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ON THE SYNTHETIC APPROACH TO THE PROTOPINE ALKALOIDS

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Abstract—The synthetic approach to the protopine alkaloids is described. Efficient construction of the alkaloid models **16a** and **16b** was accomplished by the general synthetic method consisting of photo-oxygenative ring enlargement of tetrahydrobenzindenoazepines **13a** and **13b** by singlet oxygen and further elaboration of the resultant 10-membered amido-ketone products **14a** and **14b**.

The protopine type alkaloids, one of the isoquinoline alkaloid families,[1] contain a unique 10-membered amino-ketone ring system, and have long been prepared only by way of the transformation of the protoberberine alkaloids taking advantage of their close skeletal features. The first synthesis of the protopine alkaloids was performed by Haworth and Perkin in 1926.[2] This remarkable oxidative method via the N-oxide intermediate generated in the crucial stage of their synthetic scheme has been utilized even in the modified method by Bentley's[3] or Giacopello's[4] group. Very recently, the protoberberine alkaloids were shown to be the precursor of the protopine alkaloids.[5] This gave rise to Hanaoka's *et al.* biomimetic protopine alkaloid synthesis,[6] in which photo-oxygenation of tetrahydroprotoberberine methiodide was carried out to give α-allocryptopine as well.

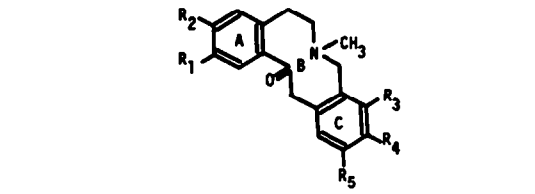
Structurally, these alkaloids represented in Table 1 are characterized by the presence of a 10-membered ring system that contains an N-Me group and a ketone CO function at C_{14}. Accordingly, the expected transannular interaction[7] between the CO group and the nitrogen lone pair is observed. For example, cryptopine and protopine do not exhibit the ketonic properties, and in the IR spectra the CO frequencies are at 1675 cm^{-1}. Each aromatic ring carries at least two O functions. The ring A substituents are located at C_2 and C_3, and the ring C O functions are more commonly found at C_9 and C_{10}, although the alkaloids of the so-called pseudo-type[8] are known with the C_{10} and C_{11} pattern. Some examples of additional O function at C_1 or C_{13} are also known.[1]

Thus, both the unique structural nature and its limited numbers of synthetic procedures promoted us to devise possible routes to the synthesis of the protopine alkaloids. The studies on the general method widely applicable to a variety of the alkaloids are on the way.[9] This paper deals with the new approach to the synthetic precursor having tetrahydrobenzindenoazepine skeleton and its efficient conversion into dibenzazecine type compounds, which have 10-membered ring system characteristic of the protopine alkaloids.

Many examples of the interaction of singlet oxygen with olefins have been studied. The oxidation of enamine has been reported to proceed by 1,2-cycloaddition followed by ready decomposition to give carbonyl and amide fragments. For instance, the morpholine enamine of desoxybenzoin (1) is oxidized and gives benzaldehyde (2) and N-benzoylmorpholine (3),[10] and also this type of oxidative cleavage is known for indene[11a] or 2-phenylindene[11b] (4) forming diketo compound 5 as shown in Fig. 2. These data inspired us to consider the possibility of carrying out the dye-sensitized photooxygenation reaction of "5, 6, 7, 12 - tetrahydro - 7 - methyl-

Table 1. The ^1H NMR spectra of **16a, b** and protopine alkaloids

Proton	Chemical Shifts (δ)						
	17a	17b	protopine[19a]	α-allo-cryptopine[19b]	cryptopine[19c]	Muramine[19b]	pseudo-protopine[19a]
N-CH_3	1.85	1.86	1.88	1.85	1.90	1.85	1.81
C_5 and C_6 -H_2	2.60, 3.02	2.50, 2.93	2.53, 2.90	2.60, 2.97	2.60, 2.97	2.60, 2.95	2.48, 2.88
C_8-H_2	3.65	3.57	3.54	3.5	3.62	3.5	3.46
C_{13}-H_2	3.86	3.84	3.75	4.0	3.79	4.1	3.64
C_1-H	7.13		6.87	6.95	7.02	7.07	6.90
C_4-H	6.74		6.60	6.64	6.71	6.69	6.58
CH_3 on A ring	3.92		—	—	3.92	3.85, 3.80	—



