 6-chloro-3,4-dihydrocarbazole-1(2H)-one[1] (**19**).

iii) The Hydroxy-aldehyde [6-Chloro-1,2,3,4-tetrahydro-1-hydroxy-9-methylcarbazole-1-carboxaldehyde] (**6**): The third eluate gave a hard oil (288 mg). IR ν_{max}^{Nujol} cm^{-1}: 3425 (OH), 1720 (CHO). NMR ($CDCl_3$) δ: 1.70—2.20 (4H, m, C_2– and C_3–H), 2.60—2.90 (2H, m, C_4–H), 3.50 (3H, s, NMe), 3.73 (1H, br.s, OH, disappeared on addition of D_2O), 7.15 (2H, dif.s, C_7– and C_8–H), 7.48 (1H, d, J=1.5 Hz, C_5–H), 9.62 (1H, s, CHO). UV λ_{max}^{EtOH} nm (log ε): 237.5 (4.54), 288 (3.76), 299 (3.80), 310 (3.73). MS *m/e*: 265 (M^++2, 33% of the intensity of M^+), 263 (M^+, $C_{14}H_{14}ClNO_2$).

Preparation of the Enamide Derivative [6-Chloro-2,3,4,4a-tetrahydro-4a,9-dimethylcarbazole-1-carboxaldehyde][12] (8)——a) 6-Chloro-2,3,4,4a-tetrahydro-4a,9-dimethyl-1H-carbazolium Iodide (**10**): Methyl iodide (4.00 g) was added to a solution of the carbazolenine [6-chloro-2,3,4,4a-tetrahydro-4a-methyl-1H-carbazole[1]] (**9**) (200 mg) in acetone (10 ml). The mixture was refluxed for 1.5 hr and evaporated to dryness *in vacuo*. Recrystallization of the residue from EtOH gave colorless needles (305 mg), mp 189°. *Anal.* Calcd for $C_{14}H_{17}ClIN$: C, 46.49; H, 4.74; N, 3.87. Found: C, 46.07; H, 5.09; N, 3.81. IR ν_{max}^{Nujol} cm^{-1}: no characteristic band. NMR ($CDCl_3$) δ: 1.30—3.55 (8H, m, aliphatic H), 1.72 (3H, s, C–Me), 4.30 (3H, s, NMe), 7.51 (1H, d, J=2.0 Hz, C_5–H), 7.53 (1H, d.d, J=2.0 and 9.5 Hz, C_7–H), 7.83 (1H, d, J=9.5 Hz, C_8–H).

b) The Enamide Derivative [6-Chloro-2,3,4,4a-tetrahydro-4a,9-dimethylcarbazole-1-carboxaldehyde] (**8**): The above carbazolium iodide (**10**) (500 mg) was added to a cold solution of 5% NaOH aq. (30 ml). The resulting oil was extracted with Et_2O. The ethereal layer was then dried over anhyd. K_2CO_3 and evaporated to dryness *in vacuo*. A solution of the oily residue (**11**) (306 mg) in dry DMF (2 ml) was added to a solution of $POCl_3$ (310 mg) in dry DMF (3 ml) under ice-cooling. The mixture was then stirred for 3 hr at room temperature, poured into water, basified with 10% NaOH aq. and extracted with Et_2O. The ethereal layer was washed with water, dried over anhyd. K_2CO_3, and evaporated to dryness *in vacuo*. Column chromatography of the residue (364 mg) on SiO_2 with 20% ethyl acetate in benzene as a solvent gave light brown needles (187 mg), mp 145.5—146.5°, which were recrystallized from cyclohexane–EtOH. *Anal.* Calcd for

