ACRIDONE STUDIES

XI.* REACTION OF SOME POLYALKOXY-10-METHYLACRIDONES WITH SODIUM METHOXIDE IN METHANOL AND IN DIMETHYL SULPHOXIDE

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Abstract

The isomeric dimethoxymethylenedioxy-10-methylacridones react with sodium methoxide in methanol to give a number of products which have been characterized. Substitution occurs on both the aromatic nucleus and the methylene group. In dimethyl sulphoxide opening of the methylenedioxy ring occurs exclusively and the rates and activation parameters of this reaction have been measured.

INTRODUCTION

In previous Parts of this series we have been concerned with product and rate studies of the four isomeric bromo-10-methylacridones with potassamide, lithium piperidide, piperidine, and sodium methoxide in methanol and in dimethyl sulphoxide,[1,2] and have shown that these compounds show a diversity of reaction pathways. Since most of the information on nucleophilic substitution of acridones prior to our work has been gained during the structural elucidation of the acridone alkaloids by Crow and Price,[3] we have now returned to these compounds for a more detailed investigation. In this paper we report the rates of reaction of the isomeric dimethoxymethylenedioxy-10-methylacridones (1), (2), and (3) with sodium methoxide, and describe the products obtained from these compounds on reaction with sodium methoxide in methanol. As in the case of the simple bromo-10-methylacridones,[2] the products from the reaction were found to depend on the solvent used.

In their elucidation of the structures of the acridone alkaloids, Crow and Price[3] found that melicopidine (1) and melicopine (2) reacted with alcoholic potassium hydroxide to open the methylenedioxy ring giving the phenols (4) and (5) respectively.

These reactions would appear to be addition–elimination substitutions via the intermediates of Scheme 1 and since the loss of formaldehyde from the intermediate would be expected to have a lower activation energy than the reverse process, loss

* Part X, *Aust. J. Chem.*, 1972, **25**, 585.

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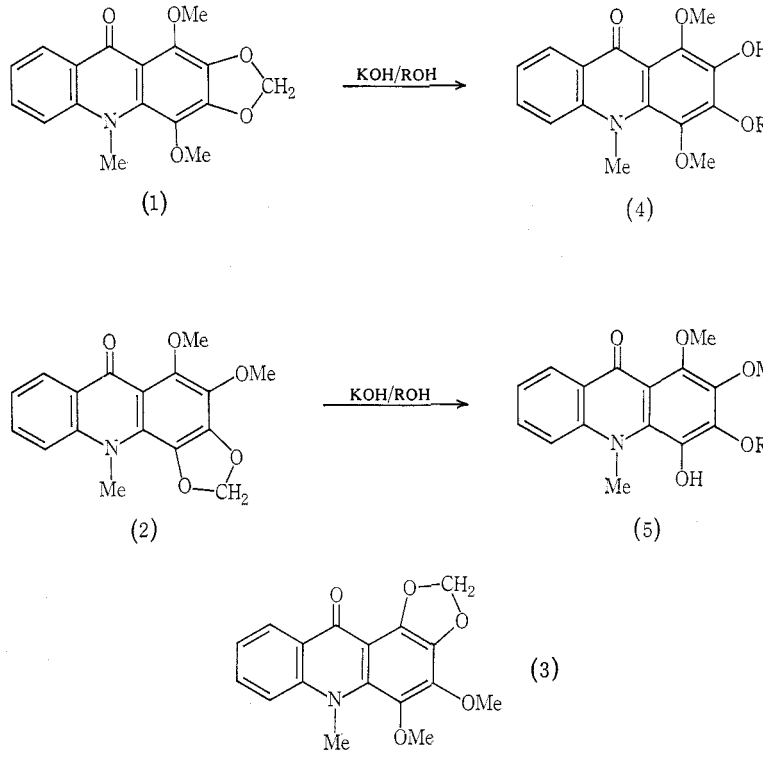
[1] Gream, G. E., Hodgeman, D. K. C., and Prager, R. H., *Aust. J. Chem.*, 1972, **25**, 569.

[2] Hodgeman, D. K. C., and Prager, R. H., *Aust. J. Chem.*, 1972, **25**, 585.

