Tetrahedron Letters No.41, pp. 4391-4394, 1968. Pergamon Press. Printed in Great Britain.

A SYNTHESIS OF SPIRO [OXINDOLE-3,2'-BICYCLO(2,2,1)HEPTENE] DERIVATIVES

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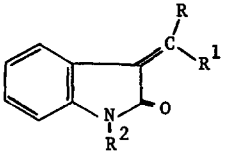
(Received in UK 8 July 1968; accepted for publication 18 July 1968)

A study of isatinylidene derivatives (I) as the dienophile component of a Diels-Alder reaction was undertaken with the object of obtaining spirooxindole derivatives of the type (II) of value in the synthesis of alkaloids of the Gelsemium species.

No previous synthesis of this nature appears to have been reported although, concurrently with this work, Johnson and co-workers (1) have reported the use of isatinylidene acetone (Ia) as a diene, and also its dimerisation involving participation as diene and dienophile.

Reaction between cyclopentadiene and a variety of isatinylidene derivatives (Ia, Ib, Ic, Ie and If) proceeded smoothly in ethanol at 40° to give good yields (60-95%) of crystalline adducts. Isatinylidene acetone is the most effective dienophile so far employed, closely followed by the dinitrile (Ib), but the adducts from the dinitrile and its N-benzyl derivative (Ic) rapidly undergo a reverse Diels-Alder reaction. Kinetic studies have been undertaken to examine the influence of the various substituents on the rate of reaction.

Satisfactory analyses were obtained for these compounds (with the exception of the dinitrile adducts) and for all the dihydro derivatives which were obtained by catalytic hydrogenation.



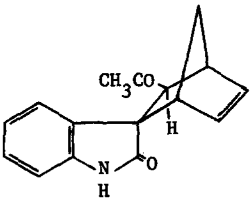
I

	a	b	c	d	e	f	g	h
R	$-COCH_3$	-CN	-CN	$-CO_2Et$	$-CO_2Et$	$-CO_2Et$	-CHO	$-CO_2H$
R^1	-H	-CN	-CN	-H	-H	-CN	-H	-H
R_2	-H	-H	$-CH_2Ph$	-H	$-CH_3$	-H	-H	-H

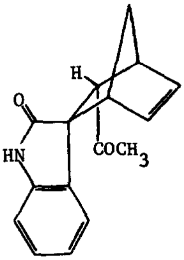
The structure of the adducts is determined both by the positions of the substituents relative to the double bond of the isatinylidene compound and also by their influence on the orientation of the Diels-Alder transition state (2).

The only relevant examination of the cis-trans isomerism of isatinylidene compounds is that of Autrey and Tahk (3) who assigned the structures on the basis of NMR studies. The dinitriles (Ib) and (Ic) were prepared to confirm their thesis that the position of the peak due to the C-4 proton was influenced by the carbonyl group in the ester (Id), aldehyde (Ig) and acid (Ih). The spectrum of the dinitrile (Ib) in acetone showed* a doublet centred at 1.90 which we assign to the C-4 proton under the deshielding influence of the cyano group and complimenting the assignment by Autrey of a doublet at 1.41 - 2.00 to the C-4 proton in all compounds of the trans series.

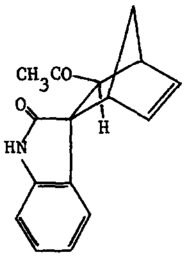
Prediction of the structure of the adduct from the ketone (Ia) and cyclopentadiene leads to the structure II if maximum overlap of the diene occurs with the isatinylidene double bond and the oxindole carbonyl group, and III if the overlap occurs with the acetyl carbonyl electrons.



II



III



IV

The NMR spectrum of the adduct obtained from isatinylidene acetone and cyclopentadiene showed two peaks due to the methyl protons of the acetyl group at 8.45 and 8.57, of relative

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* All NMR spectra were obtained using a Perkin-Elmer R10 60 Mc/s instrument with $CDCl_3$ as solvent unless otherwise specified. Chemical shifts are quoted on the τ scale.

intensity approximately 1:2, indicating the presence of two isomers which were obtained pure by chromatography on alumina; isomer A, m.p. 163-164° (dec.), CH_3 at 8.57 and isomer B, m.p. 147-149° (dec.), CH_3 at 8.45.

Heating the mixture of isomers in methanol led to a decrease in the relative intensity of the 8.45 signal with its complete disappearance after 72 hours. Chromatography of the product gave the ketone (Ia) presumably obtained from a reverse Diels-Alder reaction, together with the isomer A, which may therefore be assigned the more thermodynamically stable exo-configuration II.

This assignment has been supported by a study of the positions of the signals due to the acetyl protons in the NMR spectra of isomers A, B and their dihydro derivatives. The spatial relationship of these methyl protons and the benzene ring of the oxindole moiety, which is responsible for the shielding effect observed* is formally similar in structures II, III and their dihydroderivatives. However, inspection of a Dreiding model of the endo-isomer B reveals severe crowding between the benzene ring, bicyclo (2,2,1) heptene double bond and acetyl group which would be expected to modify the shielding of the acetyl protons and prevent the shielding behaviour of the endo- and exo-isomers following (4) the normal pattern. Removal of this interaction by hydrogenation of the double bond results in the acetyl protons of the dihydro adduct experiencing the same shielding effect as those of the dihydro derivative of isomer A (CH_3 at 8.58). The magnitude of this shielding agrees well with the correlation derived by Johnson and Bovey (5).

These data also eliminate IV as a possible structure for one of the isomers, as the acetyl protons in this molecule would not be appreciably shielded by the benzene ring.

The configuration and isomer composition of the adducts of the isatinylidene compounds Ib, Ic, Ie and If with cyclopentadiene and of If with cycloheptatriene are being investigated.

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* The methyl protons of endo-2-acetylnorbornene appear at 7.95 (CCl_4) and of the exo-isomer at 7.85. R.O. Williams. Private communication.

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