protopine[2b] $R_1+R_2=$, $R_3+R_4=$, R_5=H

α-allocryptopine[2a,b] (β-homochelidonine) $R_1+R_2=$  , R_3=R_4=OCH_3, R_5=H

hunnemannine[4c] $R_1+R_2=$  , R_3=OH, R_4=OCH_3, R_5=H

cryptopine[2b,3] R_1=R_2=OCH_3, $R_3+R_4=$  , R_5=H

cryptopalmatine[2c,3,4b] (Muramine) R_1=R_2=R_3=R_4=OCH_3, R_5=H

fagarine II[4a] R_1=R_2=, R_3=H, R_4=R_5=OCH_3

pseudoprotopine[4d] $R_1+R_2=$  , R_3=H, $R_4+R_5=$ 

Fig. 1. Synthetic protopine alkaloids.

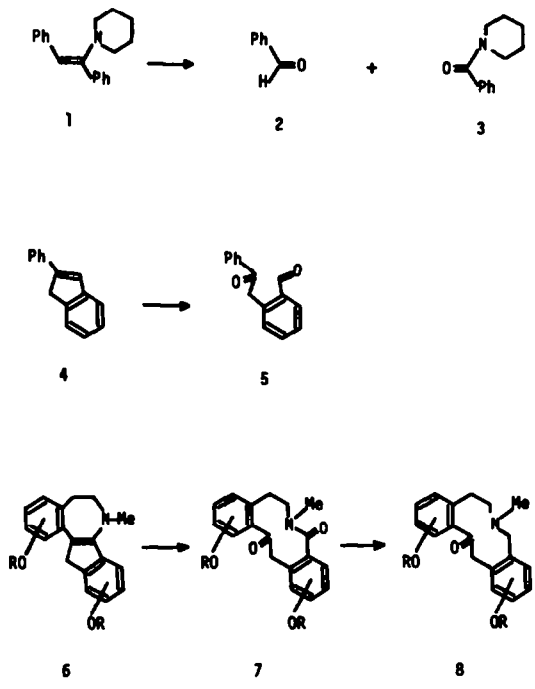


Fig. 2.

benz[d]indeno[1, 2 - *b*] - azepine" type compounds **6**, in the hope that they would have enamine- and/or indene-like properties and undergo an analogous oxidative cleavage. The scheme also depends upon further elaboration of **7** to the desired 10-membered amino-ketone **8**.

Initially, the preparation of the enamine **13** was attempted since both the starting material benzyl cyanide **9** and the synthetic scheme to benzindenoazepine type compound had been on hand.[12] Diphenylpropionitrile **10** was readily obtained (85%) from **9** and benzaldehyde by the conventional procedure:[13] condensation of benzyl cyanide with benzaldehyde and subsequent reduction of the resultant phenylcinnamonitrile with sodium amalgam to α,β-diphenylpropionitrile. Cyano group in **10** was converted to carboxy group in **11** by base-catalyzed hydrolysis followed by re-forming of N-acetyl group in 67% yield. The conversion of this acid to the desired benzindenoazepine **13** was initiated by treatment with phosphorous pentachloride. The acid chloride formed was subjected to Friedel-Crafts cyclization with aluminum chloride in nitrobenzene at 35° to give the oily indanone **12**. Basic hydrolysis of N-acetyl group of this indanone caused spontaneous cyclization between the formed amino group and indanone CO function to give the desired stable enamine **13a**, m.p. 146–147°, in 33% yield from the acid **11**.