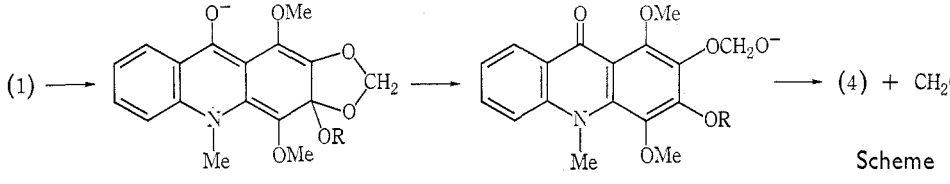
[3] Crow, W. D., and Price, J. R., *Aust. J. scient. Res.* (*A*), 1949, **2**, 255.

of methoxide ion, the first step should be rate determining and the overall reaction should follow second-order kinetics.



(1) (4) (2) (5) (3)

The reactions of the methylenedioxyacridones with sodium methoxide in refluxing methanol were first examined. The 1,2-methylenedioxy isomer (3) has not been previously described, but was easily prepared in two steps from compound (4; R = CH_3). Reaction in all cases was very slow and only in the case of melicopidine (1) was ring opening of the methylenedioxy group by the expected process the principal reaction. The reaction of melicopidine (1) occurs somewhat faster than that of melicopine (2) or (3), which is consistent with the work of Crow and Price.[3] Compounds (2) and (3) gave a complex mixture of products which are now described.

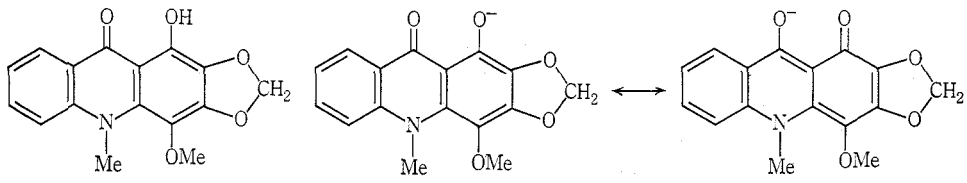


Scheme 1

Discussion

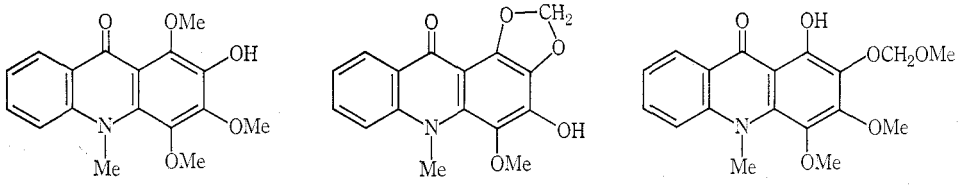
Melicopidine (1) reacted with 1·0M sodium methoxide in boiling methanol giving a 97% yield of the phenol (4; R = CH_3), together with 3% normelicopidine (6). The latter compound probably arises from the attack of methoxide ion on the

methoxyl carbon in the 1-position to yield the resonance stabilized anion (7), the negative charge on which prevents further attack on the methylenedioxy ring.

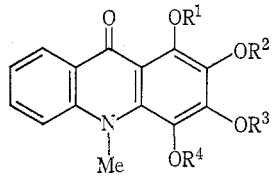


(6) (7)

3,4-Dimethoxy-1,2-methylenedioxy-10-methylacridone (3) reacted with 1·0M sodium methoxide in boiling methanol very slowly, and after 14 days 3% of starting material remained. Three products were separated by preparative thin-layer chromatography. The expected product (8) was obtained in 39% yield, together with the unexpected compounds (9) (25%) and (10) (13%).



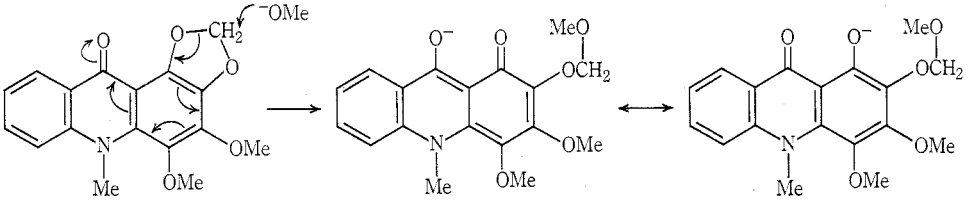
(8) (9) (10)



