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Synthesis of β-Carbolines and Azepino[4,5-*b*]indoles from Azidoacrylates

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Decomposition of azidoacrylates (**2**) derived from 2-alkylindole-3-carbaldehydes gives pharmacologically important β-carboline derivatives [(**4**), (**5**)], or azepino[4,5-*b*]indoles (**6**) in a new reaction of vinyl azides.

The recent isolation of ethyl β-carboline-3-carboxylate(β-CCE) (**4**) from human urine and brain tissue, and the demonstration that it possessed high affinity for benzodiazepine-binding brain proteins[1] has prompted a renewed interest in the chemistry of β-carbolines. In the light of our work on vinyl azides,[2] it seemed likely that the mild thermal decomposition of the azides (**2**) could constitute a new route to these pharmacologically important β-carboline derivatives. We now report that although β-CCE itself can be prepared from 2-methylindole-3-carbaldehyde by this method, attempted extension to other β-carboline-3-carboxylates gives, unexpectedly, azepino-[4,5-*b*]indoles (**6**) as major products in a new type of vinyl nitrene reaction.

Although indole-3-carbaldehydes are much less reactive than benzaldehyde, condensation of 1-methoxymethyl-2-methylindole-3-carbaldehyde (**1a**), m.p. 87—90 °C, with ethyl

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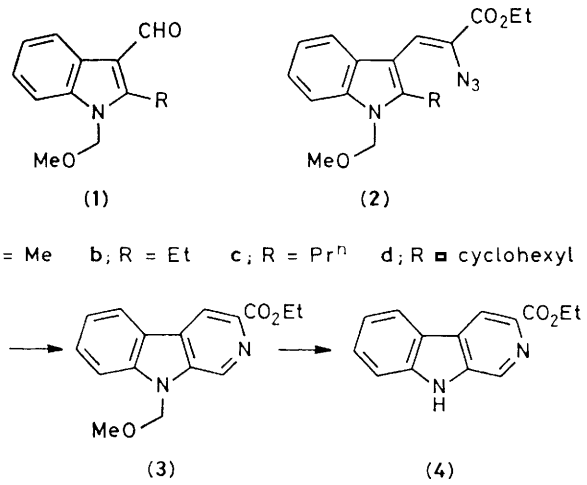
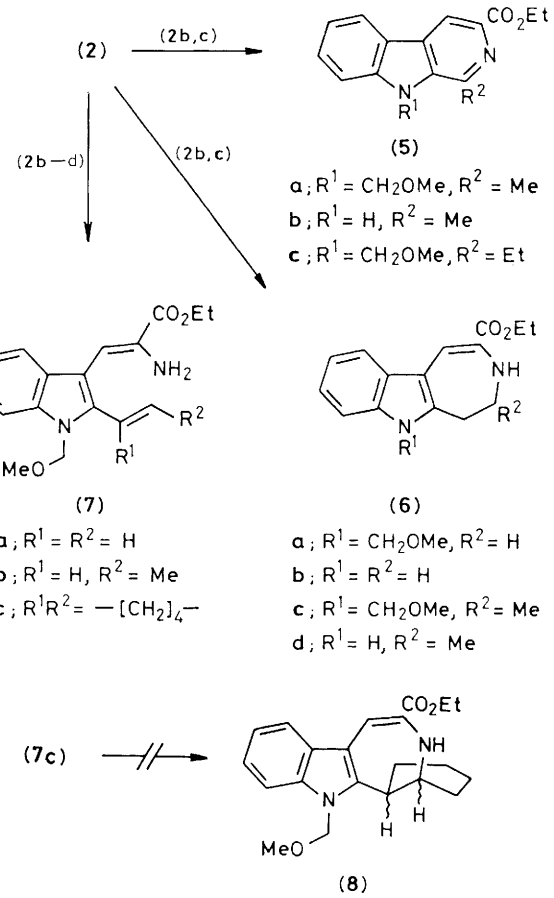


azidoacetate under the usual conditions[2] gave the azidoacrylate (**2a**) (35—45%), m.p. 90 °C (decomp.). Thermolysis of (**2a**) in xylene under nitrogen followed by work-up in air gave the expected β-carboline (**3**) (85%), m.p. 128.5—130.5 °C. The intermediate 1,2-dihydro-β-carboline could be detected by ^{1}H n.m.r. spectroscopy immediately after the thermolysis, but could not be isolated owing to its extremely rapid oxidation to (**3**) on exposure of the solution to air. Cleavage of the *N*-methoxymethyl group with aqueous acid gave β-CCE (**4**) (75%), identical with an authentic sample.

