Tetrahedron Vol. 40, No. 20, pp. 4003 to 4012, 1984
Printed in the U.S.A.

0040-4020/84 $3.00 + .00

THE SYNTHESIS OF PYRIMIDOAPORPHINES

GEORGE R. LENZ

Department of Medicinal Chemistry
G. D. Searle & Co.
4901 Searle Parkway, Skokie, Illinois 60077 U.S.A.

(*Received in USA* 30 *April* 1984)

Abstract - The reaction of 1-benzyl-3,4-dihydroisoquinolines with ethoxycarbonyl isocyanate yields exclusively the N-acylated product 2. Thermal rearrangement of these enamides at 108° C. yields the pyrimidoisoquinolines 3 which may be alkylated or ethoxycarbonylated exclusively on the pyrimidone nitrogen. The pyrimidoisoquinolines possess a stilbene chromophore and are capable of undergoing the stilbene-phenanthrene conversion. Thus irradiation of 3 in the presence of iodine as a dehydrogenating agent yields the novel pyrimidoaporphine nucleus (7-9) in good yield.

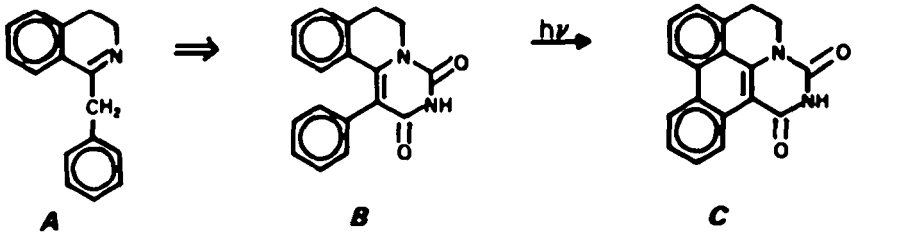
The synthesis of aporphine alkaloids has posed an intriguing synthetic problem, both for the synthetic challenge of constructing the four rings and for their wide variety of physiological activities.[1]

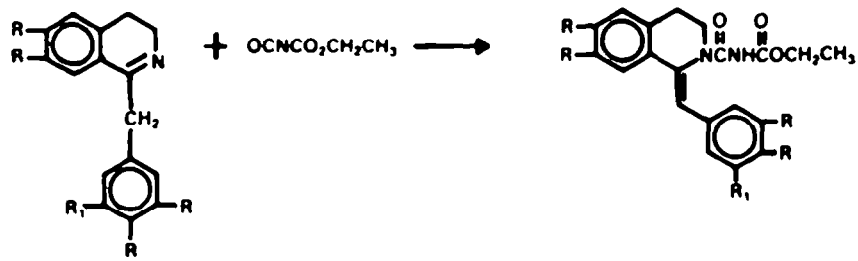
In the last few years, new types of aporphines have been discovered which possess functionality at position 7. The functional groups have included hydroxyl, methoxyl[2] as well as methyl.[3] Recently, a novel aporphine has been discovered which contains an oxazine ring fused across the 6,7-positions of a dehydroaporphine.[4] As part of our interest in constructing aporphine alkaloids with an additional heterocyclic ring fused across the 6,7-position,[5] we elected to synthesize an aporphine with a fused pyrimidone ring. Rather than modify an existing natural product as we had previously done,[5] a total synthesis of this five ring system was undertaken. The synthetic strategy involved converting a 1-benzyl-3,4-dihydroisoquinoline A into a pyrimidoisoquinoline B, followed by photochemical ring closure of the stilbene system incorporated in B into the desired compound C.[6] The conversion of B into C deserves some comment. Although the photochemical stilbene to phenanthrene conversion is well known,[7] this reaction in a diphenylpyrimidone has not been described to our knowledge. However a wide variety of vicinally phenyl substituted heterocycles readily undergo this photocyclization.[8] A five membered ring heterocycle of type B has

been synthesized and shown not to undergo photocyclization to the fused phenanthrene, possibly due to steric factors.[9]

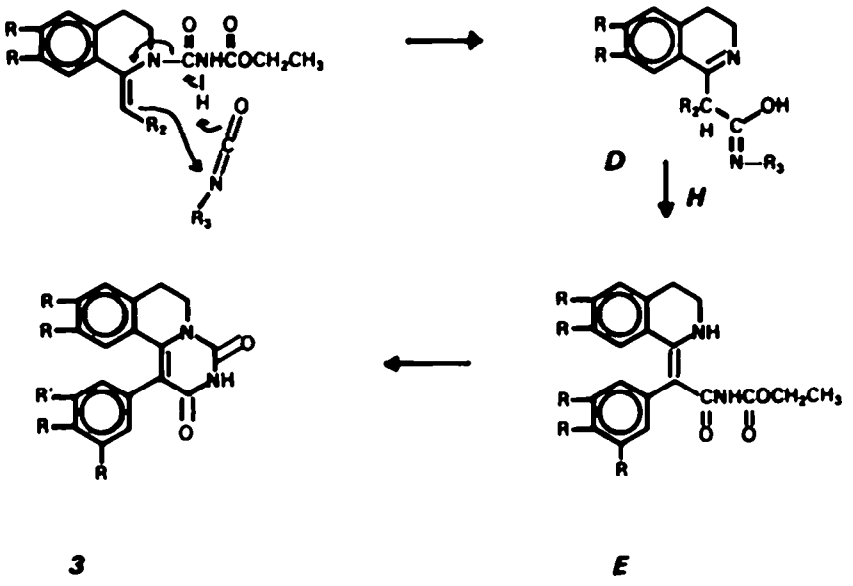
The isoquinoline enamide without the fused heterocyclic ring in B readily undergoes cyclization to the phenanthrene.[10] An added advantage to having the stilbene chromophore incorporated in a ring is the enhanced rate of phenanthrene formation due to the elimination of E-Z-isomerization as an energy wasting step. The synthesis of pyrimidoisoquinolines of type B was dependent on our recent observations on the reaction of dihydroisoquinolines with electrophiles.[11]

