ACRIDONE STUDIES

XII.* RELATIVE RATES OF REACTION OF SODIUM METHOXIDE WITH 1,2,3,4-TETRAMETHOXY-10-METHYLACRIDONE

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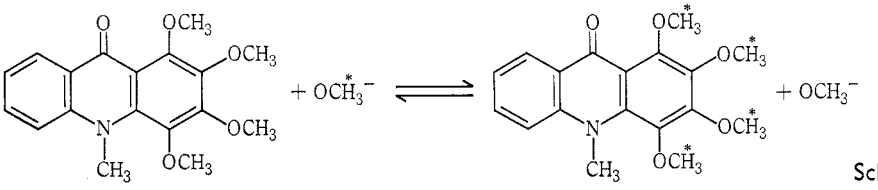
Abstract

The relative and absolute rates of exchange of the four methoxyl groups in 1,2,3,4-tetramethoxy-10-methylacridone (melicopicine) have been measured at 50°. The reaction at C 1 is more than 15 times faster than at C 3. These rates of reaction are compared with those of 1,4-dimethoxy-10-methyl-2,3-methylenedioxyacridone (melicopidine), and suggestions made to account for the differences.

Introduction

In previous parts of this series we have shown that C 1 and C 3 of 10-methylacridones are activated towards nucleophilic reagents. In simple bromo-substituted acridones C 1 is more reactive than C 3 towards amines,[1] but C 3 is more reactive towards sodium methoxide.[2] In the more highly substituted tetraalkoxyacridones, reaction appears to be faster at C 1 than at C 3.[3] To investigate this phenomenon further, and to avoid the complication introduced by differences in ground state energies and different leaving groups, we have investigated the rates of exchange of the four methoxyl groups in melicopicine (1,2,3,4-tetramethoxy-10-methylacridone), (1). The reagent used was sodium [T]methoxide (CH_2TONa), initially in dimethyl sulphoxide at 40°, conditions similar to those used to measure the rate of reaction of the methylenedioxy derivatives with sodium methoxide.[3] Under these conditions, however, the exchange reaction was found to be too fast to follow by standard sampling techniques, equilibrium (Scheme 1) being established in less than 2 min.



Scheme 1

As expected, the rate of methoxide exchange could be slowed to a measurable rate by performing the reaction in a mixture of dimethyl sulphoxide and methanol.[4]

* Part XI, *Aust. J. Chem.*, 1972, **25**, 1751.

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

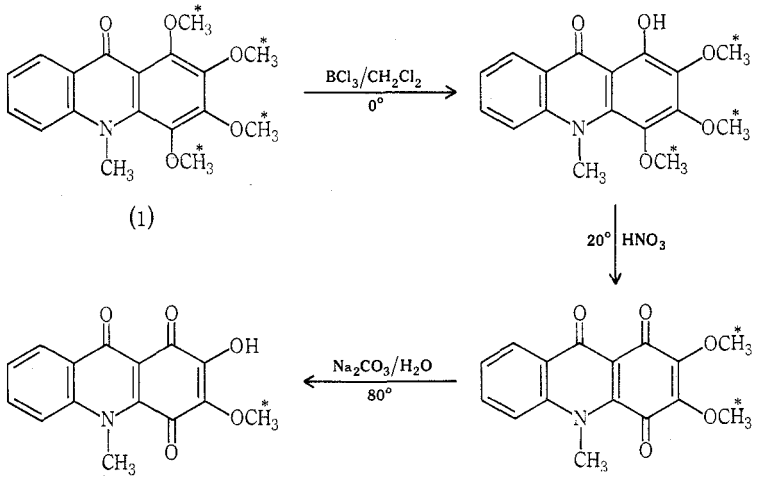
[2] Hodgeman, D. K. C., and Prager, R. H., *Aust. J. Chem.*, 1972, **25**, 585.

[3] Hodgeman, D. K. C., and Prager, R. H., *Aust. J. Chem.*, 1972, **25**, 1751.

[4] Parker, A. J., *Chem. Rev.*, 1969, **69**, 1.

Discussion

The second-order rate constant for the overall exchange process was measured at 50°, and the individual rate constants for exchange at each of the methoxyl groups have been determined by degradation. The degradation is outlined in Scheme 2, and the results are reported in Table 1. It is assumed that exchange at each site in (1) is of the same kinetic order.