Photooxygenation of the enamine **13a** was attempted[14] in a mixture of methyl alcohol and methylene chloride using rose bengal as sensitizer at 18°, keeping the solution saturated with oxygen, and irradiating with a 650 W tungsten-iodine lamp. The reaction proceeded smoothly only within 10 min. Removal of the dye and the solvents afforded a single compound **14a**, m.p. 161–164°, whose IR spectrum displayed absorption maxima at 1682 and 1620 cm^{-1} due to desoxybenzoin function and amide group, respectively. Although its ^1H NMR spectrum in deuteriochloroform at room temperature was not informative because of the existence of amide rotamers, substitution of trifluoroacetic acid for the solvent effected to fix the amide orientation and gave the fine splitting patterns at δ 3.25 (3H, s, N–CH_3), 3.2–4.3 (4H, br m, $ArCH_2CH_2N$), 4.02, 4.05 (each 3H, ds, 2 × OCH_3), 4.50 (2H, ABq J = 17, 21 Hz, $ArCH_2CO$), 7.00, 7.37 (each 1H, ds, aromatic H's). Thus, the crystalline material produced photochemically was assigned the dibenzazecindione structure **14** having 10-membered amido-ketone ring system. Successive reduction of this amide-ketone with LAH in boiling THF produced the corresponding amino-alcohol **15a**, which on treatment with activated manganese dioxide[15] at room temperature led to the desired amino-ketone **16a** in 80% yield from **14a**. The compound **16a** suggested the presence of 10-membered amino-ketone ring system in the ketone CO frequency, 1676 cm^{-1}, and its ^1H NMR spectrum as shown in Table 1 was also in good agreement with the assigned structure in Fig. 3. Now, we have proved the aforementioned assumption that the compound of benzindenoazepine type could be a synthetic precursor to the 10-membered amino-ketone ring system characteristic of protopine alkaloids, by experiments in conversion of **13a** to **16a**.

Route *a* to the compound **13a** consists of Friedel–Crafts reaction with aluminum chloride. This catalyst has been often used in order to cleave the C–O linkage of aromatic methoxy or benzyloxy compounds to the corresponding phenols.[16] Methylenedioxy group, which is commonly found in the protopine alkaloids (Fig. 1), is much more acid-sensitive than 1,2-dimethoxy group.[17] Accordingly, the reaction sequence of **10**–**12** was re-examined, and the intermediate, amino-acid **17**, m.p. 142–143°, was found to be isolable in neutral state in satisfactory yield, as shown in Fig. 4. Subsequently, the thermal and dehydrative treatment led to intramolecular

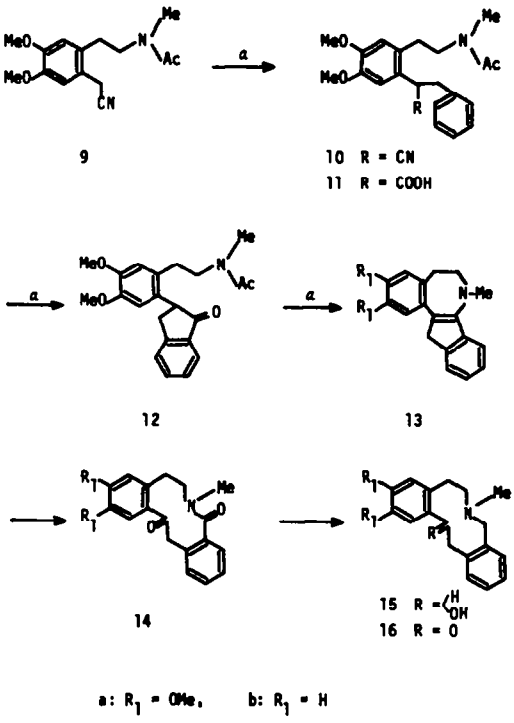


Fig. 3.

cyclization of **17** to a benzylbenzazepinone **18a** in 95% yield. When **18a** was treated with phosphoryl chloride in boiling toluene, the second intramolecular cyclization readily took place and afforded a tetracyclic compound (92%), which was identical in all respects with **13a**. Route *b via* the benzylbenzazepinone type compound **18** appears to be preferable for the compounds with acid sensitive groups such as methylenedioxy and/or benzyloxy.

In route *a* or *b*, benzyl group is arised from benzaldehyde on its condensation with the benzyl cyanide **9** and sodium-amalgam reduction of the resultant benzylidene function. Benzyl halide might be used as another benzyl source in alternative approaches, one of which would consist of electrophilic substitution reaction of it on the azepinone ring of a 3-benzazepin-2-one type compound. In fact, 1,2,4,5-tetrahydro - 3 - methyl - 3H - 3 - benzazepin - 2 - one (**19**) has been easily benzylated[18] with benzyl halide to the monobenzyl derivative **18b**, as depicted in route *b* in Fig. 4. The same treatment of **18b** with phosphoryl chloride as described for **18a** gave a new