In practice, dihydropapaverine 1b was reacted with ethoxy carbonylisocyanate[12] at room temperature to yield the novel enamide 2b in good yield. The Z-stereochemistry about the stilbene double bond was assigned by spectral means. In the carbethoxyenamides[10a] and the formyl enamides[13] derived from dihydropapaverine both geometric isomers were isolated and characterized. In these compounds, as in the simpler N-alkyl-1-benzyltetrahydroisoquinolines,[14] both the hydrogen at C8 and the methoxyl at C7 are shielded by the 1-benzylidene or benzyl group and are shifted significantly upfield in the NMR spectra. In compound 2b, the signals for both the methoxyl and C8 hydrogen are not shielded and resonate at normal values.[10a,13] In addition the UV-spectra of enamides containing a stilbene chromophore have been shown to be similar to those of cis and trans-stilbene with Z-enamides absorbing at lower energies with higher intensities like trans-stilbene and the E-enamides having a maximum at higher energy with lower intensity like cis-stilbene.[13] The enamide 2b produced from 1b and ethoxycarbonylisoocyanate possesses a maximum at 334 nm which is characteristic of the Z-isomer. In a similar manner the unsubstituted compound 2a and the pentamethoxy-enamide 2c were formed in good yield from 1-benzyl-3,4-dihydroisoquinoline 1c and ethoxycarbonylisocyanate. The stereochemistry was assigned as Z based on the same spectral arguments which were used for 2b.





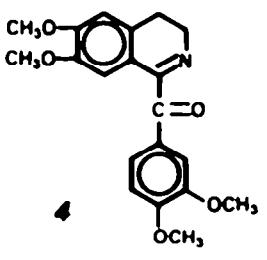
1a R = R₁ = H
1b R = OCH₃, R₁ = H
1c R = R₁ = OCH₃



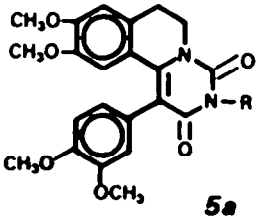
3 E

Rearrangement of the enamides to the pyrimidone was effected thermally by refluxing in toluene. Under these conditions a thermal reversion to isocyanate and dihydroisoquinoline can be detected by TLC. The isocyanate adds to the enamide double bond with elimination of the enamide N-acyl group as depicted in the scheme. Tautomerization of the C-acyl intermediate D gives E. Compounds of this type have been isolated where the substituent on the enamide double bond was other than phenyl.[11,15]

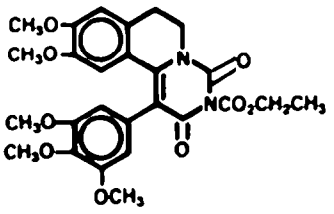
In this case compound E was unstable to the reaction conditions and spontaneously cyclized to the pyrimidoisoquinoline 3. Under these conditions, enamide 2b formed the tetramethoxy-3b in 38% yield. If the reaction was conducted under an inert atmosphere, a 47% yield of dihydropapaverine 1b was obtained. If oxygen was present, oxidation to 3,4-dihydropapaveraldine 4 occurred which complicated the isolation procedure. The pyrimidoisoquinoline structure 3 was supported by spectral and analytical data. The NMR spectrum indicated the loss of the ethoxyl carbonyl group and the occurrence of a shielded proton and a shielded methoxy methyl group which would be expected based on previous arguments.[10a,13,14] The mass spectrum confirmed the molecular formula with the molecular ion being the base peak. The only important fragmentations were the loss of a methoxyl methyl group and the loss of HNCO from the pyrimidone ring. The ultraviolet spectrum was similar to the model compound 5,6-diphenyluracil considering the enforced coplanarity of one of the phenyl rings in 3b.[16]



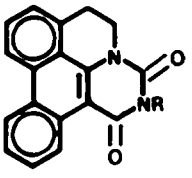
4



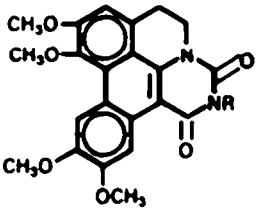
5a R = CH_3
5b R = $CO_2CH_2CH_3$



6



7a R = H
7b R = CH_3
7c R = $CO_2CH_2CH_3$

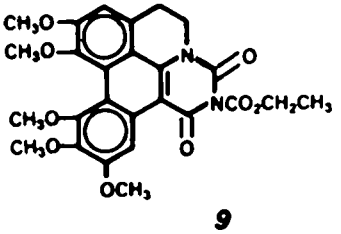


8a R = H
8b R = CH_3
8c R = $CO_2CH_2CH_3$

In a similar manner, enamides 2a and 2b were converted into the uracils 3a and 3b in 51% and 47% yield respectively.

