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A NEW ROUTE TO ISOINDOLE (BENZO[c]INDOLE) AND ITS DERIVATIVES.

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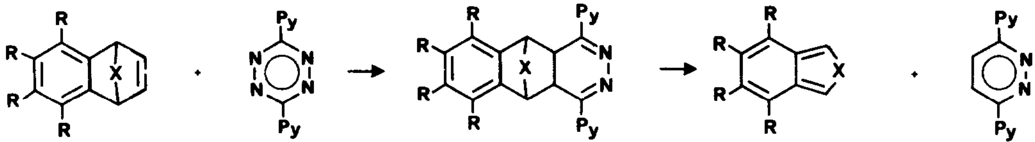
There has been a flurry of recent activity in the isoindole field. In particular Heaney and co-workers have reported[1] that flow pyrolysis of the 5,6-dihydro derivative of compound (1) forms tetrafluoro-*N*-methylisoindole (4c), and Jaques and Wallace have demonstrated[2] that an intermolecular benzyne addition is an elegant route to certain isoindoles. Bonnett and Brown have used a vapour phase pyrolysis technique to isolate the elusive and long-sought parent member (4a) of this series and fully characterised it spectrally and in adduct form.[3]

The current method is presented as an alternative route to the isoindole nucleus which is simple, quick and proceeds in high yield. The method is based on a mild fragmentation reaction[†] which depends for its success of the low activation energy attendant on cleavage of the tricyclo-[6.2.1.$0^{2,7}$]deca-3,5,9-



(1) (2) (3) (4) (5)

R = H a) X = NH b) X = $NCOOC_2H_5$
R = F c) X = NCH_3 d) X = O

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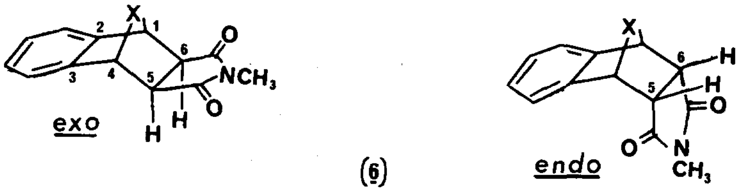
[†] *This reaction has been applied to other isobenzo systems, notably isobenzofuran*[5] *and isobenzofulvenes*[6].

triene system and aza-derivatives thereof[4]. Thus reaction of 7-aza-2:3-benzobicyclo[2.2.1]hept-7-ene*,[7] (1a) with 3,6-di(2'-pyridyl)-*s*-tetrazine (2) proceeded extremely rapidly in chloroform solution even at -25°. The reaction was followed by p.m.r. spectroscopy, but no evidence for the initial 1:1 adduct or of the derived dihydropyridazine (3) intermediate was obtained. Early formation of the pyridazine (5) was obvious, showing that cleavage of the intermediate was unusually rapid; in addition other resonances in the δ 7.5 to δ 8.0 region also appeared (fig.2c) as expected for isoindole (4a), but not clearly assigned to those reported for 4a by Bonnett and Brown[3]. However addition of *N*-methylmaleimide to this solution immediately formed a mixture of the *endo*- and *exo*-adducts† of isoindole (6a) (fig.2d). Subsequent experiments were worked up after completion of the initial cycloaddition/retroversion sequence and the isoindole (4a) sublimed from the reaction mixture at around R.T. The isoindole is sufficiently stable to be collected on a water-cooled cold finger, but the initially formed off-white sublimate rapidly darkened on exposure to air (colourless material is obtained when collected at -196°). The p.m.r. spectrum in d_6-acetone clearly supported the structure and was similar to that reported[3]; additionally the u.v. spectrum in n-hexane also corresponded. The product readily formed adducts with dienophiles.† For adduct formation it was not



(6)

