Aust. J. Chem., 1985, **38**, 1591–612

Photosolvolysis of Bridgehead Quaternary Ammonium Salts. III* Synthesis of Some 3-Benzazecine, 1*H*-2,6-Benzoxazecine and 2*H*-3,6-Benzoxazecine Derivatives and a 2*H*-1,4-Oxazocine Derivative†

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Abstract

Photosolvolysis of a mixture of *cis*- and *trans*-9,10-dimethoxy-5-methyl-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizinium iodide (2) in methanol gave, after workup, a very low yield of 8,10,11-trimethoxy-3-methyl-1,2,3,4,5,6,7,8-octahydro-3-benzazecine (3a). Similarly 1,10,11-trimethoxy-6-methyl-3,4,5,6,7,8-hexahydro-1*H*-2,6-benzoxazecine (8a) and 1,10,11-trimethoxy-6-methyl-1,4,5,6,7,8-hexahydro-2*H*-3,6-benzoxazecine (16a) were obtained in fair and low yields respectively from the *N*-methyl tetrahydro-2*H*,6*H*-[1,3]oxazino[2,3-*a*]isoquinolinium (7a) and hexahydro[1,4]oxazino[3,4-*a*]isoquinolinium (15) iodide precursors; a 1-methyl derivative (8b) of (8a) was also prepared. The ring-opened products 3-[*N*-2-{(4,5-dimethoxy-2-dimethoxymethyl)-phenyl}ethyl-*N*-methyl]aminopropan-1-ol (9a) and 3-[*N*-2-{(4,5-dimethoxy-2-1′,1′-dimethoxyethyl)-phenyl}ethyl-*N*-methyl]aminopropan-1-ol (9b) were also obtained from the [1,3]oxazino[2,3-*a*]-isoquinolinium salt derivatives. Photolysis of (2) and 9,10-dimethoxy-5-methyl-1,3,4,6,7,11b-hexahydro[1,4]oxazino[3,4-*a*]isoquinolinium iodide (15) in acidified aqueous solution afforded, after workup, the benzazecin-8-ol (3b) and hexahydro-2*H*-3,6-benzoxazecin-1-ol (16b) products respectively, but again in very low yield. Some mechanistic rationalizations of these results are given.

Photosolvolysis of 7a-(3,4-dimethoxy)phenyl-4-methyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazolium iodide (22) in methanol afforded a high yield of 8-methoxy-4-methyl-8-(3,4-dimethoxy)-phenyl-3,4,5,6,7,8-hexahydro-2*H*-1,4-oxazocine (24) in a new ring-destruction approach to this ring system. From ^{13}C n.m.r. data, the twist-boat–chair conformation was tentatively assigned to (24) in (D)chloroform solution.

Introduction

In previous papers[2,3] we reported on the photosolvolysis of annelated and reduced isoquinolinium salt precursors as a route to fused nine-membered heterocyclic systems. Applications to the preparation of 3-benzazecine, 1*H*-2,6-benzoxazecine and 2*H*-3,6-benzoxazecine derivatives are now described in this paper, together with an extension of the methodology to the synthesis of a non-annelated 2*H*-1,4-oxazocine derivative. Representatives of the first of the ten-membered ring systems, some of which show[4,5]

* Part II, *Aust. J. Chem.*, 1984, **37**, 1659.
† A preliminary report of some of these results has been published.[1]

[1] Bremner, J. B., and Winzenberg, K. N., *Chem. Ind. (London)*, 1980, 421.
[2] Bremner, J. B., and Winzenberg, K. N., *Aust. J. Chem.*, 1984, **37**, 1203.
[3] Bremner, J. B., and Winzenberg, K. N., *Aust. J. Chem.*, 1984, **37**, 1659.
[4] Herbst, D., Rees, R., Hughes, G. A., and Smith, H., *J. Med. Chem.*, 1966, **9**, 864.
[5] Yardley, J. P., Rees, R. W., and Smith, H., *J. Med. Chem.*, 1967, **10**, 1088.

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interesting pharmacological properties, have been prepared by ring destruction,[4-8] ring construction,[9,10] or ring construction–ring destruction[11] strategies. Very few representatives of the benzoxazecine ring skeleton in general have been reported,[1,12] although some 28 basic systems are possible.[13] Derivatives of the 1,4-oxazocine system are discussed later.

Results and Discussion

(*a*) *Preparation of 3-Benzazecine Derivatives*

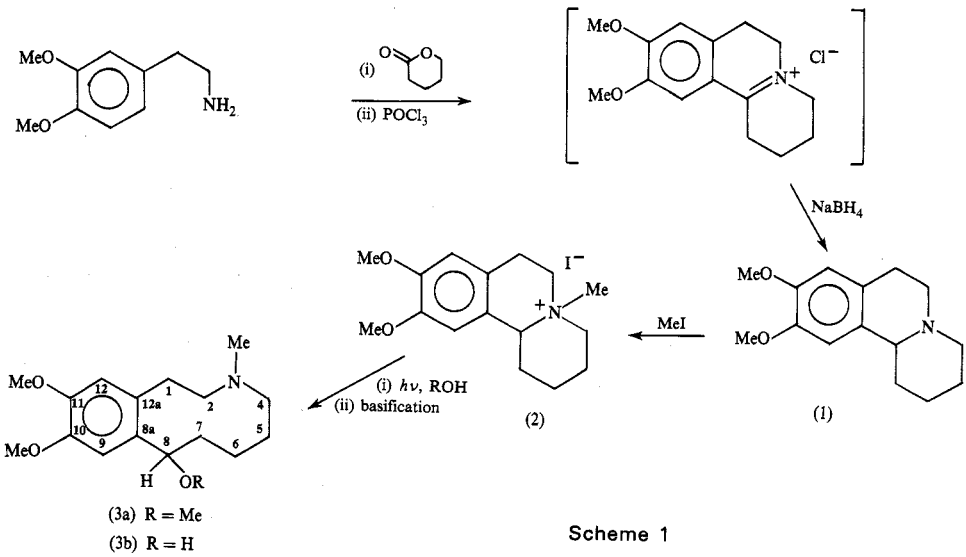
For the photosolvolytic preparation of the target octahydro-3-benzazecine derivatives, a quaternary hexahydro-2*H*-benzo[*a*]quinolizinium salt progenitor was needed. The iodide salt (2) was prepared for this purpose and was obtained[14-16] as a mixture of *cis* and *trans* diastereomers (3·4:1), in 50% yield from 2-(3,4-dimethoxyphenyl)ethanamine (Scheme 1). Fractional crystallization afforded[16] the pure *cis*-fused salt; in the ^{1}H n.m.r. spectrum of this isomer the aminomethyl group appeared as a singlet at δ 3·42. In the ^{1}H n.m.r. spectrum of the original mixture of diastereomers a singlet at δ 3·18 was ascribed to the aminomethyl group of the *trans*-fused salt.

Ultraviolet irradiation of the mixture of diastereomers of (2) in methanol, and in acidified water, afforded, after workup of the basified photolysates, the expected 3-benzazecine derivatives (3a) and (3b) respectively, although in low yields (Scheme 1 and Table 1).

The molecular formulae of (3a), and of (3b), were determined from high-resolution mass spectroscopy, and were, in each case, reinforced by elemental analysis.

The characteristic features of the ^{1}H n.m.r. spectrum of (3a) were the three-proton singlets at δ 3·07 and δ 2·05, assigned in turn to the C 8 methoxy and aminomethyl groups, and a one-proton triplet (J 8 Hz) at δ 4·75, ascribed to the hydrogen atom at C 8. Similarly, the ^{1}H n.m.r. spectrum of (3b) displayed a three-proton singlet at δ 1·98 and a one-proton doublet of doublets (J_1 10 Hz, J_2 7 Hz), centred at δ 5·16 which were assigned to the aminomethyl group and to the hydrogen atom at C 8 respectively; moreover a broad one-proton signal at δ 2·35–2·22, exchangeable with deuterium oxide, was attributed to the hydroxyl group. The presence of this

[6] Houlihan, W. J., and Manning, R. E., Fr. Pat. 1,503,238 (*Chem. Abstr.*, 1969, **70**, 11584q).
[7] Yardley, J. P., *Synthesis*, 1973, 543.
[8] Yardley, J. P., U. S. Pat. 3,856,795 (*Chem. Abstr.*, 1975, **82**, 111951y).
[9] Hamada, T., Ohmori, M., and Yonemitsu, O., *Tetrahedron Lett.*, 1977, 1519.
[10] Pecherer, B., Humiec, F., and Brossi, A., *Synth. Commun.*, 1973, **3**, 153 (*Chem. Abstr.*, 1973, **79**, 115423p).
[11] Fuks, R., Merenyi, R., and Viehe, H. G., *Bull. Soc. Chim. Belg.*, 1976, **85**, 892 (*Chem. Abstr.*, 1977, **87**, 5780k).
[12] Bremner, J. B., and Winzenberg, K. N., *Chem. Ind. (London)*, 1979, 319.
[13] Bremner, J. B., Browne, E. J., and Gunawardana, I. W. K., *Heterocycles*, 1982, **19**, 709.
[14] Child, R., and Pyman, F. L., *J. Chem. Soc.*, 1931, 36.
[15] Zymalkowski, F., and Schmidt, Fr., *Arch. Pharm. (Weinheim, Ger.)*, 1967, **300**, 229 (*Chem. Abstr.*, 1967, **67**, 73509r).
[16] Fujii, T., Nohara, M., Mitsukuchi, M., Ohba, M., Shikata, K., Yoshifuji, S., and Ikegami, S., *Chem. Pharm. Bull.*, 1975, **23**, 144.



Scheme 1

Table 1. Photolysis (Corex filter) of the 2*H*-benzo[*a*]quinolizinium salt (2), the 2*H*,6*H*-[1,3]oxazino-[2,3-*a*]isoquinolinium salts (7a,b), and the [1,4]oxazino[3,4-*a*]isoquinolinium salt (15) in hydroxylic solvents

Salt	Amount (mmol)	Solvent	Irradiation time (h)	Compounds isolated[E]
(2)[A]	1·027[C]	methanol	2·0	(3a) (2%), (2) (82%)
(2)[A]	1·027[C]	water[D]	2·0	(3b) (3%), (2) (90%)
(7a)[B]	1·022[F]	methanol	1·75	(8a) (46%), (9a) (42%)
(7a)[A]	1·071[F]	methanol	2·0	(8a) (40%), (9a) (37%)
(7b)	0·987[F]	methanol	4·0	(8b) (48%), (9b) (11%), (7b) (23%)
(15)	0·511[C]	methanol	4·0	(16a) (26%), (15) (40%)
(15)	0·895[F]	water[D]	1·75	(16b) (13%), (15) (68%)
(15)	0·713[C]	water[D]	3·0	(16b) (3%), (15) (28%)

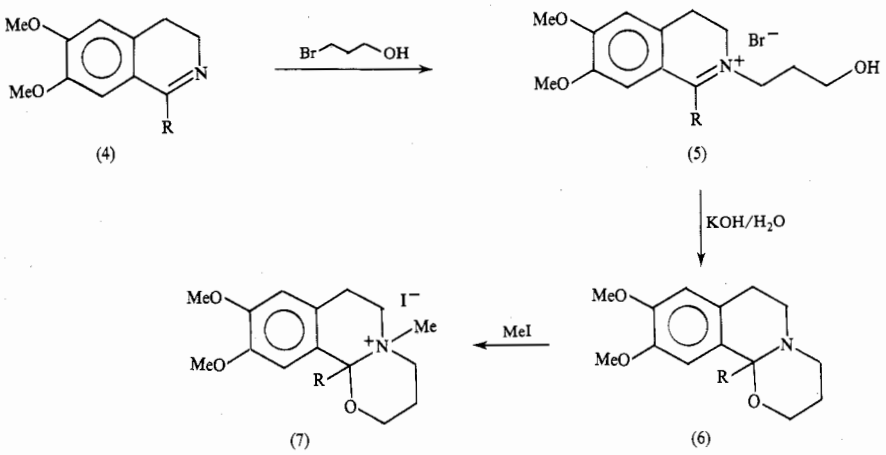
[A] Mixture of diastereomers. [B] Major diastereomer. [C] Dissolved in 100 ml of solvent. [D] Acidified to pH 1–2 by the addition of concentrated sulfuric acid. [E] Mole % yields, based on weights obtained after p.l.c. of the basified photolysate. [F] Dissolved in 200 ml of solvent.

latter group was confirmed from the infrared spectrum which exhibited a broad absorption band at 3360 cm^{-1}.