Methylation of the unsubstituted pyrimidone nitrogen in 3b was readily accomplished to form 5a in high yield using methyl iodide in dimethylformamide in the presence of potassium carbonate according to the method of Shone.[17] Similarly the carbethoxy derivatives 5b and 6 were prepared in good yield by refluxing 3b and 3c respectively in tetrachloroethane in the presence of diethylpyrocarbonate.[18]

Since a variety of unsubstituted and substituted pyrimidoisoquinolines were now available, their photocyclization into the aporphine nucleus was studied. Irradiation of 3a in the presence of iodine formed a new compound 7a in 84% yield. The photoproduct 7a was identified as the desired pyrimidoaporphine by its physical and chemical properties.



9

The elemental analysis confirmed the loss of a molecule of hydrogen while the UV spectrum has the intense absorption at 255.5 nm and the weak long wave absorptions characteristic of the phenanthrene nucleus.[20] The hydrogens in the phenanthrene cavity of the photoproduct are shifted significantly downfield because of steric interactions forcing them out of coplanarity and into the deshielding area of the aromatic pi cloud.[21] The N-methyl derivative 7b and the N-carbethoxy compound 7c was prepared by the reaction of 7a with methyl iodide and diethylpyrocarbonate respectively.

Since the unsubstituted pyrimidoisoquinoline 3a cyclized readily to the pyrimidoaporphine 7a, we were interested in determining whether N-substituted pyrimidones would photocyclize, since N-substituted imides are known to be photochemically reactive.[22] These experiments were conducted on the tetramethoxy derivatives 5. To make sure that the substituted tetramethoxy compounds would cyclize, the N-unsubstituted derivative 3b was investigated first. Irradiation, using iodine as an oxidant, furnished a single pyrimidoaporphine 8a in 86% yield. This was identified as the 1,2,9,10-tetramethoxy compound (aporphine nucleus numbering) by its NMR spectrum which showed three singlets for the aromatic hydrogen resonances. The proton in the phenanthrene cavity resonates at δ 9.49 while the C8 hydrogen appears at δ 9.23 due to strong deshielding by the proximate coplanar pyrimidone carbonyl. The remaining C3 hydrogen appears at a normal position at 7.08. The formation of a single isomer, where two are possible, in the formation of dehydroaporphines has been previously observed and has been attributed to the difference in steric interactions between a hydrogen and a methoxyl and two methoxyl groups in the intermediate dihydrophenanthrene.[10]

With this experiment in hand, the N-methyl derivative 5a was irradiated and again led to a single N-methyl pyrimidoaporphine in 67% yield. The structure was assigned as 8b based on similar NMR spectral arguments like those used for 8a. The N-carbethoxy pyrimidoaporphine 8c was likewise formed from 5b in 59% yield, indicating that the pyrimidone ring will tolerate these substituents in the photocyclization step.

The N-carbethoxy pentamethoxy derivative 6 was investigated to see whether a pyrimidoaporphine possessing 1,2,9,10,11-substitutent would be formed. This would reflect the second common oxygenation pattern in aporphines (1,2,10,11). It has previously been shown that this oxygenation pattern is not observed in the photocyclization of diverse tetramethoxy enamides.[10,13,23] The 3,4,5-trimethoxy substitution pattern on the phenyl ring in compound 6 will force the formation of the previously unobserved oxygenation pattern if photocyclization occurs since only one compound is possible. When compound 6 was irradiated a much slower photocyclization occurred to form the N-carbethoxy pentamethoxypyrimidoaporphine 9 in yield of 17%. This is much lower than that observed with the other pyrimidoisoquinolines. However the isolation of 9 does indicate that the desired alternative 1,2,10,11 oxygenation pattern is attainable, although under forcing conditions.

EXPERIMENTAL SECTION

General.--Melting points were determined on a Thomas Hoover Unimelt capillary apparatus in open capillary tubes and are uncorrected. IR spectra were run in potassium bromide unless otherwise noted. Ultraviolet and visible spectra were run in methanol unless otherwise recorded. NMR spectra were recorded on Varian

A-60A, T-60, FT-80, EM-390 or HA-100 spectrometer and were run in deuterochloroform, unless otherwise noted, using tetramethylsilane as an internal standard. The NMR results are reported in chemical shifts (δ), followed by signal shape: s, singlet; d, doublet; t, triplet; m, multiplet. The multiplicity is followed by the coupling constant where appropriate and the integrated signal intensity. Mass spectra were run on an AEI MS-30 by Dr. Jeremy Hribar and microanalyses were conducted by the Searle Microanalytical Department under the direction of Mr. E. Zielinski.