	R^1	R^2	R^3	R^4
(11)	Me	Me	H	Me
(12)	Me	H	Me	Me
(13)	Me	Me	Me	H
(14)	H	Me	Me	Me

The phenol (9) was identified from its mass spectrum, and by reformation of (3) on methylation with diazomethane. This evidence does not distinguish between (9) and the less likely 4-hydroxy-3-methoxy isomer, but the structure was shown to be (9) unequivocally by its spectral data. The ultraviolet spectrum of (9) showed similar changes in neutral and alkaline solution to compound (11); in particular a hypsochromic shift and increase in intensity of the long-wavelength band was observed on transferring to alkaline solution. The u.v. spectra of the 2- and 4-hydroxyacridones (12) and (13) showed totally different changes in alkaline solution. Further evidence for the position of the hydroxyl group in (9) was obtained from the mass spectrum of the 3,4-dimethoxy-1,2-methylenedioxy-10-methylacridone obtained on methylation with dideuterodiazomethane. The mass spectrum showed specific loss of CH_3 rather than CD_3. Since the molecular ions of methoxy-10-methylacridones preferentially lose methyl radical from the 2- or 4-position[4] methylation must have occurred in the 3-position.

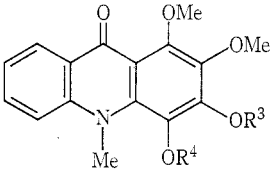
The structure of compound (10) was determined from its u.v., n.m.r., and mass spectra, and confirmed by synthesis. It had the same chromatographic properties as normelicopicine (14), and in particular, the lack of fluorescence is characteristic of a 1-hydroxyacridone. In addition, the u.v. spectra of (10) in neutral and alkaline solution were identical with those of (14) under the same conditions. The n.m.r. spectrum of (10) clearly showed the four methyl groups on oxygen or nitrogen and the methylenedioxy group. The 1-hydroxyl group resonated at δ 14·5. The mass spectrum showed the molecular ion at *m/e* 345 and the base peak at *m/e* 300 which is consistent with the loss of the CH_2OCH_3 radical from the 2-position of the acridone



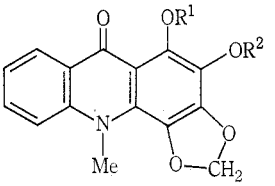
Scheme 2

nucleus. Compound (10) clearly arises by attack of methoxide ion on the methylenedioxy carbon (Scheme 2). It is interesting to note that with methoxide attack on (3), S_N2 displacement on alkyl ethers occurs to the same extent as the more common addition to the aryl ring followed by elimination. Ring opening of methylenedioxy groups in this manner is usually confined to substrates which are not activated towards nucleophilic attack on aromatic carbon.[5,6]

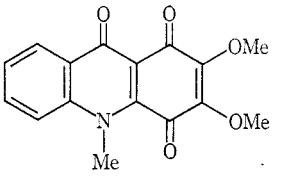
Melicopine (2) reacts with sodium methoxide in methanol more slowly than the other two isomers and the reaction results in a mixture of products even more complex than those obtained from (3). The principal product is the anticipated phenol (15), but a considerable amount of material, a mixture of several products,



	R^3	R^4
(15)	Me	H
(18)	H	OCH_2OMe



	R^1	R^2
(16)	H	Me
(17)	Me	H



(19)

remains unidentified. Among the minor products of the reaction were normelicopine (16), 2-hydroxy-1-methoxy-3,4-methylenedioxy-10-methylacridone (17), 3-hydroxy-1,2-dimethoxy-4-(α-methoxy)methoxy-10-methylacridone (18), and the quinone (19).

[4] Bowie, J. H., Cooks, R. G., Prager, R. H., and Thredgold, H. M., *Aust. J. Chem.*, 1967, **20**, 1179.

[5] Stockelbach, F. E., U.S. Pat. 1,792,716 (*Chem. Abstr.*, 1931, **25**, 2154).

[6] Ono, K., and Imoto, M., *J. chem. Soc. Japan*, 1938, **59**, 359.