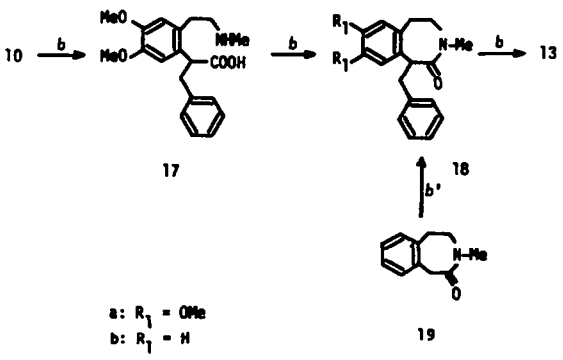


Fig. 4.

benzindenoazepine **13b** in 91% yield. Application of the above photooxygenative ring enlargement reaction to this enamine, using methylene blue this time, yielded the oily diketone **14b**, whose IR absorption maxima, 1692 and 1627 cm^{-1}, were essentially identical with those of **14a**. ^1H NMR spectrum was measured in trifluoroacetic acid to exhibit two singlet peaks at δ 3.32 and 4.67 due to N–CH_3 and C_{13}–H_2, and two triplet peaks at δ 2.82 and 3.73 ($J = 6$ Hz) for C_5–H_2 and C_6–H_2. $LiAlH_4$ reduction product, **15b** (77%), which formed in successive conversion of **14b**, accepted smooth oxidation of its benzylic OH function to ketone CO with activated manganese dioxide in chloroform. Purification of the crude material on silica tlc plates resulted in isolation of another 10-membered amino-ketone product **16b** (64%), whose ^1H NMR spectrum suggested the existence of 10-membered amino-ketone ring system characteristic of the protopine alkaloids by comparison with spectra of natural products[19] as shown in Table 1. In addition, the CO frequency in the methiodide of **16b**, m.p. 200–203°, is at 1685 cm^{-1}, in place of 1665 cm^{-1} in **16b**. This clearly exhibits that the compound **16b** has the expected transannular interaction between the CO group and the nitrogen lone pair.[7]

Thus, **16a** and **16b** which is a basic figure of protopine alkaloids and may be called "protopane", were synthesized more readily along the scheme shown in route *b* or *b'*. If these routes are accepted in synthesis of the alkaloids, their C_2 and C_3 alkoxy substituents came from appropriate alkoxy groups on benzazepinone ring system of the compound of the type **18** or **19**. C_{10} and C_{11} alkoxy functions for the pseudo-type alkaloids would be prepared by the reaction with the corresponding 3,4-alkoxybenzaldehyde or 3,4-alkoxybenzyl halide. On the contrary, the more common C_9 and C_{10} oxygen function may need a little more complicated method. For instance, the interaction of the same type of 3,4-oxygenated benzyl group with an additional protecting group of halogen atom at C_6 has been known in the preparation of protoberberine alkaloids.[20] Nevertheless, we believe that the synthesis of protopine alkaloids in this way will be accomplished, depending upon the suitable introduction of oxygen functions at the proper positions of tetrahydrobenzindenoazepine ring system, and it will be the subject in our future communication.

EXPERIMENTAL

Mps were determined on a Laboratory Devices Meltemp and are uncorrected. Infra red spectra were recorded on a Hitachi-Perkin Elmer Model 125 spectrophotometer. ^1H NMR spectra were run on $CDCl_3$ solns, unless otherwise stated, with Me_4Si as internal standard ($\delta = 0$ ppm) and resistered on a 90 MHz Hitachi R-22 spectrometer. Preparative tlc was performed on Merck silica gel 60 PF-254 (Catalog No. 7749).

2 - [2 - β - (N - *Methyl* - N - *acetylamino*)*ethyl* - 4,5 - *dimethoxyphenyl*] - 3 - *phenylpropionitrile* (**10**). To a stirred mixture of **9**[12] (5.52 g, 0.02 mol) and freshly distilled benzaldehyde (2.12 g, 0.02 mol) in 95% EtOH (15 ml) under N_2 on ice-water bath was added dropwise a NaOEt soln prepared from Na (130 mg) and abs EtOH (5 ml). The mixture was then warmed at 35° and stirred for 4 hr. To this, 95% EtOH (60 ml) and 2% Na–Hg (80 g)[21] were added. After stirring at 50° for another 4 hr, EtOH layer was separated from mercury and evaporated to leave an oily residue. Extraction with $CHCl_3$, after the addition of water in usual way, gave an oil, which was crystallized from benzene to yield **10** (6.2 g), m.p. 102°, in 85% yield. Recrystallization from EtOH gave a sample for analysis, m.p. 104–105°; IR (Nujol) 2230, 1639 cm^{-1}; ($CHCl_3$) 2230, 1630 cm^{-1}; ^1H NMR δ 1.88, 2.10 (ds, 3H, N–COMe, 1:3), 2.68 (m, 2H, $ArCH_2CH_2N$),