The Preparation of Enamide 2a.[24]--To a solution of 6.7 g (30 mmol) of 1-benzyl-3,4-dihydroisoquinoline[24] 1a in 75 ml of ether, 4 ml of ethoxycarbonylisocyanate[25] was added. The vigor of the reaction caused the solvent to boil and the solution turned light yellow and rapidly deposited 8.25 g (24.6 mmol, 82%) of enamide 2a. The compound was filtered and washed with ether to yield 2a: mp 122-125° C.; IR 3420 (sharp) cm^{-1}, 1780, 1695, 1500; UV 231 nm (ε 15,500), 250 (12,000), 269 (min, 9500), 302 (17,500); NMR δ 7.0-8.0 (m,11H), 3.98 (q,2H), 3.33-4.67 (broad m,2H), 3.05 (broad m,2H), 1.08 (t,3H).

Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.40; H, 5.99; N, 8.33. Found: C, 71.36; H, 5.83; N, 8.11.

Tetramethoxyenamide 2b.--A solution of 10 g[26] (29.3 mmol) of 1-3'4'-dimethoxybenzyl-6,7-dimethoxy-3,4-dihydroisoquinoline[26] 1b in 250 ml of toluene was dried by refluxing using a Dean-Stark trap. The heat source was removed and when the internal solution temperature reached 60° C., 4 ml of ethoxycarbonylisocyanate was introduced and the mixture stirred magnetically overnight. A heavy cream-colored precipitate formed which was filtered and washed with ether to yield 8.0 g (17.53 mmol, 60%) of enamide 2b. Recrystallization from ethyl acetate-methylene chloride gave an analytical sample of 2b: mp 151-153° C.; IR 3420 cm^{-1}, 3300, 1780, 1760, 1698, 1610, 1520; UV 220 nm (end, ε 30,500), 265 (min, 8750), 296 (shoulder, 13,500), 334 (26,500); NMR δ 7.33 (s, 1H, NH, exchanged with D_2O), 6.65-7.25 (m,6H), 3.93 (q,2H), 3.90 (s,12H), 2.50-3.83 (broad m,4H), 1.13 (t,3H).

Anal. Calcd for $C_{24}H_{28}N_2O_7$: C, 63.14; H, 6.18; N, 6.14. Found: C, 62.70; H, 6.22; N, 6.30.

Pentamethoxyenamide 2c.--A solution of 10.0 g (27.0[27] mmol) of 1-3',4',5'-trimethoxybenzyl-6,7-dimethoxy-3,4-dihydroisoquinoline[27] 1c in 200 ml of benzene was dried, under nitrogen, by refluxing using a Dean-Stark trap. After cooling to rt, 5 ml of ethoxycarbonylisocyanate was introduced. After 1 hr, the majority of the benzene was evaporated and ether was added and 10 g (20.6 mmol, 76%) of enamide 2c collected. TLC on silica in ethyl acetate indicated two closely moving spots which indicated that crude 2c was probably a mixture of E-Z isomers.[10a] Since this point had already been investigated and was immaterial to the thermal cyclization, it was not pursued.[13] The pure Z-isomer 2c could be readily isolated by recrystallization of crude material from ethyl acetate-petroleum ether: mp 138-143.5° C.; IR 3420 cm^{-1}, 1785, 1695, 1520; UV 220 nm (end, ε 30,500), 265 (min, 7750), 330 (23,000); NMR δ 7.32 (s,1H, NH, exchanges with D_2O), 7.20 (s,1H), 6.83 (s,1H), 6.80 (s,1H), 6.66 (s,1H), 3.33-4.67 (broad m,2H), 3.93 (q,2H), 3.89 (s,15H), 2.97 (broard m,2H), 1.13 (t,3H).

Anal. Calcd for $C_{25}H_{30}N_2O_8$: C, 61.72; H, 6.22; N, 5.76. Found: C, 61.62; H, 6.37; N, 5.53.

General Procedure for the Thermal Rearrangement of the Enamides 2 into the Pyrimidoisoquinolines 3.--A solution of enamide 2 in toluene, approximately 1 g per 10 ml, was refluxed under nitrogen until the starting material disappeared by TLC, generally 2-4 hours. Usually a precipitate of the pyrimidone 3 formed which could be filtered, leaving behind the dihydroisoquinoline 1 in solution. If the refluxing solution was left open to the air, oxidation of 1 to the keto-imine compound occurred and complicated the isolation procedure[28] since it was also relatively insoluble in toluene. 3,4-Dihydropapaveraldine[28] 4 was isolated and identified in the rearrangement of 1b to 3b.

Pyrimidoisoquinoline 3a.--Six grams (17.8 mmol) of 2a were refluxed in toluene for 4 hrs and, upon cooling, 2.65 g (9.13 mmol, 51%) of 3a crystallized: mp 267.5-270° C. (dimethylformamide-ethyl acetate); IR 3160 cm^{-1}, 1690, 1680, 1590; UV 221 nm (min, 14,000), 238 (19,500), 273 (3750), 303 (sh, 12,000), 320 (14,500); NMR δ (DMF + d_7), 8.01 (s, 1H, NH, exchanges with D_2O), 7.26 (m,7H), 6.84 (m,2H), 4.02 (t,2H), 3.09 (t,2H).

Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.46; H, 4.86; N, 9.65. Found: C, 74.31; H, 5.08; N, 9.52.

The dihydroisoquinoline 1a was detected by TLC on silica using ethyl acetate and 1:1 ethyl acetate-toluene as solvent systems, however it was not isolated.

