A NOVEL REARRANGEMENT OF A PAPAVERINE DERIVATIVE INTO ISOQUINO [1,2-b]-QUINAZOLINE DERIVATIVE

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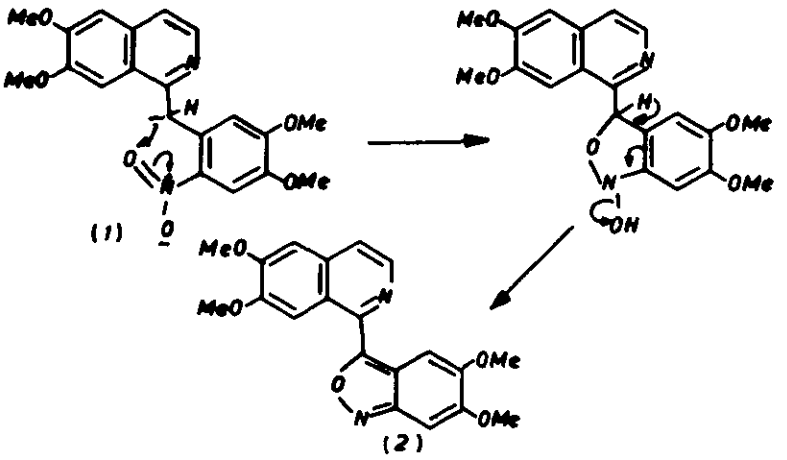
Abstract - Anthranilopapaverine (2) was rearranged by pyrolysis or photolysis into a new heterocycle (3). The structure of (3) has been elucidated by X-ray crystallography and by spectroscopic methods. Pyrolysis of (2) also gives an isomeric mesoionic azaberbinone (5).

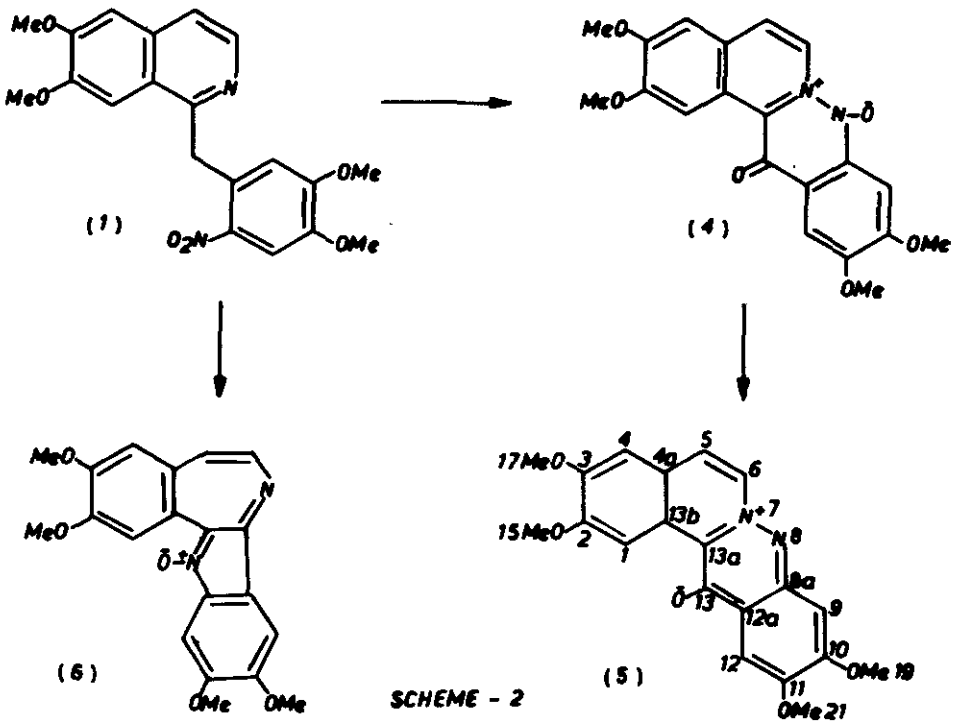
Nitration of the benzylisoquinoline alkaloid, 'papaverine', affords 6'-nitropapaverine (1). On refluxing in methanolic solution it gives the anthranilopapaverine (2), (Scheme-1)[1]. Cava has



SCHEME - 1

previously reported that when nitropapaverine (1) is treated with iodine and sodium acetate it affords a red azaberbinone N-oxide (4)[2]. On reduction of the N-oxide, the azaberbinone (5) was obtained. Kametani[3] has also reported a rearrangement reaction of nitropapaverine (1) by heating it with triethyl phosphite to give a heterocycle to which structure (6) was assigned (Scheme-2). Other anthranils are also known to give rearranged products on thermolysis[4-7].

