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PHOTOINDUCED OXYGENATION OF TRYPTAMINES BY AROMATIC AMINE N-OXIDES[1]

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Abstract—Irradiation (1) (253·7 nm) of N_a,N_b-dimethyltryptamine with pyridine N-oxide or benzo[c]cinnoline N-oxide in CH_2Cl_2 yielded 1,8-dimethyl-3a-hydroxy-1,2,3,3a,8-8a,-hexahydropyrrolo[2,3-b]indole (**19**), while with visible light N_b-(4-cyanobutadienyl)-N_a,N_b-dimethyltryptamine (**21**) was obtained. This method was applied to trimethyltryptamine and the corresponding oxindole (**34**) and the N-formyl derivative (**20**) were obtained.

Autoxidation of indoles has come in much attention in recent years [2a] and the reaction of molecular oxygen with indoles to form 3-hydroperoxyindolenines, 3-hydroxyindolenines or its rearranged products such as **4**, has been well rationalized.[2b] The interest in these reactions, moreover, has been greatly stimulated by the similarity of those to the metabolic transformation of tryptophan to kynurenine.[3] Furthermore, the operation of an analogous reaction to the autoxidation of indoles could account for the occurrence of 2-acylindole alkaloids such as vobasine **6**.[4]

Tryptophan derivatives, however, undergoes a variety of oxidative pathways other than the cleavage of 2,3-bond in the pyrrole ring. The biologically important and frequent occurrence in nature, of tryptophan derivatives, is the oxidation of the benzene ring, e.g. 5-hydroxytryptophan,[5] serotonine,[5] dehydrobufotenine **7**[6] and the sporidesmins **8**.[7]

In recent years there has been considerable interest and speculation concerning the nature of biological oxidation of aromatic substrates with concomitant NIH shift.[8] The importance of arene oxides such as **9** and **10** as a primary intermediate in the oxidation of aromatic compounds *in vivo* has been suggested.[9]

Chemical epoxidation of aromatic double bond was successfully made by photoysing pyridine N-oxide in the presence of aromatic compounds, which serves as a useful model reaction for such oxidations catalyzed by monooxygenases.[10] It has also been reported that photo-induced oxygenation by pyridine[11a] and pyridazine N-oxides[11b] of ethylenic and aromatic compounds gave the oxygen atom addition product to the C=C double bond, whereas, insertion reaction of O atom to the C–H bond took place in the case of saturated compounds.

It was considered that enzymatic formation of the epoxide at the most reactive 2,3 position of tryptamines **11** and followed cyclization will result in formation of 3a-hydroxypyrroloindoles **13** in one step, which is a unique ring system found in sporidesmins and brevianamide E **15**,[12] as shown in Chart 1. On the other hand, **12** (R=Me) will be expected to form oxindole **14**.

The present paper reports our findings on the oxygenation of tryptamines by photolysing aromatic amine N-oxides (**17**, **32**) and isolation and identification of 1,8-dimethyl-3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole **19**, butadienyl cyanide **21**, and oxindole **34**.

Oxidation of N_a,N_b-dimethyltryptamine **16** *by pyridine N-oxide* **17** *with low pressure mercury lamp*

N_a,N_b-Dimethyltryptamine **16** in CH_2Cl_2 with 2·0 moles of **17** was irradiated with 253·7 nm for 1 h. A gradual disappearance of the starting material was determined by TLC and the UV spectrum. One of new spots which showed a deep blue fluorescence under 254 nm light and gave a negative color test with Ehrlich's reagent, was separated as the main product in 11·6% yield by preparative TLC. The structure assignment as the expected compound **19** was fully supported by elemental analysis of its picrate and by spectral data. Thus, the mass spectrum exhibited the characteristic fragment peaks (a), (b), (c) besides the molecular ion peak, which can be rationalized on the basis of the structure **19**. The UV absorption spectrum was typical of a PhNCN system having maxima at 250, 303 nm, and the hypsochromic shift of 8 nm for both bands was observed in addition of an acid.[13] The IR spectrum of **19** in $CHCl_3$ contained a sharp band at 3650 cm^{-1}, a broad band at 3340 cm^{-1}, assigned to the OH streching. The NMR spectrum of **19** in $CDCl_3$ confirms the presence of a methine proton N–CH–N at δ 4·25 as a singlet[14] and a broad OH