Tetramethoxy-pyrimidoisoquinoline 3b.--Three grams (6.57 mmol) of enamide 2b were refluxed in toluene and, upon cooling, 1.05 g (2.50 mmol, 38%) of 3b crystallized: mp 245-248.5°C. (methylene chloride-toluene), IR 3200 cm^{-1}, 1715 sh, 1690 (broad), 1600, 1520; UV 225 nm (ϵ 26,000), 242 (sh, 19,000), 265 (min, 8000), 279 (9500), 295 (min, 7500), 334 (14,500); NMR δ 9.67 (s, 1H, NH, exchanges with D_2O), 6.80 (m,3H), 6.67 (s,1H), 6.53 (s,1H), 4.10 (m,2H), 3.87 (s,3H), 3.83 (s,3H), 3.77 (s,3H), 3.20 (s,3H), 3.10 (t,2H); MS m/e (rel.%) 410 au (parent, 100%), 395 ($-CH_3$, 43%), 366 (-HNCO-H, 14%), 352 ($-CH_3$,-HNCO, 19%).

Anal. Calcd for $C_{23}H_{22}N_2O_6 \cdot H_2O$: C, 61.67; H, 5.65; N, 6.54. Found: C, 61.88; H, 5.57; N, 6.35.

The microanalytical service reported that 3b was very hygroscopic and gained weight rapidly upon being weighed for combustion analysis. Different samples of 3b depending upon their exposure to air and subsequent vacuum drying over refluxing toluene analyzed for varying amounts of water from a hemihydrate to a hydrate, although all other spectral and physical properties remained constant.

The mother liquors from the formation of 3b were extracted with dil hydrochloric acid. The acidic extract was made basic with sodium hydroxide and extracted with chloroform. The organic solution was dried with sodium sulfate and evaporated to yield 1.043 g (3.06 mmol, 47%) of dihydropapaverine 1b.[26]

Pentamethoxy-pyrimidoisoquinoline 3c.--Seven grams (14.4 mmol) of enamide 2c were refluxed in toluene and, upon cooling, 3 g (6.81 mmol, 47%) of 3c crystallized: mp 259.5-264° C.; IR 1720 cm^{-1}, 1680, 1660, 1595, 1515; UV 220 nm (ϵ 34,000), 243 (sh, 19,000), 275 (sh, 8250), 288 (min, 6750), 332 (16,250); NMR δ 9.40 (s, 1H, NH, exchanges with D_2O), 6.66 (s,1H), 6.53 (s,1H), 6.45 (s,2H), 4.14 (t,2H), 3.88 (s,3H), 3.84 (s,3H), 3.74 (s,6H), 3.28 (s,3H), 2.93 (t,2H).

Anal. Calcd for $C_{23}H_{24}N_2O_7 \cdot 0.5\ H_2O$: C, 61.45; H, 5.61; N, 6.23. Found: C, 61.83; H, 5.52; N, 6.15.

N-Methylation of 3b.--Three grams (7.32 mmol) of 3b were dissolved in 25 ml of DMF and 2.5 ml of methyl iodide and 3 g of potassium carbonate added. The mixture was stirred magnetically for three days after which the majority of the solvent was removed on a rotary evaporator. The residue was poured into water and extracted with three one hundred ml portions of benzene. After drying with sodium sulfate, the solvent was evaporated to leave an oil which crystallized immediately upon trituration with ethyl acetate. Recrystallization from ethyl acetate-ether yielded 2.85 g (6.72 mmol, 92%) of 5a: mp 197-199° C.; IR 1695 cm^{-1}, 1645, 1600, 1515; UV 225 nm (ϵ 29,000), 244 (sh, 20,750), 265 (min, 9500), 278 (10,500), 294 (min, 8750), 332 (16,250); NMR δ 6.82 (m,3H), 6.67 (s,1H), 4.13 (broad t,2H), 3.90 (s,3H), 3.87 (s,3H), 3.80 (s,3H), 3.46 (s,3H), 3.23 (s,3H), 2.08 (t,2H).

Anal. Calcd for $C_{23}H_{24}N_2O_6 \cdot 0.5\ H_2O$: C, 63.73; H, 5.81; N, 6.46. Found: C, 63.37; H, 5.64; N, 6.40.

The analytical sample of 5a, like that of 3b, rapidly gained weight upon exposure to air. The analytical sample of 5a was allowed to stand open to the air overnight and then analyzed correctly for a hemihydrate.

Carbethoxylation of Pyrimidone 3b.--A solution of 1.007 g (2.40 mmol) of 3b in 5 ml of 1,1,2,2-tetrachloroethane and 1 ml of diethylpyrocarbonate was refluxed for 4.5 hr. The solvent was removed under reduced pressure and the residue recrystallized from ethyl acetate-petroleum ether to yield 1.065 g of 5b (2.21 mmol, 92%): mp 188-190°C.; IR 1790 cm^{-1}, 1710, 1665, 1600, 1520; UV 244 nm (ϵ 22,000), 265 (min, 9000), 281 (11,000), 297 (min, 8000), 338 (16,000); NMR δ 6.80 (m,3H), 6.68 (s,1H), 6.57 (s,1H), 4.52 (q,2H), 4.08 (broad t,2H), 3.90 (s,3H), 3.86 (s,3H), 3.79 (s,3H), 3.22 (s,3H), 2.93 (t,2H), 1.43 (t,3H).