In view of the interesting chemistry exhibited during these rearrangement reactions it was decided to subjected the anthranilopapaverine (2) directly to thermolysis as well as photolysis and to investigate the structures of any rearranged products.



SCHEME - 2

When the anthranilopapaverine (2) was heated at its melting point, it was found to be converted to two other compounds. The first of these was isolated as a colourless crystalline solid, mp 276-278°C (3). The second compound isolated from the reaction mixture was bright yellow crstayls, mp 278-280°C (decomp.) unreacted starting material was also obtained. Structure (5) for the second product of the thermolysis product was assigned by us on the following evidence. Accurate mass measurement of its molecular ion peak at m/z 366 afforded its molecular formula as $C_{20}H_{18}N_2O_5$. In its ir spectrum it showed no peak for the carbonyl group. The ^{1}H-nmr spectrum showed four

3H singlets at δ4.15, δ 4.05, δ 4.00 and δ 3.99 accounting for four methoxy groups. Four singlets integrating for one proton each appeared at δ 10.29 (H-1), δ 7.70 (H-12), δ 7.03 (H-9) and δ 6.96 (H-4). Two 1H doublets resonated at δ 8.32 and δ 7.46, each with J=6Hz, which were assigned to H-6 and H-5 respectively. The unusually low field value of δ 10.29 for H-1 was indicative of the presence of an oxygen atom in the vicinity of H-1. The same downfield appearance of H-1 has been reported by Hanaoka et al. in the comparable berberine- phenolbetaine[8]. Two dimensional nuclear Overhauser enhancement studies (NOESY) were carried out to ascertain the assignments. The data as well as the ^{13}C-nmr spectrum (broadband & DEPT, Table-I) supported the structure (5) assigned to the thermolysis product.

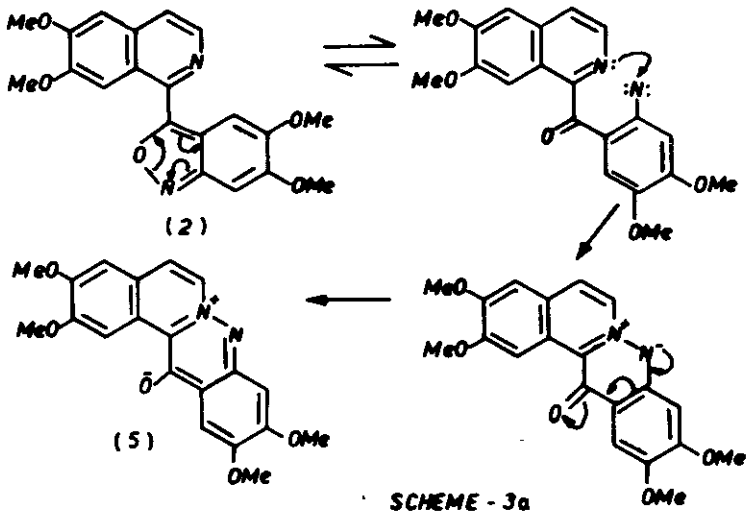
Table-I: ^{1}H and ^{13}C NMR Data* of Compound-5.

^{1}H NMR					^{13}C NMR			
Hydrogen Atom	δ	No. of Protons	m	J(Hz)	Carbon Atom	δ	Carbon Atom	δ
H - 1	10.29	1	s	-	C_1	121.75	C_{11}	150.00
H - 4	6.96	1	s	-	C_2	151.33	C_{12}	108.79
H - 5	7.46	1	d	6($J_{5,6}$)	C_3	151.07	C_{12a}	124.93
H - 6	8.32	1	d	6($J_{6,5}$)	C_4	101.91	C_{13}	169.00
H - 9	7.03	1	s	-	C_{4a}	116.03	C_{13a}	121.75
H - 12	7.70	1	s	-	C_5	106.09	C_{13b}	121.00
H - 15	4.15	3	s	-	C_6	132.04	C_{15}	56.43
H - 17	4.05	3	s	-	C_{8a}	124.17	C_{17}	56.37
H - 19	4.00	3	s	-	C_9	102.56	C_{19}	56.00
H - 21	3.99	3	s	-	C_{10}	144.69	C_{21}	56.27

* Numbering as in structure 5 of Scheme-2.