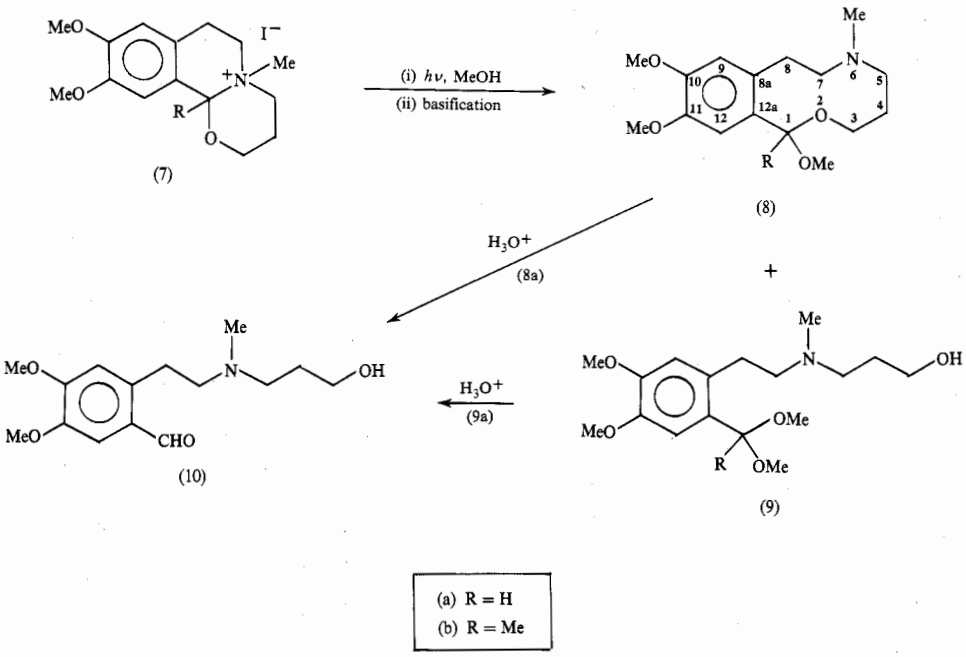
The ^{13}C n.m.r. spectra of (3a) and (3b) were consistent with the proposed structures. The chemical shifts of the methylene carbon atoms of (3a) and (3b) were tentatively assigned by comparison with the calculated[17a,18] chemical shifts (in parentheses) as follows: (3a), (3b): C 1, 30·0, 30·1 (34·7, 34·7); C 2, 58·9, 58·9 (56·7, 56·7); C 4, 52·3, 52·2 (55·6, 55·6); C 5, 28·1, 27·9 (28·4, 28·4); C 6, 20·0, 20·2 (25·4, 24·4); C 7, 38·1, 39·7 (39·4, 41·4). The assignment of the tertiary sp^3 C 8 atom of both compounds was apparent from the observed doublet multiplicity in each

[17] Wehrli, F. W., and Wirthlin, T., 'Interpretation of Carbon-13 N.M.R. Spectra' (*a*) p. 36; (*b*) p. 54; (*c*) p. 28 (Heyden & Son: London 1978).

[18] Breitmaier, E., and Voelter, W., '^{13}C N.M.R. Spectroscopy' (Monographs in Modern Chemistry, Ed. H. F. Ebel) Vol. 5, p. 119ff. (Verlag Chemie: Weinheim 1974).



Scheme 2



Scheme 3

case, in the proton-coupled spectrum. Moreover, in the proton-coupled spectrum of (3a) the aliphatic methoxyl carbon appeared as the characteristic doublet of quartets ($^1J_{C-H}$ 140 Hz, $^3J_{C-O-C-H}$ 3 Hz) indicative of long-range coupling to the hydrogen atom C 8.

(*b*) *Synthesis of 2,6-Benzoxazecine Derivatives*

The starting 2*H*,6*H*-[1,3]oxazino[2,3-*a*]isoquinoline derivatives (6a) and (6b) were prepared in 65% and 55% yield respectively from the 3,4-dihydroisoquinolines (4a) and (4b) after the method of Schneider and Kämmerer[19] (Scheme 2). Reaction of these tricyclic bases with iodomethane afforded the quaternary salts (7a) and (7b) required as progenitors of the 2,6-benzoxazecine derivatives.

Spectroscopic (^{1}H n.m.r.) analysis indicated that (7a) had been obtained as a mixture of diastereomers of which only the major one, comprising about two thirds of the mixture, could be obtained pure by repeated fractional recrystallization. The resonance from the aminomethyl group in the major isomer appeared at δ 3·38 and in the minor isomer the corresponding resonance appeared at δ 3·02. From an examination of the ^{1}H n.m.r. spectra of the methiodide salts of quinolizidine derivatives, it has been shown[20] that the aminomethyl group absorbs at lower field in the *cis*-fused salts than in the *trans*-fused analogues, and, on the basis of this finding, a *cis* relationship between H 11b and the aminomethyl group of the major diastereomer of (7a) is tentatively assigned (cf. also ref.[16]).

Ultraviolet irradiation of the 2*H*,6*H*-[1,3]oxazino[2,3-*a*]isoquinolinium salts (7a) and (7b) in methanol afforded the expected 1*H*-2,6-benzoxazecine derivatives (8a) and (8b) in moderate yield (Scheme 3 and Table 1). The acetals (9a) and (9b) were also obtained from this reaction. In the case of (7a) essentially the same product distribution and overall yield was observed from the irradiation of the mixture of diastereomers of (7a) as from irradiation of the pure major diastereomer, indicating that photosolvolysis was insensitive to this particular stereochemical aspect.

The assignment of structures (8a) and (8b) is supported by analytical and spectroscopic data. A detailed account of the structural elucidation of (8a) only is presented below.

Microanalysis of (8a) indicated an empirical formula of $C_{16}H_{25}NO_4$, and this was shown to be the molecular formula from high-resolution mass spectroscopy.

The 270 MHz ^{1}H n.m.r. spectrum of (8a) exhibited two three-proton singlets at δ 3·53 and 2·13 attributed in turn to the methoxy group at C 1 and to the aminomethyl group. A one-proton singlet at δ 5·59 was ascribed to the hydrogen atom at C 1; the chemical shift of this proton was almost identical to that of the corresponding proton in the analogous 2,5-benzoxazonine derivative.[3]

A partial assignment of the methylene protons of the medium-ring was made with the aid of proton decoupling experiments. A multiplet at δ 3·59–3·42 was assigned to the hydrogen atoms at C 3. Irradiation of this resonance resulted in a simplification of another multiplet at δ 1·58–1·44 which could thus be assigned to the hydrogen atoms at C 4. Irradiation of this upfield signal collapsed the C 3 protons to an AB quartet, partly obscured by the C 1 methoxyl resonance, indicative of

[19] Schneider, W., and Kämmerer, E., *Arch. Pharm.* (*Weinheim, Ger.*), 1966, **299**, 817.
[20] Crabb, T. A., Newton, R. F., and Jackson, D., *Chem. Rev.*, 1971, **71**, 109.

residual geminal coupling of these protons. More significantly, this irradiation simplified a one-proton resonance at δ 2·23–2·14 and the upfield part of a four-proton multiplet at δ 2·74–2·61. Accordingly, these latter two signals were attributed to the hydrogen atoms at C 5. The remaining downfield part of the multiplet at δ 2·74–2·61 and a one-proton multiplet at δ 3·07–3·04 were ascribed to the hydrogen atoms at C 7 and C 8.

The ^{13}C n.m.r. spectrum of (8a) was consistent with the proposed structure. The methylene carbon resonances were again tentatively assigned by comparison with the calculated[17a,18] chemical shifts (in parentheses) as follows: C 3, 60·3 (70·4); C 4, 27·4 (29·9); C 5, 50·5 (53·4); C 7, 60·0 (56·7); C 8, 30·6 (34·7). The assignment of C 4 was unequivocally verified by a selective proton decoupling experiment, however C 3, C 5 and C 7 could not be unambiguously assigned by this technique. Nevertheless, from the proton-coupled spectrum the $^1J_{C-H}$ coupling constants of the resonances at δ 50·5, δ 60·0 and δ 60·3 were 132, 132 and 141 Hz respectively, which indicated that the last resonance was most probably[17b] associated with C 3. In the proton coupled spectrum the aliphatic methoxyl carbon appeared as a doublet of quartets ($^1J_{C-H}$ 141 Hz, $^3J_{C-O-C-H}$ 3 Hz) indicative of long-range coupling to the hydrogen atom at C 1.

Acid hydrolysis of (8a) afforded the expected aldehyde (10) in high yield. The infrared spectrum of this compound exhibited absorption bands at 3380 cm^{-1}, and at 1690 and 1675 cm^{-1} ascribable to the hydroxyl and aldehyde groups. Furthermore, the ^1H n.m.r. spectrum of (10) showed a downfield one-proton singlet at δ 10·15 assigned to the aldehydic proton.

The structures (9a) and (9b) assigned to the ring-opened acetal photolysis products rest on spectroscopic data, and in the case of (9a), structural confirmation was forthcoming from its conversion in high yield to the aldehyde (10) by acid hydrolysis.

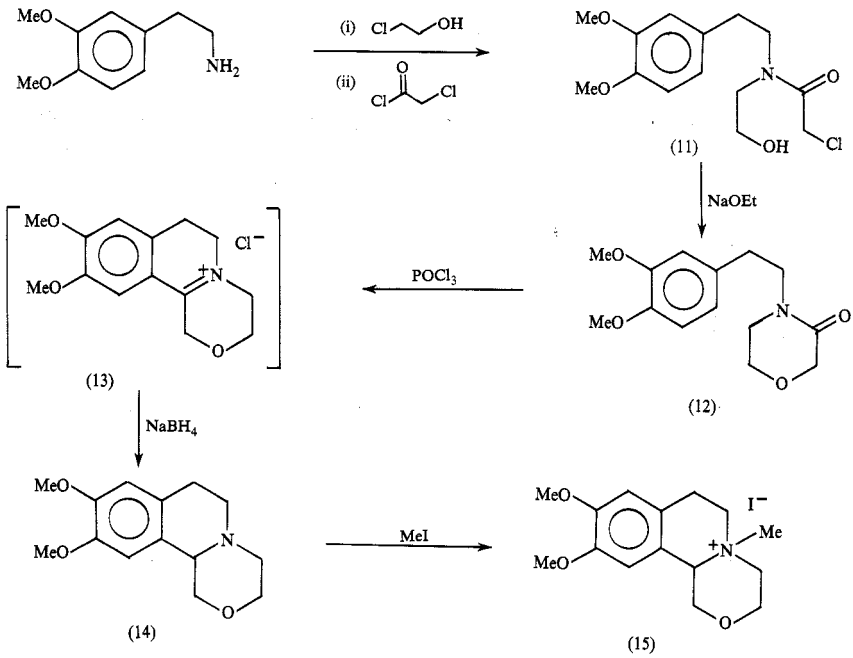
(*c*) *Synthesis of Some 3,6-Benzoxazecine Derivatives*

The [1,4]oxazino[3,4-*a*]isoquinolinium salt (15), required as a potential photochemical precursor of derivatives of the 2*H*-3,6-benzoxazecine system, was prepared in 11% yield from 2-(3,4-dimethoxyphenyl)ethanamine after a patented[21] method (Scheme 4). In contrast to the results described by the authors of the patent, the Bischler–Napieralski cyclization of the lactam (12) derived from (11), did not proceed satisfactorily. Pure (13) could not be obtained, and it was necessary to directly reduce the reaction mixture with sodium tetrahydroborate. Crude (14) crystallized from the reduction mixture but was obtained pure, in 21% yield from (12), only after repeated recrystallization.