$C_{15}H_{16}ClNO$: C, 68.83; H, 6.16; N, 5.35. Found: C, 68.82; H, 6.26; N, 5.21. IR ν_{max}^{Nujol} cm^{-1}: 1621 (CHO). NMR (CCl_4) δ: 1.33 (3H, s, C–Me), 1.40—3.00 (6H, m, C_2–, C_3–, and C_4–H), 3.57 (3H, s, NMe), 6.65 (1H, d, J=8.5 Hz, C_8-H), 7.07 (1H, d, J=2.5 Hz, C_5–H), 7.14 (1H, d.d, J=2.5 and 8.5 Hz, C_7–H), 9.95 (1H, s, CHO). UV λ_{max}^{EtOH} nm (log ε): 236 (3.85), 258 sh (3.55), 354.5 (4.49). MS m/e: 263 (M^++2, 33.6% of the intensity of M^+), 261 (M^+).

The Mono-dithioacetal [6-Chloro-1-ethylenedithiomethyl-1,2,3,4-tetrahydro-9-methylcarbazole] (12)——BF_3–OEt_2 (0.2 ml) was added to a suspension of the dialdehyde (**4**) (100 mg) and 1,2-ethanedithiol (0.2 ml) in AcOH (2 ml). The mixture was allowed to stand for 3 hr at room temperature, poured into water and extracted with Et_2O. The ethereal layer was washed with 5% $NaHCO_3$ aq., dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was chromatographed on SiO_2 with benzene–cyclohexane (1 : 1) as a solvent. The first eluate gave colorless leaflets (56 mg), mp 148—150°, which were recrystallized from EtOH–benzene. *Anal.* Calcd for $C_{16}H_{18}ClNS_2$: C, 59.44; H, 5.62; N, 4.26. Found: C, 59.33; H, 5.60; N, 4.32. IR ν_{max}^{Nujol} cm^{-1}: no characteristic band. NMR ($CDCl_3$) δ: 1.70—3.60 (11H, m, C_1–, C_2–, C_3–, C_4–H and SCH_2CH_2S), 3.73 (3H, s, NMe), 4.96 (1H, d, J=8.3 Hz, $CH\langle^{S}_{S}$), 7.13 (2H, dif.s, C_7– and C_8–H), 7.41 (1H, d, J=1.5 Hz, C_5–H). UV λ_{max}^{EtOH} nm (log ε): 239 (4.60), 288 sh (3.85), 296 (3.88), 304 sh (3.82). MS m/e: 325 (M^++2, 46.7% of the intensity of M^+), 323 (M^+).

The Bis-dithioacetal [6-Chloro-1,1-bis(ethylenedithiomethyl)-1,2,3,4-tetrahydro-9-methylcarbazole] (13)——The second eluate gave colorless needles (49 mg), mp 214—216°, which were recrystallized from EtOH–benzene. *Anal.* Calcd for $C_{19}H_{22}ClNS_4$: C, 53.30; H, 5.18; N, 3.27. Found: C, 53.45; H, 5.12; N, 3.30. IR ν_{max}^{Nujol} cm^{-1}: no characteristic band. NMR ($CDCl_3$) δ: 1.94—2.82 (6H, m, C_2–, C_3– and C_4–H), 3.00—3.35 (8H, m, $SCH_2CH_2S\times2$), 3.99 (3H, s, NMe), 5.48 (2H, s, $CH\langle^{S}_{S}\times2$), 7.15 (2H, dif.s, C_7– and C_8–H), 7.44 (1H, d, J=1.5 Hz, C_5–H). UV λ_{max}^{EtOH} nm (log ε): 239.5 (4.61), 290 sh (3.95), 299 (3.97), 308 sh (3.88). MS m/e: 429 (M^++2, 52.4% of the intensity of M^+), 427 (M^+).

1-Methyl-6-chloro-NMe-THC [6-Chloro-1,2,3,4-tetrahydro-1,9-dimethylcarbazole] (14)——Raney nickel[13] [prepared from alloy (6 g)] was added to a solution of the mono-dithioacetal (**12**) (130 mg) in acetone (15 ml), and the suspension was refluxed for 2 hr. The catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo*. Column chromatography of the residue (100 mg) on SiO_2 with cyclohexane as a solvent yielded an oil (60 mg), which was identified by direct comparison with an authentic sample prepared as follows.