2.90, 2.94 (ds, 3H, N–Me, 3:1), 3.17 (d, 2H, J = 3.5 Hz, NC–CH–CH_2Ph), 3.40 (m, 2H, CH_2N), 3.85, 3.90 (s, each 3H, 2 × OMe), 4.43 (t, 1H, J = 3.5 Hz, NC–CH), 6.56, 6.71 (ds, 1H, aromatic H, 1:3.2), 6.83, 6.88 (ds, 1H, aromatic H) and 7.0–7.4 (m, 5H, aromatic H's). Found: C, 71.95; H, 7.14; N, 7.53. Calc for $C_{22}H_{26}N_2O_3$: C, 72.10; H, 7.15; N, 7.65.

2 - [2 - *β* - (N - *Methyl* - N - *acetylamino*)*ethyl* - 4,5 - *dimethoxyphenyl*] - 3 - *phenylpropionic acid* (11). A mixture of 10 (1 g) and 50% aq EtOH (15 ml) containing KOH (1.5 g) was refluxed under N_2 for 20 hr. The solvents were azeotropically distilled with benzene. The residue was treated with Ac_2O (15 ml) on a steam bath for 1 hr, and then the mixture was evaporated on a rotary evaporator. A residual material was basified with dil NaOH aq, and washed with CH_2Cl_2. This alkaline soln, after acidification with conc HCl, was extracted with $CHCl_3$. The extract, after drying, was evaporated to leave an oil, which crystallized from 95% EtOH to give 11 (0.71 g, 67%), m.p. 176°. Recrystallization from the same solvent gave an analytical sample, m.p. 180–181°; IR (Nujol) 1710, 1592 cm^{-1}; 1720, 1625 cm^{-1}; ^1H NMR *δ* 1.82, 2.03 (ds, 3H, N–COMe, 1:1.9), 2.62 (m, 2H, Ar–CH_2CH_2–N), 2.83, 2.86 (ds, 3H, N–Me, 1.4:1), 3.2–3.5 (m, 2H, CH_2–N), 3.84, 3.89 (ds, each 3H, 2 × OMe), 4.12 (t, 1H, J = 7 Hz, HOOC–CH), 6.49, 6.60 (ds, 1H, aromatic H, 1:1.5) and 6.9–7.3 (m, 6H, aromatic H's). Found: C, 68.60; H, 7.01; N, 3.63. Calc for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63.

5,6,7,12 - *Tetrahydro* - 2,3 - *dimethoxy* - 7 - *methylbenz*[*d*]*indeno* - [1,2 - *b*]*azepine* (13a). To a stirred solution of 11 (1.5 g, 3.9 mmol) in a mixture of dry benzene (25 ml), dry $CHCl_3$ (20 ml) and dry nitrobenzene (6.5 ml) was added PCl_5 (1.11 g, 4.7 mmol). The mixture was continuously stirred at room temp overnight, and concentrated to about 5 ml. It was diluted with nitrobenzene (7 ml) and then, after cooling on the ice-water bath, powdered $AlCl_3$ (1.04 g, 7.8 mmol) was added. After stirring at 35° for 5 hr, the mixture was shaken with ice-water (30 ml) and nitrobenzene was removed by steam distillation. The residue was extracted with $CHCl_3$ and the extracts were washed with 1N–NaOH and water. The alkaline washings were acidified with conc HCl and extracted with $CHCl_3$, and then 0.17 g, m.p. 175°, of the starting acid 12 was recovered. On the other hand, the $CHCl_3$ extracts were washed with water and dried over Na_2SO_4. Evaporation of $CHCl_3$ gave crude 12 as an oil (1.17 g); IR ($CHCl_3$) 1693, 1630 cm^{-1}. This was heated in 50% aq EtOH (30 ml) containing 10% KOH to reflux under N_2 for 21 hr. EtOH was removed on a rotary evaporator. Extraction with CH_2Cl_2 and crystallization from benzene yielded the enamine 13a (0.35 g), m.p. 145–146° in 29.2% (33%, calculated on recovered acid). Recrystallization from 95% EtOH afforded an analytical sample, m.p. 146–147°; IR (Nujol) 1601, 1590, 1578, 1555 cm^{-1}; ($CHCl_3$) 1587, 1573, 1552 cm^{-1}; ^1H NMR *δ* 3.03 (*s*, 3H, N–Me), 3.02, 3.26 (m, each 2H, C_5- and C_6–H_2), 3.85 (s, 2H, C_{12}–H), 3.90, 3.96 (ds, each 3H, 2 × OMe), 6.73, 7.10 (ds, each 1H, C_4- and C_1-H) and 7.15–7.65 (m, 4H, aromatic H's). Found: C, 78.22; H, 6.88; N, 4.40. Calc for $C_{22}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56.