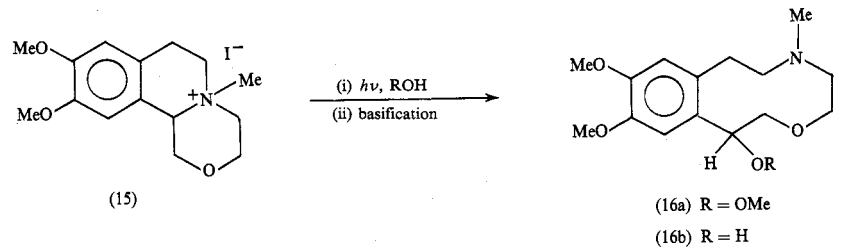
Ultraviolet irradiation of (15) in methanol or acidified water afforded low yields of the expected 2*H*-3,6-benzoxazecine derivatives (16a,b) (Scheme 5 and Table 1).

The salient features of the ^1H n.m.r. spectrum of the alcohol (16b) were a one-proton triplet (*J* 6 Hz) at δ 5·20 and a three-proton singlet at δ 2·33 which were ascribed to the hydrogen atom at C 1 and to the aminomethyl group. A broad one-proton singlet, exchangeable with deuterium oxide, centred at δ 4·02 was attributed to the hydroxy group; the infrared spectrum of (16b) displayed a broad absorption band at 3400 cm^{-1} confirming the presence of the alcohol.

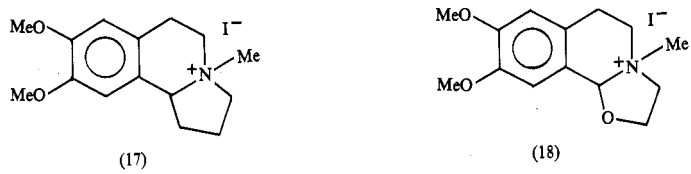
[21] E. Merck, A.-G., Neth. Appl. 6,611,733 (*Chem. Abstr.*, 1968, **68**, 49621w).



Scheme 4



Scheme 5



In the 270 MHz ^{1}H n.m.r. spectrum of the 2*H*-3,6-benzoxazecine derivative (16a), two three-proton singlets at δ 3·22 and δ 2·25 were assigned in turn to the aliphatic methoxy and methylamino groups. A downfield one-proton triplet at δ 4·80 (J 6 Hz) was assigned to the hydrogen atom at C1. Irradiation of this triplet collapsed a partly obscured two-proton doublet (J 6 Hz) centred at about δ 3·84 to a singlet. This signal was thus assigned to the hydrogen atoms at C2. Accordingly a two-proton multiplet at δ 3·74–3·57 could be ascribed to the hydrogen atoms at C4. Irradiation of these C4 protons simplified another two-proton multiplet at δ 2·88–2·81 so that these signals could be attributed to the hydrogen atoms at C5. The remaining one-proton multiplet at δ 3·08–2·94, two-proton multiplet at δ 2·72–2·62 and one-proton multiplet at δ 2·30–2·20 were ascribed to the hydrogen atoms at C7 and C8.

The ^{13}C n.m.r. spectrum of (16a) was in accord with the proposed structure. Reasonable agreement between experimental and calculated (in parentheses) chemical shifts for the ring methylene carbons were obtained as follows: C2, 76·4 (80·7); C4, 70·5 (69·7); C5, 59·7 (55·7); C7, 57·5 (56·7); C8, 31·3 (34·7). The validity of the C2, C5 and C7 assignments were confirmed by selective proton decoupling. The aliphatic methoxyl carbon appeared as a doublet of quarterts ($^1J_{C-H}$ 140 Hz, $^3J_{C-O-C-H}$ 3·5 Hz) in the proton coupled spectrum, indicative of long-range coupling to the hydrogen atom at C1.

(*d*) *Mechanistic Points*

The low yields of the 3-benzazecine derivatives obtained would appear to be a result of the slow rate of photosolvolysis of the 2*H*-benzo[*a*]quinolizinium salt (2) in both solvents; most of this salt was recovered unchanged from each photolysis. The yield of (3b) could not be increased to any significant extent by extended irradiation of (2) in water. This is probably as a consequence of the photoinstability of the 3-benzazecine (3b). In support of this view, it was shown in a separate experiment that the two-hour irradiation of (3b) in water acidified to pH 1 afforded a complex mixture of products, and only a small amount (8%) of unchanged (3b) was recovered.

The rate of photosolvolysis of the 2*H*-benzo[*a*]quinolizinium salt (2) is strikingly slower than that[2] of the corresponding pyrrolo[2,1-*a*]isoquinolinium salt (17). Stereoelectronic factors may account for this unexpected effect.

An inspection of models indicated that the carbonium ion intermediate generated, cf.[2,22], from heterolysis of the C11b–N bond of (2) may adopt a thermodynamically favourable conformation in which the lone-pair orbital of the nitrogen atom and the empty p orbital of the C8 carbonium ion effectively overlap (Fig. 1). An intermediate of this type might more readily collapse back to (2), before either water or methanol molecules could diffuse to the C8 carbonium ion and effect solvolysis.

If the photo-induced heterolysis of the C11b–N bond in (2) were reversible, then irradiation of the *cis*-fused diastereomer of (2) should result in the partial conversion of this isomer to the thermodynamically more stable[16] *trans*-fused salt. In the event, irradiation of the *cis*-fused salt in methanol afforded (3a), in less than 5% yield, together with unchanged (2), in 92% yield. However, ^{1}H n.m.r. analysis of the recovered salt showed that none of the *trans*-fused diastereomer was present.

[22] Cristol, S. J., and Bindel, T. H., in 'Organic Photochemistry' (Ed. A. Padwa) Vol. 6, p. 333ff. (Marcel Dekker: New York 1983).

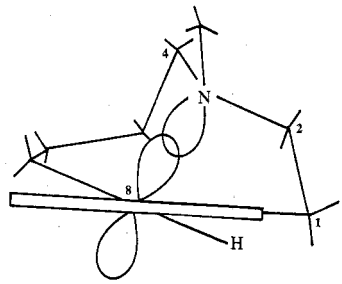
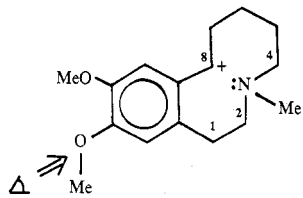


Fig. 1. View along the C 11–O bond of a conformation of the carbonium ion intermediate generated from heterolysis of the C 11b–N bond of the quaternary ammonium salt (2); not all atoms are shown.



This result does not invalidate the mechanism outlined above, for the activation energy barrier between the photochemically derived carbonium ion intermediate and the *trans*-fused diastereomer of (2) may be higher than that between the carbonium ion intermediate and the *cis*-fused isomer. It is possible, for example, that a tight association between the cation and the tertiary amino group in the carbonium ion intermediate, and a rapid reformation of the C 11b–N bond might preclude the conformational changes required for formation of the *trans*-fused salt.

Support for the existence of an activation energy barrier between the carbonium ion intermediate and the *trans*-fused salt was forthcoming from another experiment. A 70% recovery of (2) was obtained when the *cis*-fused salt was irradiated for two hours in refluxing methanol; ^{1}H n.m.r. analysis of the recovered salt showed it to be comprised of a mixture (3·7:1) of the *cis*- and *trans*-fused diastereomers. No (3a) was obtained from this experiment. However, in a separate experiment it was shown that (3a) was reactive under these conditions: no (3a) was recovered from the two hour photolysis of the hydrochloride salt of (3a) in refluxing methanol and, furthermore, no 9,10-dimethoxy-5-methyl-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]-quinolizinium chloride appeared to have been formed from ^{1}H n.m.r. analysis of the water-soluble photo-products. It should also be noted that in a blank experiment no *trans*-fused (2) was formed when a methanol solution of the *cis*-fused salt was refluxed under argon in the absence of ultraviolet irradiation.

In the case of the pyrrolo[2,1-*a*]isoquinolinium salt (17), an inspection of models indicated that an effective orbital interaction between the lone-pair orbital of the nitrogen atom and the empty p orbital of the C 7 carbonium ion was impossible in the thermodynamically favoured conformations of the carbonium ion intermediate generated from heterolysis of the C 10b–N bond of this salt. The closest this intermediate may come to effective orbital overlap is shown in Fig. 2. Accordingly solvent molecules might compete more successfully for the cationic C 7 atom than the internal nucleophilic nitrogen atom.

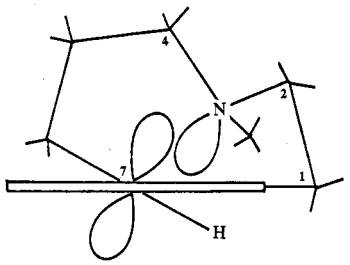
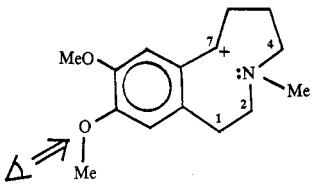


Fig. 2. View along C 10–O bond of a conformation of the carbonium ion intermediate generated from heterolysis of the C 10b–N bond of the quaternary ammonium salt (17); not all atoms are shown.



Further inspection of models showed that this orbital overlap mechanism could not operate with the carbonium ion intermediates derived from the oxazolo[2,3-*a*]-isoquinolinium salt (18), and related salts, and this was thus in accord with the observed[3] facile photosolvolysis of these salts.

The orbital overlap mechanism could, however, be potentially effective again with the carbonium ion intermediates derived from the methiodide salts (7a,b) and (15), and could help explain their slow rates of photosolvolysis. Furthermore, both the solvolysis products (8a) and (8b) appeared to be photolabile based on the observation of the acetals (9a,b).

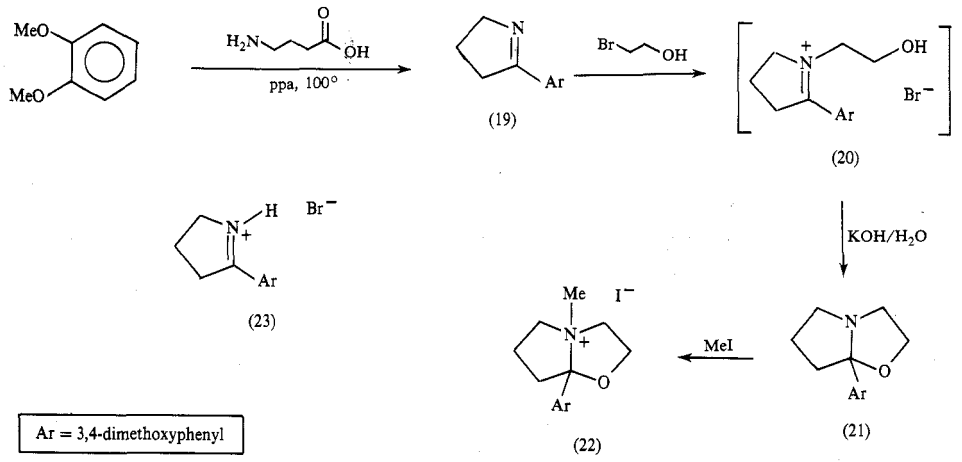
Nevertheless photosolvolysis proceeds more efficiently with the 2*H*,6*H*-[1,3]-oxazino[2,3-*a*]isoquinolinium salts (7a,b) than with the 2*H*-benzo[*a*]quinolizinium salt (2) or the [1,4]oxazino[3,4-*a*]isoquinolinium salt (15), presumably due largely to the extra stabilization of the carbonium ion intermediates by the adjacent oxygen in the first-mentioned cases.