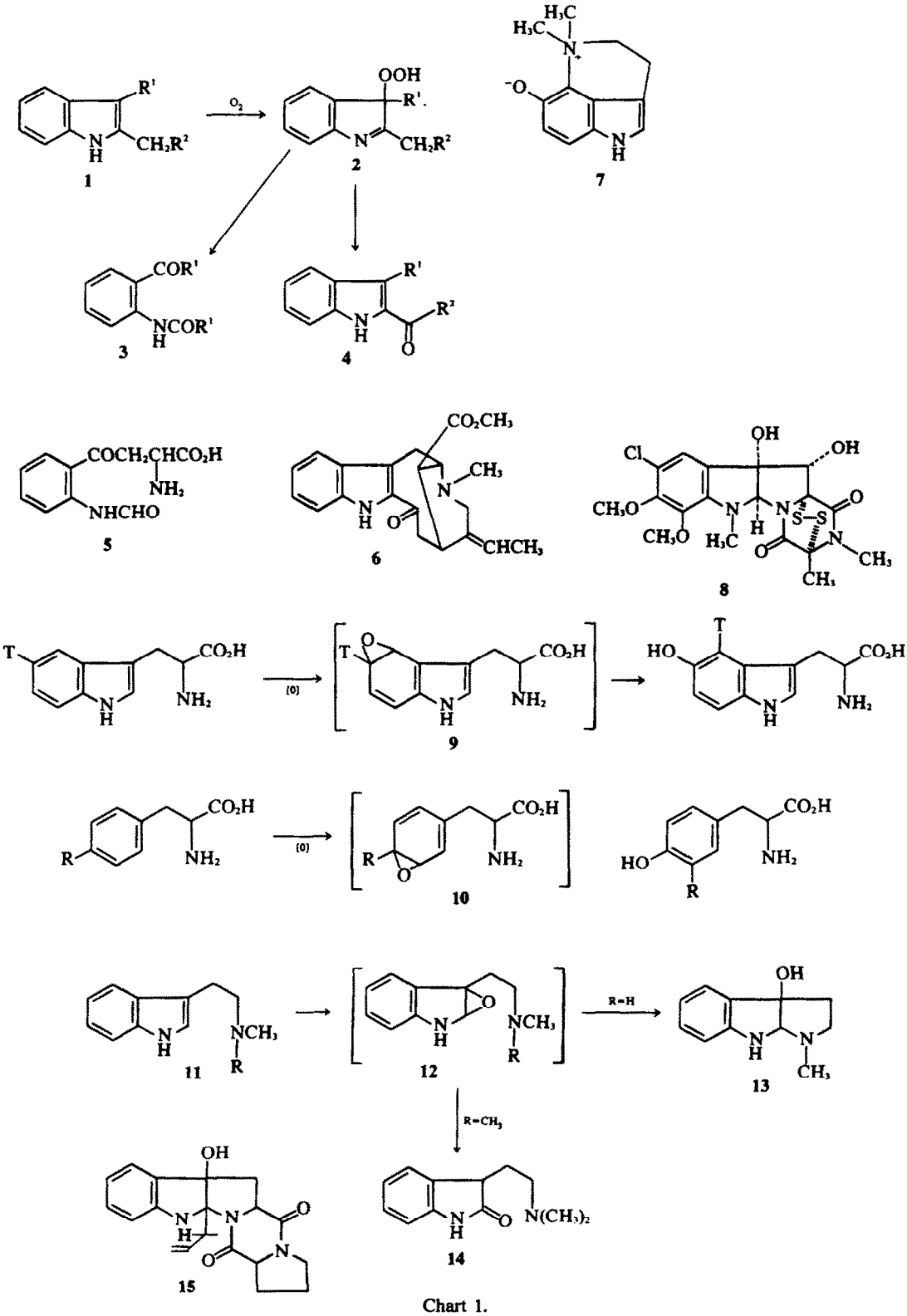
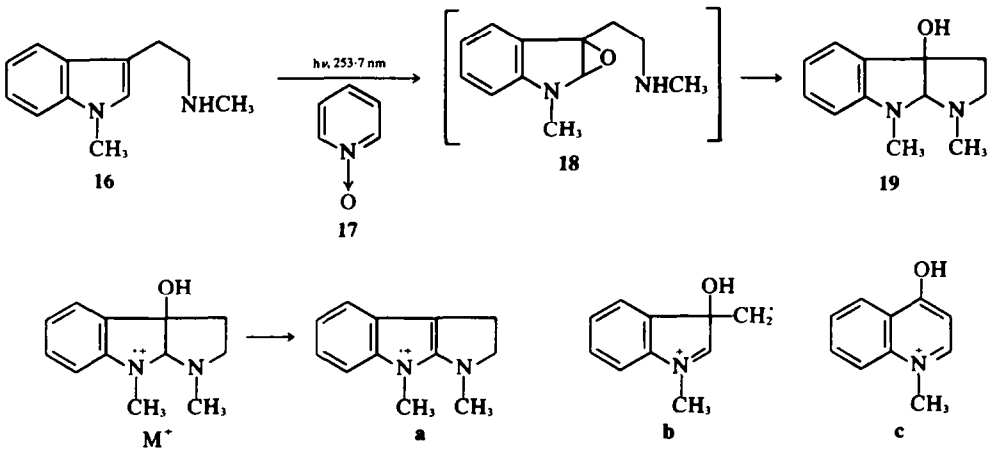


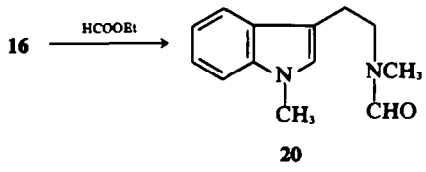
Chart 1.



peak at δ 4·44 which disappeared upon addition of D_2O.

Anhydro analogs of **19** have been reported and which were converted by steps of oxidation and reduction to 3a-hydroxypyrroloindoles.[15] 2-Alkyl-3a-hydroxypyrroloindole has also been prepared by the reduction of the corresponding oxime with LAH.[16] Our one step production of this structure probably proceeds by participation of the ethylamine side chain in opening an intermediate 2,3-oxide **18**.

The yield of **19** were not much altered when the molar ratios of **17/16** were varied from 1·5 to 5 as shown in Table 1 and falls in the range of 8-11%. In addition, a small amount of one of by-products, which displayed a positive color test with Ehlrich's reagent, was isolated from the reaction mixture and identified as N_b-formyl-*Na*,N_b-dimethyltryptamine **20** (0·8%). The structure assignments rest on comparisons of its spectral data and the R_f value on TLC with those of the authentic specimen prepared from the reaction of **16** with ethylformate. The NMR spectrum of **20** in $CDCl_3$ showed N_b-methyl protons, α-proton and formyl proton as a doublet, respectively, indicating the presence of a hindered internal rotation of the amide bond. The coalescence temperature was found at 128 ± 2° in DMSO and $\Delta G^{\neq}$ was calculated to be 20·6 kcal/mole. Similar effect attributed to *cis* and *trans* rotational isomers in the spectrum of N-acetyl-N-methyltrypt-



amine has been observed.[17] The N-alkylation of **16** with CH_2Cl_2 and followed hydrolysis and oxidation were presumably involved in the formation of **20**, although the mechanism is not certain.