Alternative Synthesis of 1-Methyl-6-chloro-NMe-THC [6-Chloro-1,2,3,4-tetrahydro-1,9-dimethylcarbazole] (14)——To a solution of 1-methyl-6-chloro-THC[1] (**16**) (150 mg) in acetone (5 ml), 50% KOH aq. (0.75 ml) and dimethyl sulfate (0.6 ml) were added. The mixture was stirred for 4.5 hr at room temperature, poured into water, and extracted with Et_2O. The ethereal layer was washed with water, dried over anhyd. K_2CO_3, and evaporated to dryness *in vacuo*. Column chromatography of the residue (356 mg) on SiO_2 with cyclohexane as a solvent gave a pale yellow oil (131 mg), bp 190° (1.5 mmHg, bath temperature). *Anal.* Calcd for $C_{14}H_{16}ClN$: C, 71.94; H, 6.90; N, 5.99. Found: C, 71.98; H, 6.86; N, 5.86. IR ν_{max}^{liquid} cm^{-1}: no characteristic band. NMR (CCl_4) δ: 1.27 (3H, d, J=7.5 Hz, C_1–Me), 1.60—3.10 (7H, m, C_1–, C_2–, C_3–, and C_4–H), 3.60 (3H, s, NMe), 6.97 (2H, dif.s, C_7– and C_8–H), 7.26 (1H, dif.s, C_5–H). UV λ_{max}^{EtOH} nm (log ε): 238.5 (4.57), 287 sh (3.78), 295 (3.82), 303 sh (3.78). MS m/e: 235 (M^++2, 30% of the intensity of M^+), 233 (M^+).

1,1-Dimethyl-6-chloro-NMe-THC [6-Chloro-1,2,3,4-tetrahydro-1,1,9-trimethylcarbazole] (15)——Raney nickel[13] [prepared from alloy (8 g)] was added to a solution of the bis-dithioacetal (**13**) (94 mg) in acetone (15 ml), and the mixture was refluxed for 1 hr. The catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo*. Column chromatography of the residue (45 mg) on SiO_2 with cyclohexane as a solvent gave colorless leaflets (25 mg), mp 77—79°, which were recrystallized from pentane. This material was identified by direct comparison with an authentic sample prepared as follows.

Alternative Synthesis of 1,1-Dimethyl-6-chloro-NMe-THC [6-Chloro-1,2,3,4-tetrahydro-1,1,9-trimethylcarbazole] (15)——A mixture of N_1-(*p*-chlorophenyl)-N_1-methylhydrazine[5] (**17**) (781 mg) and 2,2-dimethylcyclohexanone[6] (**18**) (630 mg) in AcOH (5 ml) was gently refluxed for 1 hr, poured into water, and extracted with Et_2O. The ethereal layer was washed with 5% $NaHCO_3$ aq., dried over anhyd. K_2CO_3, and evaporated to dryness *in vacuo*. Column chromatography of the residue (1.17 g) on SiO_2 with cyclohexane as a solvent gave colorless leaflets (374 mg), mp 80—81°, which were recrystallized from pentane. *Anal.* Calcd for $C_{15}H_{18}ClN$: C, 72.71; H, 7.32; N, 5.65. Found: C, 72.85; H, 7.32; N, 5.52. IR ν_{max}^{Nujol} cm^{-1}: no characteristic band. NMR (CCl_4) δ: 1.41 (6H, s, 1,1-dimethyl), 1.55—1.95 (4H, m, C_2– and C_3–H), 2.50—2.70 (2H, m, C_4–H), 3.77 (3H, s, NMe), 6.99 (2H, dif.s, C_7– and C_8–H), 7.28 (1H, dif.s, C_5–H). UV λ_{max}^{EtOH} nm (log ε): 238.5 (4.58), 287 sh (3.79), 295 (3.81), 303 sh (3.79). MS m/e: 249 (M^++2, 36.8% of the intensity of M^+), 247 (M^+).