Anal. Calcd for $C_{25}H_{26}N_2O_8$: C, 62.23; H, 5.43; N, 5.81. Found: C, 61.97; H, 5.42; N, 5.62.

Carbethoxylation of Pyrimidone 3c.--A solution of 1.2 g (2.73 mmol) of 3c in 7 ml of 1,1,2,2-tetrachloroethane and 2 ml of diethylpyrocarbonate was refluxed for 40 hr. After 16 hr, an additional ml of diethylpyrocarbonate was added. After removal of the solvent the residue was crystallized from ether-petroleum ether to yield 850 mg (1.67 mmol, 61%) of 6: mp 171-174° C.; IR 1790 cm^{-1}, 1715, 1670, 1590, 1520; UV 220 nm (end, ϵ 32,000), 227 (sh, 27,500), 241 (min, 19,000), 245 (19,500), 278 (7500), 291 (min, 6250), 340 (15,750); NMR δ 6.69 (s,1H), 6.63 (s,1H), 6.45 (s,2H), 4.51 (q,2H), 4.09 (t,2H), 3.89 (s,3H), 3.83 (s,3H), 3.74 (s,6H), 3.28 (s,3H), 2.95 (t,2H), 1.44 (t,3H).

Anal. Calcd for $C_{26}H_{28}N_2O_9$: C, 60.92; H, 5.51; N, 5.47. Found: C, 60.61; H, 5.59; N, 5.20.

Photochemical Ring Closure of the Pyrimidoisoquinoline 3a to Pyrimido-aporphine 7a.--A suspension of 1.00 g (3.44 mmol) of **3a** in 560 ml of toluene was stirred magnetically while a stream of nitrogen was passed through the solution. After the addition of a few crystals of iodine, the mixture was irradiated through a Pyrex filter with a 450 watt medium pressure mercury arc. After 9 hr, starting material had been consumed and 750 mg of the product **7a** was collected. The irradiation vessel was washed with 250 ml of toluene and combined with the filtrate which was, in turn, washed with dil sodium sulfite solution. The resultant light yellow solution was dried with sodium sulfate and reduced in volume to approximately 25 ml and a further 80 mg of **7a** collected for a total yield of 830 mg (2.88 mmol, 84%). An analytical sample was recrystallized from dimethylformamide: mp 317-320° C.: IR 3190 cm^{-1}, 1695, 1600; UV 230 nm (ε 22,000), 248 (sh, 42,000), 254.4 (54,000), 261.5 (min, 34,000), 263.5 (35,000), 288.5 (min, 7000), 294.5 (9500), 307 (min, 4500), 318.5 (6500), 325 (min, 6000), 333.5 (7500), 344 (min, 4500), 351 (7500), 360 (min, 3500), 369 (9000); NMR δ (DMSO + d_6) 9.80 (m,1H), 8.75 (m,2H), 7.5-8.0 (m,4H), 4.27 (t,J=6.5 Hz,2H), 3.33 (t,2H).

Anal. Calcd for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 74.92; H, 4.45; N, 9.55.

N-Methylation of the Pyrimidoaporphine 7a.--To a stirred solution of 208 mg (0.72 mmol) of **7a** in 5 ml of dimethylformamide was added 0.5 ml of methyl iodide and 0.8 g of potassium carbonate. After stirring for 88.5 hr, the excess methyl iodide was removed on a rotary evaporator and remaining mixture slowly diluted with distilled water to yield 205 mg (0.68 mmol, 94%) of the N-methyl compound **7b**: mp 255.5-256.5° C.; IR 1700 cm^{-1}, 1655, 1615 w; UV 229 nm (sh, 21,500), 246 (sh, 40,000), 253.5 (52,000), 260.5 (min, 35,500), 263 (36,000), 288 (min, 7250), 294 (9750), 307 (min, 5000), 317.5 (6750), 323.5 (min, 6000), 332 (7500), 342 (min, 4500), 349.5 (8000), 358.5 (min, 3500), 367.5 (9500); NMR δ 9.83 (m,1H), 8.52 (m,1H), 7.3-7.75 (m,5H), 4.42 (t,2H), 3.57 (s,3H), 3.20 (t,2H).

Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.08; H, 4.81; N, 9.21.

N-Carbethoxylation of Pyrimidoaporphine 7a.--Compound **7a**, 316 mg (1.08 mmol), was refluxed for 1.5 hr in 2 ml of dimethylformamide and 1 ml of diethylpyrocarbonate. Upon cooling, light yellow crystals formed. After dilution with 20 ml of ether and filtering, 323 mg (0.90 mmol, 83%) of the N-carbethoxylated derivative **7c** was obtained: mp 215-219° C.; IR 1795 cm^{-1}; 1710, 1670, 1655 sh, 1615; UV 231 nm (sh, 22,000), 249 (sh, 43,000), 255.5 (55,000), 265 (36,000), 271 (sh, 31,500), 285 (sh, 10,000), 291 (min, 4000), 296 (10,000), 308 (min, 4500), 321 (6500), 326 (min, 6250), 335.5 (7750), 345 (min, 5400), 353.5 (7750), 362.5 (min, 4500), 371.5 (9000).