(1)

Scheme 2

Table 1

SECOND-ORDER RATE CONSTANTS FOR OMe EXCHANGE IN MELICOPICINE WITH MeONa (In Me_2SO–MeOH 5 : 1 at 50°)

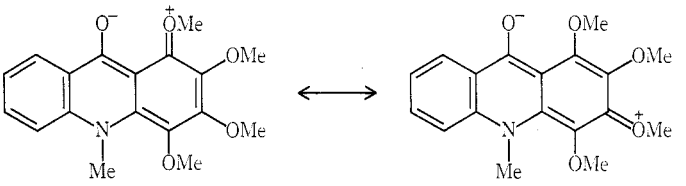
Methoxyl group	1-OMe	2-OMe	3-OMe	4-OMe
10^4k (l. mol^{-1} s^{-1})	55	0·67	3·6	0·96

The rate of exchange of the methoxyl groups of melicopicine is seen to be in the relative order $1 \gg 3 > 4 > 2$. Again, with polyalkoxy substituents,[3] substitution is found to occur faster in the 1-position than the 3-position. Assuming that activation for substitution is due to the carbonyl group, bromoacridones have an $o : p$ rate ratio towards methoxide of less than one,[2] and the polyalkoxyacridones have an $o : p$ rate ratio of greater than one. A similar change from an *ortho* : *para* ratio of less than 1 to a ratio of greater than 1 has been observed and discussed by Bamkole and Hirst[5] in relation to the rate of reaction of 2,4-difluoronitrobenzene with sodium methoxide.

In the present context it is possible to rationalize this reversal in $o : p$ rate ratio for the alkoxy compounds in terms of resonance involving the canonical forms (1a) and (1b), in which the positive charge is partly distributed in the 1- and 3-methoxyl groups. With the larger, less electron-releasing bromine atom this resonance occurs to a much smaller extent. Since the canonical form (1a) involves a much smaller

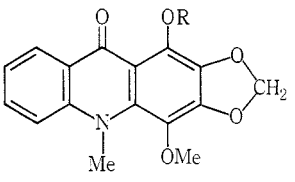
[5] Bamkole, T. O., and Hirst, J., *Chem. Commun.*, 1971, 69.

physical separation of charges than does (1b) it might be argued that the former would contribute to a greater degree to the overall structure. This would favour nucleophilic substitution in the 1-position in the alkoxy-10-methylacridones.

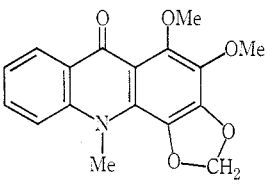


(1a) (1b)

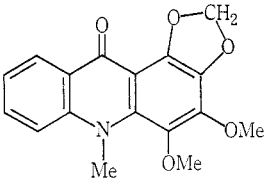
The difference in the relative rates of substitution between the 1- and 3-positions (*c.* 15) in methoxyl exchange is considerably greater than the relative rates of ring opening in the compounds (4) and (3) (*c.* 2·5) or (4) and (2) (*c.* 0·7). Since the latter



(2) R = Me (5) R = H



(3)



(4)

rates were measured only in dimethyl sulphoxide and involve a different leaving group, the rates of methoxyl exchange in melicopidine (2) and melicopicine (1) have been compared under the conditions of Table 1. The relative rates of exchange at C1 and C4 in melicopidine were determined by comparing the radioactivity of labelled melicopidine (2) and normelicopidine (5). The rate constants calculated for methoxyl exchange at C1 and C4 in (2), estimated from competition experiments with (1), and the rate of opening of the methylenedioxy ring, obtained by conventional methods, are listed in Table 2.

TABLE 2

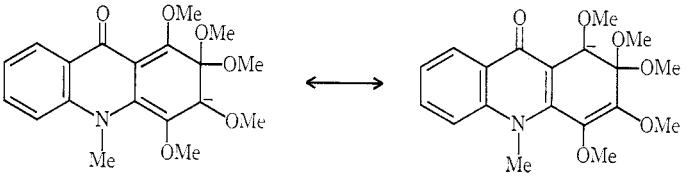
RATE CONSTANTS FOR OMe EXCHANGE AT C 1 AND C 4 AND OCH_2O RING OPENING IN (2)

(In Me_2SO–MeOH 5 : 1 at 50°)

Reaction site	1-OMe	4-OMe	3-OCH_2O
10^4k (l. mol^{-1} s^{-1})	20	2·2	30·3

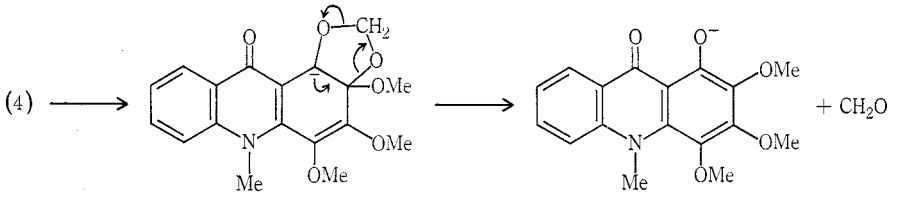
It can be seen that although the rate of exchange of the 1-methoxyl group is of the same order in (1) and (2), there is a considerable difference in the rate of reaction at C3, the methylenedioxy group being replaced almost ten times as easily as the methoxyl group. We suggest that this is a consequence of the higher ground-state energy of (2), resulting in a decrease in the activation energy for reaction at C3, but not at C1. It is interesting to speculate that the increase of reactivity of the

4-methoxyl group in (2) compared with that in (1) may be a consequence of the polarization of the σ electrons away from C4, a consequence of the strain in the methylenedioxy ring.[6] Methoxyl exchange at the 2- and 4-positions of (1), and at the 4-position of (2), is unexpected, as the intermediates (cf. (6)) are stabilized only inductively.