The latter compound (19) appears to come from the phenol (15) during separation by t.l.c. on silica gel, the rates of demethylation and oxygenation being enhanced in the presence of silica (see[7] for similar silica-induced reactions). The 2-hydroxy compound (17), which was identified by its mass spectrum, gave melicopine on methylation with diazomethane, and the melicopine formed on methylation with dideuterodiazomethane showed specific loss of the CD_3 radical indicating that methylation had occurred in the 2-position.[4] This product is the first we have encountered resulting from attack at a methyl group unactivated by resonance effects of the carbonyl group; presumably inductive activation by the other electron-withdrawing groups is sufficient.

The compound (18) was identified from its mass spectrum, which showed a large fragment ion corresponding to the loss of the fragment CH_2OCH_3.[4] Again, as in the formation of (12), methylenedioxy ring opening occurs in the sense assisted by the carbonyl group.

The large number of products formed in the reactions of (2) and (3) in methanol prevented determination of the rates of methylenedioxy ring opening for these compounds in methanol. For melicopidine (1), the second-order rate constant for ring opening of the methylenedioxy group at 65° was found to be $4{\cdot}0\times10^{-6}$ l. mol^{-1} s^{-1}.

When these reactions were carried out in dimethyl sulphoxide as solvent, the reactions in all cases were clean, and the products were almost entirely the expected phenols (8) and (15). The rates of methylenedioxy ring opening of (1), (2), and (3) were therefore measured in this system and are recorded in Table 1.

TABLE 1

SECOND-ORDER RATE CONSTANTS FOR REACTION OF DIMETHOXYMETHYLENEDIOXY-10-METHYLACRIDONES WITH SODIUM METHOXIDE IN DIMETHYL SULPHOXIDE

[NaOMe] varied between 0·046M and 0·305M. k determined for rate of disappearance of starting material (405 nm) or rate of appearance of product (492 nm)

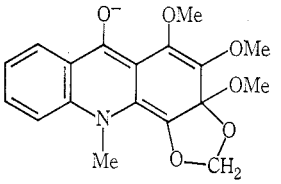
Compound	T (K)	k (l. mol^{-1} s^{-1})	$\Delta H\ddagger$ (kJ mol^{-1})	$\Delta S\ddagger$ (J K^{-1} mol^{-1})	Compound	T (K)	k (l. mol^{-1} s^{-1})
(1)	293·8	$1{\cdot}80\times10^{-2}$	38·5±3·0	113±8	(1)	303·0	$3{\cdot}19\times10^{-2}$
(2)	293·8	$5{\cdot}24\times10^{-3}$	47·4±3·2	96±8	(2)	303·0	$1{\cdot}06\times10^{-2}$
(3)	293·8	$1{\cdot}23\times10^{-2}$			(8)	303·0	$4{\cdot}45\times10^{-4}$

There is seen to be a rate enhancement of approximately 10^4 on transferring the reaction with melicopidine from methanol to dimethyl sulphoxide. This is consistent with previous observations for anion–neutral molecule reactions in dipolar aprotic solvents.[8] In dimethyl sulphoxide the product (8) was observed to react with sodium methoxide at a measurable rate, but the nature of this reaction has not been investigated as it was observed the product contained at least three components.

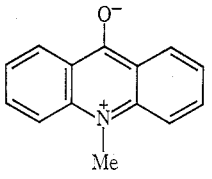
Reaction of the methylenedioxyacridones with methoxide ion is a two-step process in which the first step is expected to be rate-determining, and since formation of the intermediates (e.g. (20)) is an endothermic process, the transition states for these reactions will closely resemble the respective intermediate.[9] It is possible to

[7] Joshi, V. S., Damodaram, N. P., and Dev, S., *Tetrahedron*, 1971, **27**, 475.
[8] Parker, A. J., *Chem. Rev.*, 1969, **69**, 1.
[9] Hammond, G. S., *J. Am. chem. Soc.*, 1955, **77**, 334.

rationalize the observed differences in rate in terms of electronic activation effects and in terms of the geometry of the transition states. Since reaction of methoxide with (1) and (2) both involve nucleophilic attack at C3, it is necessary to look for



(20)



