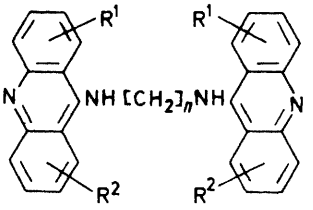
Synthesis of 10-Alkyl- and 10,10′-Alkyl-linked 9-Aminoacridinium Salts

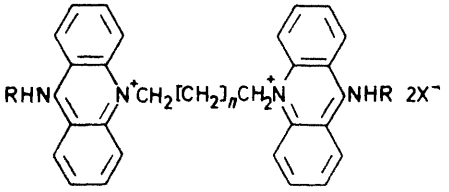
By R. MORRIN ACHESON* and EDWIN C. CONSTABLE
(*Department of Biochemistry, South Parks Road, Oxford* OX1 3QU)

Summary Potassium 9(10*H*)-acridone with α,ω-diiodoalkanes in dimethylformamide or acetonitrile gave α,ω-bis-(9-oxo-9,10-dihydroacridin-10-yl)alkanes, which were converted into the corresponding 9-aminoacridinium salts by successive treatment with phosphorus trichloride oxide, primary amines, and acid.

ACRIDINES possess a large number of biological effects[1] and the intercalation of aminoacridines into DNA is a subject of current intensive study [2–6] A series of bis-9-aminoacridines, linked through the exocyclic nitrogen atoms by aliphatic chains, has been prepared by Le Pecq *et al* ,[2] Canellakis *et al* ,[3] and Wright [4] It has been shown that both acridine rings of these bis-derivatives can intercalate if the linking chain is just long enough to span one base pair, and this is the case for (**1**, $R^1 = R^2 = H$, $n = 6$) [3] The acridine systems in this case must enter the helix by a mode away from the side chain Substituents in the carbocyclic rings affect the intercalation [5]



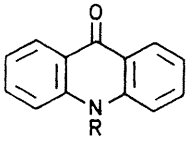
(1)



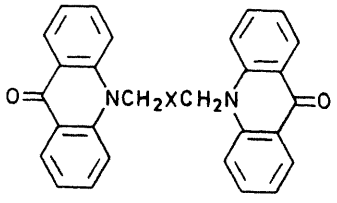
(2)

In order to find out whether bis-intercalation was possible from other orientations of the acridine ring system, isomers of (**1**) were prepared The compounds desired had structure (**2**) and could, in principle, be obtained from the reaction of 9-aminoacridine with α,ω-dihalogenoalkanes, a procedure recently shown to be successful with acridine itself [7] Although the ring alkylation of 9-aminoacridine proceeds well with methyl and ethyl iodides, higher halides and α,ω-dihalogenoalkanes undergo mainly Hofmann elimination,[8] inseparable mixtures of ring- and *exo*-*N*-alkylated acridines were usually formed under other conditions reported[9] since our experiments Our attempts to alkylate the anion of 9-aminoacridine, obtained with sodium hydride suspended in tetrahydrofuran, caused mainly *exo*-*N*-alkylation

We have now found, contrary to Blanchard *et al* [10] for 2-methoxy-9(10*H*)-acridone, that the potassium salt of acridone in dimethylformamide or MeCN with alkyl iodides or tosylates gave exclusively the 10-alkylacridones (**3**) in 25—85% yield, several other solvents, or alkylations with alkyl chlorides or bromides gave little *N*-alkylation Bifunctional alkylating agents, such as 1,6-di-iodohexane, obtained from the bromo-analogues with sodium iodide in MeCN, gave the very insoluble $\alpha\ \omega$-*N*,*N*′-linked bisacridones (**4**) and (**5**) in 28–60% yield These with phosphorus trichloride oxide gave the corresponding 9-chloroacridinium salts which, with ammonia or primary amines, yielded iminoacridans, which were converted by acids into the corresponding salts [*e g* (**2**, R = H, $n = 6$), 30% yield]



(3) R = Et, Bu^n, n-C_7H_{15}, n-$C_{16}H_{33}$, $PhCH_2$, $MeO_2C[CH_2]_5$



(4), X = -$[CH_2]_n$-, n = 4,5,6,8,10,12

(5), X = -$[CH_2]_2O[CH_2]_2$-

and the analogue (R = H) from (**5**) (76%), free from isomers This type of procedure could also be used in the synthesis of 9-aminoacridinium or similar salts linked from the heterocyclic nitrogen atoms through a suitable chain to any other position of an acridine ring or to another moiety

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[1] R M Acheson, ed , 'The Acridines,' 2nd edn , Interscience–Wiley, New York, 1973
[2] J B Le Pecq, M Lebret, J Barbet, and B H Rogues, *Proc Natl Acad Sci USA*, 1975, **72**, 2915
[3] L P G Wakelin, M Romanos, T K Chen, D Glaubiger, E S Canellakis, and M J Waring, *Biochemistry*, 1978, **17**, 5057, and papers cited therein
[4] R G M Wright, D Phil thesis, Oxford University, 1978
[5] R G M Wright, L P G Wakelin, A Fieldes, R M Acheson, and M J Waring, *Biochemistry*, accepted for publication, and papers cited therein
[6] J W Pawlak and J Konopa, *Br J Pharmacol* , 1979, **28**, 3391
[7] W-S Chen, G H Cocolas, C J Cavallito, and K J Chai, *J Med Chem* , 1977, **20**, 1617
[8] R M Acheson and C W C Harvey, *J Chem Soc , Perkin Trans* 1, 1976, 465
[9] J P Gaby, J Elquero, E J Vincent, A-M Gaby, and J Barbet, *Heterocycles*, 1980, **14**, 311
[10] C Blanchard, J -M Fabre, C Montginoul, B A Chaffia, E Torreilles, and L Giral, *J Heterocycl Chem* , 1978, **15**, 149