To confirm the structure, the rearrangement of 6'-nitropapaverine to the azaberbinone N-oxide (4) and reduction of the N-oxide to the azaberbinone (5) was repeated according to the conditions reported by Cava et al.[2] The resulting azaberbinone was isolated and compared (t.l.c., spectroscopy) with the product obtained by us from the direct thermolysis of the anthranilopapaverine (2) and the two were found to be identical. This established that one of the two products obtained from the thermolysis reaction was indeed the azaberbinone (5). The azaberbinone probably arises by the initial ring opening of the 5-membered ring in the anthranil (2) to afford a nitrene. The nitrene then undergoes cyclization to afford the azaberbinone (5) (Scheme-3a). An alternative

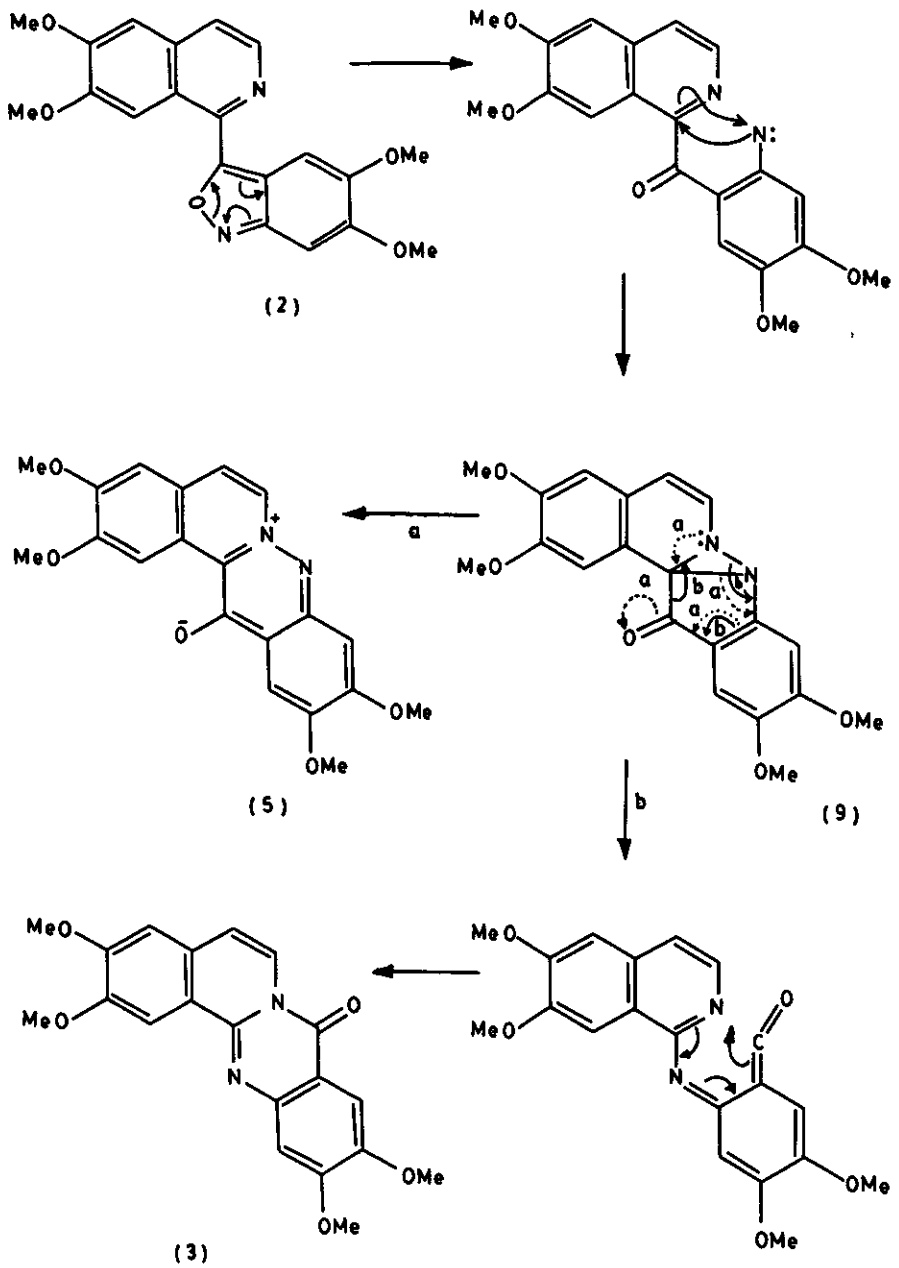
mechanism for the formation of (5) is presented in Scheme-3b. This involves an initial formation of a nitrene which can cyclize to afford a pentacyclic intermediate (9). This can undergo the opening to (5) or afford (3) through a ketene intermediate.



