9-Acridinylguanidines. Mono-, Bis-, Tris-, and Tetrakis-9-acridinyl Derivatives of Guanidine connected *via* Polymethylene Linkers

John B. Hansen,* Tove Thomsen, and Ole Buchardt*

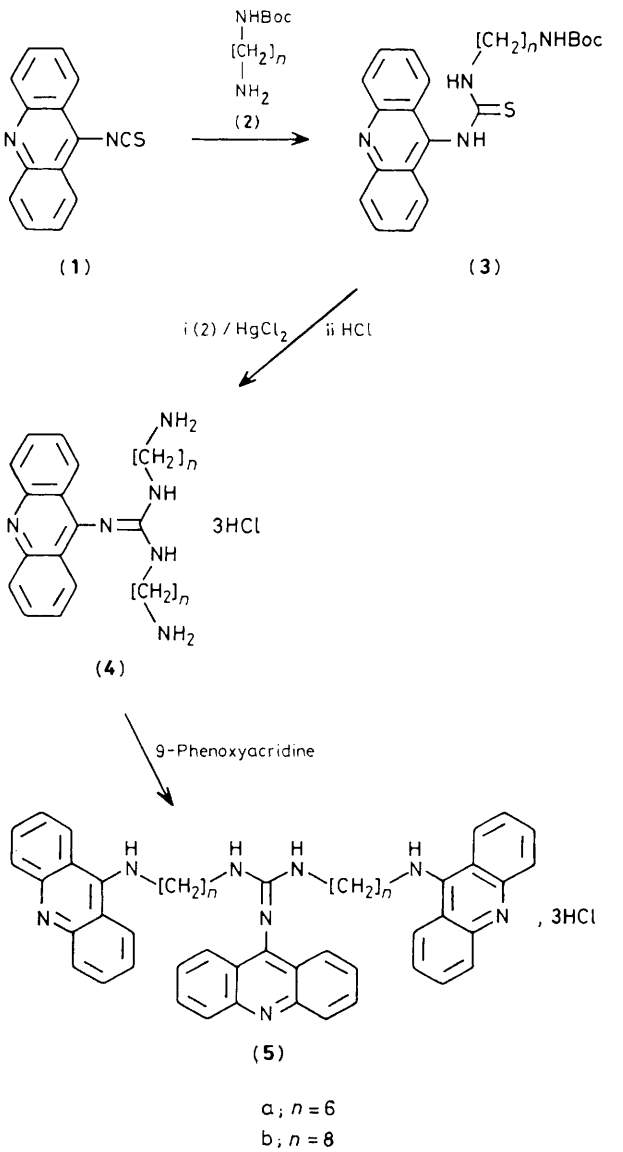
Chemical Laboratory II, The H. C. Ørsted Institute, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen Ø, Denmark

9-Isothiocyanatoacridine is converted into 9-guanidyl derivatives of acridine containing one, two, three, or four 9-aminoacridine groups separated by polymethylene linkers of variable length.

9-(Aminoalkyl)aminoacridines exhibit a variety of biological effects, and are pharmacologically important as antiparasitic and cytostatic agents.[1] They bind to double stranded DNA by intercalation in such a way that the 9-amino group appears to be in the direction of the DNA minor groove.[2] The strength of this binding[2] and the DNA site specificity are influenced by electrostatic interactions and hydrogen bonds between the substituents on the 9-amino group of the acridines, and some of the DNA-bases, especially the guanines, as well as to the phosphate groups in the DNA helix.[3] The protonation of amino groups in the side-chain of these intercalators at physiological pH appears to be important for their DNA-binding and their biological functions.[4]