Irradiation of **17** *with* 200 *W mercury lamp in the presence of* **16**

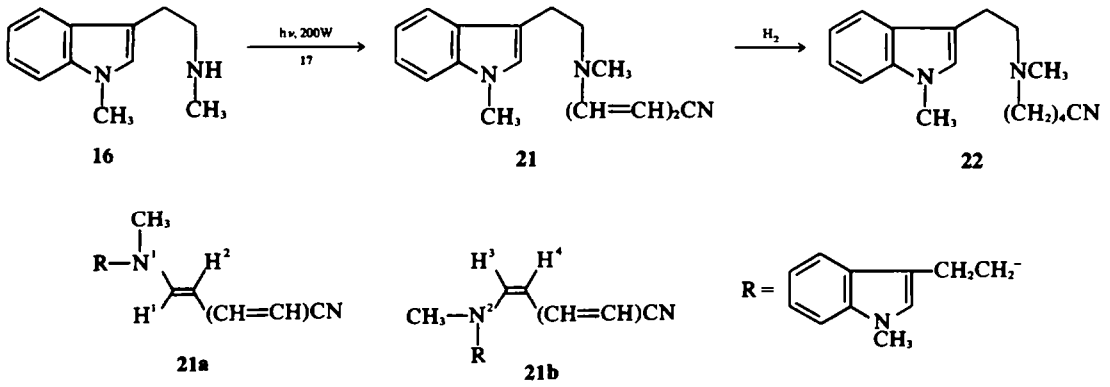
However, irradiation of **16** with **17** in CH_2Cl_2 with a 200 W mercury lamp gave rise to the butadienyl cyanide **21** as the main product in 20% yield, in the presence or absence of air, and **19** was not obtained. The NMR spectrum in $CDCl_3$ exhibited four olefinic protons as multiplets (δ 4·30–5·55, 6·40–6·70), indicating that the butadienyl group must be present as **21**. In addition, its conjugation with the nitrile group was suggested from the UV spectrum (λ_{max}225 and 339 nm) as well as the IR spectrum of the nitrile group ($\nu_{C\equiv N}$2195 cm^{-1}). The mass spectrum, likewise, supported the structure **21**, giving a molecular ion peak at *m/e* 265 and a fragment peak at *m/e* 121 $CH_2{=}\overset{+}{N}(CH_3)$-$(CH{=}CH)_2CN$. Although the stereochemistry of the butadienyl group is not determined yet, further examination of the olefinic protons showed **21** was a roughly 1 : 1 mixture consisting of the part structure of *trans* **21a** and *cis* **21b** as depicted [δ 4·65(d, H^1, $J_{1,2}$ = 15 Hz), 4·36(d, H^3, $J_{3,4}$ = 10 Hz), 5·05(t, H^2), 5·41(t, H^4), 2·80(s, N^1–Me), 2·85(s, N^2–Me)]. Moreover, **21**, which showed the NMR spectrum the entirely same as that obtained above, was obtained when **16** was immediately added to the preirradiated CH_2Cl_2 soln of **17**.[18]

The structure of **21** was further confirmed by selective hydrogenation (Pd/C) in MeOH with 2

Table 1. Irradiation (253·7 nm) of **16** with **17** in CH_2Cl_2

Molar ratio 17/16	Yield (%) 20	Recovered yield (%) 16	17
1·5	9	21	78
2·0	11·6	27	—[a]
2·5	10·5	—[a]	—[a]
3·0	7·4	70	42
5·0	7·4	31	70

[a] Isolation was not attempted.



moles of H_2 uptake to give the saturated nitrile **22**.

Irradiation of **16** in various reaction conditions was summarized in Table 2, showing the reaction was dependent on a wavelength and a solvent used. It is apparent that **19** was obtained only when irradiated at 253·7 nm in CH_2Cl_2 in the presence or absence of air. However, upon irradiation of **16** at 253·7 nm in CH_2Cl_2 in a N_2 atmosphere, **21** was isolated besides **19** and became the sole product when the reaction was run in MeOH or irradiated with 200 W lamp. Since **21** decomposed rapidly in CH_2Cl_2 by irradiation at 253·7 nm in an open air, it appears resonable that the yield of **21** was lower when the nitrogen purge was omitted.

Mechanism of the formation of cyanobutadienyl derivatives

Methylaniline **23**, as with **16**, readily gave a butadienyl cyanide **24** upon irradiation (200 W) of **17** (3 mole equivalent) in 27% yield. Subsequent catalytic hydrogenation of **24** over 10% Pd/C gave the corresponding amine **26** in 90% yield. Changing the relative ratios of **23** to **17** had no marked effect on the yield of **24** as listed in Table 3 and the HCl salt of **23** became the main product when the reaction was run in excess of **23**. In addition, a small amount of **25** was isolated, which was identical with that obtained by the reaction of **23** with CH_2O.[19] On the other hand, irradiation of **23** without

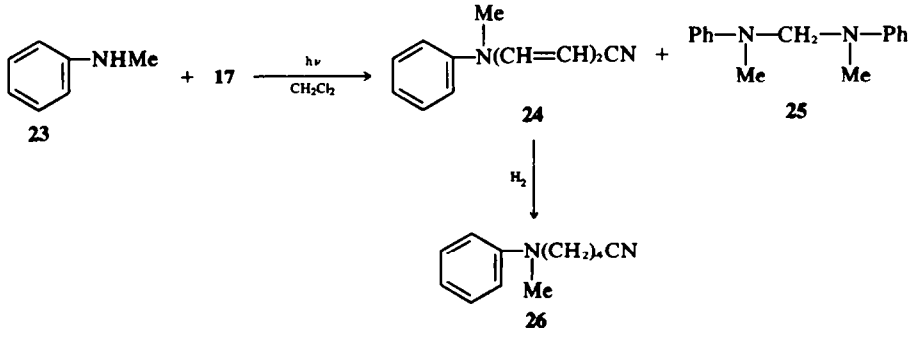


Table 2. Irradiation of **16** with **17** in various reaction conditions

Light source	Moral ratio 17/16	Solvent	Reaction time (h)	Air or N_2	Yield(%) 19	21
253·7 nm	2·5	CH_2Cl_2	1	air	10·5	
253·7 nm	2	CH_2Cl_2	1	N_2	4[a]	6
253·7 nm	3	CH_3OH	1	air		11
253·7 nm	3	CH_3OH	1	N_2		12
200 W	3	CH_2Cl_2	3	air		14
200 W	3	CH_2Cl_2	3	N_2		20

[a]The yield obtained when 100 mg of **16** was used. The other reactions were run with **16** (1 g or more, Experimental).

Table 3. Irradiation (200 W) of 23 with 17 in CH_2Cl_2

Mol. equiv 23	17	Products yield (%) 24[b]	23 HCl salt	25
1/3	1	9	0	[a]
1/2	1	9	0	[a]
1	1	8	0	[a]
3	1	10	42–27	5·3
1	0	0	70	0

[a] Isolation was not attempted although the presence of 25 in the reaction mixture was detected.
[b] The yield was calculated based on 17.

17 gave the HCl salt of 23 in 70% yield.