SCHEME - 3a

The first product (3) of the thermolysis reaction was colourless. It showed an amidic carbonyl at 1660 cm^{-1}. Its uv spectrum showed absorptions at λ max 387, 367, 350, 300, 288, 275, 265, 238 nm indicating a highly conjugated heterocyclic system. The mass spectrum of the product showed the M^+ peak at m/z 366.1199 corresponding to the formula $C_{20}H_{18}N_2O_5$. Other major fragments were present at m/z 351 (60 %), 321 (19 %), 307 (9 %), 277 (7 %), 183 (32 %). The molecular ion was seen to readily lose a methyl group to afford the ion at m/z 351. Elimination of a - CH_2O moiety from the fragment m/z 351 gave a moderately intense peak at m/z 321. Similarly loss of CH_3 from the peak at m/z 321 gave the fragment at m/z 307. A peak at m/z 183 corresponded to the dimethoxy-substituted isoquinoline ion.

The ^{1}H-nmr spectrum (300 MHz) showed two doublets at δ 6.94 (1H, d, $J_{5,6}$=7Hz) and δ 8.62 (1H,d,$J_{6,5}$=7Hz) corresponding to H-5 and H-6 respectively. The other protons showed singlets at δ 8.32 (1H,s,H-9), δ 7.66 (1H,s,H-1), δ7.20 (1H,s,H-12), δ 6.93 (1H,s,H-4), and three singlets at δ4.13 (3H), δ4.07 (3H) and δ 4.02 (6H) for the four methoxy groups (Table-II).



SCHEME 3b

Table-II: ^{1}H and ^{13}C NMR Data* of Compound-3.

^{1}H NMR					^{13}C NMR			
Hydrogen Atom	δ	No. of Protons	m	J(Hz)	Carbon Atom	δ	Carbon Atom	δ
H - 1	7.66	1	s	-	C_1	112.48	C_{10}	144.67
H - 4	6.93	1	s	-	C_2	148.47	C_{11}	144.89
H - 5	6.94	1	d	$7(J_{5,6})$	C_3	150.2	C_{12}	105.69
H - 6	8.62	1	d	$7(J_{6,5})$	C_4	107.16	C_{12a}	153.14
H - 9	8.32	1	s	-	C_{4a}	110.49	C_{13a}	155.90
H - 12	7.20	1	s	-	C_5	107.36	C_{13b}	121.36
H - 15	4.13	3	s	-	C_6	120.82	C_{15}	56.46
H - 17	4.02	3	s	-	C_8	158.58	C_{17}	56.35
H - 20	4.07	3	s	-	C_{8a}	127.99	C_{20}	56.24
H - 22	4.02	3	s	-	C_9	106.69	C_{22}	56.35

* Numbering as in X-ray structure.

In order to establish the relative positions of the various protons, NOE difference studies were carried out (Fig.1). Irradiation of the C-11 OCH_3 (δ 4.02) resulted in 8.3 % NOE effect on H-12 (δ7.20). Similarly irradiation of C-10 OCH_3 (δ4.07) resulted in 3.1% NOE effect on H-9 (δ8.32). Irradiation of C-2 OCH_3 (δ4.13) resulted in 2 % NOE effect on H-1 (δ7.66), while irradiation of δ 6.94(H-4 & H-5) gave a 2.7 % NOE effect on H-6 (δ8.62). Irradiation at δ 8.32 (H-9) resulted in 7 % NOE effect on C-10 OCH_3 (δ4.07). Similarly irradiation of H-12 (δ7.20) showed NOE effect of about 5 % on the C-11 OCH_3 (δ4.02). 2 D-NOESY studies also substantiated the NOE difference results.[9]

The ^{13}C-nmr spectrum showed the presence of 20 signals. Polarization transfer studies (DEPT) established that there are four OCH_3 carbons and six CH carbons while the remaining ten carbon atoms were quaternary. The amidic C=O carbon atom resonated at a rather upfield value of δ158.58 indicative of the presence of an electron donating aromatic ring system in conjugation to it (Table-II).