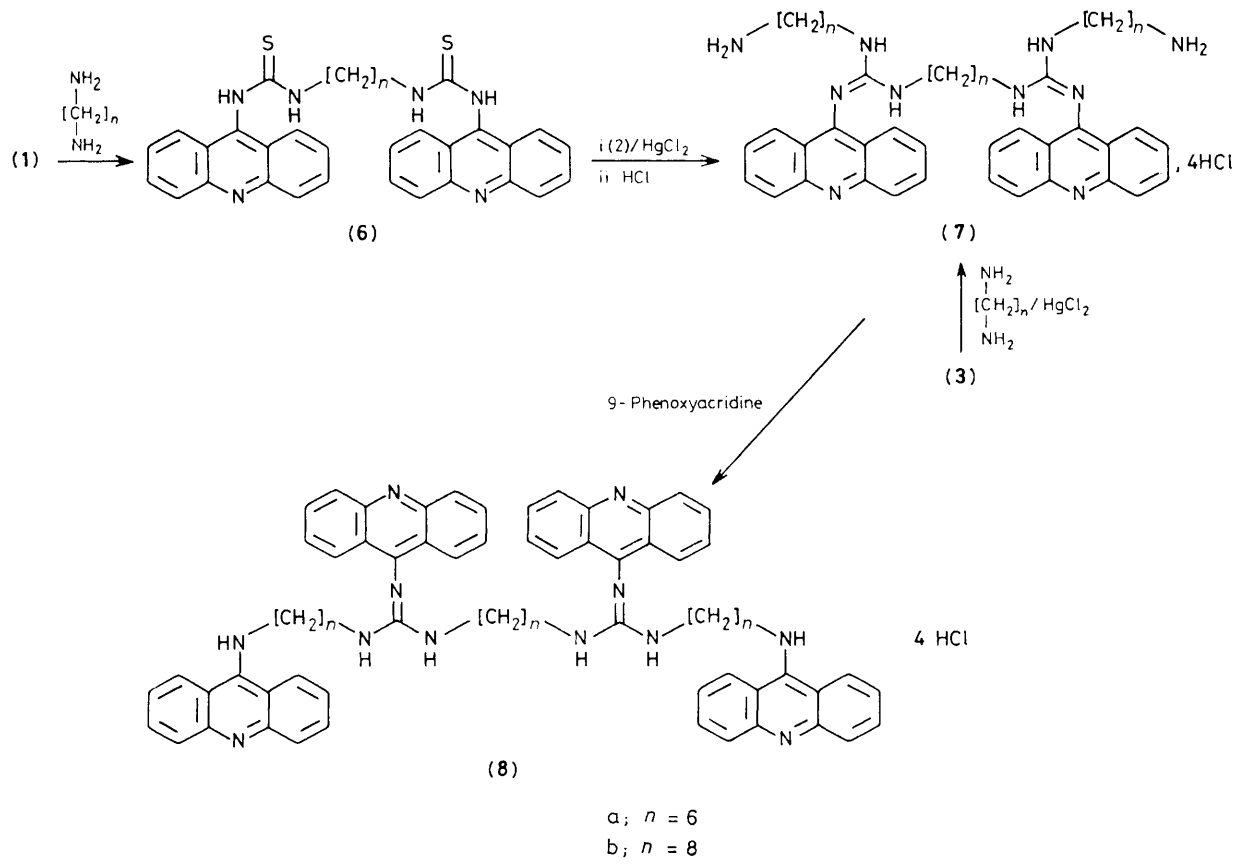
By connecting two intercalating ligands *via* aliphatic chains, bisintercalating agents with very high affinity for DNA have been prepared in the search for, *e.g.*, new antitumour drugs,[5] and we have previously described the synthesis[6] as well as some biophysical and biological properties of a series of such tri-, di-, and mono-9-aminoacridines.[7] In the present paper we report the synthesis of the hitherto unknown mono- and di-9-guanidylacridines (**4**) and (**7**), and their transformation into the potential tris- and tetrakis-intercalating compounds, (**5**) and (**8**). Treatment of 9-isothiocyanatoacridine (**1**) with aliphatic primary amines gave the corresponding *N*-(9-acridinyl)-*N'*-alkylthioureas in good yield (toluene, reflux 30 min) as described previously.[8] The thiourea (**3b**), prepared from *N*-(Boc)octane-1,8-diamine (Boc = Bu^{t}OCO) (**2b**)[9] and (**1**) was allowed to react with (**2b**), HCl in the presence of $HgCl_2$ and Et_3N (reflux, acetonitrile, 5 h) to give the corresponding 9-guanidylacridine, possibly *via* the corresponding di-imide.[10] This was subsequently treated with *ca.* 1 M HCl in glacial acetic acid (room temperature, 30 min) to remove the Boc-protecting groups to give (**4b**) (85% yield). Treatment of (**4b**) with 9-phenoxyacridine in phenol (100—120 °C, 1.5 h) gave the trisacridine (**5b**) (46% yield) (Scheme 1).