Photoinduced isomerization of 17 has been known to give 2-formylpyrrole[20] and the intermediacy of 1,2-oxazepine has been suggested, whose presence was recently demonstrated by isolating benzol[c.f]-1,2-oxazepine.[21] The mechanism of the formation of the cyanobutadienyl derivatives (21, 24) is not entirely clear but it is assumed that 16 effects a base-catalyzed opening of 27 in a manner analogous to the known base-catalyzed ring opening of isoxazoles[22] giving 28 which then reacts with 16 to give 21. Although the formation of 28 by irradiation of pyridine N-oxide has not been reported, our experimental data suggest that the conversion of 27 to 28 may occur possibly by photochemical or thermal [1, 3]-sigmatropic rearrangement, followed by condensation of the resulting 28 with 16, as a possible alternative. Supporting this mechanism, is the isolation of photoisomer analogous 28, *viz*, β-formamidoacrylonitrile 30, by irradiation of pyrimidine N-oxide[23] or the formation of the thermal rearranged product 31.[24] Our results are in agreement with those previous observations that photoisomerization of 17 was favoured in a polar solvent such as EtOH, whereas deoxygenation predominated in CH_2Cl_2.[25]

Oxidation of 16 *by photolysing benzo[c]cinnoline N-oxide*

Benzo[c]cinnoline N-oxide 32 was reported incapable of undergoing photoinduced isomerization but photolysis causes only deoxygenation.[26] Therefore, 32 was chosen in place of 17 and the oxidation of 16 in various reaction conditions was carried out. The results are shown in Table 4. Optimum conditions for obtaining 19 appeared to be the use of 100 W medium pressure lamp. However, the yield of 19 was not improved as compared with that obtained by the use of 17.

Oxidation of N_a,N_b,N_b-*trimethyltryptamine* 33 *by photolysing* 17

Irradiation of 33 in CH_2Cl_2 with 2 moles of 17 for 30 min at 253·7 nm gave the oxindole 34 in 0·7% yield. Prolonged irradiation did not improve the yield of 34. When 33 in CH_2Cl_2 with 3 moles of 17 was irradiated with 200 W lamp, 20 was isolated in 1·1% yield besides a trace of 34.

It has been shown that photochemical deoxy-

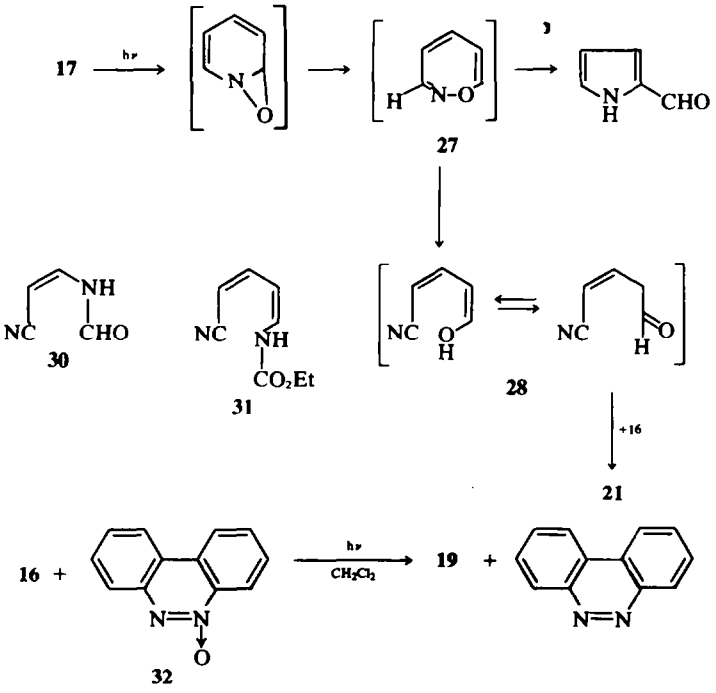
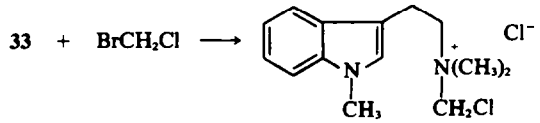


Table 4. Irradiation of **16** with **32** in CH_2Cl_2 in various reaction conditions

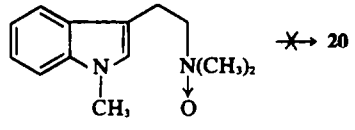
Light source	Filter	Reaction time (h)	Yield (%) **19**	Yield (%) benzo[c]-cinnoline	Recovery (%) **16**	Recovery (%) **32**
253·7 nm	—	9	8	4·4	36	84
100 W	pyrex	3	12	7·4	25	79
400 W	—	2	3	10·0	14	61
400 W	pyrex	2	6	14·4	19	70

Molar ratio **32**/**16** = 3.

genation became predominant over photoisomerization when a triplet sensitizer such as benzophenone was used.[27] Therefore, benzophenone sensitization of this reaction was carried out for 5 h. In addition to two photoproducts **34**(0·1%) and **20**(0·7%), chloromethyl-dimethyl-2-(β-N-methylindolyl)ethyl ammonium chloride **35a**, m.p., 74–76°, was obtained from the aqueous layer in 10% yield. It gave an immediate precipitate with an aqueous silver nitrate. Its picrate, m.p., 167–168° gave a positive Beilstein test and was identical with a specimen prepared by the chloromethylation of **33** with $ClCH_2Br$. The NMR spectrum taken in CF_3COOH showed a sharp singlet at δ 5·15 due to N–CH_2–Cl proton.



35b



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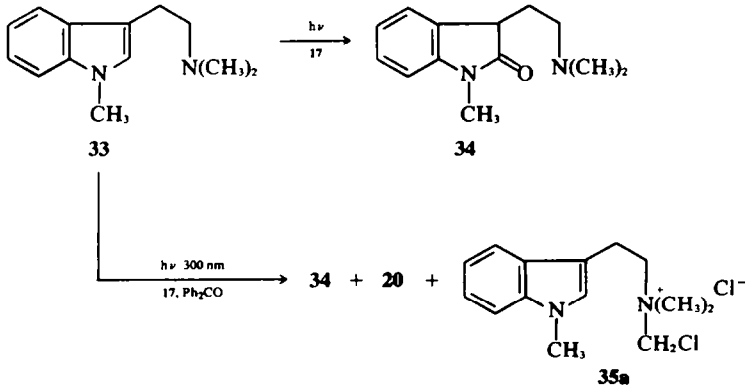
In the oxidation of **33**, as with the dimethyltryptamine **16**, indole 2,3-oxide was postulated, as an intermediate to **34**. On the other hand, treatment of the N_b-oxide **36**, which was prepared by the reaction of **33** with *m*-Cl–$C_6H_4CO_3H$ in $CHCl_3$,[28] under these reaction conditions did not give **20** and rules it out as an intermediate. Therefore, the trace of N-formyltryptamine **20** found in the photolysis mixture of **33** probably arises from the direct oxygenation of Me group. Though the mechanism of this oxygen transfer reaction is not known, photoinduced oxygenation of the Me group (C–CH_3, O–CH_3) by aromatic amine N-oxide has been reported.[10,11]

Our results show that monooxygenases model reactions produce 3a-hydroxypyrrolo[2,3-b]indole ring system and an oxindole, suggesting possible pathways in the biogenesis of a number of 3a-hydroxy-tricyclic-pyrroloindoles as well as oxindole alkaloids.