5,6,7,8,13,14 - *Hexahydro* - 7 - *methyl* - 2,3 - *dimethoxydibenz*[*c*, *g*] - *azecine* - 8,14 - *dione* (14a). A soln of 13a (200 mg) and rose bengal (6 mg) in MeOH (70 ml) and CH_2Cl_2 (10 ml), contained in a Pyrex test tube (30 × 150) equipped with a sintered glass bubbler, was cooled with a stream of cold water from the side of the tube. O_2 gas was introduced through the bubbler, and then the mixture was irradiated by a tungsten-iodine lamp (Elmo movie light El-650) at 18 ± 1° for 10 min. The solvents were removed *in vacuo*. The residue was dissolved in benzene, washed with water and dried over Na_2SO_4. The benzene soln, after decolorization with active carbon (Norit A), was concentrated to give crystals of 14a (185 mg), m.p. 161–164°, in 84% yield. Recrystallization from 95% EtOH afforded an analytical sample, m.p. 171–172°; IR (Nujol) 1682, 1620 cm^{-1}; ^1H NMR (CF_3COOH) *δ* 3.25 (s, 3H, N–Me), 3.2–4.3 (br m, 4H, ArCH_2CH_2N), 4.02, 4.05 (ds, each 3H, 2 × OMe), 4.50 (ABq, 2H, J = 17, 21 Hz, ArCH_2CO), 7.00, 7.37 (ds, each 1H, aromatic H's). Found: C, 71.05; H, 6.34; N, 3.92. Calc for $C_{20}H_{21}O_4N$: C, 70.78; N, 6.24; N, 4.13.

5,6,7,8,13,14 - *Hexahydro* - 7 - *methyl* - 14 - *hydroxy* - 2,3 - *dimethoxydibenz*[*c*, *g*]*azecine* (15a) and 5,6,7,8,13,14 - *hexahydro* - 7 - *methyl* - 2,3 - *dimethoxydibenz*[*c*, *g*]*azecin* - 14 - *one* (16a). To a boiling suspension of LAH (130 mg) in dry THF (10 ml). 14a (130 mg) in dry THF (8 ml) was added under N_2. The mixture was refluxed for 3 hr and then cooled. Water (0.5 ml) in THF (10 ml) was added to decompose the excess hydride. Inorganic ppt was removed by suction filtration. THF was evaporated on a rotary evaporator to leave an oily residue, which was dissolved in $CHCl_3$ and washed with water. Drying and evaporation of the soln left an oil (130 mg), one half (65 mg) of which, on two crystallizations from ether-MeOH, afforded an analytically pure sample of 15a (54 mg), m.p. 144–146°, in 86% yield, based on a half of starting material; IR (Nujol) 3370 cm^{-1}; ^1H NMR *δ* 2.13 (s, 3H, N–Me), 2.1–3.2 (m, 5H, C_5–H_2, C_6H_2, C_8–H), 3.36 (d, 1H, J = 14 Hz, C_{12}–H), 3.50 (dd, 1H, J = 2. 15 Hz, C_{13}–H), 3.88, 3.95 (ds, each 3H, 2OMe), 4.11 (d, 1H, J = 14 Hz, C_8–H), 6.65, 7.20 (ds, each 1H, C_4- and C_1–H), 7.1–7.4 (m, 4H, aromatic H's). Found : C, 73.30; H, 7.88; N, 4.36. Calc for $C_{20}H_{25}O_3N$: C, 73.36; H, 7.70; N, 4.28.