(6)

No evidence was found[3] for a similar reaction of sodium methoxide at the unactivated position of the methylenedioxy ring of the methylenedioxyacridones in dimethyl sulphoxide or methanol. This would proceed, in the case of (4), to give normelicopicine (from (7)).



(7)

Experimental

General experimental details have been given previously.[2] Light petroleum refers to a fraction of b.p. 55–65°. Radioactive samples were counted on a Packard Tri-Carb 2003 liquid scintillation spectrometer.

Rate of Methoxide Exchange of Melicopicine (1) with Sodium Methoxide

(A) *In dimethyl sulphoxide.*—Tritium-labelled sodium methoxide[7] was prepared from sodium and tritium-labelled methanol, CH_2TOH (approx. 1·3 mCi/mmol). A solution of labelled sodium methoxide in methanol-free dimethyl sulphoxide was prepared essentially as described previously.[2]

Tritiated sodium methoxide in dimethyl sulphoxide (50 ml of 0·0021M solution, 0·11 mmol) was added to melicopicine (21·8 mg, 0·066 mmol) in dimethyl sulphoxide (3·0 ml) at 40·0°. Samples (5·0 ml) were removed at intervals and the reaction quenched with dilute acid. Melicopicine was extracted into chloroform and the extract evaporated under reduced pressure, dimethyl sulphoxide being removed at 0·01 mmHg. The residue was made up to 5·0 ml in toluene, and 2·0 ml of this solution added to 15·0 ml of scintillation solution and the radioactivity determined. The results showed that the equilibrium radioactivity, $6{\cdot}35 \times 10^4$ d/m, was attained in less than 2 min. (Activities measured on Ekco N664A liquid scintillation counter.) Thin-layer chromatography of each fraction showed no chemical change in the melicopicine.

[6] Streitwieser, A., Ziegler, G. R., Mowery, P. C., Lewis, A., and Lawler, R. G., *J. Am. chem. Soc.*, 1968, **90**, 1357.

[7] Prager, R. H., and Thredgold, H. M., *Aust. J. Chem.*, 1969, **22**, 1477.

(B) *In dimethyl sulphoxide–methanol.*—To a solution of melicopicine (100·0 mg) in dimethyl sulphoxide (1·0 ml) thermostated at 50·0° was added a solution of radioactive sodium methoxide in dimethyl sulphoxide–methanol, 4 : 1 (5·0 ml; 0·50M). The mixture was maintained at 50° and 0·5 ml aliquots were removed at 1, 3, 5, 7, 10, 13, 16, 19, 22, and 25 min intervals. Each aliquot was worked up as described above, but the melicopicine in each fraction was recrystallized from ether–light petroleum before *c.* 1 mg was counted. The pseudo first-order rate constant was determined by the method of McKay,[8] affording a second-order rate constant of $5 \cdot 98 \times 10^{-3}$ l. mol^{-1} s^{-1}.

Degradation of Radioactive Melicopicine (1)

The graph of specific radioactivity against time for the exchange reaction above indicated that equilibrium had been achieved essentially after 17 min. The above reaction with 100 mg of melicopicine was repeated and quenched after 0·5 and 9 min, times which were well before equilibrium had been attained. On degradation of the isolated melicopicine, both samples gave relative ratios of activities within ±5%.

(A) *Normelicopicine (5).*—Melicopicine (100 mg) was dissolved in methylene chloride (2 ml) at 0°, and a 15% solution of BCl_3 in methylene chloride (0·5 ml) was added slowly. The mixture was stirred at 0° for 2 min and washed with water. The organic phase was dried (Na_2SO_4) and separated into its constituents by preparative t.l.c. using benzene–ether 5 : 1 on silica. Normelicopicine (65%) was obtained, m.p. and mixed m.p. 124–125°. Subsequently the conventional method[9] with 5M HCl in methanol was used, as it was shown that when radioactive melicopicine (100 mg) was refluxed with 5M HCl (2 ml) in methanol, the melicopicine removed after 10, 30, and 40 min had identical specific activities.