(21)

factors other than electronic ones which may affect the rate of formation of the intermediate. It is possible to rationalize the slow rate of reaction of (2) compared with that of (1) in terms of the carbon–carbon bond lengths in the benzenoid ring of the acridone nucleus. There is considerable evidence that a significant proportion of the acridinium canonical form (21) contributes to the structure of acridone[10] so that acridone would be expected to exhibit similar bond fixation to that occurring in acridine. The bond lengths of acridine have been measured,[11] and it has been found that the C1–C2 and C3–C4 bonds are somewhat shorter than the C2–C3 bond. In addition, Hückel molecular orbital calculations[12] have shown the C1–C2 and C3–C4 bonds of acridone have a higher bond order than the C2–C3 bond. Examination of Dreiding molecular models shows the five-membered methylenedioxy ring to be considerably strained and, furthermore, shows this strain should decrease as the carbon–carbon bond of the five-membered ring is shortened. Melicopine (2) will therefore have a lower ground-state energy than melicopidine (1). The strain energy of the methylenedioxy rings will be the same in both intermediates, and nearly the same in both transition states. This will result in a higher activation energy for melicopine than for melicopidine. Unfortunately, the experimental enthalpies of activation, shown in Table 1, are too similar for any definite conclusions to be drawn. It is pertinent to comment on the difficulty experienced in measuring the rate constants, which were extremely sensitive to the quality of the sodium methoxide solution used. Even when reagents were prepared in the same way using anhydrous reagents in the absence of oxygen, the base reagent had to be discarded after several hours, as the rate was considerably reduced by traces of oxygen or moisture. The values in Table 1 were all recorded with the same stock solution.

The ground state energies of the isomers (2) and (3) are expected to be very nearly the same and the changes in ring strain on formation of the transition state will be essentially the same for both compounds. The observed difference in reaction rate of these compounds must, therefore, reflect the difference in electronic activation effects of the carbonyl and alkoxyl groups on addition–elimination substitution by methoxide ion in the 1- and 3-positions of the dimethoxymethylenedioxy-10-methylacridones. The results indicate that with alkoxy leaving groups, substitution occurs

[10] Albert, A., "The Acridines." p. 184. (Arnold: London 1966.)
[11] Phillips, D. C., *Acta crystallogr.*, 1956, **9**, 237.
[12] Roney, B. D., unpublished data.

faster in the 1-position than in the 3-position, the reverse of that found with the bromo-10-methylacridones.[2] This observation is being investigated in greater detail.

Experimental

(*a*) *Reagents and Starting Material*

General experimental details have been given previously.[2,13] Light petroleum refers to a fraction of b.p. 55–65°. Methanol and dimethyl sulphoxide were purified by the manner previously described.[2] N.m.r. spectra were obtained on a Varian T60 instrument in $CDCl_3$ with TMS as internal standard.

3,4-Dimethoxy-1,2-methylenedioxy-10-methylacridone

A mixture of 1,2-dihydroxy-3,4-dimethoxy-10-methylacridone[3] (1·5 g), diiodomethane (10 ml), and anhydrous potassium carbonate (2·0 g) was heated under reflux in acetone (50 ml) for 24 hr. The solution was concentrated, water was added, and the mixture was extracted with chloroform. Column chromatography on silica gel, eluting with chloroform, gave 3,4-dimethoxy-1,2-methylenedioxy-10-methylacridone (0·80 g, 51%), m.p. 217·5–223·5° (from acetone). Sublimation at 210°/0·01 mm gave yellow *crystals*, m.p. 219–221° (Found: C, 65·4; H, 4·8; N, 4·4. $C_{17}H_{15}NO_5$ requires C, 65·2; H, 4·8; N, 4·5%). The mass spectrum included peaks at *m/e* 313 (76%) (M^+), 298 (100) (M^+-CH_3), and 178 (28). N.m.r. spectrum: three s, each 3, 3·75, 3·92, and 4·20, (NCH_3 and two OCH_3); s, 2, 6·18, (OCH_2O); m, 3, 7·0–7·8, (H 5, H 6, H 7); d of d, 1, 8·38, (H 8), 7 Hz, 2 Hz.

(*b*) *Reactions of the Dimethoxymethylenedioxy-10-methylacridones with Sodium Methoxide in Methanol*

(i) *3,4-Dimethoxy-1,2-methylenedioxy-10-methylacridone* (*3*)

3,4-Dimethoxy-1,2-methylenedioxy-10-methylacridone (246 mg) in 1·0M sodium methoxide in methanol (20 ml) was gently refluxed under an atmosphere of nitrogen on a water-bath for 14 days; thin-layer chromatography showed that only trace amounts of starting material remained. Solvent was removed and the residue acidified and extracted with chloroform. The products were separated by thick-layer chromatography on silica gel; developing solvent was benzene–ethyl acetate (2 : 1). Four orange or yellow bands separated and are described in order of decreasing R_F.