A soln of the other half (65 mg) in $CHCl_3$ (10 ml) was stirred at room temp with activated MnO_2[15] (650 mg) for 1 hr. Removal of inorganic ppt and solvent, followed by treatment with ether-MeOH, gave crystals (50 mg) of 16a, m.p. 167–169°, in 80% yield. Recrystallization from the same solvent system afforded a pure sample, m.p. 170–171°; IR (Nujol) 1676 cm^{-1}; ^1H NMR *δ* 1.85 (m, 3H, N–Me), 2.60, 3.02 (m, each 2H, C_6–H_2 and C_5–H_2), 3.65 (br s, 2H, C_8–H_2), 3.86 (br s, 2H, C_{13}–H_2), 3.92 (s, 6H, 2 × OMe), 6.74 (s, 1H, C_4–H), 7.13 (s, 1H, C_1–H), 7.2–7.4 (m, 4H, aromatic H's). Found: C, 73.68; H, 7.18: N, 4.19. Calc for $C_{20}H_{23}O_3N$: C, 73.82; H, 7.12; N, 4.30.

2 - [2 - *β* - (N - *Methylamino*)*ethyl* - 4,5 - *dimethoxyphenyl*] - 3 - *phenyl-propionic acid* (17). Compound 10 (3 g) was heated in 50% aq EtOH (45 ml) containing 10% NaOH for 20 hr. After cooling, this soln was made to pH 7 by addition of conc HCl at first and 2N HCl near the end point of neutralization. Insoluble material was filtered off. Concentration of a clear filtrate gave a ppt, which was washed with 70% aq EtOH and dried to give 17 (2.6 g, 92%), m.p. 222°. Recrystallization from 70% aq EtOH afforded an analytical sample, m.p. 223°; IR (Nujol) 3200–2100, 1630, 1600 cm^{-1}. Found: C, 70.19; H, 7.43; N, 3.99. Calc for $C_{20}H_{25}O_4N$: C, 69.95; H, 7.33; N, 4.08.

1,2,4,5 - *Tetrahydro* - 7,8, - *dimethoxy* - 3 - *methyl* - 1 - *benzyl* - 3H - 3 - *benzazaepin* 2 - *one* (18a). A suspension of 17 (1.50 g) in xylene (30 ml) was refluxed under a Dean–Stark tube for 16 hr. A clear soln obtained was evaporated, and the residue triturated with benzene to lead to crystals of 18a (1.20 g, 85%), m.p. 142–143°.

An analytical sample was prepared by recrystallization from benzene, and melted at 141°; IR (Nujol) 1650 cm^{-1}; ^1H NMR 2.96 (s, 3H, N–Me), 2.9–4.2 (m, 6H, ArCH_2CH_2N and CH_2Ph), 3.73, 3.84 (ds, each 3H, 2 × OMe), 4.43 (t, 1H, J = 7.5 Hz, Ar_2CH–CO), 6.59, 6.63 (ds, each 1H, aromatic H's) and 7.1–7.4 (m, 5H, aromatic H's). Found : C, 73.99; H, 7.12; N, 4.24. Calc for $C_{20}H_{23}O_3N$: C, 73.82; H, 7.12; N, 4.30.

Reaction of 18a *with phosphoryl chloride.* The amide 18a (163 mg, 0.5 mmol) in dry toluene (3 ml) was refluxed with $POCl_3$ (230 mg, 1.5 mmol) for 7 hr. To the cooled mixture water (3 ml) and 2N NaOH was added and the alkaline soln was extracted with CH_2Cl_2. Organic layer was washed with water, dried and evaporated. The solid obtained was recrystallized with 95% EtOH to give 141 mg of the enamine, m.p. 144–145°, which was identical in all respects with compound 13a.

5,6,7,12 - *Tetrahydro* - 7 - *methylbenz*[*d*]*indeno*{1,2 - *b*]*azepine* (13b). To a stirred soln of crystals of 18b (1.06 g, 4.0 mmol) in boiling dry toluene (12 ml), $POCl_3$ (1.1 ml, 12 mmol) was added. and the mixture was refluxed under N_2 for 15 hr. The cooled mixture was then treated with dil NaOH aq and CH_2Cl_2. The organic extracts were combined, washed with water and dried over Na_2SO_4. Evaporation of the solvent left a light-brown oil, which was dissolved in ether and, after addition of decolorized carbon (Norit A), filtered through a thin layer of Celite power under suction. The solvent was evaporated to dryness to afford an oil of 14b (0.89 g, 91%), which appeared as a single spot (*Rf* 0.8) on silica tlc plate developed with 3% MeOH–CH_2Cl_2; IR (Neat) 1660, 1591, 1551 cm^{-1}; ^1H NMR *δ* 2.90–3.40 (m, 4H, Ar–CH_2CH_2–N), 3.07 (s, 3H, N–Me), 3.86 (s, 2H, C_{12}–H_2), 6.90–

7.0 (m, 8H, aromatic H's).