EXPERIMENTAL

M.Ps are uncorrected. IR spectra were recorded on Hitachi G-3 model and Hitachi 215-spectrometers. UV spectra were recorded in 95% EtOH on Hitachi EPS-3T spectrophotomer. NMR spectra were determined with JEOL JNM4H-100 and a Varian Associates HA-100 spectrometers in $CDCl_3$ (otherwise stated) with TMS as internal standard. The chemical shift was expressed by the δ-value in ppm. Mass spectra were obtained on a Hitachi RMU-6E mass spectrometer. The irradiation



(100 W, 200 W) was carried out by means of an immersed and quarz water-jaketed medium pressure mercury lamp (Ohsawa). The light source (253·7 nm), a 10 W low-pressure mercury lamp was centrally situated in the soln in Pyrex test tube (30 mm × 195 mm). The temperature was maintained below 20° by ice cooling during illumination.

Oxygenation of **16** *by photolysing* **17** *with* 10 *W mercury lamp*

A soln of **16**(1·61 g, 8·5 mM) and **17**(1·63 g, 17 mM) in CH_2Cl_2 (2260 ml) was divided into Pyrex test tubes and each tube was irradiated with 10 W mercury lamp for 1 h with ice cooling. The mixture was evaporated and the residue was thick layer chromatographed (silica gel 520 g/CH_2Cl_2: Et_3N = 4 : 1). The upper band was extracted with CH_2Cl_2 to afford **19**(201 mg, 11·6%), which was further purified twice by preparative TLC (SiO_2/CH_2Cl_2: Et_3N = 4 : 1), giving a pale yellow oil, **19**, which solidified upon cooling: λ_{max}^{EtOH} nm(ε) 250(6500), 303(2360); $\lambda_{max}^{EtOH\text{-}HCl}$ nm(ε) 242(6100), 295(2460): NMR 2·25(m, CH_2), 2·51(s, N_b–Me), 2·60-3·00(m, CH_2–N), 2·91(s, N_a–Me), 4·25(s, N–CH–N), 4·44(broad s, OH), 6·47(d, 1H), 6·72(t, 1H), 7·18(m, 2H): IR and mass spectra see text. Picrate, m.p., 180–183° (MeOH) (Found: C, 50·00; H, 4·56; N, 15·79. $C_{18}H_{19}O_8N_5$ requires: C, 49·88; H, 4·42; N, 16·16%). The extraction of the lower band with CH_2Cl_2: MeOH(6 : 1) gave **16**(425 mg, 27%). The most polar fraction was extracted with CH_2Cl_2 : MeOH(3 : 1) to give an oil (441 mg) which was dissolved in CH_2Cl_2 and washed with H_2O. The residue, on evaporation of the CH_2Cl_2 and washed with H_2O. The residue, on evaporation of the CH_2Cl_2 extracts, was thick layer chromatographed (silica gel/n-BuOH: H_2O = 5 : 1). The upper band extracted with CH_2Cl_2 : MeOH(6 : 1) yielded **20** (14 mg, 0·8%) which was identified by comparison of the spectral data (IR, NMR, mass, UV) and R_f vlaue with an authentic specimen.

Irradiation of **16** *and* **17** *in* MeOH *with* 10 *W lamp*

A soln of **16**(100 mg, 0·53 mM) and **17**(152 mg, 1·6 mM) in MeOH(80 ml) was irradiated with 10 W lamp for 1 h with ice cooling. The solvent was evaporated. The residue (253 mg) was thick layer chromatographed (silica gel 40 g/CH_2Cl_2: Et_3N = 5 : 1) and the upper band afforded, upon extraction with CH_2Cl_2, an oil **21**(17 mg, 11%). From the more polar fraction, **16**(8 mg, 8%) and **17**(105 mg, 69%) were recovered.

Irradiation of **16** *and* **17** *in* CH_2Cl_2 *with* 200 *W lamp*

A soln of **16**(1·0 g, 5·3 mM) and **17**(1·5 g, 16 mM) in CH_2Cl_2 (240 ml) was irradiated using Vycor filter 791 for 3 h under N_2. The CH_2Cl_2 soln was washed with H_2O and dried. The residue (1·03 g), on evaporation, was separated by preparative TLC (silica gel 100 g/CH_2Cl_2 : Et_3N = 20 : 1). The upper band yielded, upon extraction with CH_2Cl_2–MeOH(9 : 1), **21**(297 mg, 20%) which was further purified by alumina column chromatography. Elution with benzene–hexane gave **21** as a yellow oil: λ_{max}^{EtOH} nm (ε) 225(35000), 340(30400); $\nu_{max}^{CHCl_3}$ 2195(C≡N), 1622 cm^{-1} (C=C); *m/e* (relative intensity) 265(6) M^+, 157(13), 144(100), 121(13); NMR 2·80 and 2·85(s, N_b–Me), 2·60–3·10(m, CH_2), 3·20–3·55(m, CH_2–N), 3·73(s, N_a–Me), 4·30–5·55, 6·40–6·70(m, vinyl H), 6·81(s, α–H), 7·00–7·60(m, aromatic H); Ehrlich test positive.