(*e*) *Preparation of a* 2H-*1,4-Oxazocine Derivative*

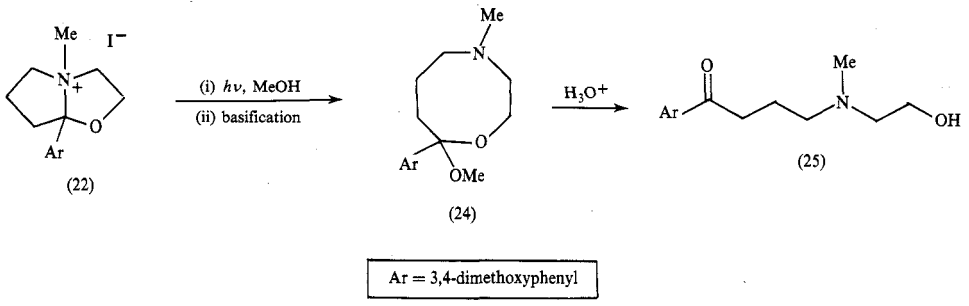
Further to the work described in this paper and previously,[1-3] it was reasoned that if the light-absorbing aromatic ring was present as a substituent at the bridgehead carbon, rather than fused, then photosolvolysis should enable access to non-fused medium-ring derivatives. Realization of this strategy was achieved in the synthesis of a 2*H*-1,4-oxazocine derivative[13] from a hexahydropyrrolo[2,1-*b*]oxazolium salt, as described in detail below. The known representatives of this particular eight-membered ring system have largely been made[23-26] by ring construction approaches involving condensation reactions. Prinzbach and co-workers have made[27]

[23] Kabbe, H.-J., and Joop, N., *Justus Liebigs Ann. Chem.*, 1969, **730**, 151.
[24] Hopwood, J. J., U. S. Pat. 3,591,544 (*Chem. Abstr.*, 1971, **75**, 153053t).
[25] Dulux Australia Ltd., Br. Pat. 1,325,454 (*Chem. Abstr.*, 1974, **80**, 4054v).
[26] Bodanszky, M., U. S. Pat. 3,704,246 (*Chem. Abstr.*, 1973, **78**, 58801p).
[27] Prinzbach, H., Müller, K.-H., Kaiser, C., and Hunkler, D., *Tetrahedron Lett.*, 1980, **21**, 3475.

sulfonamide derivatives of the fully unsaturated 4*H*-1,4-oxazocine system employing a thermal cycloreversion process, while a claim is also made[28] in a patent of a 4-heptenoic acid derivative of this latter system.



Scheme 6



Scheme 7

Although a synthetic route to 7a-phenyl-substituted 2,3,7,7a-tetrahydropyrrolo-[2,1-*b*]oxazol-5(6*H*)-one derivatives was reported,[29] no 7a-phenyl-substituted 2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole compounds were known at the time this work was begun.* Moreover, reduction of the former amides would, most probably, not have afforded the corresponding hexahydro derivatives, but rather products arising from the reductive fission of the C 7a–O bond of the initially formed

* The preparation of 7a-aryl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazoles was reported[30] subsequently.

[28] Glaxo Group Ltd, Jpn. Pat. 18,671 (1982) (*Chem. Abstr.*, 1982, **96**, 217560z).
[29] Aeberli, P., Gogerty, J. H., Houlihan, W. J., and Iorio, L. C., *J. Med. Chem.*, 1976, **19**, 436.
[30] Kourounakis, P., Hunter, W. H., and Morris, P. G., *Arzneim.-Forsch.*, 1979, **29**, 983 (*Chem. Abstr.*, 1979, **91**, 140756e).

hexahydro derivatives.[31] However, other hexahydropyrrolo[2,1-*b*]oxazole derivatives have been reported,[32,33] and the key step in their synthesis involved the cyclization of *N*-2-hydroxyethyl-3,4-dihydro-2*H*-pyrrolium salts. It was envisaged that (21) could be readily obtained from the 3,4-dihydro-2*H*-pyrrole derivative (19)[34] by this approach (Scheme 6).

Unfortunately, in the event, difficulties were encountered in the quaternization of (19) with 2-bromoethanol. Various solvents were tried, and although acetonitrile was adopted, a mixture of (20) and the hydrobromide salt (23) was obtained; the hydrogen bromide most probably arises[35] from the dehydrobromination of the 2-bromoethanol. Most of the hydrobromide salt (23) could be removed by fractional crystallization. The residue from the mother liquors was dissolved in water and extracted with ether to remove unchanged (19). Treatment of the aqueous solution with potassium hydroxide gave, after purification by p.l.c., the pyrrolo[2,1-*b*]oxazole derivative (21) as a colourless oil. The yields of (23) and (21) were 27 and 22% respectively. Reaction of (21) with iodomethane afforded, in 79% yield, the required 2*H*-1,4-oxazocine progenitor (22). The spectroscopic data for (23), (21) and (22) were consistent with the proposed structures, and satisfactory analyses were obtained for (23) and (22).

The synthetic utility of this approach to the pyrrolo[2,1-*b*]oxazole derivative (21), and hence its methiodide salt, is limited by the difficulty of effecting quaternization of (19) with 2-bromoethanol. It was thought that the oxazolidine annelation might be more readily achieved by reaction of (19) with oxiran.[36,37] However, in a trial experiment no reaction was observed.

Ultraviolet irradiation (Corex filter) of (22) in methanol gave the 2*H*-1,4-oxazocine derivative (24) in 89% yield (Scheme 7).

The structural assignment of (24) was based largely upon spectroscopic data. Microanalysis indicated an empirical formula of $C_{16}H_{25}NO_4$, and this was confirmed as the molecular formula from the high-resolution mass spectrum.

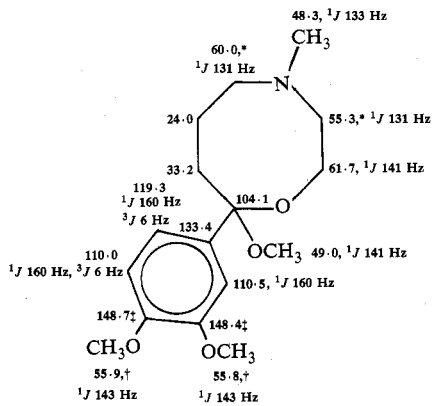


Fig. 3. ^{13}C n.m.r. data for the hexahydro-2*H*-1,4-oxazocine derivative (24).

[31] Leonard, N. J., and Musker, K. W., *J. Am. Chem. Soc.*, 1960, **82**, 5148.
[32] Audeh, C. A., and Lindsay Smith, J. R., *J. Chem. Soc. B*, 1971, 1745.
[33] Moehrle, H., Kamper, C., and Feil, R., *Z. Naturforsch., Teil B*, 1976, **31**, 99 (*Chem. Abstr.*, 1976, **84**, 121724g).
[34] Koller, W., and Schlack, P., *Chem. Ber.*, 1963, **96**, 93.
[35] Donetti, A., and Bellora, E., *Tetrahedron Lett.*, 1973, 3573.
[36] Schneider, W., and Müller, B., *Arch. Pharm. (Weinheim, Ger.)* 1961, **294**, 360.
[37] Filer, C. N., Granchelli, F. E., Soloway, A. H., and Neumeyer, J. L., *J. Org. Chem.*, 1978, **43**, 672.

Salient features of the ^1H n.m.r. spectrum of (24) were two three-proton singlets at δ 2·95 and δ 2·42 which were assigned to the aliphatic methoxyl group at C 8 and to the aminomethyl group respectively. A complex two-proton multiplet between δ 4·40 and 3·30 was ascribed to the hydrogen atoms at C 2.

The ^{13}C n.m.r. spectrum of (24) was consistent with the proposed structure. The ^{13}C chemical shifts of the proton decoupled spectrum are shown in Fig. 3, together with some coupling constants, deduced from the proton coupled spectrum.

The assignment of the carbon atoms of the 3,4-dimethoxyphenyl substituent is supported by comparison with those of a model compound.[38] The resonances from the methylene carbon atoms of the medium-ring were tentatively assigned by comparison of the observed shifts with the calculated[17a,18] (in parentheses) chemical shifts: C 2, 61·7 (69·7); C 3, 55·3 (55·7); C 5, 60·0 (55·1); C 6, 24·0 (20·9); C 7, 33·2 (46·9). Further support for the assignment of C 2, C 3 and C 5 was forthcoming from a consideration of the $^1J_{C-H}$ coupling constants[17b] for these atoms. The resonances from the aminomethyl and aliphatic methoxyl carbon atoms were separated by only 0·7 ppm, but here also the signals could be unambiguously assigned from a comparison[17b] of the $^1J_{C-H}$ coupling constants.

Acid hydrolysis of (24) afforded the ketone (25) in 83% yield. Elemental analyses and spectroscopic data were in accord with the proposed structure for the hydrolysis product.

(*f*) *Conformation of (24)*

Carbon-13 n.m.r. spectroscopy provides a useful probe for the investigation of molecular conformation, since the ^{13}C chemical shift is particulary sensitive to minor conformational variations. In this context the most salient features of the ^{13}C n.m.r. spectrum of the 2*H*-1,4-oxazocine derivative (24) are the significant upfield shifts of 8·0 and 13·7 ppm for C 2 and C 7 respectively compared with the calculated values for these atoms noted above. Upfield shifts of this type occur whenever two proton-bearing carbon atoms are in a *γ-gauche* relative orientation.[17c] Assuming this steric perturbation to be operative for C 2 and C 7, it is possible to make a tentative selection of the preferred molecular geometry of the medium-ring of (24).

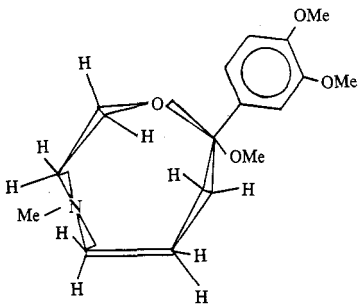


Fig. 4. Suggested preferred conformation of (24) in $CDCl_3$.

From a consideration of molecular models a *γ-gauche* relative orientation between C 2 and C 7 is not possible in conformations of (24) which resemble the crown, chair–chair, twist-chair–chair and boat–boat conformations[39] of cyclooctane. This

[38] Shamma, M., and Hindenlang, D. M., 'Carbon-13 N.M.R. Shift Assignments of Amines and Alkaloids' p. 111 (Plenum Press: New York 1979).

[39] Anet, F. A. L., *Fortschr. Chem. Forsch.*, 1974, **45**, 169.

interaction is possible in conformations which resemble the twist-boat, boat–chair and twist-boat–chair of cyclooctane. However, *γ-gauche* relative orientations between other methylene groups also exist in the two first-mentioned conformations, for example between C3 and C6 in the former and between C5 and C2 in the latter, yet there is no evidence for upfield shifts for either C5, C3 or C6 in the observed ^{13}C n.m.r. spectrum of (24). No methylene groups other than those at C2 and C7 exist in a *γ-gauche* relative orientation in the twist-boat–chair conformation which is thus tentatively assigned (Fig. 4) as the predominant one for (24) in (D)chloroform solution.

It is of interest to note that semi-empirical calculations of relative energies of cyclooctane indicate[40] the boat–chair form to be of lowest energy, however there are a number of other conformations, including the twist-boat–chair, which have rather similar energies.

X-ray crystallographic studies have confirmed[39,41] that 'simple' cyclooctane derivatives, as well as azocane,[42] exist predominantly in the boat–chair conformation while heavily substituted cyclooctanes as well as heterocyclic eight-membered rings possessing several heteroatoms, are known to exist[39] to a greater or lesser extent in crown family forms.

Experimental

General experimental notes with respect to this section are the same as those described in Part I.[2]

For photolyses in methanol the usual workup involved concentration in vacuum to a volume of about 10 ml, basification to pH 9 with concentrated aqueous ammonia, dilution to a volume of about 20 ml with distilled water, and extraction with chloroform (3 × 30 ml).

Iodomethane used in the preparation of the methiodide salts was distilled off anhydrous potassium carbonate.

All organic solvent extracts were dried with anhydrous sodium sulfate.