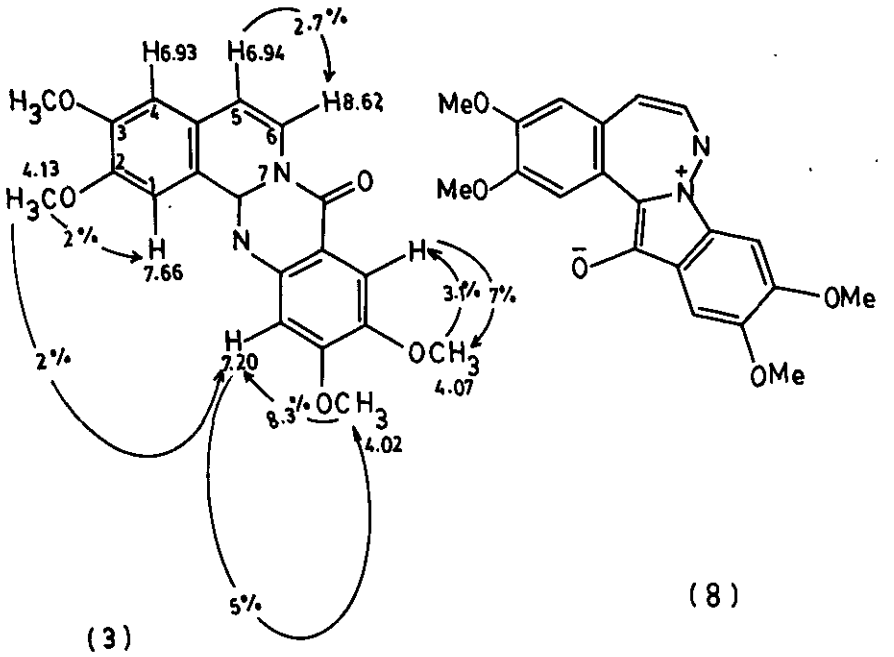


FIGURE-1

X-ray crystallographic analysis showed the product to possess structure (3) and led to the rejection of the alternative structure (8) considered for the product[10]. Compound (3) crystallized in the monoclinic space group $P2_1/n$ ($P2_1/c$, alternate setting) with a=7.345 (2), b=16.687 (6), c=16.744 (4) A°, and β=105.62 (2)°. An approximate crystal density of 1.35 g/cc indicated that one molecule of composition $C_{20}H_{18}N_2O_5 \cdot C_2H_5OH$ formed the asymmetric unit. All unique diffraction maxima with $2\theta < 114°$ were collected using graphite monochromated Cu $K\bar{\alpha}$ radiation (1.54178 A°) and variable speed, 1° ω -scans. Of the 2031 reflections collected in this manner, only 650 (32%) were judged observed [$F_o > 3\ \sigma(F_o)$] after correction for Lorentz, polarization, and background effects. A phasing model was found using direct methods, and most of the nonhydrogen atoms were visible on the first E-synthesis[11]. Hydrogen atoms were located on a Δ F-synthesis following partial refinement of the nonhydrogen atoms. Block diagonal least-squares refinements with anisotropic nonhydrogen atoms and isotropic hydrogens have converged to a conventional crystallographic residual of 0.06 for the observed reflection[12].