Anal. Calcd for $C_{21}H_{16}N_2O_4$: C, 69.99; H, 4.47; N, 7.77. Found: C, 70.33; H, 4.82; N, 7.97.

Ring Closure of the Tetramethoxy-pyrimidoisoquinoline 3b.--Compound **3b**, 523 mg (1.28 mmol), was partially dissolved in 300 ml of benzene and irradiated as described for **3a** for 5.25 hr. The ppt. then was mostly product while the filtrate was mostly **3b**. The irradiation volume was increased to 600 ml and additional iodine added. After an additional 5.25 hr irradiation, TLC on silica using 1:9 methanol-chloroform, only product **8a** was present. The precipitate and the residue after evaporation of the irradiation solution was dissolved in chloroform and washed with dil sodium sulfite solution and then dried with sodium sulfate and evaporated. The residue was crystallized from ethyl acetate-ether to yield **8a**, 448 mg (1.10 mmol, 86%); mp 302-304° C.; IR 3180 cm^{-1}, 2850, 1690 (broad), 1600, 1535, 1520; UV (methylene chloride) 255 nm (sh, 26,000), 264 (42,000), 270 (min, 33,500), 278.5 (41,000), 306 (sh, 13,000), 325 (min, 4250), 335 (5750), 341 (min, 5500), 351 (6500), 361 (min, 5000), 373 (7500), 381 (min, 7000), 392 (9250); NMR δ 9.49 (s,1H), 9.23 (s,1H), 8.53 (broad s, 1H, NH, exchanges with D_2O), 7.08 (s,1H), 4.38 (t,2H), 4.12 (s,3H), 4.09 (s,3H), 4.07 (s,3H), 3.89 (s,3H), 3.30 (t,3H).

Anal. Calcd for $C_{22}H_{20}N_2O_6 \cdot 0.5\ H_2O$: C, 63.30; H, 5.07; N, 6.71. Found: C, 63.35; H, 4.96; N, 6.51.

Ring Closure of the N-Methyl Tetramethoxypyrimidoisoquinoline 5a.--A solution of 1.078 g (2.54 mmol) and 140 mg of iodine in 190 ml of benzene was irradiated under nitrogen with a 450 watt medium pressure mercury arc for 4.75 hr. The irradiation was interrupted and a polymeric coating was removed from the immersion well with chloroform, followed by a benzene wash. An additional 91 mg of iodine were added and the irradiation continued for a further nine hours.

The rose-colored solution was washed with dilute sodium bisulfite solution to yield a faintly yellow solution, which was dried with sodium sulfate. After evaporation, the oily residue was crystallized from a small amount of methanol to yield 609 mg (1.44 mmol, 57%) of the N-methyl-pyrimidoaporphine **8b**: mp 216° C.; IR 1700 cm^{-1}, 1655, 1620, 1600, 1535, 1515; UV 235 nm (ε 17,500), 243 (min, 17,000), 262 (39,000), 268 (min, 37,000), 273 (37,500), 290 (sh, 24,500), 302 (sh, 12,500), 322 (min, 4500), 330 (5250), 344 (5750), 356 (min, 4750), 368 (5750), 382 (6250); NMR δ 9.50 (s,1H), 9.17 (s,1H), 7.03 (s,1H), 4.35 (t,2H), 4.08 (s,3H), 4.03 (s,3H), 4.02 (s,3H), 3.85 (s,3H), 3.52 (s,3H), 3.21 (t,2H).

Anal. Calcd for $C_{23}H_{22}N_2O_6$: C, 65.39; H, 5.25; N, 6.63. Found: C, 65.50; H, 5.34; N, 6.33.

N-Carbethoxy-tetramethoxy-pyrimidoaporphine 8c.--A solution of 1.002 g (2.08 mmol) of **5b** in 600 ml of benzene containing a few mg of iodine was irradiated for five hours. After work up as described for **5a**, 593 mg (1.23 mmol, 59%) of **8c** were obtained: mp 257.5-260.5°C. (ethyl acetate-ether); IR 1790 cm^{-1}, 1700, 1660, 1620, 1595; UV 265 nm (ε 54,000), 271 (min, 49,000), 280 (52,000), 309 (sh, 18,500), 327 (min, 5500), 339 (7500), 345 (min, 7000), 354 (8500), 370 (min, 7000), 387 (10,250), 393 (min, 10,000), 402 (10,250).

Anal. Calcd for $C_{25}H_{24}N_2O_8$: C, 62.49; H, 5.04; N, 5.83. Found C, 62.78; H, 5.13; N, 5.88.

N-Carbethoxy-pentamethoxy-pyrimidoaporphine 9.--A solution of 450 mg of **6** (0.88 mmol) in 190 ml of benzene containing a few crystals of iodine was irradiated as described for **5a** for 15.5 hr. Work-up and crystallization of the oil from ethanol yielded 74 mg (0.15 mmol, 17%), of **9** as a hemihydrate: mp 175-180° C.; IR 1795 cm^{-1}, 1715, 1660, 1600, 1515; UV 220 nm (end, 21,000), 228 (min, 17,500), 236 (sh, 19,000), 243 (sh, 20,750), 269 (47,500), 290 (29,000), 317 (sh, 13,750), 334 (min, 6250), 368 (10,000), 388 (9000); NMR δ 8.95 (s,1H), 7.09 (s,1H), 4.58 (q,2H), 4.33 (t,2H), 4.07 (s,9H), 3.99 (s,3H), 3.68 (s,3H), 3.31 (t,2H), 1.48 (t,3H).