9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-2H-benzo[a]*quinolizine* (*1*)

The title compound (1) was prepared by use of a modification of the methods of Child and Pyman,[14] and Zymalkowski and Schmidt.[15]

A mixture of 2-(3,4-dimethoxyphenyl)ethanamine (18·2 g, 0·100 mol) and 5-pentanolide (11·73 g, 0·117 mol) was heated under nitrogen at 140° for 4 h. To the crude *N*-[2-(3,4-dimethoxyphenyl)-ethyl]-5-hydroxypentanamide thus obtained was added toluene (100 ml) followed by phosphorus oxychloride (20 ml). This mixture was refluxed for 2 h and allowed to cool. Light petroleum (b.p. 40–60°) (100 ml) was added and the upper organic layer decanted. The remaining oil was dissolved in ice-water (300 ml), the solution basified to pH 7 with concentrated aqueous ammonia, and extracted with chloroform (3 × 75 ml). The dried chloroform extracts were evaporated to afford a red gum which was extracted with diethyl ether (5 × 100 ml). As the combined diethyl ether extracts were concentrated an exothermic reaction, presumably cyclization of the 1-(4-chlorobutyl)-6,7-dimethoxy-3,4-dihydroisoquinoline intermediate, commenced. The residue obtained from evaporation of the ethereal extract was dissolved in 25% aqueous ethanol (100 ml) and excess sodium tetrahydroborate (*c.* 5 g) added. The mixture was stirred at room temperature for 2 h and then the solvents were evaporated. Water (100 ml) was added and the emulsion extracted with chloroform (3 × 50 ml). The residue obtained from the dried chloroform extracts was extracted with boiling light petroleum (b.p. 60–80°). Evaporation of these light petroleum extracts afforded the title compound (1) (14·2 g,

[40] Hendrickson, J. B., *J. Am. Chem. Soc.*, 1967, **89**, 7036, 7043, 7047.
[41] Miller, R. W., and McPhail, A. T., *J. Chem. Res.* (*S*), 1979, 285.
[42] Anet, F. A. L., Degen, P. J., and Yavari, I., *J. Org. Chem.*, 1978, **43**, 3021.

57%), m.p. 58–60° (lit.[14] 59–60°). ^{1}H n.m.r. δ ($CDCl_3$): 6·70, 6·56, 2s, 2×ArH; 3·83, s, 2×OCH_3; 3·20–1·20, m, 13H.

9,10-Dimethoxy-5-methyl-1,3,4,6,7,11b-hexahydro-2H-benzo[a]*quinolizinium Iodide* (2)

To a solution of (1) (5·55 g, 22·4 mmol) in dry acetone (20 ml) was added iodomethane (5 ml). The solution was allowed to stand at room temperature for 1 h. The precipitate which had formed was recrystallized from methanol to afford the *methiodide salt* (2) (7·60 g, 87%), m.p. 236° (lit.[14] 236°). The ^{1}H n.m.r. spectrum of (2) indicated[16] a mixture of *cis* and *trans* diastereomers (3·4:1). ^{1}H n.m.r. δ ($(CD_3)_2SO$): 7·23, s, ArH; 7·18, s, ArH; 4·90–4·25, m, H 11b; 4·20–1·80, m, 12H; 4·12, s, 2×OCH_3; 3·40, s, 2·32H, NCH_3 of *cis* diastereomer; 3·18, s, 0·68H, NCH_3 of *trans* diastereomer. λ_{max} (log ε) 220 (4·30), 283 (3·55), 287sh (3·51); λ_{min} 216 (4·28), 254 nm (2·92).

Fractional recrystallization of the diastereomeric mixture (5·475 g), after the method of Fujii *et al.*[16], afforded the *cis* diastereomer of (2) (1·010 g), m.p. 232–234° (dec.) (lit.[16] 229–230° (dec.)). ^{1}H n.m.r. δ ($(CD_3)_2SO$): 7·23, s, ArH; 7·18, s, ArH; 4·90–4·25, m, H 11b; 4·20–1·80, m, 12H; 4·12, s, 2×OCH_3; 3·42, s, NCH_3.

Photolysis of the Mixture of Diastereomers of the 2H-Benzo[a]*quinolizinium Salt* (2) *in Methanol*

A solution of (2) (400 mg, 1·027 mmol) in methanol (100 ml) was irradiated for 2 h and evaporated to dryness. Water (25 ml), basified to pH 9 by the addition of concentrated aqueous ammonia, was added and the solution obtained was extracted with diethyl ether (3 × 30 ml). The aqueous solution was then evaporated to dryness and extracted with boiling chloroform (3 × 30 ml). P.l.c. (chloroform/5% methanol) of the residue (30 mg) from the dried diethyl ether extracts gave (R_F 0·70) *8,10,11-trimethoxy-3-methyl-1,2,3,4,5,6,7,8-octahydro-3-benzazecine* (3a) (5 mg, 2%) as a colourless solid. Recrystallization from light petroleum (b.p. 40–60°) gave the 3-benzazecine (3a) as colourless prismatic needles, m.p. 83–84° (Found: C, 69·9; H, 9·5; N, 4·7. $C_{17}H_{27}NO_3$ requires C, 69·6; H, 9·3; N, 4·8%). Mass spectrum: *m/e* 293 ($M^{+\bullet}$, accurate mass 293·1990; $C_{17}H_{27}NO_3$ requires $M^{+\bullet}$, 293·1991), 278, 262. ^{1}H n.m.r. δ ($CDCl_3$): 6·82, 6·74, 2s, 2ArH; 4·75, t, *J* 8 Hz, H 8; 3·89, 3·87, 2s, 2×OCH_3; 3·07, s, 8-OCH_3; 3·30–1·10, m, 12H; 2·05, s, NCH_3. ^{13}C n.m.r. δ ($CDCl_3$): 148·3,* C 11[A]; 147·9, C 10[A]; 132·9, C 12a[B]; 132·4, C 8a[B]; 111·0, C 12; 108·2, C 9; 78·5, C 8; 58·9, C 2[D]; 55·8, 11-OCH_3[C]; 55·7, 10-OCH_3[C]; 55·5, 8-OCH_3; 52·3, C 4[D]; 43·6, NCH_3; 38·1, C 7; 30·0, C 1; 28·1, C 5; 20·0, C 6. λ_{max} (log ε) 225sh (3·99), 282 (3·47), 287sh (3·43); λ_{min} 254 nm (2·92).

Many other products were detected by p.l.c. but, due to the small amount of material involved, none were investigated further.

The combined chloroform extracts were evaporated to afford unchanged (2) (326 mg, 82%).

Photolysis of the cis *Diastereomer of the 2H-Benzo*[a]*quinolizinium Salt* (2) *in Methanol*

A solution of the *cis* diastereomer of (2) (243 mg, 0·624 mmol) in methanol (150 ml) was irradiated for 1 h at room temperature, and then worked up in the same manner as described above.

^{1}H n.m.r. analysis of the residue (9 mg) from the ether extract showed that it was comprised mainly of (3a).

Unchanged (2) (224 mg, 92%) was obtained from the evaporation of the aqueous extract; ^{1}H n.m.r. analysis showed that only the *cis* diastereomer of (2) was present.

In another experiment, a solution of the *cis* diastereomer of (2) (250 mg, 0·642 mmol) in refluxing methanol (150 ml) was irradiated for 2 h, and then evaporated to dryness. Water (30 ml), basified to pH 9 by the addition of concentrated aqueous ammonia, was added and the solution extracted with diethyl ether (3 × 30 ml). The aqueous solution was evaporated to dryness and the residue extracted with boiling chloroform (3 × 30 ml).

^{1}H n.m.r. analysis of the residue (94 mg) from the ether extract showed it to be a complex mixture, and no (3a) could be detected.

The residue (174 mg) from the chloroform extracts was shown to be a mixture of the *cis* and *trans* diastereomers of (2) (3·7:1).

* Each assigned resonance in this and the following ^{13}C n.m.r. spectra showed the expected multiplicity in the proton coupled spectra. Assignments of resonances indicated with the same superscripts may be interchanged.

In a blank experiment a solution of the *cis* diastereomer of (2) (111 mg) in methanol (50 ml) was refluxed in the dark under argon for 2 h, and then evaporated to dryness. None of the *trans* diastereomer of (2) was detected in the residue from ^{1}H n.m.r. analysis.

Photolysis of the Hydrochloride Salt of (3a) in Refluxing Methanol

To a solution of (3a) (236 mg) in methanol (5 ml) was added concentrated hydrochloric acid (10 drops). The solution was evaporated to dryness and the glass thus obtained dissolved in methanol (150 ml). This solution was irradiated under reflux for 2 h, and then worked up as described for the photolysis of the *cis* diastereomer of (2) in refluxing methanol.

The residue (148 mg) from the ether extract was shown to be a complex mixture from ^{1}H n.m.r. analysis, and no unchanged (3a) was detected.

The residue (109 mg) from the chloroform extract was also shown to be a complex mixture from ^{1}H n.m.r. analysis, and neither *cis*- nor *trans*-9,10-dimethoxy-5-methyl-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizinium chloride appeared to be present.

Photolysis of the Mixture of Diastereomers of the 2H-Benzo[a]quinolizinium Iodide (2) in Water

A solution of (2) (400 mg, 1·027 mmol) in water (100 ml) acidified to pH 1–2, by the addition of concentrated sulfuric acid, was irradiated for 2 h. P.l.c. (chloroform/7% methanol) of the residue from the first chloroform extract, obtained in the same manner as described[2] for the irradiation of (17) in acidified water, gave (R_F 0·65) the alcohol *10,11-dimethoxy-3-methyl-1,2,3,4,5,6,7,8-octahydro-3-benzazecin-8-ol* (3b) (8 mg, 3%) as a colourless solid. Recrystallization from diethyl ether gave the 3-benzazecin-8-ol (3b) as colourless prisms, m.p. 118·5–119·5° (Found: C, 68·7; H, 9·1; N, 5·0. $C_{16}H_{25}NO_3$ requires C, 68·8; H, 9·0; N, 5·0%). Mass spectrum: *m/e* 279 ($M^{+\bullet}$, accurate mass 279·1834; $C_{16}H_{25}NO_3$ requires $M^{+\bullet}$, 279·1834), 264, 261. ^{1}H n.m.r. δ ($CDCl_3$): 6·83, s, H 9; 6·56, s, H 12; 5·16, dd, J_1 10, J_2 7 Hz, H 8; 3·82, s, 2 × OCH_3; 3·10–1·00, m, 12H; 2·35–2·22, broad s, exchanged with D_2O, OH; 1·98, s, 3H, NCH_3. ^{13}C n.m.r. δ ($CDCl_3$): 148·3, C 11[A]; 147·7, C 10[A]; 135·2, C 12a[B]; 131·4, C 8a[B]; 111·4, C 12; 108·3, C 9; 69·2, C 8; 58·9, C 2[D]; 55·8, 11-OCH_3[C]; 55·7, 10-OCH_3[C]; 52·2, C 4[D]; 43·6, NCH_3; 39·7, C 7; 30·1, C 1; 27·9, C 5; 20·2, C 6. ν_{max} ($CHCl_3$): 3360 (m, OH) cm^{-1}. λ_{max} (log ε) 225sh (4·09), 282 (3·55), 287sh (3·51); λ_{min} 253 nm (2·86).

Another fraction (R_F 0·30) afforded unchanged (2) (27 mg, 7%). Many uninvestigated minor products were present.

The second chloroform extract was evaporated to afford unchanged (2) (330 mg, 83%).

In another experiment a solution of (2) (400 mg, 1·027 mmol) in water acidified to pH 1–2 was irradiated for 6 h. Analytical t.l.c. of the residue (50 mg) from the first chloroform extract showed that only a trace of the 3-benzazecin-8-ol (3b) was present.

Photolysis of the 3-Benzazecin-8-ol Derivative (3b) in Water

A solution of (3b) (250 mg) in water (200 ml) acidified to pH 1–2, by the addition of concentrated sulfuric acid, was irradiated for 2 h. The solution was basified to pH 9 with concentrated aqueous ammonia, and extracted with chloroform (5 × 20 ml). The residue from the dried chloroform extract was subjected to p.l.c. (chloroform/6% methanol) to afford unchanged (3b) (20 mg, 8%). Many other products were present, but were not investigated.

9,10-Dimethoxy-3,4,7,11b-tetrahydro-2H,6H-[1,3]oxazino[2,3-a]isoquinoline (6a)

Reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline (4a) (cf. 3) with 3-bromopropan-1-ol after the method of Schneider and Kämmerer[19] afforded, in 68% yield, after recrystallization from methanol/ethyl acetate, 2-(3-hydroxypropyl)-6,7-dimethoxy-3,4-dihydroisoquinolinium bromide (5a), m.p. 192–193° (lit.[19] 192°).

