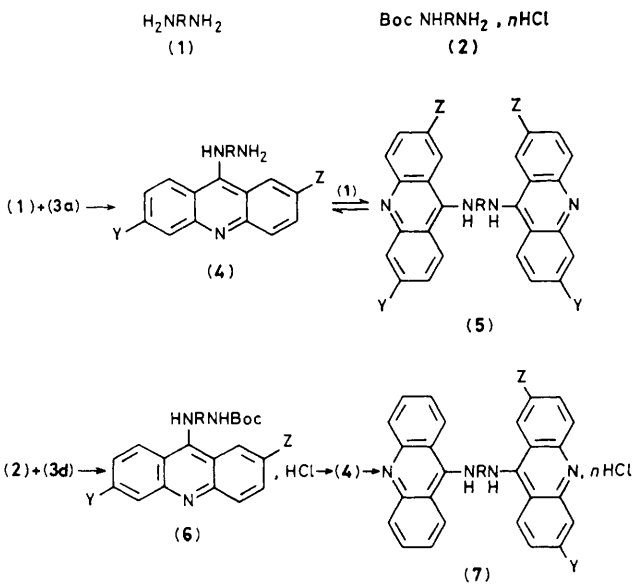
A Novel Synthesis of Tri-, Di-, and Mono-9-acridinyl Derivatives of Tetra-, Tri-, and Di-amines

John B. Hansen and Ole Buchardt

Chemical Laboratory II, The H. C. Ørsted Institute, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen Ø, Denmark

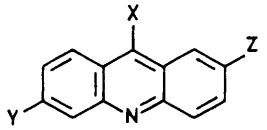
Mono-9-acridinyl derivatives, potential polyintercalating hetero-di-9-acridinylamines, and homo- or hetero-tri-9-acridinylamines were prepared from partially Boc-protected polyamines.

The naturally occurring polyamines, *e.g.*, putrescine (butane-1,4-diamine), spermidine [*N*-(3-aminopropyl)-*N*-(4-aminobutyl)amine], and spermine [*N*,*N*′-di-(3-aminopropyl)butane-1,4-diamine] are important for the regulation of both normal and neoplastic cells.[1] They have high affinities for nucleic acids and exhibit a variety of effects on the biosynthesis and



a,R=-$[CH_2]_6$-; b,R=-$[CH_2]_8$-; c,R=-$[CH_2]_3N[CH_2]_3$-; d,R=-$[CH_2]_3N$⟨⟩$N[CH_2]_3$-

(4), (6), and (7): Y = Cl, Z = OMe, n = 1, 2, 3, or 4



(3)

a, X = Cl, Y = Z = H
b, X = Y = Cl, Z = OMe
c, X = OPh, Y = Z = H
d, X = OPh, Y = Cl, Z = OMe

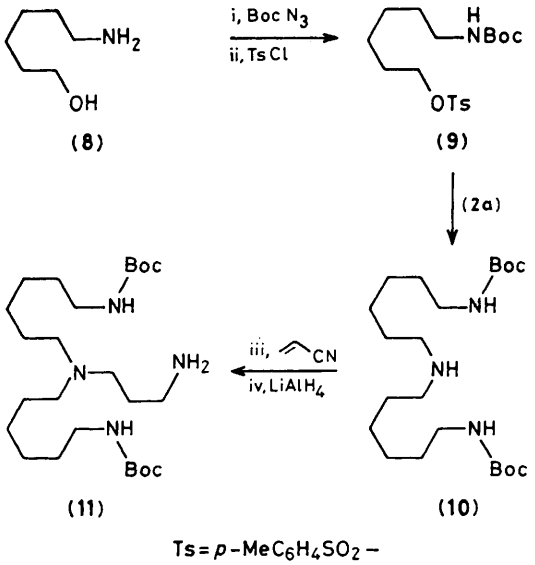
metabolism of DNA.[2] This, combined with the well established DNA-intercalation and other biologically important properties of 9-acridinylamines,[3] means that the 9-acridinyl derivatives of such amines are very interesting.[4] They are potential anti-tumour drugs, and when attached to aryl azido-groups or diazo-compounds[5] can act as photoaffinity labelling reagents in the study of chromatin.[6]

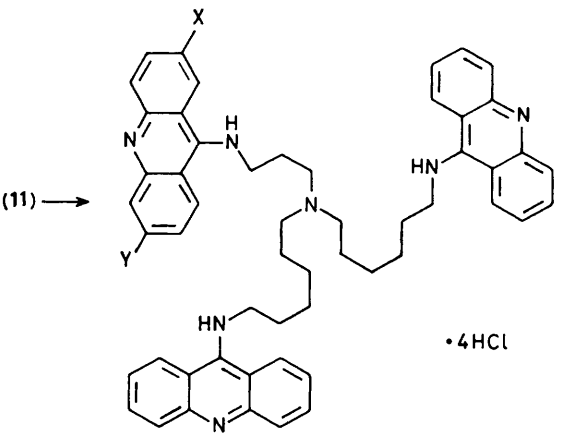
In the present paper we report (i) the first practical synthesis of mono-acridinyl derivatives (**4**) of the amines in question, (ii) their transformation into the hitherto unknown hetero-di-acridines (**7**), and (iii) the synthesis of the potential tris-intercalating derivatives, (**12**) and (**13**).