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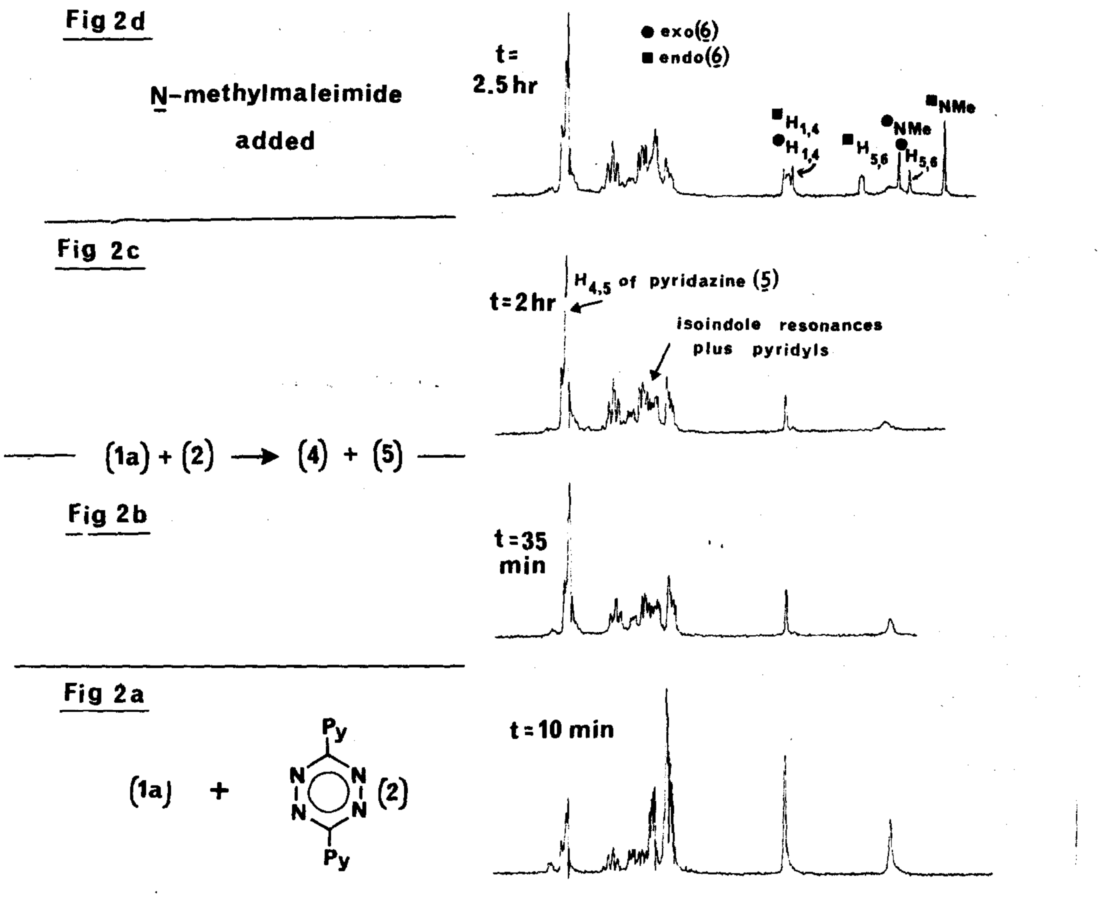
* For this route to be really attractive, a simple route to this starting material was required. This has been achieved by the addition of benzyne (generated from anthranilic acid[8]) to N-carbethoxy pyrrole in refluxing dioxan (40-50% yield), followed by hydrolysis with 10% sodium hydroxide (84% yield).

† exo- and endo- adducts were formed with N-methylmaleimide, maleic anhydride and these were distinguished by p.m.r. spectroscopy. The exo- adducts showed singlets for $H_{1(4)}$ and $H_{5(6)}$. The corresponding protons in the endo isomer were multiplets (AA'BB').

necessary to isolate the isoindole as the potential dienophile could be added either at the start of the reaction (if electron deficient) or after completion of the initial reaction (if it reacted separately with the *s*-tetrazine).

FIGURES

Figure 2. Progress of reaction of olefin 1a with *s*-tetrazine(2) in $CDCl_3$ at -30°.



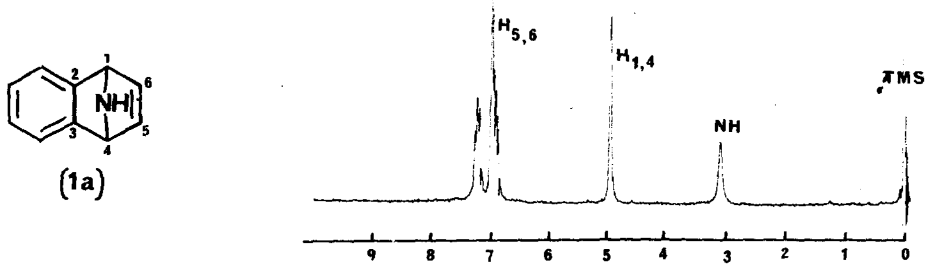


Figure 1. 100MHz spectrum of (1a) in $CDCl_3$.

In a similar way the following isoindoles were prepared and again isolated by sublimation from the reaction mixtures.

a) *N*-carbethoxy isoindole*,[9] (4b) (m.p. *ca.* 35°, rapidly polymerised on melting. Mass spectral molecular weight found 189.0790, calculated 189.0790 [$C_{11}H_{11}NO_2$]. P.m.r. ($CDCl_3$) δ 1.46 (3H, t) and 4.52 (2H, q) ethoxy group, 6.70-7.05 (2H, m) and 7.20-7.52 (2H, m) $C_{3,4,5,6}$-H and 7.70 (2H, 2) $C_{2,7}$-H.

b) 3,4,5,6-Tetrafluoro-*N*-methyl isoindole[9] (4c) (m.p. 178°). *m/e* found 203.0361, calculated 203.0358 [$C_9H_5F_4N$] p.m.r. ($CDCl_3$) δ 4.02 (s, 2H, *N*-methyl), δ 7.21 (m, 2H, $C_{2,7}$-H). Each of these isoindoles was further characterised by adduct formation[9]; the latter compound (4c) reacting much slower than either of the indoles lacking the fluorine substituents.

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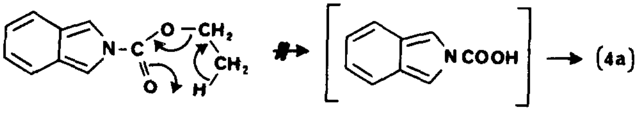
* *This compound did not form the isoindole on vapour phase pyrolysis at 500-700°, and contrasts with the known thermal breakdown of other urethanes.*[10]



(4b) (7)

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