N_a,N_b-*Dimethyl*-N_b-(4-*cyanobutyl*) *tryptamine* **22**

Compound **21** (300 mg, 1·1 mM) in EtOH–CH_3CO_2Et (30 ml–20 ml) was hydrogenated over 10% Pd/C at room temp and atm pressure. The reaction was discontinued after the absorption of 2 molar equiv of H_2 and the solvent was evaporated to give the crude product (281 mg, 92%, TLC one spot). **22**(226 mg) was further purified by preparative TLC (Silica gel 40 g/CH_2Cl_2 : NH_3 = 1 : 1). The less polar band gave unreacted **21**(12 mg, 5%) upon extraction with CH_2Cl_2. The lower band gave **22**(177 mg, 72%) as an oil: ν_{max}^{KBr} 2245 cm^{-1} (C≡N); *m/e* (relative intensity) 269(4), 158(3), 144(15), 125(100); NMR 1·64(m, C–CH_2–CH_2–C), 2·20–3·05(m, 8 H, CH_2), 2·33(s, N_b–Me), 3·74(s, N_a–Me), 6·88(s, α–H), 7·00–7·65(m, aromatic H). HCl salt, m.p., 185–186° (MeOH–ether) (Found: C, 66·76; H, 7·90; N, 13·49; Cl, 12·12. $C_{17}H_{24}N_2Cl$ requires: C, 66·70; H, 7·91; N, 13·47; Cl, 11·59%).

N_a,N_b-*Dimethyl*-N_b-*formyltryptamine* **20**

A soln of **16**(1·0 g, 5·3 mM) and HCO_2Et(11·7 g) in toluene (30 ml) was refluxed for 6 h and evaporated. The residue was taken up in benzene and washed with dil HCl, water, dried, and evaporated. The residue was chromatographed on alumina. The elution with benzene yielded **20**(985 mg, 86%) as an oil: λ_{max}^{EtOH} nm (ε) 225(34700), 278(4520), 289(5100), 300(4000); $\nu_{max}^{CCl_4}$ 1682 cm^{-1} (C=O); *m/e* (relative intensity) 216(20) M^+, 157(57), 144(100); NMR 2·87 and 2·91(s, N_a–Me), 2·80–3·10(m, C–CH_2–C), 2·90–3·70(m, CH_2–N), 3·72(s, N_a–Me), 6·80, and 6·90(s, α–H), 7·00–7·70(m, aromatic H), 7·79 and 8·04(s, N–CHO). Ehrlich test positive. Picrate, m.p., 79–80° (iso-PrOH-iso-Pr_2O), orange needles (Found: C, 51·04; H, 4·38; N, 15·37. $C_{19}H_{19}O_8N_5$ requires: C, 51·23; H, 4·30; N, 15·73%).

Irradiation of methylaniline in CH_2Cl_2 *with* **17**

(1) Irradiation of a soln of **23**(1·0 g, 9·3 mM) and **17**(2·63 g, 27·9 mM) using Vycor filter 791 for 3 h under N_2 in CH_2Cl_2 (260 ml), yielded, on evaporation, an oil(3·8 g) which was chromatographed on alumina (100 g). Elution with hexane–benzene (19 : 1 ~ 9 : 1) gave **23**(126 mg, 12·6%). Elution with hexane–benzene (1 : 19 ~ 1 : 4) gave **24**(457 mg, 27%), which was further purified by column chromatography (silica gel/benzene) to give an oil, **24**; λ_{max}^{EtOH} nm (ε) 242·5(4730), 349(43000); $\nu_{max}^{CHCl_3}$ cm^{-1} 2195(≡N), 1620(C=C); *m/e* (relative intensity) 184(64) M^+, 144(27), 132(5), 107(45), 106(47); NMR 3·22 and 3·28(s, N–Me), 4·58–5·95(m, olefinic H), 6·68–7·45(m, aromatic H). Elution with CH_2Cl_2 gave **17**(1·84 g, 70%).

(2) After irradiation of **23**(3 g, 28 mM) and **17**(885 mg, 9·3 mM) in the similar reaction conditions described above, the residue was chromatographed on silica gel (40 g). The column was eluted successively with benzene, benzene–CH_2Cl_2 and CH_2Cl_2–MeOH. The earlier fraction (1·222 g) eluted with benzene and benzene–CH_2Cl_2 (1 : 1) showed three spots on TLC (silica gel/benzene). Elution with CH_2Cl_2–MeOH(14 : 1) yielded the crude HCl salt of **23**(1·08 g, 27%, m.p., ~ 102) which was recrystallized from acetone to give m.p., 116–120°, no depression with an authentic specimen. Elution with CH_2Cl_2 : MeOH(5 : 1) yielded **17**(478 mg, 53%). The residue (1·222 g) obtained on evaporation of the earlier fraction was rechromatographed on alumina. Elution with hexane–benzene (9 : 1 ~ 2 : 1) gave a residue, which showed three spots on TLC (silica gel/benzene), was resolved by preparative TLC (silica gel/benzene). The upper band, yielded **25**(171 mg, 5·4%) upon extraction

with CH_2Cl_2. The lower band, gave **23**(80 mg), upon extraction with CH_2Cl_2. **25**: λ_{max}^{EtOH} nm (ϵ) 249·5(22300), 296(4370); $\nu_{max}^{CHCl_3}$ cm^{-1} 1600, 1510; *m/e* (relative intensity) 226(18) M^+, 120(100), 107(21); NMR 2·69 and 2·77(s, N–Me), 4·19(s, N–CH_2–N), 6·57–7·35(m, aromatic H). Elution with hexane–benzene (2:1) gave **23**(232 mg, total 312 mg, 10%). Further elution with hexane–benzene (2:1) ~ benzene yielded **24**(167 mg, 9·7%, calculated based upon **17**).

N-(4-*Cyanobutyl*)-N-*methylaniline* **26**

A soln of **24**(490 mg, 2·7 mM) in EtOH (50 ml) was reduced with H_2 at room temp and atm pressure in presence of 5% Pd/C(200 mg) for 6 h until 2 molar equiv of H_2 was absorbed, and filtered and evaporated to give **26**(449 mg, 89·6%), b.p. 0·35 150°, colorless oil: λ_{max}^{EtOH} nm (ϵ) 255(15200), 302(1900): $\nu_{max}^{CHCl_3}$ 2245 cm^{-1} (C≡N); *m/e* (relative intensity) 188(13) M^+, 120(100), 105(5), 91(3); NMR 1·68(m, C–CH_2CH_2–C), 2·3(m, CH_2CN), 2·87(s, N–Me), 3·30(m, N–CH_2), 6·65–6·80, 7·09–7·31(m, aromatic H). (Found: C, 75·84; H, 8·55; N, 14·52. $C_{12}H_{16}N_2$ requires: C, 76·55; H, 8·57; N, 14·88%).