Reaction of (**1**) with hexane-1,6-diamine or octane-1,8-diamine in toluene gave the dithioureas (**6a,b**) (95% yield), which by reaction with (**2**) ($HgCl_2$, Et_3N, acetonitrile, reflux 5 h) followed by treatment with HCl–glacial acetic acid (30 min, room temperature) gave the di-(9-guanidylacridines) (**7a,b**) (50—60% yield) (Scheme 2). Alternatively, (**7a,b**) were prepared from (**3a,b**) and the corresponding diamine in an analogous manner in 50% yield. The di-thioureas (**6a,b**) were also treated with 9-(6-ethylaminohexylamino)acridine[7] or with 9-(6-aminohexylamino)acridine[6,7] in the presence of mercury(II) chloride and triethylamine, but this treatment did not give the di-guanidyl derivatives. In the case of 9-(6-aminohexylamino)acridine, 1,6-di-(9-aminoacridinyl)hexane was formed, owing to 'dismutation'[6] of the monoacridine. The tetraacridines (**8a,b**) were prepared by the reaction of (**7**) with 9-phenoxyacridine in phenol (100—120 °C, 1.5 h, 65% yield). Furthermore, we have prepared the unsubstituted 9-guanidylacridine by treatment of guanidine hydrochloride with 9-phenoxyacridine (phenol, 120 °C, 1 h, 60% yield). The only previously described related compound is 2-guanidylacridine, prepared from 2-aminoacridine and cyanamide.[11] All new compounds reported gave satisfactory ^{1}H n.m.r. spectra and chemical analyses.



Scheme 1

The synthetic methods outlined here, besides allowing the formation of the present compounds, can be used to prepare a wide variety of biophysically and biologically interesting reagents.



Scheme 2

This work was supported by the Danish Medical Science Research Council, with a grant to J. B. H.

Received, 20th June 1983; Com. 816

References

1 'The Acridines,' ed. R. M. Acheson, 2nd edn., Wiley-Interscience, New York, 1973.
2 J. B. Hansen, T. Koch, O. Burchardt, P. E. Nielsen, M. Wirth, and B. Nordén, *Biochemistry*, in the press; W. D. Wilson and R. L. Jones, in 'Intercalation Chemistry,' eds. M. S. Whittingham and A. J. Jacobson, Academic Press, New York, 1982, p. 445.
3 J. Markovits, B. Gaugain, B. P. Roques, and J.-B. Le Pecq, in 'Intermolecular Forces,' ed. B. Pullman, Reidel, The Netherlands, 1981, pp. 285—298 and references cited therein.
4 D. Pelaprat, R. Oberlin, I. Le Guen, and B. P. Roques, *J. Med. Chem.*, 1980, **23**, 1330.
5 R. G. McR. Wright, L. P. G. Wakelin, A. Fieldes, R. M. Acheson, and M. J. Waring, *Biochemistry*, 1980, **19**, 5825; D. Pelaprat, A. Delbarre, I. Le Guen, B. P. Roques, and J.-B. Le Pecq, *J. Med. Chem.*, 1980, **23**, 1336 and references cited therein.
6 J. B. Hansen and O. Buchardt, *J. Chem. Soc., Chem. Commun.*, 1983, 162.
7 J. B. Hansen, E. Langvad, F. Frandsen, and O. Buchardt, *J. Med. Chem.*, 1983, in the press.
8 A. De Leenheer, J. E. Sinsheimer, and J. H. Burckhalter, *J. Pharm. Sci.*, 1972, **61**, 273.
9 J. B. Hansen, M. C. Nielsen, U. Ehrbar, and O. Buchardt, *Synthesis*, 1982, 404.
10 H. Ulrich and A. A. R. Sayigh, in 'Neuere Methoden der Präparativen Organischen Chemie,' band VI, ed. W. Foerst, Verlag Chemie, Weinheim, 1970, pp. 211—229.
11 R. Royer, *J. Chem. Soc.*, 1949, 1665.