(A) *1-Hydroxy-3,4-dimethoxy-2-(α-methoxy)methoxy-10-methylacridone* (10) (36 mg, 13%), m.p. 100–102° (from chloroform–light petroleum) (Found: C, 62·8; H, 5·5; N, 3·9. $C_{18}H_{19}NO_6$ requires C, 62·6; H, 5·6; N, 4·0%). U.v. spectrum (in 95% ethanol): λ_{max} (neutral solution) 249, 273, 309, 419; (alkaline solution) 252, 275, 322, 433 nm. The mass spectrum included peaks at *m/e* 345 (25%) (M^+) and 300 (100) with a metastable ion at *m/e* 261. N.m.r. spectrum: four s, each 3, 3·67, 3·75, 4·05, and 4·15 (NCH_3 and three OCH_3); s, 2, 5·24, (OCH_2O); m, 3, 7·0–7·9, (H 5, H 6, H 7); d of d, 1, 8·40, (H 8), 7 Hz, 2 Hz; s, 1, 14·5, (OH, exchanged with D_2O). Methylation of this compound with diazomethane overnight in ether–methanol gave a non-crystalline oil identical (by thin-layer chromatography and i.r. spectrum) with a sample of 1,3,4-trimethoxy-2-(α-methoxy)methoxy-10-methylacridone prepared from 2-hydroxy-1,3,4-trimethoxy-10-methylacridone and chlorodimethyl ether; n.m.r. spectrum: five s, each 3, 3·56, 3·73, 3·85, 3·90, and 4·00 (NCH_3 and four OCH_3); s, 2, 5·05, (OCH_2O); m, 3, 6·9–7·7, (H 5, H 6, H 7); d of d, 1, 8·17, (H 8), 8 Hz, 2 Hz.

Attempts to synthesize (10) by selective demethylation of this synthetic ether by BCl_3 or alcoholic HCl were not completely satisfactory. With HCl, even for short periods, the products were (12) and 1,2-dihydroxy-3,4-dimethoxy-10-methylacridone[3] in the ratio of *c.* 1 : 2. BCl_3 yielded mainly the latter compound, but the neutral fraction (20%) contained four compounds of which the first eluted from silica was (10) (11% overall), identical with the sample above.

(B) 3,4-Dimethoxy-1,2-methylenedioxy-10-methylacridone (3) (7 mg, 3%), m.p. and mixed m.p. 220–221°.

[13] Prager, R. H., and Thredgold, H. M., *Aust. J. Chem.*, 1968, **21**, 229.

(C) 2-Hydroxy-1,3,4-trimethoxy-10-methylacridone (12) (95 mg, 39%), m.p. and mixed m.p. 170–171°.

(D) 3-Hydroxy-4-methoxy-1,2-methylenedioxy-10-methylacridone (9) (59 mg, 25%), m.p. 244–246° (from aqueous ethanol). The mass spectrum included peaks at *m/e* 299 (63%) (M^+), 284 (100) ($M^+ - CH_3$), and 254 (24) with metastable ions at *m/e* 270 and 230. U.v. spectrum (in 95% ethanol): λ_{max} (log ϵ) (neutral solution) 280 (4·52), 418 nm (3·65); (alkaline solution) 252 (4·40), 289 (4·37), 370 nm (4·04). Methylation with dideuterodiazomethane gave deuterated 3,4-dimethoxy-1,2-methylenedioxy-10-methylacridone, m.p. and mixed m.p. 217–218°; the mass spectrum included peaks at *m/e* 316 (58%), 315 (73), 314 (69), 301 (74), 300 (100), and 299 (100).

(ii) *Melicopidine (1)*

Melicopidine (986 mg) was heated under reflux in 1·0M sodium methoxide in methanol (50 ml) for 6 days and worked up as described above. Separation by thick-layer chromatography on silica gel (benzene–ethyl acetate, 2 : 1) gave normelicopidine (6) (28 mg, 3%), m.p. and mixed m.p. 211–212°, and 2-hydroxy-1,3,4-trimethoxy-10-methylacridone (8) (960 mg, 97%), m.p. and mixed m.p. 170–171°.