Treatment of (5a) with 20% aqueous potassium hydroxide gave[19] in 95% yield the title compound (6a), m.p. 78–81° (lit.[19] 82–83°). ^{1}H n.m.r. δ ($CDCl_3$): 6·88, 6·61, 2s, 2 × ArH; 4·83, s, H 11b; 4·40–3·60, m, $(H2)_2$; 3·89, 3·86, 2s, 2 × OCH_3; 3·40–1·90, m, 7H; 1·50–1·20, m, 1H.

9,10-Dimethoxy-5-methyl-3,4,7,11b-tetrahydro-2H,6H-[1,3]oxazino[2,3-a]isoquinolinium Iodide (7a)

To a solution of (6a) (12·4 g, 49·7 mmol) in dry acetone (50 ml) was added excess iodomethane (10 ml). The solution was allowed to stand at room temperature for 1 h, and then evaporated to

dryness. The residue was crystallized from acetone to give the *methiodide salt* (7a), (16·4 g, 84%), m.p. 219–222°. The ^{1}H n.m.r. spectrum of (7a) indicated a mixture of diastereomers (1:2). ^{1}H n.m.r. δ ($CDCl_3$): 6·87, broad s, ArH; 6·72, broad s, ArH; 6·45, s, 0·33 H, H 11b of minor isomer; 6·27, s, 0·67 H, H 11b of major isomer; 4·70–1·80, m, 10H; 3·89, s, 2×OCH_3; 3·38, s, 2H, NCH_3 of major isomer; 3·02, s, 1H, NCH_3 of minor isomer.

The diastereomeric mixture (14·4 g) was recrystallized three times from chloroform/acetone to afford a pure sample of the major isomer of (7a) (4·97 g), m.p. 231–232° (Found: C, 45·6; H, 5·7; N, 3·5. $C_{15}H_{22}INO_3$ requires C, 46·0; H, 5·7; N, 3·6%). ^{1}H n.m.r. δ ($CDCl_3$/CD_3OD); 6·98, 6·78, 2s, 2×ArH; 6·12, s, H 11b; 4·65–1·80, m, 10H; 3·89, s, 2×OCH_3; 3·24 s, NCH_3. λ_{max} (log ε) 219sh (4·28), 281 (3·48), 285sh (3·44); λ_{min} 257 nm (2·80).

Photolysis of the Major Diastereomer of the 2H,6H-[1,3]Oxazino[2,3-a]isoquinolinium Salt (7a) in Methanol

A solution of the major diastereomer (7a) (400 mg, 1·022 mmol) in methanol (200 ml) was irradiated for 1·75 h. The photolysate residue, obtained after the usual workup, was subjected to p.l.c. (chloroform/8% methanol).

Fraction 1 (R_F 0·55) afforded *1,10,11-trimethoxy-6-methyl-3,4,5,6,7,8-hexahydro-1H-2,6-benzoxazecine* (8a) (140 mg, 46%) as a colourless solid. Recrystallization from light petroleum (b.p. 40–60°) gave (8a) as rosettes of prisms, m.p. 63–64° (Found: C, 65·3; H, 8·2; N, 4·7. $C_{16}H_{25}NO_4$ requires C, 65·1; H, 8·6; N, 4·7%). Mass spectrum: *m/e* 295 ($M^{+\bullet}$, accurate mass 295·1782; $C_{16}H_{25}NO_4$ requires $M^{+\bullet}$, 295·1784), 294, 280, 264. ^{1}H n.m.r. (270 MHz) δ ($CDCl_3$): 7·08, s, H 12; 6·69, s, H 9; 5·59, s, H 1; 3·87, 3·86, 2s, 2×OCH_3; 3·59–3·42, m, $(H3)_2$; 3·53, s, 1-OCH_3; 3·07–3·04, m, 1H; 2·74–2·61, m, 4H; 2·23–2·14, m, 1H; 2·13, s, NCH_3; 1·58–1·44, m, $(H4)_2$. ^{13}C n.m.r. δ ($CDCl_3$): 148·7, C 10^A; 146·6, C 11^A; 132·9, C 8a^B; 129·8, C 12a^B; 112·1, C 9; 110·5, C 12; 102·8, C 1; 60·3, C 3; 60·0, C 7^C; 55·8, 55·8, 10,11-OCH_3; 55·2, 1-OCH_3; 50·5, C 5^C, 45·1, NCH_3; 30·6, C 8; 27·4, C 4. λ_{max} (log ε) 233 (4·00), 281 (3·41), 286sh (3·36); λ_{min} 220 (3·85), 256 nm (2·95).

Fraction 2 (R_F 0·45) afforded the acetal *3-[N-2-{(4,5-dimethoxy-2-dimethoxymethyl)phenyl}ethyl-N-methyl]aminopropan-1-ol* (9a) (140 mg, 42%) as a colourless oil. Mass spectrum: *m/e* 327 (M), 312, 296, 102 $H_2C{=}N^+(CH_3)CH_2CH_2CH_2OH$). ^{1}H n.m.r. δ ($CDCl_3$): 7·14, s, ArH; 6·72, s, ArH; 5·47, s, $CH(OCH)_3)_2$; 4·60, broad s, exchanged with D_2O, OH; 3·92, s, 2×$ArOCH_3$; 3·84, t, *J* 6 Hz, CH_2OH; 3·38, s, $CH(OCH_3)_2$; 3·00–2·45, m, 6H, $ArCH_2CH_2NCH_2$; 2·40, s, NCH_3; 1·76, m, *J* 6 Hz, $(H2)_2$. ν_{max} (thin film): 3380 (broad, m, OH) cm^{-1}.

To a solution of (9a) (140 mg, 0·428 mmol) in acetone (5 ml) was added iodomethane (1 ml). The solution was allowed to stand at room temperature for 1 h and then evaporated to dryness. The residue was crystallized from methanol/diethyl ether to afford the *methiodide salt* of (9a) (147 mg, 73%) as colourless needles, m.p. 134–135° (Found: C, 45·9; H, 6·8. $C_{18}H_{32}INO_5$ requires C, 46·1; H, 6·9%). ^{1}H n.m.r. ($CDCl_3$): 7·15, s, ArH; 6·97, s, ArH; 5·39, s, $CH(OCH_3)_2$; 3·97, 3·87, 2s, 2×$ArOCH_3$; 3·90–2·90, m, 9H, includes OH; 3·36, s, 12H, $C(OCH_3)_2$ and $N(CH_3)_2$; 2·25–1·90, m, 2-CH_2. λ_{max} (log ε) 222 (4·31), 280 (3·53), 285sh (3·49); λ_{min} 216 (4·29), 256 nm (3·05).

Hydrolysis of the 1H-2,6-Benzoxazecine (8a) and the Acetal (9a) with Dilute Hydrochloric Acid

The 1*H*-2,6-benzoxazecine (8a) (140 mg, 0·473 mmol) was treated with dilute hydrochloric acid, in the same manner as described[3] for the hydrolysis of the analogous 2,5-benzoxazecine derivative, to afford the aldehyde, *2-[2-(N-3-hydroxypropyl-N-methyl)amino]ethyl-4,5-dimethoxybenzaldehyde* (10) (126 mg, 95%) as an oil. Mass spectrum: *m/e* 281 ($M^{+\bullet}$, accurate mass 281·1633; $C_{15}H_{23}NO_4$ requires $M^{+\bullet}$, 281·1627), 263, 102 ($H_2C{=}N^+(CH_3)CH_2CH_2CH_2OH$). ^{1}H n.m.r. δ ($CDCl_3$): 10·15, s, CHO; 7·35, s, ArH; 6·76, s, ArH; 4·55, s, exchanged with D_2O, OH; 3·98, 3·93, 2s, 2×OCH_3; 3·78, t, *J* 6 Hz, CH_2OH; 3·42–3·00, m, 2H; 2·84–2·55, m, 4H; 2·40, s, NCH_3; 1·75, m, *J* 6 Hz, $(H2)_2$. ν_{max} (thin film): 3380 (broad, m, OH), 1690, 1675 (both s, C=O) cm^{-1}.

To a solution of the aldehyde (10) (113 mg, 0·402 mmol) in acetone (10 ml) was added iodomethane (1 ml). The solution was allowed to stand for 1 h, and then evaporated to dryness. The residue was crystallized from methanol/diethyl ether to afford the *methiodide salt* of (10) (107 mg, 63%) as colourless needles, m.p. 171–172° (Found: C, 45·1; H, 6·0. $C_{16}H_{26}INO_4$ requires C, 45·4; H, 6·2%). ^{1}H n.m.r. δ ($CDCl_3$): 9·90, s, CHO; 7·30, 7·28, 2s, 2×ArH; 4·06, 3·94, 2s, 2×OCH_3; 4·00–2·80, m, 4×CH_2 and OH; 3·33, s, $N(CH_3)_2$; 2·24–1·85, m, 2H.

Treatment of the acetal (9a) (140 mg, 0·428 mmol) with dilute hydrochloric acid as described above also afforded the aldehyde (10) (113 mg, 94%).

Photolysis of the Mixture of Diastereomers of the 2H,6H-[1,3]Oxazino[2,3-a]isoquinolinium Salt (7a) in Methanol

A solution of the mixture of diastereomers of (7a) (419 mg, 1·071 mmol) in methanol (200 ml) was irradiated for 2 h to afford, after the usual workup, the 1*H*-2,6-benzoxazecine derivative (8a) (128 mg, 40%) and the acetal (9a) (130 mg, 37%).

9,10-Dimethoxy-11b-methyl-3,4,7,11b-tetrahydro-2H,6H-[1,3]oxazino[2,3-a]isoquinoline (6b)

To a solution of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (4b) cf.3 (9·93 g, 48·4 mmol) in dry toluene (50 ml) was added 3-bromopropan-1-ol (8·8 g). The mixture was heated to 80° for 12 h. The precipitate which had formed was collected and recrystallized from methanol/ethyl acetate to afford 2-(3-hydroxypropyl)-6,7-dimethoxy-1-methyl-3,4-dihydroisoquinolinium bromide (5b) (9·70 g, 58%), m.p. 203° (lit.[19] 203°).

Treatment of (5b) with 20% aqueous potassium hydroxide gave[19] in 95% yield the title compound (6b) as an oil. ^{1}H n.m.r. δ ($CDCl_3$): 6·93, s, ArH; 6·57, s, ArH; 4·20–1·50, m, 5×CH_2; 3·90, 3·88, 2s, 2×OCH_3; 1·70, s, exchanged with D_2O, 11b-CH_3.

9,10-Dimethoxy-5,11b-dimethyl-3,4,7,11b-tetrahydro-2H,6H-[1,3]oxazino[2,3-a]isoquinolinium Iodide (7b)

Reaction of (6b) with iodomethane as described by Schneider and Kämmerer[19] afforded the methiodide salt (7b), in 58% yield after recrystallization from propan-1-ol/ethyl acetate, m.p. 219–220° (lit.[19] 221°). ^{1}H n.m.r. δ ($CDCl_3$): 6·79, 6·73, 2s, 2×ArH; 4·50–2·90, m, 8H, 2,4,6 and 7-CH_2; 3·93, 3·90, 2s, 2×OCH_3; 3·62, s, NCH_3; 2·80–2·10, m, 1H, H3; 1·93, s, 11b-CH_3; 2·00–1·60, m, 1H, H3. λ_{max} (log ε) 218sh (4·25), 282 (3·51), 287sh (3·49); λ_{min} 257 nm (2·81).

Photolysis of the 2H,6H-[1,3]Oxazino[2,3-a]isoquinolinium Salt (7b) in Methanol

A solution of (7b) (400 mg, 0·987 mmol) in methanol (200 ml) was irradiated for 4 h. The photolysate residue, obtained after the usual workup, was subjected to p.l.c. (chloroform/8% methanol).

