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Synthesis and Anticancer Properties of a Hindered Amino-diester

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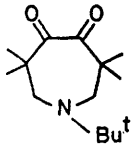
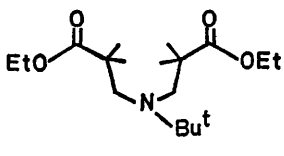
Summary A new synthesis of di-neopentyl-substituted amines is described and the anticancer properties of one of these compounds is discussed.

As part of a synthetic scheme leading toward the formation of tetrasubstituted amino-dione (I), we have used a novel approach for the synthesis of precursor (IIa) which involves reaction of two equivalents each of ethyl α-bromoisobutyrate and magnesium[1] with (III) at 0° for 3 h in ether.

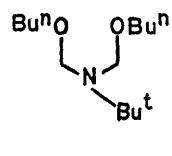
Because of the synthetic potential of this type of reaction and the significant anticancer activity exhibited by diester (IIa), we have studied this type of dialkylation reaction with several different bromoesters and now report our results as well as a possible explanation for the anticancer properties of diester (IIa).



(I)



(IIa)

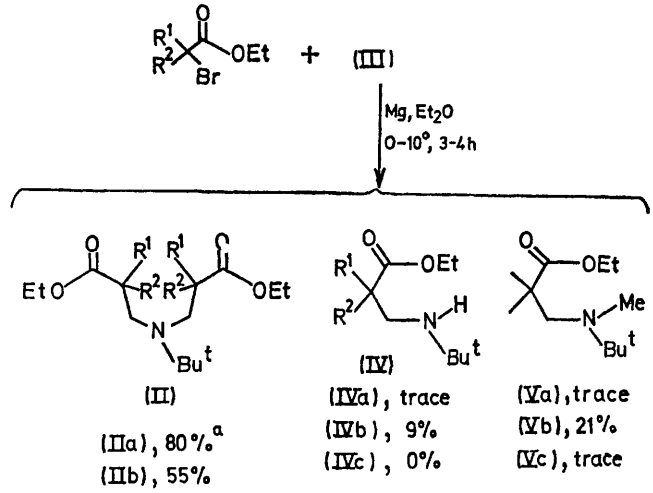


(III)

Amine (III) was synthesized using the general procedure of Gaines and Swanson.[2]

The reaction of amine (III) and magnesium with ethyl α-bromoisobutyrate, ethyl α-bromopropionate, and ethyl α-bromoacetate is shown in the Scheme. Ethyl α-chloroacetate gave no reaction under our conditions.

An examination of the yields obtained for the dialkylated amines (II) shows that the yield of product decreases as the number of enolizable protons increases and as the steric factors preventing self-condensation of the bromoester decrease. A small amount of monoalkylation was noted in these reactions [N–H (IV) and N–Me (V) monoalkylated amines were characterized by their spectra]. Amine (IVb) was converted to (Vb) in 80% yield after reaction with trioxane in ethanol followed by reduction with $NaBH_4$.[3]



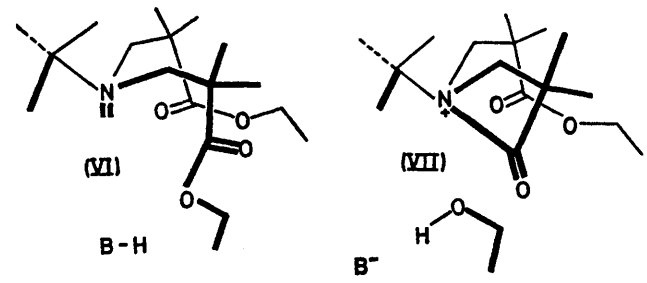
Scheme

[a] Yields are isolated material after purification by spinning band distillation.

Diester t-butyl amine (IIb) and (IIc) were identified by their spectral data.†

Amine (IIa) was shown to have significant activity *in vivo* against lymphocytic leukemia (PS).‡ Careful model studies of this very hindered di-neopentyl substituted amino-diester show that the preferred geometry of this molecule (VI) is such that there is a good possibility that its mode of action (bridging RNA or DNA strands) is similar to that of the well known nitrogen mustard dialkylating agents, except in this case the active species would not be the three membered ring aziridine ion, but rather a β-lactam ion (VII)§ as shown in the Figure.

Recent data shows that several related compounds bearing similar structural features also exhibit reasonable anti-tumour activity (Le, PS tests);‡ however, the less substituted amino diesters (IIb) and (IIc), which are not conformationally held in a favourable geometry, do not show appreciable activity.



FIGURE

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† Structure assignments are supported by analytical, i.r., n.m.r., and mass spectral data.

‡ Tested by the National Cancer Institute of N.I.H. (USA). PS=P388 lymphocytic leukemia; Le=L–1210 lymphoid leukemia.

§ It seems unlikely a compound with structure (VII) actually exists in solution; it should be considered a 'limit drawing.'

[1] Alkylamine formation by mono-alkylation of simple amino-acetals with organo-magnesium compounds has been reported; C. Glacet and G. Adrian, *Bull. Soc. chim. France*, 1971, 638.

[2] J. R. Gaines and A. W. Swanson, *J. Heterocyclic Chem.*, 1971, **8**, 249.

[3] Procedure of J. Lundstrom, *Acta. Pharm. Suec.*, 1971, **8**, 485.