Alternative Synthesis of 6-Chloro-NMe-THC-1-one [6-Chloro-3,4-dihydro-9-methylcarbazole-1(2H)-one][11] (5b)——To a suspension of 6-chloro-NH-THC-1-one [6-chloro-3,4-dihydrocarbazole-1(2H)-one][1] (**19**) (220 mg) in acetone (5 ml), 10% KOH aq. (1.5 ml) and dimethyl sulfate (0.13 ml) were added. The mixture was stirred at room temperature for 45 min, poured into water, and extracted with Et_2O. The ethereal layer was dried over anhyd. K_2CO_3 and evaporated to dryness *in vacuo*. Column chromatography of the residue (123 mg) on SiO_2 with benzene as a solvent gave colorless needles (108 mg), mp 131—133°,[11] which were recrystallized from EtOH.

6-Chloro-NMe-THC-1-one (5b) from the Hydroxy-aldehyde (6)——Active MnO_2[14] (800 mg) was added to a solution of the hydroxy-aldehyde (**6**) (105 mg) in $CHCl_3$ (7 ml). The suspension was stirred at room temperature for 1.25 hr and MnO_2 was filtered off. The filtrate was evaporated to dryness *in vacuo* to yield colorless needles (75 mg), mp 130—131°. This material was identical with an authentic sample.

Vilsmeier-Haack Reaction of NMe-THC (1a) with DEF——NMe-THC (**1a**) (0.40 g) was added to a cold solution of $POCl_3$ (0.40 g) in anhyd. DEF (2.3 ml). The mixture was heated at 100—105° (bath temperature) for 2.5 hr. When the reaction was over, the mixture was worked up by the procedure described in the case of 6-chloro-NMe-THC (**1b**). The crude product (470 mg) was chromatographed on SiO_2 with benzene as a solvent. The first eluate gave the starting material (59 mg).

The Fully Aromatized Aldehyde [1,9-Dimethylcarbazole-3-carboxaldehyde][3] (2a)——The second eluate gave colorless needles (128 mg), mp 166—167.5°, after recrystallization from EtOH–benzene. *Anal.* Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.49; H, 5.87; N, 6.26. IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O). NMR (DMSO-d_6) δ: 2.88 (3H, s, C_1–Me), 4.13 (3H, s, NMe), 7.10—7.70 (4H, m, C_2–, C_6–, C_7–, and C_8–H), 8.13 (1H, d, J=7.5 Hz, C_5–H), 8.44 (1H, d, J=2.0 Hz, C_4–H), 9.93 (1H, s, CHO). MS *m/e*: 223 (M^+). The mother liquor of recrystallization gave a mixture of three components. Preparative TLC on SiO_2 with the solvent system hexane–Et_2O (3: 1) gave an additional amount of this material (7 mg; total yield 135 mg) from the portion with moderate *Rf* value.

NMe-THC-1-one[3,4-Dihydro-9-methylcarbazole-1(2H)-one][8] (5a)——In the preparative TLC described above, the portion showing the largest *Rf* value gave colorless plates (10 mg), mp 100.5—102° (lit.[8] mp 102.5—103°), which were recrystallized from hexane. *Anal.* Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.41; H, 6.66; N, 6.87. IR ν_{max}^{Nujol} cm^{-1}: 1646 (C=O). UV λ_{max}^{EtOH} nm (log ε): 240 (4.29), 310 (4.34). MS *m/e*: 199 (M^+).