Fraction 1 (R_F 0·70) afforded *1,10,11-trimethoxy-1,6-dimethyl-3,4,5,6,7,8-hexahydro-1H-2,6-benzoxazecine* (8b) (147 mg, 48%) as a colourless solid. Recrystallization from light petroleum (b.p. 60–80°) gave colourless needles of (8b), m.p. 103–104° (Found: C, 66·2; H, 8·6; N, 4·5. $C_{17}H_{27}NO_4$ requires C, 66·0; H, 8·8; N, 4·5%). Mass spectrum: *m/e* 309 ($M^{+\bullet}$, accurate mass 309·1955; $C_{17}H_{27}NO_4$ requires $M^{+\bullet}$, 309·1940), 294, 278. ^{1}H n.m.r. δ ($CDCl_3$): 7·30, s, H12; 6·76, s, H9; 3·90, s, 2×OCH_3; 3·70–1·20, m, 10H, 5×CH_2; 3·40, s, 1-OCH_3; 2·17, s, NCH_3; 1·58, s, 1-CH_3.

To a solution of (8b) (100 mg, 0·323 mmol) in dry acetone (10 ml) was added excess iodomethane (1 ml). The solution was allowed to stand at room temperature for 2 h and then evaporated to dryness. The residue was recrystallized from methanol to afford the *methiodide salt* of (8b), (120 mg, 82%) as colourless needles, m.p. 228–229° (dec.) (Found: C, 48·0; H, 6·8. $C_{18}H_{30}INO_4$ requires C, 47·9; H, 6·7%). ^{1}H n.m.r. δ ($CDCl_3$): 7·02, 6·95, 2s, 2×ArH; 4·30–2·80, m, 8H, (H3)$_2$, (H5)$_2$, (H7)$_2$, (H8)$_2$; 3·90, 3·86, 2s, 2×OCH_3; 3·52, 3·39, 2s, $N(CH_3)_2$; 3·19, s, 1-OCH_3; 2·30–2·00, m, (H4)$_2$; 1·52, s, 1-CH_3. λ_{max} (log ε) 232 (4·15), 280 (3·59), 285sh (3·51); λ_{min} 221 (4·10), 255 nm (2·89).

Fraction 2 (R_F 0·40) afforded the crude acetal *3-[N-2-{(4,5-dimethoxy-2-1′,1′-dimethoxyethyl)-phenyl}ethyl-N-methyl]aminopropan-1-ol* (9b) (37 mg, 11%) as an oil, which was subjected twice to further p.l.c. (chloroform/10% methanol) to afford pure (9b) (15 mg) as a colourless oil. Mass spectrum; *m/e* 341 ($M^{+\bullet}$, accurate mass 341·2214; $C_{18}H_{31}NO_5$ requires 341·2202), 326, 310, 102 ($H_2C{=}N^+$-$(CH_3)CH_2CH_2CH_2OH$). ^{1}H n.m.r. δ ($CDCl_3$): 7·12, 6·68, 2s, 2×ArH; 4·44, broad s, exchanged with D_2O, OH; 3·88, s, 2×OCH_3; partly obscured t, *J* 9 Hz, CH_2OH; 3·20, s, $C(OCH_3)_2$; 3·10–2·25, m, $ArCH_2CH_2NCH_2$; 2·39, s, NCH_3; 1·90–1·60, m, (H2)$_2$, 1·56, s, 1-CH_3. ν_{max} (thin film): 3380 (broad, m, OH) cm^{-1}.

Fraction 3 (R_F 0·25) gave unchanged (7b) (93 mg, 23%).

9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro[1,4]oxazino[3,4-a]isoquinoline (14)

The title compound (14) was prepared[21] after a patented method.

To a solution of 2-(3,4-dimethoxyphenyl)ethanamine (21·4 g, 0·118 mol) in dry toluene (100 ml) was added redistilled 2-chloroethanol (9·6 g, 0·119 mol). The mixture was refluxed for 2 h and then allowed to cool. The toluene was decanted from the viscous oil which had separated. This oil was washed with light petroleum (b.p. 40–60°) (100 ml) and treated with 5% sodium hydroxide (100 ml). The emulsion which formed was extracted with chloroform (3 × 50 ml). The dried chloroform extracts were evaporated to afford 2-[*N*-2-(3,4-dimethoxyphenyl)ethyl]aminoethanol which was dissolved in dichloromethane (150 ml) and cooled to 0°. A solution of freshly redistilled chloroacetyl chloride (8 ml, 0·101 mol) in dichloromethane (25 ml) was added dropwise with stirring over 0·5 h. The solution was stirred for a further 0·5 h at 0° and then a solution of sodium hydrogen carbonate (20 g in 100 ml of water) was added. The mixture was allowed to stand at room temperature for 1 h. The organic phase was collected, and washed with 5% hydrochloric acid (2 × 50 ml) followed by water (30 ml), and dried. Evaporation of the dichloromethane gave 2-chloro-{*N*-2(3,4-dimethoxyphenyl)ethyl-*N*-2-hydroxyethyl}ethanamide (11) (26·8 g, 75%) which was dissolved in dry ethanol (100 ml) and added to a solution of sodium ethoxide, prepared by the addition of sodium (6 g, 0·26 g atom) to ethanol (100 ml). The mixture was stirred at room temperature for 12 h, and evaporated to dryness. Water (100 ml) was added and the emulsion extracted with chloroform (2 × 100 ml). The chloroform extracts were washed with 5% hydrochloric acid (2 × 50 ml) followed by water (50 ml), dried and evaporated to afford the amide *N*-2-(3,4-dimethoxyphenyl)ethyl-5,6-dihydro-2*H*,4*H*-1,4-oxazin-3-one (12) (19·0 g, 81%) as a viscous gum. ^{1}H n.m.r. ($CDCl_3$): 6·82, broad s, 3 × ArH; 4·17, s, OCH_2CO; 3·90, s, 2 × OCH_3; 3·85–3·50, m, 4H; 3·30–3·12, m, 2H; 2·98–2·75, m, 2H. ν_{max} (thin film): 1660 (s, C=O) cm^{-1}.

To a solution of the amide (12) (7·5 g, 28·3 mmol) in dry toluene (50 ml) was added phosphorus oxychloride (8 ml). The mixture was refluxed for 2 h, cooled and evaporated under vacuum. The gummy residue was dissolved in 25% aqueous ethanol (100 ml). The stirred solution was taken to pH 6–7 by the addition of solid potassium carbonate, and sodium tetrahydroborate (5 g) was added portionwise. After stirring for 1·5 h the solution was evaporated to dryness. Water (150 ml) was added and the emulsion extracted with diethyl ether (3 × 100 ml). The residue from the dried diethyl ether extracts afforded, after recrystallization (3 times) from diethyl ether, the title compound (14) (1·5 g, 21%), m.p. 118–120° (lit.[21] 118–120°). Mass spectrum: *m/e* 249 (M), 248, 234, 218. ^{1}H n.m.r. δ ($CDCl_3$): 6·63, 6·55, 2s, 2 × ArH; 4·33, d, *J* 7 Hz, H 11b; 3·85, s, 2 × OCH_3; 3·95–2·40, m, 10H, 5 × CH_2.

9,10-Dimethoxy-5-methyl-1,3,4,5,6,7,11b-hexahydro[1,4]oxazino[3,4-a]isoquinolinium Iodide (15)

A solution of (14) (720 mg, 2·89 mmol) in dry acetone (10 ml) was treated with iodomethane (1·5 ml) and allowed to stand at room temperature for 3 h. The precipitate which had formed was recrystallized from methanol/diethyl ether to afford colourless needles of the *methiodide salt* (15), (970 mg, 86%), m.p. 275° (Found: C, 45·9; H, 5·8. $C_{15}H_{22}INO_3$ requires C, 46·0; H, 5·7%). ^{1}H n.m.r. δ (CD_3)$_2$SO): 7·54, s, 2 × ArH; 5·35–3·60, m, 11H; 4·40, s, 2 × OCH_3; 3·77, s, NCH_3. λ_{max} (log ε) 220 (4·26), 283 (3·51), 288sh (3·47); λ_{min} 217 (4·24), 255 nm (2·77).

Photolysis of the [1,4]Oxazino[3,4-a]isoquinolinium Salt (15) in Methanol

A solution of (15) (200 mg, 0·511 mmol) in methanol (100 ml) was irradiated for 4 h. The methanol was evaporated and dilute aqueous ammonia (40 ml; pH 9) was added. The aqueous solution was extracted with diethyl ether (3 × 30 ml). P.l.c. (chloroform/6% methanol) of the residue (80 mg) from the dried diethyl ether extracts gave (R_F 0·50) *1,10,11-trimethoxy-6-methyl-1,4,5,6,7,8-hexahydro-2H-3,6-benzoxazecine* (16a) (39 mg, 26%) as a colourless oil, which crystallized on prolonged standing at 0°. Recrystallization from diethyl ether/light petroleum (b.p. 40–60°) afforded (16a) as colourless prisms, m.p. 58–59° (Found: C, 65·3; H, 8·5; N, 4·4. $C_{16}H_{25}NO_4$ requires C, 65·1; H, 8·6; N, 4·7%). Mass spectrum: *m/e* 295 ($M^{+\bullet}$, accurate mass 295·1787; $C_{16}H_{25}NO_4$ requires $M^{+\bullet}$, 295·1784), 280, 264. ^{1}H n.m.r. (270 MHz) δ ($CDCl_3$): 6·85, s, H 12; 6·63, s, H 9; 4·80, t, *J* 6 Hz, H 1; 3·87, 3·86, 2s, 2 × OCH_3; 3·84, d, *J* 6 Hz, (H 2)$_2$; 3·74–3·57, m, (H 4)$_2$; 3·22, s, 1-OCH_3; 3·08–2·94, m, 1H; 2·88–2·81, m, (H 5)$_2$; 2·72–2·62, m, 2H; 2·30–2·20, m,

1H; 2·25, s, NCH_3. ^{13}C n.m.r. δ ($CDCl_3$): 148·2, C10^A; 147·8, C11^A; 133·0, C8a^B; 130·9, C12a^B; 112·2, C9; 108·4, C12; 79·5, C1; 76·4, C2; 70·5, C4; 59·7, C5; 57·5, C7; 56·4, 1-OCH_3; 55·8, 55·8, 10,11-OCH_3; 44·8, NCH_3, 31·3, C8. λ_{max} (log ε) 232 (3·99), 283 (3·52), 287sh (348); λ_{min} 220 (3·95), 255 nm (2·69).

Iodomethane (1 ml) was added to a solution of (16a) (70 mg, 0·237 mmol) in dry acetone (10 ml). The solution was allowed to stand at room temperature for 1 h and evaporated to dryness. The residue was crystallized from methanol/diethyl ether to afford colourless needles of the *methodide salt* of (16a) (90 mg, 87%), m.p. 219–220° (Found: C, 46·8; H, 6·3; N, 3·2. $C_{17}H_{28}INO_4$ requires C, 46·7; H, 6·5; N, 3·2%). ^1H n.m.r. δ ($CDCl_3$/CD_3OD): 6·87, 6·83, 2s, 2×2ArH; 4·90–4·65, m, H1; 4·20–3·00, m, 10H, 5×CH_2; 3·92, 3·88, 2s, 2×OCH_3; 3·52, 3·42, 2s, $N(CH_3)_2$; 3·34, s, 1-OCH_3.

Some other fractions were also collected: R_F 0·30, 6 mg; R_F 0·40, 16 mg; R_F 0·55, 13 mg; R_F 0·90, 4 mg; however due to the small quantity of material involved, these latter fractions were not investigated.

The aqueous solution from the original photolysate was taken to dryness and the residue extracted with boiling chloroform/20% methanol (3×30 ml). The combined chloroform/methanol extracts were evaporated to afford unchanged (15) (80 mg, 40%).