The mono-9-acridinyl derivatives (**4**) of the polyamines (**1**) are interesting both biologically and as synthons, *e.g.*, for the preparation of hetero-di-9-acridinylamines (**7**). Compounds of type (**4**) were previously prepared in poor yields (<10%) by treating the polyamines (**1**) with 9-chloroacridines (**3a**), and it was inferred that the poor yield was due to 'dismutation' of the preformed (**4**) into the homo-di-9-acridinylamines (**5**) and the parent amines (**1**).[7]

Compounds (**4**) were obtained in good yield by initial partial protection of the polyamines, for which several methods are known.[8,9] The mono-Boc-protected amines (**2**) were prepared[9] and treated with 2-methoxy-6-chloro-9-phenoxyacridine (**3d**) in phenol to give compounds (**6**)† which were de-protected

† All new compounds showed satisfactory elemental analysis and ^{1}H n.m.r. spectroscopic properties.





(**12**); X = Y = H
(**13**); X = OMe, Y = Cl

Scheme 1. (**11**) → (**12**): i, HCl; ii, (**3c**). (**11**) → (**13**): i, (**3b**); ii, HCl, iii, (**3c**).

with HCl in HOAc to give the hydrochlorides of compounds (**4**) in 70—90% yield. The hydrochlorides were stable in the solid form, and it was found that they did not 'dismutate' in methanol, or in aqueous solution (pH 7; 10 mM tris-buffer) within 24 h at room temperature. However, in basic solution (MeOH–Et_3N; 9:1) reversible 'dismutation' takes place at rates which are dependent upon the substitution pattern of the acridines and the character of the linking chains (R).[10] The 9-acridinylamines (**4a—d**) were transformed into the hetero-di-9-acridinylamines (**7a—d**) in high yields (60—90%) by treatment with 9-phenoxyacridine (**3d**), and isolated as the hydrochlorides, (**7a**)·2HCl, (**7b**)·2HCl, (**7c**)·3HCl, and (**7d**)·4HCl.

The potential tris-intercalating compounds (**12**) and (**13**) were prepared from 6-aminohexan-1-ol (**8**), which was Boc-protected (dimethyl sulphoxide; Et_3N; 91%) and converted into the tosylate (**9**) (pyridine; 0 °C; 40%). In the next step (**9**) reacted with (**2a**) (reflux in MeCN; 58%) to give (**10**) to which was added acrylonitrile (reflux in toluene; 40 h; 91%), and the product was reduced with $LiAlH_4$ in dry ether[11] to give (**11**) (90%) which was converted into (**12**) by removal of

the protective groups followed by treatment with 9-phenoxyacridine [(**3c**); phenol; 100—120 °C; 1.5 h; 70% yield from (**11**)]. Alternatively, (**11**) was treated with 2-methoxy-6,9-dichloroacridine [(**3b**); phenol; 100—120 °C; 1.5 h; 44%], deprotected and finally treated with (**3c**) as above to give (**13**) (65%) (Scheme 1). Compounds (**10**)—(**13**) were preferentially isolated and purified in the form of their hydrochlorides.

The synthetic pathways presented should be useful for the preparation of other derivatives of biologically important amines, and potential polyintercalating compounds containing different intercalating groups.

We are grateful to the Danish Medical Science Research Council for financial support to J.B.H.

Received, 15th November 1982; Com. 1306

References

1 P. J. Tofilon, S. M. Oredsson, D. F. Deen, and L. J. Marton, *Science*, 1982, **217**, 1046.
2 C. W. Tabor and H. Tabor, *Annu. Rev. Biochem.*, 1976, **45**, 285.
3 'The Acridines,' ed. R. M. Acheson, 2nd edn., Interscience–Wiley, New York, 1973.
4 R. G. M. Wright, L. P. G. Wakelin, A. Fields, R. M. Acheson, and M. T. Waring, *Biochemistry*, 1980, **19**, 5825.
5 P. E. Nielsen, J. B. Hansen, T. Thomsen, and O. Buchardt, *Experientia*, submitted for publication.
6 P. E. Nielsen, *FEBS Lett.*, 1981, **135**, 173; P. E. Nielsen, *Eur. J. Biochem.*, 1982, **122**, 283.
7 Z. Ledochowski and A. Chimak, *Rocz. Chem.*, 1959, **33**, 1207; B. S. Stefanska and A. Ledochowski, *ibid.*, 1972, **46**, 1637; E. S. Canellakis, Y. H. Shaw, W. E. Hanners, and R. A. Schwartz, *Biochem. Biophys. Acta*, 1976, **418**, 277.
8 R. J. Bergeron, P. S. Burton, K. A. McGovern, and S. Kline, *Synthesis*, 1981, 732; R. J. Stolowich and C. W. Porter, *ibid.*, 1982, 689.
9 J. B. Hansen, M. C. Nielsen, U. Ehrbar, and O. Buchardt, *Synthesis*, 1982, 404.
10 J. B. Hansen, E. Langvad, F. Frandsen, and O. Buchardt, *J. Med. Chem.*, submitted for publication.
11 M. Hamura and J. Quick, *J. Org. Chem.*, 1979, **44**, 1166.