The 7-Formylated Product [1,2,3,4-Tetrahydro-9-methylcarbazole-7-carboxaldehyde][4] (3a)——The portion showing the smallest *Rf* value on preparative TLC gave colorless needles (28 mg), mp 114—115° (lit.[4] mp 113—114°), which were recrystallized from EtOH. *Anal.* Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 79.15; H, 6.78; N, 6.42. IR ν_{max}^{Nujol} cm^{-1}: 1672 (C=O). NMR ($CDCl_3$) δ: 1.89 (4H, m, C_2– and C_3–H), 2.72 (4H, m, C_1– and C_4–H), 3.67 (3H, s, NMe), 7.52 (2H, dif.s, C_5– and C_6–H), 7.77 (1H, dif.s, C_8–H), 10.01 (1H, s, CHO). UV λ_{max}^{EtOH} nm (log ε): 236.5 (4.16), 247 (4.15), 265.5 (4.22), 315.5 (4.09). MS *m/e*: 213 (M^+).

Vilsmeier-Haack Reaction of 6-Chloro-NMe-THC (1b) with 1.3 Mol Eq. $POCl_3$ (Table I) at Several Concentrations——6-Chloro-NMe-THC (**1b**) (0.400 g) was added to a cold solution of $POCl_3$ (0.363 g) in anhyd. DMF [1.20 g (10.5 mol eq.) or 4.80 g (42.0 mol eq.)]. The mixture was then heated at 70° or 100° (bath temperature) for 45 min, and worked up as described in the case of the 3 mol eq. experiment. The reaction mixture was chromatographed on SiO_2 with benzene as a solvent. The starting 6-chloro-NMe-THC (**1b**), the mono-aldehyde (**20**), and a mixture of three other components were eluted in that order. Recrystallization of the mixture from EtOH–benzene gave the fully aromatized aldehyde [6-chloro-1,9-dimethylcarbazole-3-carboxaldehyde] (**2b**). The residue which was obtained from the mother liquor of the recrystallization was subjected to preparative TLC with Et_2O–hexane (1: 2) as a solvent system to give 6-chloro-NMe-THC-1-one (**5b**), the 7-formyl derivative (**3b**), and **2b**. The presence of 6-chloro-1,9-dimethylcarbazole (**21**) (1/100 of **1b**) was detected in the mother liquor of recrystallization of recovered **1b** by gas chromatography (retention time, **1b**; 11.1 min; **21**: 17.1 min).

The Mono-aldehyde [6-Chloro-1,2,3,4-tetrahydro-9-methylcarbazole-1-carboxaldehyde] (**20**): Colorless prisms, mp 109—111°, after recrystallization from hexane–EtOH or cyclohexane. *Anal.* Calcd for $C_{14}H_{14}ClNO$: C, 67.88; H, 5.70; N, 5.65. Found: C, 68.02; H, 5.67; N, 5.65. IR ν_{max}^{Nujol} cm^{-1}: 1722 (CHO). NMR ($CDCl_3$) δ: 1.70—3.83 (7H, m, C_1–, C_2–, C_3– and C_4–H), 3.59 (3H, s, NMe), 7.14 (2H, s, C_7– and C_8–H), 7.44 (1H, d, J=2.0 Hz, C_5–H), 9.67 (1H, d, J=3.0 Hz, CHO). UV λ_{max}^{EtOH} nm (log ε): 235.5 (4.56), 287 sh (3.75), 296 (3.77), 303 sh (3.75). MS *m/e*: 249 (M^++2, 37.2% of the intensity of M^+), 247 (M^+).

7-Formylated Product [6-Chloro-1,2,3,4-tetrahydro-9-methylcarbazole-7-carboxaldehyde] (**3b**): Pale yellow needles, mp 140—141°, after recrystallization from hexane. *Anal.* Calcd for $C_{14}H_{14}ClNO$: C,67.88; H, 5.70; N, 5.65. Found: C, 67.74; H, 5.59; N, 5.64. IR ν_{max}^{Nujol} cm^{-1}: 1667 (C=O). NMR (CCl_4) δ: 1.88 (4H, m, C_2– and C_3–H), 2.63 (4H, m, C_1– and C_4–H), 3.63 (3H, s, NMe), 7.24 (1H, s, C_5–H), 7.62 (1H, s, C_8–H), 10.33 (1H, s, CHO). UV λ_{max}^{EtOH} nm (log ε): 247 (4.18), 272 (4.21), 327.5 (4.09). MS *m/e*: 249 (M^++2, 33.4% of the intensity of M^+), 247 (M^+).