Photolysis of the [1,4]Oxazino[3,4-a]isoquinolinium Salt (15) in Water

A solution of (15) (350 mg, 0·895 mmol) in water (200 ml) acidified to pH 1–2, by the addition of concentrated sulfuric acid, was irradiated for 1·75 h. The solution was worked up in the same manner as described[2] for the photolysis of (17) in water. P.l.c. (chloroform/10% methanol) of the residue (71 mg) from the first chloroform extract afforded (R_F 0·40) *10,11-dimethoxy-6-methyl-1,4,5,6,-7,8-hexahydro-2H-3,6-benzoxazecin-1-ol* (16b) (33 mg 13%) as a colourless solid. Recrystallization from methanol/diethyl ether gave (16b) as prisms, m.p. 139–140° (Found: C, 63·8; H, 8·3; N, 5·1. $C_{15}H_{23}NO_4$ requires C, 64·0; H, 8·3; N, 5·0%). Mass spectrum: *m/e* 281 (M), 266, 263, 250. ^1H n.m.r. δ ($CDCl_3$): 6·95, s, H12; 6·57, s, H9; 5·20, t, *J* 6 Hz, H1; 4·02, broad s, exchanged with D_2O, OH; 3·85, s, 2×OCH_3; 3·90–3·55, m, $(H2)_2$, $(H4)_2$; 3·00–2·20, m, $(H5)_2$, $(H7)_2$, $(H8)_2$; 2·33, s, NCH_3. ν_{max} ($CHCl_3$): 3400 (broad, m, OH) cm^{-1}.

Many minor products were observed from p.l.c. but these compounds were not investigated. The second chloroform/methanol extract was evaporated to afford unchanged (15) (239 mg, 68%).

In another experiment, a solution of (15) (279 mg, 0·713 mmol) in water (100 ml) at pH 1–2 was irradiated 3 h. Workup as before afforded (16b) (5 mg, 3%) together with unchanged (15) (78 mg, 28%).

5-(3,4-Dimethoxyphenyl)-3,4-dihydro-2H-pyrrole (19)

The title compound (19) was prepared from 4-aminobutanoic acid in 74% yield after the method of Koller and Schlack,[34] m.p. 78° (lit.[34] 89°). ^1H n.m.r. δ ($CDCl_3$): 7·57, d, *J* 2 Hz, H2′; 7·24, dd, J_1 9 Hz, J_2 2 Hz, H6′; 6·85, d, *J* 9 Hz, H5′; 4·15–3·85, m, $(H2)_2$; 3·94, 3·90, 2s, 2×OCH_3; 3·02–3·80, m, $(H4)_2$; 2·00, m, *J* 8 Hz, $(H3)_2$.

7a-(3,4-Dimethoxyphenyl)-2,3,5,6,7,7a-hexahydropyrrolo[2,1-b]oxazole (21)

The imine (19) (1·54 g, 7·54 mmol) was added to a solution of 2-bromoethanol (1·60 g, 12·80 mmol) in dry acetonitrile (8 ml), and the mixture heated to 85° for 7 h. The acetonitrile was evaporated and the residual gum dissolved in a minimum volume of methanol. Addition of ethyl acetate afforded colourless needles of (23), the *hydrobromide salt* of (19), (0·59 g, 27%), m.p. 239–240° (Found: C, 50·3; H, 5·7; Br, 28·2. $C_{12}H_{16}BrNO_2$ requires C, 50·4; H, 5·7; Br, 27·9%). ^1H n.m.r. δ ($CDCl_3$/CD_3OD): 8·05, d, *J* 2 Hz, H2′; 7·65, dd, J_1 8 Hz, J_2 2 Hz, H6′; 7·04, d, *J* 8 Hz, H5′; 4·40–4·15, m, 1H exchanged with D_2O, $(H2)_2$ and NH; 4·07, 4·03, 2s, 2×OCH_3; 3·67–3·45, m, $(H4)_2$; 2·60–2·25, m, $(H3)_2$. ν_{max} (Nujol): 1625 (s, C=N) cm^{-1}.

The residue from the mother liquors was dissolved in water (30 ml). The solution was washed with diethyl ether (3×30 ml), treated with 20% aqueous potassium hydroxide (20 ml) and then extracted with diethyl ether (4×30 ml). The residue from the dried diethyl ether extracts was subjected to p.l.c. (chloroform/3% methanol).

Fraction 1 (R_F 0·55) afforded unchanged (19) (29 mg, 2%).

Fraction 2 (R_F 0·50) afforded the *title compound* (21) (419 mg, 22%) as a colourless oil, which decomposed on prolonged storage at 0°. Mass spectrum: *m/e* 249 ($M^{+\bullet}$, accurate mass 249·1369; $C_{14}H_{19}NO_3$ requires $M^{+\bullet}$, 249·1365), 234, 218, 165. ^{1}H n.m.r. δ ($CDCl_3$): 7·20–7·05, m, H 2′ and H 6′; 6·83, d, *J* 9 Hz, H 5′; 4·10–1·80, m, 10H; 3·92, 3·88, 2s, 2×OCH_3.

7a-(3,4-Dimethoxyphenyl)-4-methyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-b]oxazolium Iodide (22)

A solution of (21) (757 mg, 3·04 mmol) in acetone (5 ml) was treated with iodomethane (about 1 ml) and allowed to stand at room temperature for 12 h. The solvents were evaporated and the residue recrystallized twice from methanol/diethyl ether to afford the *salt* (22) (935 mg, 79%) as colourless granules, m.p. 174–175° (Found: C, 46·2; H, 5·5; I, 32·5. $C_{15}H_{22}INO_3$ requires C, 46·0; H, 5·7; I, 32·4%). ^{1}H n.m.r. δ ($CDCl_3$): 7·45–7·20, m, H 2′ and H 6′; 6·98, d, *J* 8 Hz, H 5′; 4·90–3·60, m, 6H, (H 2)$_2$, (H 3)$_2$, (H 5)$_2$; 4·03, 3·93, 2s, 2×OCH_3; 3·40–2·35, m, (H 6)$_2$, (H 7)$_2$; 3·00, s, NCH_3. λ_{max} methanol (log ε) 240sh (4·10), 280 (3·61), 285sh (3·57); λ_{min} 263 nm (3·28).

Unsuccessful Attempts at the Quaternization of the Imine (19) with 2-Bromoethanol

To a solution of the imine (19) (1 g) in acetone (20 ml) was added 2-bromoethanol (1 ml). The mixture was refluxed for 18 h; only unchanged (19) could be detected by t.l.c. Similarly no quaternization reaction occurred when (19) (1 g) was refluxed with 2-bromoethanol (1 ml) in benzene (20 ml) for 6 h.

The imine (19) (1 g) was refluxed with 2-bromoethanol (1 ml) in butan-2-one (20 ml) for 15 h. The precipitate which had formed was filtered off and recrystallized from methanol/ethyl acetate to afford (23), (410 mg, 29%). Analytical t.l.c. of the filtrate showed the presence of a large amount of unchanged (19), together with a little polar material which was not investigated.

The hydrobromide salt (23) (210 mg, 15%) was also obtained when the imine (19) (1 g) was refluxed with 2-bromoethanol (2 ml) in toluene (20 ml) for 11 h.

Attempted Reaction of the Imine (19) with Oxiran

A solution of (19) (710 mg) in dry methanol (50 ml) and freshly redistilled oxiran (5 g) was allowed to stand at room temperature overnight. Analysis by t.l.c. showed that most of the imine (19) remained unchanged. A trace of polar material was present but was not investigated.

Photolysis of the Pyrrolo[2,1-b]oxazolium Salt Derivative (22) in Methanol

A solution of (22) (400 mg, 1·02 mmol) in methanol (250 ml) was irradiated for 1·25 h. P.l.c. (chloroform/6% methanol) of the photolysate residue obtained after the usual workup, afforded (R_F 0·50) *8-methoxy-4-methyl-8-(3,4-dimethoxyphenyl)-3,4,5,6,7,8-hexahydro-2H-1,4-oxazocine* (24) (268 mg, 89%) as a colourless oil which crystallized on prolonged standing at 0°. Recrystallization from light petroleum (b.p. 40–60°) gave (24) as colourless prisms, m.p. 75–76° (Found: C, 65·2; H, 8·3; N, 4·8. $C_{16}H_{25}NO_4$ requires C, 65·1; H, 8·6; N, 4·7%). Mass spectrum: *m/e* 295 ($M^{+\bullet}$, accurate mass 295·1813; $C_{16}H_{25}NO_4$ requires $M^{+\bullet}$, 295·1783), 280, 264. ^{1}H n.m.r. δ ($CDCl_3$): 7·20–7·05, m, 2ArH; 6·84, d of d, J_1 10 Hz, J_2 4 Hz, (H 6); 4·40–3·40, m, 2-CH_2; 3·92, s, 2×OCH_3; 3·10–0·80, m, 8H; 2·95, s, 8-OCH_3; 2·42, s, NCH_3. ^{13}C n.m.r. δ ($CDCl_3$): see Fig. 3.

A solution of (24) (143 mg, 0·484 mmol) in acetone (5 ml) was treated with iodomethane (1 ml) and allowed to stand at room temperature for 1 h. The solvents were evaporated and the residue crystallized from methanol/diethyl ether to afford the *methiodide salt* of (24) (169 mg, 80%) as fine colourless crystals, m.p. 155–156° (Found: C, 46·3; H, 6·6; I, 28·8. $C_{17}H_{28}INO_4$ requires C, 46·7; H, 6·5; I, 29·0%). ^{1}H n.m.r. δ ($CDCl_3$): 7·13, broad d, *J* 9 Hz, H 5′ or H 6′; 7·02–6·82, m, 2ArH; 4·70–3·30, m, (H 2)$_2$, (H 3)$_2$, (H 5)$_2$; 3·95, 3·92, 2s, 2×OCH_3; 3·70, 3·62, 2 broad s, $N(CH_3)_2$; 2·93, s, 8-OCH_3; 2·70–1·20, m, (H 6)$_2$, (H 7)$_2$. λ_{max} methanol (log ε) 222 (4·31), 278 (3·51), 283sh (3·45); λ_{min} 213 (4·22), 252 nm (2·83).

Hydrolysis of the 2H-1,4-Oxazocine Derivative (24) with Dilute Hydrochloric Acid

The 1,4-oxazocine (24) (125 mg, 0·423 mmol) was added to distilled water (10 ml) acidified by the addition of concentrated hydrochloric acid (1 ml). This solution was stirred at room temperature

for 0·5 h, then basified to pH 9 with concentrated aqueous ammonia and extracted with chloroform (3 × 30 ml). P.l.c. (chloroform/10% methanol) of the residue from the dried and evaporated chloroform extracts gave (R_F 0·65) the ketone derivative *4-(N-2-hydroxyethyl-N-methyl)amino-1-(3,4-dimethoxyphenyl)butan-1-one* (25) (99 mg, 83%) as a pale yellow solid. Recrystallization from methanol/diethyl ether gave (25) as colourless needles, m.p. 83–84° (Found: C, 63·8; H, 8·2; N, 4·9. $C_{15}H_{23}NO_4$ requires C, 64·0; H, 8·3; N, 5·0%). Mass spectrum: *m/e* 281 ($M^{+\bullet}$, accurate mass 281·1646; $C_{15}H_{23}NO_4$ requires $M^{+\bullet}$, 281·1627), 266, 263, 250, 165. ν_{max} ($CHCl_3$): 3400 (s, OH), 1675, 1665 (s, C=O) cm^{-1}. ^1H n.m.r. ($CDCl_3$): 7·70–7·50, m, H 2′, H 6′ 6·91, d, *J* 8 Hz, H 5′; 3·97, s, 6H, 2 × OCH_3; 3·61, t, *J* 5 Hz, CH_2OH; 2·98, t, *J* 6 Hz, 2H; 3·03, broad s, 1H, exchanged with D_2O, OH; 2·65–2·40, m, 4H; 2·27, s, NCH_3; 1·94, m, *J* 6 Hz, $(H3)_2$. λ_{max} (methanol) (log ε) 228 (4·30), 273 (4·11), 303 (3·97); λ_{min} 215 (4·02), 244 (3·30), 290 nm (3·92).

Acknowledgments

A grant in support of this work from the Australian Research Grants Committee, and a Commonwealth Postgraduate Research Award (to K.N.W.) are gratefully acknowledged. We thank the Upjohn Company (Kalamazoo, Michigan, U.S.A.) for their support, and Mr J. C. Bignall and Mr M. Power (Central Science Laboratory University of Tasmania) for the determination of the mass spectra, and Dr A. J. Jones (of the former National N.M.R. Centre, Canberra) for the measurement of ^1H n.m.r. and ^{13}C n.m.r. spectra.

Manuscript rceived 18 March 1985