Irradiation (100 *W*) *of* **16** *with* **32**

Irradiation of a soln of **16**(94 mg, 0·5 mM) and **32**(196 mg, 1 mM) in CH_2Cl_2 (100 ml) with 100 W lamp using Pyrex filter for 3 h under N_2, yielded, on evaporation, the residue (340 mg) which was thick layer chromatographed (silica gel 60 g/CH_2Cl_2: Et_3N = 6:1) and separated into 5 fraction. The least polar fraction 1 was extracted with CH_2Cl_2. The residue (209 mg), on evaporation, which showed two spots on a chromatoplate, was resolved by thick layer chromatography (silica gel 40 g/CH_2Cl_2). The upper band afforded, upon extraction with CH_2Cl_2, **32**(154 mg, 79% recovery). The lower band yielded dibenzopyridazine (14 mg, 7·4%). The less polar fraction 2 was extracted with (CH_2Cl_2:MeOH = 15:1) to give **19**(12 mg, 12%) which showed one spot (silica gel/CH_2Cl_2: Et_3N = 6:1) and was identified with the spectral data as well as the R_f value on TLC. The starting material **16**(23 mg, 25%) was recovered from the more polar fraction 3 when extracted with CH_2Cl_2–MeOH(9:1).

Irradiation(10 *W*) *of* **33** *in* CH_2Cl_2 *with* **17**

A soln of **33**(505 mg, 2 mM) and **17**(475 mg, 5 mM) in CH_2Cl_2 (800 ml) was divided into 10 Pyrex tubes (33 × 195 mm) and each tube was irradiated at 253·7 nm for 30 min with ice cooling. The mixture was concentrated to 200 ml and water was added. The aqueous layer was evaporated to dryness to give an oil (1·15 g) which was subjected to preparative TLC (silica gel 200 g/CH_2Cl_2:MeOH:NH_3 = 70:8:3). The upper fraction 1 gave **33**(89 mg) upon extraction with CH_2Cl_2–NH_3(4:1). The more polar fraction 2 yielded an oil (8 mg) upon extraction with CH_2Cl_2–MeOH–NH_3(4:1:1) which was further purified by preparative TLC (silica gel/CH_2Cl_2:MeOH:NH_3 = 70:8:3) to give **34**(4 mg, 0·7%). Ehrlich test negative; λ_{max}^{EtOH} nm 229 sh, 255, 290 sh; *m/e* (relative intensity) 218(11), 160(7), 147(14), 72(22), 58(100); NMR 2·35(s, N_b–Me), 3·18(s, N_a–Me). Picrate, m.p., 135–148° (lit[29] m.p., 168°); $\nu_{max}^{CHCl_3}$ 1710 cm^{-1} (C=O).

Irradiation (200 *W*) *of* **33** *in* CH_2Cl_2 *with* **17**

(1) Irradiation of **33**(1·1 g, 5·45 mM) and **17**(1·56 g, 16·4 mM) in CH_2Cl_2 (250 ml) using Vycor filter (791) for 2 h. The reaction mixture was extracted with H_2O. The aqueous layer, upon evaporation, yielded, the residue (2·06 g) which showed the presence of **34** on TLC (silica gel/CH_2Cl_2:MeOH:NH_3 = 25:1:0·5), was chromatographed on silica gel (100 g). The first elution with CH_2Cl_2–MeOH–NH_3 (10:1:0·5) gave **33**(393 mg, 39%). The second elution with the same solvent gave **17**(1·1g, 71%). The CH_2Cl_2 layer gave, upon evaporation, an oil(0·96 g) which was separated by preparative TLC (silica gel 200 g/benzene–acetone = 5:1). The less polar fraction was extracted with CH_2Cl_2–MeOH(1:1) to give **20**(13 mg, 1·1%). The more polar fraction afforded the mixture of **33** and **17**(386 mg) upon extraction with CH_2Cl_2–MeOH–NH_3(4:4:1).

(2) Irradiation(200 W) of **33**(3·76 g, 20 mM) in CH_2Cl_2 (11) with **17**(6·4 g, 67 mM) and benzophenone(4·14 g, 17 mM) using Pyrex filter (774) was carried out for 5 h under N_2 and extracted with H_2O. The residue (9·31 g), on evaporation of H_2O, was chromatographed on alumina (100 g). Elution with hexane–benzene(1:1) gave **33**(815 mg, 22%). Further elution with the same solvent gave the residue (795 mg) which showed three spots, was separated by preparative TLC (silica gel 80 g/CH_2Cl_2:MeOH:NH_3 = 25:1:0·5). The less polar band gave **33**(30 mg) upon extraction with CH_2Cl_2–MeOH–NH_3 (4:1:1). The middle band, extracted with the same solvent, gave **34**(5 mg, 0·1%). The lower band gave **17**(433 mg, 7%). Elution with CH_2Cl_2 gave **17**(4·54 g, 71%). Elution with MeOH gave a brown residue (1·28 g) which showed almost one spot on TLC (silica gel/CH_2Cl_2:MeOH:NH_3 = 15:5:1), was purified by preparative TLC (alumina 200 g/benzene:EtOH = 6:1). An oil (848 mg, partially crystallized) was obtained and crystallized from i-PrOH-i-Propyl ether to give **35a**(560 mg, 10%). Three recrystallizations gave m.p., 149–151°, colorless needles, identical with that obtained by the reaction of **33** with CH_2Cl_2: λ_{max}^{EtOH} 223, 278, 287, 298 nm; NMR (CF_3COOH) 3·00–3·50(m, CH_2) 3·34(s, N_b–Me), 3·70–4·00(m, CH_2–N), 3·89(s, N_a–Me), 5·10(s, N_b–CH_2–Cl), 7·20–7·70(m, aromatic H). Picrate, m.p., 160·5–161°(dec) (EtOH), yellow needles, Beilstein test positive. Mixed m.ps and a comparison of the IR spectra confirmed its identity with the specimen prepared by the reaction of **33** with $BrCH_2Cl$. The organic layer (CH_2Cl_2) was evaporated to give an oil(5·58 g) which was chromatographed on alumina (120 g). Elution with hexane afforded benzophenone (3·24 g, 78%). Elution with hexane–benzene (1:1) gave **33**(516 mg, 14%). Elution with benzene–CH_2Cl_2 (1:1) gave an oil (143 mg), which showed several spots on TLC (no spot corresponding to benzopinacol), and resolved by preparative TLC (silica gel 40 g/benzene:acetone = 5:1) to give **20**(28 mg, 0·7%). Picrate, m.p., 78–81°, which was identified by the comparison with the authentic sample prepared as above.