(iii) *Melicopine (2)*

Melicopine (1·05 g) was refluxed under nitrogen in 1·0M sodium methoxide in methanol for 14 days and was worked up as described above. The crude product (1·16 g) was separated into its constituents by repeated thick-layer chromatography on silica gel developing with benzene–ethyl acetate (2 : 1). All products present were isolated and are described in order of decreasing R_F.

(A) Normelicopine (16) (65 mg, 6%), m.p. and mixed m.p. 234–235°.

(B) Melicopine (2) (45 mg, 4%), m.p. and mixed m.p. 176–178°.

(C) 4-Hydroxy-1,2,3-trimethoxy-10-methylacridone (15) (410 mg, 39%), identical with a sample prepared by the method of Crow and Price.[3]

(D) An unidentified fraction (380 mg) which appeared to be a mixture of several compounds.

(E) A further unidentified product (15 mg). The mass spectrum of this compound included peaks at *m/e* 322 (21%), 321 (88), 307 (30), 306 (100), 292 (37), and 262 (31).

(F) 3-Hydroxy-1,2-dimethoxy-4-(α-methoxy)methoxy-10-methylacridone (18) (15 mg, 1·3%) m.p. 60°. The mass spectrum of this compound included peaks at *m/e* 345 (33%) and 300 (100) with a metastable ion at *m/e* 261.

(G) 2-Hydroxy-1-methoxy-3,4-methylenedioxy-10-methylacridone (17) (25 mg, 2·4%) as bright yellow, fluorescing needles, m.p. 228–232°. The mass spectrum of this compound included peaks at *m/e* 299 (100%), 284 (55), 281 (90), 280 (47), 270 (17), 256 (15), 254 (31), and 252 (22) (Found *m/e* 299·079604. $C_{16}H_{13}NO_5$ requires 299·079365). Methylation of this compound with dideuterodiazomethane gave melicopine, m.p. 178°, (identical by thin-layer chromatography) the mass spectrum of which included peaks at *m/e* 316 (20%), 315 (30), 314 (41), 313 (32), and 298 (100).

(H) 2,3-Dimethoxy-10-methylacridone-1,4-quinone (19), (55 mg, 5·5%), m.p. and mixed m.p. 200–201°.

(c) Kinetics of Reaction of Melicopidine with Sodium Methoxide in Methanol

A solution of melicopidine (250 mg, 0·800 mmol) in 1·00M sodium methoxide in methanol (25 ml) was maintained at 65° under nitrogen. Samples (5 ml) were removed after 2·5, 6·75, 13·8, 23·2, and 30·6 hr and the reaction was quenched with dilute hydrochloric acid. The product was extracted with chloroform, the extract evaporated, and the residue dissolved in deuterochloroform (0·7 ml). The reaction was followed by n.m.r. spectroscopy by comparison of the integrated intensities of the methylenedioxy resonance (a singlet at δ 6·1) and the H 8 resonance (a doublet at 8·4) which is present in both melicopidine and in the product, 2-hydroxy-1,3,4-trimethoxy-10-methylacridone. From this ratio the concentration of melicopidine in the reaction mixture was determined and the pseudo-first order rate constant[14] obtained.

[14] Frost, A. A., and Pearson, R. G., "Kinetics and Mechanism." 2nd Edn, p. 13. (Wiley: New York 1961.)

(d) Kinetics of the Reactions of the Dimethoxymethylenedioxy-10-methylacridones with Sodium Methoxide in Dimethyl Sulphoxide

The kinetics were measured spectrophotometrically in a Unicam SP700 spectrophotometer equipped with a thermostated cell housing, and following the disappearance of the starting material at 405 nm or the appearance of product at 492 nm. The reaction was initiated by injecting a solution of the acridone in dimethyl sulphoxide (30 μl) into the sample cell containing sodium methoxide in dimethyl sulphoxide (2·6 ml; *c.* 0·09M). Rate constants were determined graphically from a plot of $\ln [(A_\infty - A_0)/(A_\infty - A_t)]$ against time. Duplicate runs were reproducible to within 5%. Beer's law was obeyed by all starting materials and products over the concentration range used.

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