Anal. Calcd for $C_{26}H_{26}N_2O_9 \cdot 0.5\ H_2O$: C, 60.10; H, 5.24; N, 5.39. Found: C, 59.84; H, 5.13; N, 5.41.

REFERENCES

1. (a) M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York, (1972) p. 195; (b) M. Shamma and J.L. Moniot, "Isoquinoline Alkaloids Research 1972-1977", Plenum Press, New York (1978) 123.

2. H. Guinaudeau, M. LeBoeuf and A. Cave, Lloydia, **38**, 275 (1975); ibid, J. Nat. Proc., **42**, 325 (1979).

3. M. LeBoeuf, D. Cortes, R. Hocquemiller, A. Cave and P. Potier, C. R. Seances Acad. Sci., Ser. II, **295**, 191 (1982).

4. F. Roblot, R. Hocquemiller and A. Cave, C. R. Seances Acad. Sci., Ser. II, **293**, 373 (1981).

5. G.R. Lenz and F.J. Koszyk, J. Chem. Soc. Perkin Trans. I, 1273 (1984).

6. G.R. Lenz, Synthesis, 489 (1978).

7. (a) F.R. Stermitz, Org. Photochem, **1**, 247 (1967); (b) E.V. Blackburn and C.J. Timmons, Q. Rev. Chem. Soc., **23**, 482 (1969).

8. (a) J.L. Cooper and H.H. Wasserman, Chem. Commun., 200 (1969); (b) A. Coutre, A. LaBlache-Combier and H. Ofenburg, Tetrahedron, **41**, 2023 (1975).

9. (a) I. Ninomiya, I. Furutani, O. Yamamoto, T. Kiguchi and T. Naito, Heterocycles, **9**, 853 (1978); (b) I. Ninomiya and T. Naito, Heterocycles, **10**, 237 (1978).

10. (a) N.C. Yang, G.R. Lenz and A. Shani, Tetrahedron Lett., 2941 (1966); (b) M.P. Cava, M.J. Mitchell, S.C. Havlicek, A. Lindert and R.J. Spangler, J. Org. Chem., **35**, 175 (1970); (c) S.M. Kupchan, J.L. Moniot, R.M. Kanojia and J.B. O'Brien, J. Org. Chem., **36**, 2413 (1971).

11. G.R. Lenz, C.M. Woo and B.L. Hawkins, J. Org. Chem., **47**, 3049 (1982).

12. B.A. Arbuzov and N.N. Zobova, Synthesis, 461 (1974).

13. G.R. Lenz, J. Org. Chem., 42, 1117 (1977).

14. (a) D.R. Dalton, M.P. Cava and K.T. Buck, Tetrahedron Lett., 2687 (1965); (b) D.R. Dalton, K.C. Ramey, H.J. Gisler, Jr., L.J. Lendvay and A. Abraham, J. Amer. Chem. Soc., 91, 6367 (1969).

15. (a) M.D. Nair and S.R. Mehta, Indian J. Chem., 7, 684 (1969); (b) R. Richter, Chem. Ber., 105, 82 (1972).

16. J.P. Wajon and J.P. Areus, Rec. Trav. Chim. Pay-Bas., 76, 79 (1957).

17. R.L. Shone, J. Heterocyclic Chem., 9, 1175 (1972).

18. A. Vincze, R.E.L. Henderson, J.J. MacDonald and N.J. Leonard, J. Amer. Chem. Soc., 95, 2677 (1973).

19. C.W. Mallory and F.B. Mallory, Org. Photochem. Syn., 1, 55 (1971).

20. W.V. Mayneord and E.M.F. Roe, Proc. Roy. Soc. (London), A158, 634 (1937).

21. J.A. Pople, W.G. Schneider and H.J. Bernstein, "High Resolution Nuclear Magnetic Spectroscopy", John Wiley and Sons, New York (1959), 247.

22. Y. Kanaoka, Acct. Chem. Res., 11, 407 (1978).

23. (a) G.R. Lenz, J. Org. Chem., 39, 2846 (1974); (b) G.R. Lenz, J. Org. Chem., 41, 2201 (1976).

24. W.M. Whaley and W.H. Hartung, J. Org. Chem., 14, 650 (1949).

25. R.W. Lamon, J. Heterocyclic Chem., 6, 261 (1969).

26. J.S. Buck, R.D. Haworth and W.H. Perkin, Jr., J. Chem. Soc., 2176 (1924).

27. E. Spath and K. Bohm, Ber. Dtsch. Chem. Ges., 55, 2989 (1922).

28. (a) J.S. Buck, R.D. Haworth and W.H. Perkin, Jr., J. Chem. Soc., 125, 2176 (1924); (b) J.S. Buck, W.H. Perkin, Jr. and J.S. Stevens, J. Chem. Soc., 127, 1472 (1925).