The azidoacrylates (**2b—d**) were similarly prepared from the known 2-alkylindoles *via* the aldehydes (**1b—d**), although increasing size of the 2-substituent led to lower yields in the condensation reaction. Decomposition of the azide (**2b**) in xylene gave two major products in approximately equal amounts. That one compound was the expected β-carboline (**5a**), m.p. 105—106 °C, was immediately apparent from its ^{1}H n.m.r. spectrum which contained the low-field singlet for H-4 at δ 8.75, and from its t.l.c. behaviour which exhibited characteristic intense blue fluorescence under u.v. light. Acid cleavage of the *N*-methoxymethyl group gave the known ethyl harman-3-carboxylate (**5b**) (95%). The other thermolysis product was assigned the 3,4,5,6-tetrahydroazepino[4,5-*b*]-indole structure (**6a**) on the basis of its spectral properties: ν_{max} 3380 (NH) and 1690 (C=O) cm^{-1}; δ ($CDCl_3$) 3.29 (2H, t, *J* 5.1 Hz), 3.48 (2H, t, *J* 5.1 Hz), and 6.93 (1H, s) in addition to signals for the ester ethyl, *N*-methoxymethyl, and aromatic protons. Acid hydrolysis of (**6a**) gave the crystalline azepinoindole (**6b**) (65%), m.p. 152—154 °C.

The thermolysis of (**2b**) was also investigated in other solvents. Thus, it was found that in 1,2-dichlorobenzene the β-carboline (**5a**) was the only isolated product (45%) whereas the formation of the azepinoindole (**6a**) (60%) was favoured by the use of the more polar dimethylformamide (DMF) as thermolysis solvent, in which no (**5a**) was formed. When the thermolysis was conducted at a lower temperature in refluxing benzene, a new compound was observed as the major product, the ^{1}H n.m.r. spectrum of which established the structure as the enamine (**7a**). The enamine, which was characterised as its *N*-acetyl derivative, could not be purified since attempted chromatography on, or stirring with, silica gel caused cyclisation to the azepinoindole (**6a**). On heating in solution, the enamine gave (**5a**) and/or (**6a**), the results closely paralleling those obtained from the azide (**2b**) itself.

In the thermolysis of the azide (**2c**) almost exclusive azepinoindole formation was observed, with only traces of β-carboline (**5c**) being detected by t.l.c. Thus heating the azide in xylene or, better, DMF gave the azepinoindole (**6c**) (50%),



characterised as the *N*-unsubstituted compound (**6d**), m.p. 180—182 °C. In benzene, the enamine (**7b**) was the major product, and although more stable than (**7a**) it could be cyclised to (**6c**) by heating in DMF.

Tetrahydroazepino[4,5-*b*]indoles have not been prepared before, although the 1,2,3,4,5,6-hexahydro-derivatives are quite well known, and indeed have been used as intermediates in alkaloid synthesis.[3] The azepinoindole skeleton also occurs in nature, and therefore an attempt was made to extend our method to the synthesis of (**8**), a compound related to the *Iboga* alkaloid catharanthine. Therefore, the cyclohexyl substituted azide (**2d**) was decomposed in benzene to give the expected cyclohexenyl enamine (**7c**). However, the enamine proved thermally stable, and has not as yet been induced to cyclise to (**8**), being recovered unchanged from heating in xylene or 1,2-dichlorobenzene. Heating the enamine (**7c**), or the azide (**2d**) in refluxing DMF resulted in complex mixtures.

Although the formation of β-carbolines is similar to the preparation of other annelated pyridines from vinyl azides[2,4,5] the formation of seven-membered rings represents a new type of vinyl azide reaction. The results are best rationalised by the intermediacy of vinyl nitrenes which undergo a 1,6-hydrogen shift to give an imine which can cyclise to give pyridines in the case of azides (**2a—c**), or undergo a further hydrogen shift to give enamines (**7**) as the kinetic product, in a mechanistic scheme similar to that proposed by Japanese workers in their studies on the decomposition of vinyl azides derived from benzofuran-2-carbaldehyde.[5] However, the formation of seven-membered rings from enamines related to (**7**) was not observed. Although azepinoindole formation can be explained by intramolecular addition of the amino-group to the conjugated system, little is known about such cyclisations, and it

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remains to be seen whether seven-membered ring formation is peculiar to vinyl azides derived from indole-3-carbaldehydes.

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