(B) *2,3-Dimethoxy-10-methylacridone-1,4-quinone.*—Normelicipicone (50 mg) was dissolved in conc. HNO_3 (1 ml) at 20° and shaken for 3 min, then poured into water (10 ml). The mixture was extracted with chloroform (4 × 2 ml), the extract dried, and evaporated. The solid residue (quantitative yield) was recrystallized from chloroform–light petroleum, m.p. and mixed m.p. 200–201°.[10] Because of its relatively low solubility in toluene, the dimethoxy and hydroxy quinone were counted in a mixture of scintillator (15 ml) and methanol (0·6 ml).

(C) *2-Hydroxy-3-methoxy-10-methylacridone-1,4-quinone.*—The dimethoxyquinone (30 mg) was warmed with 5% aqueous sodium carbonate (10 ml) until it dissolved (*c.* 10 min) to form a deep purple solution. The solution was cooled, acidified, and extracted with chloroform (5 × 2 ml). Extraction with chloroform before acidification was used to remove any starting material, but the extract was completely colourless. The chloroform extract yielded an orange crystalline residue (30 mg) which was recrystallized twice from ethanol–light petroleum as orange needles, m.p. and mixed m.p. 230–232°.[7]

The activities were (expressed as counts/mg during 100 s): melicopicine $4 \cdot 09 \times 10^3$; normelicopicine $3 \cdot 55 \times 10^2$; dimethoxyquinone $2 \cdot 93 \times 10^2$; hydroxyquinone $2 \cdot 37 \times 10^2$. All samples were corrected for quenching, and the activity is the average of two recrystallized samples.

Relative Rates of Reaction of Melicopidine (3) and Melicopicine (1)

A mixture of melicopidine (70·0 mg) and melicopicine (70·0 mg) was dissolved in dimethyl sulphoxide (1·0 ml) at 50·0°, and added to a 0·50M solution of sodium methoxide in methanol (CH_2TOH $1 \cdot 88 \times 10^8$ counts/ml during 100 s; 0·4 ml)–dimethyl sulphoxide (1·0 ml) thermostated at 50·0°. Half the mixture was quenched with water after 1·5 min, the other half after 10 min. The mixture was acidified and extracted with chloroform (4 × 2 ml) and the chloroform extract chromatographed on a thin layer of silica gel, developing with benzene–ethyl acetate 4 : 1. The upper band consisted of melicopicine, and was recrystallized twice from ether–light petroleum, m.p. and mixed m.p. 132–134°. The second band, m.p. 95–100°, was mainly melicopidine, but could not be adequately purified by recrystallization, and was rechromatographed. The main band was recrystallized from ether–light petroleum, and had m.p. and mixed m.p.

[8] McKay, H. A. C., *Nature*, 1938, **142**, 997.
[9] Crow, W. D., and Price, J. R., *Aust. J. scient. Res.* (*A*), 1949, **2**, 255.
[10] Crow, W. D., and Price, J. R., *Aust. J. scient. Res.* (*A*), 1949, **2**, 282.

with melicopidine 117–119°. The third band was identical with 2-hydroxy-1,3,4-trimethoxy-10-methylacridone, and weighed only 3·0 mg (7·7%) in the first aliquot.

The melicopidine and melicopicine were separately demethylated to the respective nor-compounds by refluxing with alcoholic 5M HCl for 30 min. The nor-compounds were isolated by preparative t.l.c., using the above solvent system, and the pure compounds were recrystallized from chloroform–light petroleum. Samples were recrystallized until subsequent specific activities were within ±5%. The activities were (expressed as counts/mg during 100 s): melicopicine $3{\cdot}60\times10^3$; normelicopicine $2{\cdot}50\times10^2$; melicopidine $1{\cdot}39\times10^3$; normelicopidine $1{\cdot}40\times10^2$.

Kinetics of the Reaction of Melicopidine (2) with Sodium Methoxide

Melicopidine (16·81 mg) was dissolved in dimethyl sulphoxide (5·0 ml) at 50·0°. To this solution was added a solution of sodium methoxide in dimethyl sulphoxide (5 ml) and methanol (2 ml) at 50°. The final concentration of sodium methoxide was 0·417M. The mixture was kept at 50·0° and 2·0 ml aliquots were taken at 2-min intervals, quenched with water, and extracted with chloroform. The chloroform extract was evaporated, the dimethyl sulphoxide removed at 0·1 mmHg, and the residue made up to 5·0 ml in chloroform. An aliquot (100 μl) was applied as a strip to a silica thin-layer plate (all six samples on one 20-cm plate) and the chromatogram was developed with benzene–ethyl acetate 2 : 1. The melicopidine was eluted from the plate with 95% ethanol and made up to 5·0 ml in a volumetric flask. The concentration was determined from the optical density at 277 nm, the spectroscopic reference being obtained by similar elution of a blank part of the same silica plate.

Acknowledgments

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