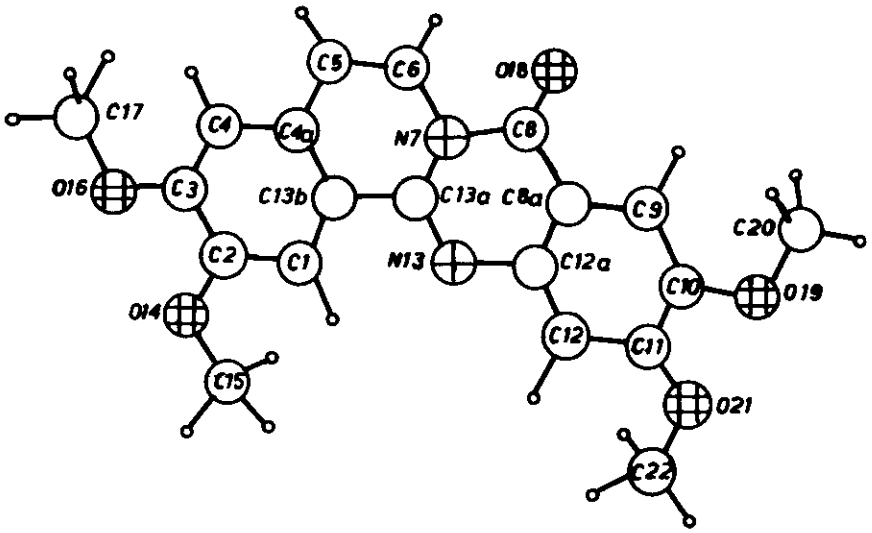
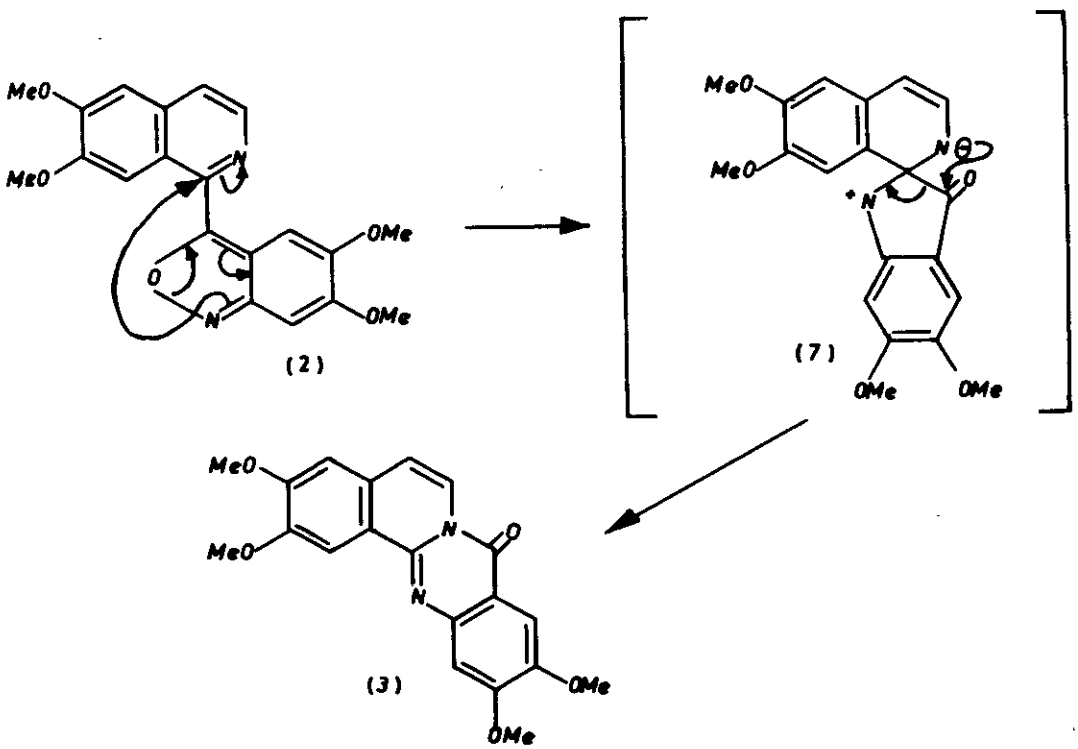


FIGURE. 2. A computer generated perspective drawing of the final X-ray model of compound 3



SCHEME - 4

A computer generated perspective drawing of the final x-ray model of compound (3) is presented in Fig.2.

A possible mechanism for the formation of (3) is shown in Scheme-4. The reaction may alternatively proceed through a nitrene followed by the formation of a five membered spiro intermediate (7). Cleavage of (7) can give rise to (3).