Chloromethyl-dimethyl-2-(β-1-*methylindolyl*)*ethyl ammonium bromide* **35b**

A soln of **33**(505 mg, 2 mM) in bromochloromethane(10 ml) was stirred for 4·5 h and the excess $BrCH_2Cl$ was evaporated. The residue was recrystallized from i-PrOH-i-Pr_2O to give **35b**, colorless plates, m.p., 144–147°, 828 mg(100%). Picrate, m.p., 159–161° (dec) (MeOH–EtOH). (Found: C, 49·91; H, 4·64; N, 14·50. $C_{20}H_{22}N_5O_7Cl$ requires: C, 50·06; H, 4·62; N, 14·59%).

Chloromethyl-dimethyl-2-(β-1-*methylindolyl*)*ethyl ammonium chloride* **35a**

A soln of **33**(505 mg, 2 mM) in CH_2Cl_2 (50 ml) was stir-

red for 23 days at room temp. The residue(810 mg, 100%), on evaporation, was crystallized from i-PrOH-i-Pr_2O to give **35a**, colorless prisms, 511 mg(71%), m.p., 150–151°.

Synthesis of **36**

To a soln of **33**(1·07 g, mM) in $CHCl_3$ (200 ml) was added *m*-Cl-C_6H_4-CO_3H (1·2 g, 76% purity, 5 mM) in $CHCl_3$ (30 ml) at 1–2° and stirred for 30 h at room temp. The soln was passed through alumina column (110 g). Elution with $CHCl_3$ gave **33**(111 mg, 10%). Elution with $CHCl_3$–MeOH(3:1) gave **36**(1·16 g, *ca* 100%). m.p., 56–58°; *m/e* (relative intensity) 216(0·6) M-2H, 202(2) M–O, 174(2), 157(100), 148(8), 128(8), 115(32); NMR 3·20–3·50(m, CH_2), 3·60(s, N-Me_2), 3·85(s, N_a–Me), 3·70–4·10(m, CH_2–N), 7·10–7·65(m, aromatic H), picrate, 137–139·5°, yellow prisms.

Reduction of **36** *by* AcOH-Zn

To a soln of **36**(15 mg) in $MeCO_2H$ (0·5 ml) was added Zn-powder (30 mg) and stirred for 2 days at room temp. The residue, on evaporation, was subjected to preparative TLC (alumina 5 g/benzene:EtOH = 6:1). The extraction with CH_2Cl_2–MeOH–NH_3 (4:1:0·5) afforded **33**(11 mg, 80%) which was identified by the comparison with an authentic sample, picrate, m.p., 173–176° (EtOH).

Irradiation(10 *W*) *of* **36** *in* CH_2Cl_2

A soln of **36**(15 mg) in CH_2Cl_2 was irradiated for 1 h with 10 W lamp and evaporated. The residue was examined by TLC (alumina/benzene–EtOH = 6:1) and **36** was not found. The TLC develpoped with CH_2Cl_2–MeOH–NH_3 (20:1:1) on silica gel did not show the presence of **33** and with benzene–acetone (5:1) on silica gel showed no spot corresponding **20**. Likewise, irradiation of **36** in CH_2Cl_2 with 200 W lamp was carried out but **20** was not obtained.

Oxidation of other tryptamines

The oxidation of N_b-dimethyltryptamine **37a** in CH_2Cl_2 or H_2O by photolyzing **17** with 100 W mercury lamp was carried out, but only a trace of N_b-formyl-N_b-methyltryptamine **38a** was obtained. The oxidation of N_b-monomethyltryptamine **37b** (1 g, 5·74 mM) in CH_2Cl_2 (250 ml) by photolyzing **17**(1·65 g, 13 mM) with 200 W mercury lamp for 5 hr, gave HCl salt of **37b** as insoluble ppts, m.p., 171–173°(7%). A small amount of **38a** and N_b-(4-cyanobutadienyl)-N_b-methyltryptamine were obtained chromatography and followed preparative TLC of the mother liquor, and N_b-formyltryptamine **38b** was not obtained.

N_b-methyl-N_b-*formyltryptamine* **38a**

A soln of **37b** (290 mg, 1·7 mM) in HCO_2Et (25 ml) was refluxed for 10 h. The residue, on evaporation, was subjected to preparative TLC silica gel/benzene:acetene = 5:1). The extraction with CH_2Cl_2 of the lower band, gave **38a** (205 mg, 74%), an oil; λ_{max}^{EtOH} nm (ϵ) 221·5(34000), 282(5400), 290·5(4600); $\nu_{max}^{CHCl_3}$ 1670 cm^{-1}; *m/e* (relative intensity) 202(12) M^+, 144 (9·6), 143(70), 131(11), 130(100); NMR 2·83 and 2·89(s, N_b–Me), 2·95(m, CH_2–C), 3·57(m, CH_2–N), 6·88 and 6·97 (d, α–H), 7·05–7·60(m, aromatic H), 7·72 and 8·02(s, NCHO), 8·40(broad s, NH). Picrate, m.p., 107·5–109·5° (i-PrOH), orange needles. (Found: C, 50·16; H, 4·08; N, 15·83. $C_{18}H_{17}N_5O_8$ requires: C, 50·12; H, 3·92; N, 16·24%).

N_b-*formyltryptamine* **38b**

A soln of tryptamine (1 g, 6·2 mM) in HCO_2Et(25 ml) was refluxed for 7 h. The residue (1·23 g), on evaporation, was subjected to column chromatogrpahy (silica gel/CH_2Cl_2) to give **38b**(1·025 g, 87%), an oil; λ_{max}^{EtOH}nm (ϵ) 222(33300), 283(5300), 291(4600); $\nu_{max}^{CHCl_3}$ cm^{-1} 3485, 3440, 3320(NH), 1685(C=O); *m/e* (relative intensity) 188(17) M^+, 143(55), 130(100); NMR 2·92(t, CH_2), 3·53(m, CH_2N), 5·71(broad s, N_bH), 6·93(d, α–H), 7·99(d, NCHO), 8·04(broad s, N_aH), picrate, m.p., 93·5–94·5° (MeOH–ether). (Found: C, 48·33; H, 3·79; N, 16·87. $C_{17}H_{15}N_5O_8$ requires: C, 48·93; H, 3·62; N, 16·78%).

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