The Fully Aromatized Aldehyde [6-Chloro-1,9-dimethylcarbazole-3-carboxaldehyde[3] (**2b**):] Colorless needles, mp 171—173° (lit.[3] mp 168—169°), after recrystallization from EtOH–benzene. *Anal.* Calcd for $C_{15}H_{12}ClNO$: C, 69.90; H, 4.69; N, 5.44. Found: C, 69.86; H, 4.52; N, 5.42. IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O). NMR (DMSO-d_6) δ: 2.86 (3H, s, C_1–Me), 4.11 (3H, s, NMe), 7.42 (1H, d.d, J=9.2 and 2.5 Hz, C_7–H), 7.59 (1H, d, J=9.2 Hz, C_8–H), 7.63 (1H, dif. s, C_2–H), 8.19 (1H, d, J=2.5 Hz, C_5–H), 8.48 (1H, d, J=2.5 Hz, C_4–H), 9.93 (1H, s, CHO). MS *m/e*: 259 (M^++2, 36.6% of the intensity of M^+), 257 (M^+).

The Mono-dithioacetal (12) from the Mono-aldehyde (20)——BF_3–OEt_2 (0.09 ml) was added to a solution of the mono-aldehyde (**20**) (68 mg) and 1,2-ethanedithiol (0.09 ml). The mixture was allowed to stand for 8.5 hr at room temperature, poured into water, and extracted with Et_2O. The ethereal layer was washed with 5% $NaHCO_3$ aq., dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The oily residue was subjected

to preparative TLC with benzene–cyclohexane (1: 1) to give colorless leaflets (83 mg), mp 147—149°, which were recrystallized from benzene–EtOH. This material was identical with the sample obtained from the dialdehyde (**4**).

Vilsmeier-Haack Reaction of the Mono-aldehyde (20)——$POCl_3$ (185 mg) was added to a solution of the mono-aldehyde (**20**) (150 mg) in DMF (0.5 ml). The mixture was heated at 100° for 45 min, poured into water, basified with 10% Na_2CO_3 aq., and extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was subjected to preparative TLC on SiO_2 with benzene as a solvent.

a) 6-Chloro-1,9-dimethylcarbazole (**21**): Purification of the portion (46 mg) showing a larger *Rf* value on preparative TLC on SiO_2 with the solvent system hexane–Et_2O (2.5: 1) gave colorless needles (40 mg), mp 99.5—100.5°, which were recrystallized from hexane. *Anal.* Calcd for $C_{14}H_{12}ClN$: C, 73.20; H, 5.27; N, 6.10. Found: C, 73.09; H, 5.21; N, 6.04. IR ν_{max}^{Nujol} cm^{-1}: no characteristic band. NMR (CCl_4) δ: 2.73 (3H, s, aromatic Me), 3.93 (3H, s, NMe), 6.85—7.90 (6H, m, aromatic H). UV ν_{max}^{EtOH} nm (log ε): 242.5 (4.60), 252 (4.42), 267 (4.41), 288.5 (3.90), 298.5 (4.15), 327 (3.30), 340 (3.52), 355 (3.55). MS *m/e*: 231 (M^++2, 35% of the intensity of M^+), 229 (M^+).

b) The Fully Aromatized Product (**2b**): The portion showing a smaller *Rf* value in the first preparative TLC gave colorless needles (52 mg), mp 170—172°, which were recrystallized from EtOH–benzene. This material was identical with an authentic sample (**2b**) (mp 171—173°).