Photooxygenation of 5,6,7,12 - tetrahydro - 7 - methylbenz[d] - indeno[1,2 - b]azepine (**13b**). A soln of the oily **13b** (0.89 g) and methylene blue (25 mg) in MeOH (50 ml) and CH_2Cl_2 (10 ml) was kept saturated with O_2 and irradiated with a tungsten-iodine lamp at 18–20° as described for **13a**. After 30 min, none of the starting enamine was detected on a silica gel tlc plate. The solvents were evaporated on a rotary evaporator below 35°. Purification of the residual oil by preparative tlc (silica gel, 5% MeOH–CH_2Cl_2) and extraction of the *Rf* 0.3 band with 1:2 MeOH–CH_2Cl_2, followed by washing the resultant oil in CH_2Cl_2 with water led to 0.78 g of **14b** as an oily substance (77%), which showed the following spectral data; IR (Neat) 1692, 1627 cm^{-1}; ^1H NMR (CF_3COOH) δ 2.82, 3.73, (br t, each 2H, J = 6 Hz, C_5–H_2 and C_6–H_2), 3.32 (s, 3H, N–Me), 4.67 (s, 2H, C_{13}–H) and 6.5–8.0 (m, 8H, aromatic H's).

5,6,7,8,13,14 - Hexahydro - 7 - methyl - 14 - hydroxydibenz[d, g] - azecine (**15b**). The above **14b** (0.765 g) in dry THF (30 ml) was added dropwise into a stirred suspension of LAH (1.0 g) in dry boiling THF (45 ml). The mixture was refluxed for 3 hr and then cooled in an ice-water bath. The excess hydride was decomposed by addition of water (3 ml) containing 4% NaOH. The resultant inorganic ppt and the solvent were removed in the same manner as described for the compound **15a** to give an oil, which was purified on preparation tlc as described above. *Rf* 0.5 band gave the oily **15b** (0.605 g, 83%), which exhibited peaks as follows; IR (Neat) 3370 cm^{-1}; ^1H NMR δ 2.14 (s, 3H, N–Me), 2.4–3.2 (m, 5H, C_5–H_2, C_6–H_2 and C_8–H), 3.35 (d, 1H, J = 14 Hz, C_8–H), 3.48 (dd, 1H, J = 2, 8 Hz, C_{13}–H), 4.06 (d, 1H, J = 14 Hz, C_8–H), 7.00–7.40 (m, 8H, aromatic H's). The methiodide was obtained by heating **15b** with excess MeI in MeOH, recrystallized from MeOH, and melted at 189.5–191.5°. Found: C, 55.59; H, 5.96; N, 3.41; I, 29.90. Calc for $C_{19}H_{24}ONI$: C, 55.75; H, 5.91; N, 3.42; I, 31.00.

5,6,7,8,13,14 - Hexahydro - 7 - methyldibenz[d,g]azecin - 14 - one (protopane) (**16b**). A mixture of **15b** (0.267 g) and the activated MnO_2[15] (3 g) in EtOH-free chloroform (14 ml) was stirred at room temp for 3 hr. The ppt was filtered off and the solvent was evaporated. The oily residue was purified by preparative tlc (silica gel, 5% MeOH–CH_2Cl_2). *Rf* 0.2 band gave an oil, which was dissolved in CH_2Cl_2, washed with water and dried over Na_2SO_4. Evaporation of the solvent gave an oil (0.170 g, 64%) of **16b**; IR (Neat) 1665 cm^{-1}; ^1H NMR δ 1.86 (s, 3H, N–Me), 2.50, 2.93 (m, each 2H, Ar–CH_2CH_2–N), 3.57 (s, 2H, N–CH_2–Ar), 3.84 (s, 2H, Ar–CH_2–CO) and 7.0–7.5 (m, 8H, aromatic H's). Methiodide, mp 200–203° (MeOH) was yielded in the usual way: IR (Nujol) 1685 cm^{-1}. Found: C, 56.07; H, 5.32; N, 3.23; I, 31.14. Calc for $C_{19}H_{22}ONI$: C, 56.03; H, 5.44; N, 3.43; I, 31.15.

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