The substance (3) was also prepared in almost quantitative yields from anthranil (2) by uv photolysis in methanol. The photolytic rearrangement probably proceeds through a similar mechanism as the thermolysis reaction involving ring D inversion[13-15].

EXPERIMENTAL

All melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Infrared (ir) spectra were measured with a JASCO A-302 spectrometer and ultraviolet (uv) spectra with a Shimadzu UV 240 spectrometer. ^{1}H-nmr and ^{13}C-nmr spectra were recorded in $CDCl_3$ with a Bruker WP-100 SY & Bruker AM-300 FT NMR spectrometers with tetramethylsilane as an internal standard. Mass spectra were taken on Finnigan MAT 112 S & MAT 312 mass spectrometers connected to PDP 11/34 & MAT 188 computer system. Tlc was carried out on glass plates using 0.25mm thick Merck silica gel 60 F-254; column chromatography was performed with silica gel BDH mesh 60-120. Irradiation was carried out with high pressure mercury lamp in the presence of Pyrex filter. Abbreviations used s=singlet, d=doublet, t=triplet, m=multiplet and dd=double doublet.

Anthranilopapaverine (2)- A mixture of 6'-nitropapaverine (1) (6.0 g, 0.015M) and KOH (120 g) in methanol (1.2 lit) was refluxed on a water bath for 12 h, cooled to room temperature and filtered, washed with water and methanol. The resulting residue was recrystallised with chloroform and n-hexane to give anthranilopapaverine (2) (3.3g; 57.7 %) as yellow needles, mp 240-242°C ($CHCl_3$/n-hexane); UV $\lambda_{max}^{Dioxane}$ nm (log ε): 385 (4.37), 255 (4.53), $\lambda_{min}^{Dioxane}$ nm (log ε): 320 (3.91). IR ν_{max}^{KBr} cm^{-1}: 3450, 2940, 2820, 1618, 1545. MS m/z (%): 366 (M^+, 20%), 365 (86%), 350 (base peak), 320 (20%), 301 (12%), 276 (10%), 248 (4%), 188 (15%), 127 (7%), 103 (7%), 83 (62%). ^{1}H-NMR ($CDCl_3$) : δ 3.98 (6H, s, OCH_3 x 2), δ 4.02 and δ 4.08 (6H,s, OCH_3), δ 6.79 (1H, s, H-3), δ 7.06 (1H, s, H-6), δ 7.5 (1H, d, $J_{7,8}$ = 5.4 Hz, H-7), δ 7.52 (1H, s, H-4'), δ 8.35(1H, s, H-7'), δ 8.53 (1H, d, $J_{8,7}$ = 5.4Hz, H-8).

Thermolysis Products (3) and (5) Anthranilopapaverine (2) (500 mg, 1.3 mmole) was heated at 240-245°C for 5 min. in a stream of nitrogen in a metal bath. The resulting residue (500 mg) was dissolved in $CHCl_3$ (15 ml) and chromatographed on silica gel with $CHCl_3$:CH_3OH (20:1) as the eluent. Initial fractions gave unreacted (2) (60%), followed by (3) and lastly (5) (5%). Fractions containing (3) were dried under reduced pressure and recrystallized to afford (3) (60 mg, 12%) as colourless crystals, mp 276-278°C ($CHCl_3$-hexane). UV $\lambda_{max}^{Dioxane}$ nm (log ε): 238 (4.53), 265 (4.76), 275 (4.75), 288 (4.84), 300 (4.79), 350 (4.35), 367 (4.53), 387 (4.55), $\lambda_{min}^{Dioxane}$ nm (logε): 245 (4.45), 260 (4.75), 275 (4.7), 295 (4.72), 315 (3.8), 355 (4.33), 395 (4.26). IR ν_{max}^{KBr} cm^{-1} : 3400, 2900, 2816, 1660, 1610, 1570, 1530. MS m/z (%): 366.1190 (M^+, $C_{20}H_{18}N_2O_5$ base peak), 351 (60 %), 321 (19%), 277 (7%), 183 (32%). ^{1}H-nmr and ^{13}C-nmr ($CDCl_3$) see Table 2.

Compound (5): mp 278-280°C (decomp.)