Vilsmeier Reaction of 6-Chloro-1,9-dimethylcarbazole (21)——6-Chloro-1,9-dimethylcarbazole (**21**) (55 mg) was added to a solution of $POCl_3$ (0.044 ml) in anhyd. DMF (0.5 ml). The mixture was heated at 100° (bath temperature) for 45 min, and worked up as described in the case of 6-chloro-NMe-THC (**1b**). The residue was subjected to preparative TLC with benzene. The portion showing a larger *Rf* value gave the starting **21** (36 mg). The portion showing a smaller *Rf* value gave colorless needles (8 mg), mp 172—174°, which were recrystallized from EtOH–benzene. This material was identical with an authentic sample of the fully aromatized aldehyde (**2b**).

Treatment of the Dialdehyde (4) with 50% KOH in EtOH——A suspension of the dialdehyde (**4**) (200 mg) in EtOH (5 ml) was treated with 50% KOH aq. (0.5 ml), with stirring. The mixture was stirred for 20 min at room temperature (the whole became clear), then gently refluxed for 5 min, poured into water, and extracted with Et_2O. The ethereal layer was washed with water, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. Recrystallization of the residue from EtOH gave the 6-chloro-NMe-THC-1-one (**5b**) (150 mg), mp 130—133°.

Treatment of the Mono-aldehyde (20) with 10% NaOH in EtOH——A solution of the mono-aldehyde (**20**) (100 mg) in EtOH (3 ml) was treated with 10% NaOH aq. (1.0 ml). The mixture was refluxed for 1 hr, and worked up in the manner described above. Recrystallization of the crude material from EtOH gave the ketone (**5b**) (61 mg), mp 130—133°.

References and Notes

1) *a*) Part XV: Y. Murakami and H. Ishii, *Chem. Pharm. Bull.*, **29**, 699 (1981); *b*) A part of this study was presented at the 5th Congress of Heterocyclic Chemistry, Gifu, Japan, November, 1972.
2) Location: *a*) *2-2-1, Miyama, Funabashi, 274, Japan*; *b*) *1-33, Yayoi-cho, Chiba, 260, Japan.*
3) P. Bruck, *Chem. Commun.*, **1970**, 1690.
4) N.F. Kucherova, V.P. Edakov, and N.K. Lochetlov, *Zhur. Obschei. Khim.*, **271**, 1049 (1957) [*Chem. Abstr.*, **52**, 3763 (1958)].
5) *a*) H.-H. Stroh, D. Henning, and J. Klandler, *Z. Chem.*, **3**, 426 (1963) [*Chem. Abstr.*, **60**, 7940*c* (1964)]; *b*) H.-H. Stroh and G. Westphal, *Chem. Ber.*, **97**, 83 (1964).
6) *a*) F.E. King, T.J. King, and J.G. Topliss, *J. Chem. Soc.*, **1957**, 919; *b*) W.S. Johnson and H. Posvic, *J. Am. Chem. Soc.*, **69**, 1361 (1947).
7) Unfortunately we could not follow Bruck's conditions, because his report[3] was published only as a communication.
8) L.J. Dolby and D.L. Booth, *J. Org. Chem.*, **30**, 1550 (1965).
9) The C_6 position of an indole nucleus corresponds to the C_7 position of THC.
10) Ng. Ph. Buu-Hoi and Ng. Hoan, *J. Am. Chem. Soc.*, **73**, 98 (1951).
11) A.N. Grinev and I.N. Nikolaeva, *Arm. Khim. Zh.*, **28**, 1007 (1975) [*Chem. Abstr.*, **85**, 21002*x* (1976)]. In this report, the melting point of this substance is not given.
12) The method follows Fritz's report. H. Fritz, *Chem. Ber.*, **92**, 1809 (1959).
13) R. Mozingo, D.E. Wolf, S.A. Harris, and K. Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1943).
14) I.M. Goldman, *J. Org. Chem.*, **34**, 1979 (1969).