Photolysis Product (3) - The anthranil (2) (50mg) was subjected to UV photolysis in methanol with a high pressure mercury lamp for 1 h at 2-5°C in the presence of a Pyrex filter, with simultaneous bubbling of the solution with nitrogen. Evaporation of the solution afforded a crystalline mass (48mg, 97% yield). The product was identified as (3) by spectroscopic studies.

Azaberbinone N-Oxide (4)- A solution of 1.05 g (4.15mmole) of I_2 in warm n-propanol (12.5ml) was added during 2 min to a refluxing solution of 6'-nitropapaverine (2) 0.96g (2.5 mmole) and 1.25g of anhydrous sodium acetate in 30 ml of n-propanol. Heating was continued for 20 min and 40 ml of water was then added and the reaction mixture cooled to 20°C. After standing for 45 min the reaction mixture was filtered and washed (n-propanol-water) to give (4) as a red compound (0.35g, 36.4% yield), mp 114-116°C (AcOH-H_2O). UV $\lambda_{max}^{Dioxane}$ nm (logε): 232 (4.59), 252 (4.51), 349 (4.1). IR ν_{max}^{KBr} cm^{-1}: 3425, 2950, 1670, 1620, 1590, 1555, 1510. MS m/z : 382 (M^+, 32%), 366 (14%), 352 (16%), 336 (15%), 323 (25%), 307 (11.8%), 295 (11%), 279 (20%), 251 (9%), 205 (8%), 188 (48%), 85 (67%), 83 (base peak, 100%). ^{1}H-NMR ($CDCl_3$): δ8.56 (1H, s, H-9), δ8.2 (1H, d, $J_{6,5}$=5.4Hz, H-6), δ7.52 (1H, d, $J_{5,6}$=5.4Hz, H-5), δ 7.37 (1H, s, H-12), δ7.06 (1H, s, H-1), δ6.67(1H, s, H-4), δ4.08, δ4.1, δ4.02, δ3.94 (12H, s, 4xOCH$_3$).

Azaberbinone (5)- To a solution of the red compound (4) (192mg, 1.9mmole) in AcOH (15 ml) was added $NaHSO_3$ (0.15 g) in water (15 ml) and the reaction mixture was warmed on a steam bath for 10 min. Water (20 ml) was added to the reaction solution. After standing for 1 h, azaberbinone (5) separated as yellow needles (50mg, 30%), mp 278°C(decomp.)(30% AcOH in H_2O). UV $\lambda_{max}^{Dioxane}$ nm (logε) 265 (4.5), 280 (4.4), 321 (4.0) 388 (4.02), 406 (4.08), 430 (4.3), 457 (4.5). $\lambda_{min}^{Dioxane}$ nm (log ε): 275 (4.4), 305 (3.95), 355 (3.66), 395 (3.99), 415 (4.05), 445 (4.1).

IR ν_{max}^{KBr} cm^{-1}: 3350, 2900, 1610, 1567. MS m/z : 366.1199 (M^+, $C_{20}H_{18}N_2O_5$, base peak), 351 (99.8 %), 335 (6 %), 321 (22 %), 307 (16.2 %), 277 (12.2 %), 249 (10 %), 221 (8 %), 187 (11 %), 183 (16 %), 149 (14 %), 83 (56 %). ^{1}H-nmr and ^{13}C-nmr ($CDCl_3$) see Table-1.

ACKNOWLEDGEMENT

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11. All crystallographic calculations were done on a PRIME 9950 computer operated by the Cornell Chemistry Computing Facility. Principal programs employed were : REDUCE and UNIQUE, data reduction programs by M.E. Leonowicz, Cornell University, 1978; MULTAN 80, and RANTAN 80, systems of computer programs for the automatic solution of crystal structures from x-ray diffraction data (locally modified to perform all Fourier calculations including Patterson synthesis) written by P. Mian, S.E. Hull, L. Lessinger, G. Germain, J.P. Declercq and M.M. Woolfson, University of York, England, 1980; BLS78A, an anisotropic block diagonal least squares refinement written by K. Hirotsu and E. Arnold, Cornell University, 1980: PLUTO78, a locally modified crystallographic illustration program by W.D.S. Motherwell, Cambridge Crystallographic Data Centre, 1978; and BOND, a program to calculate molecular parameters and prepare tables written by K. Hirotsu and

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12. Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, U.K. They will give a complete literature citation when ordering.

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