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THE DIELS-ALDER REACTION OF ISOPRENE WITH 2-OXOINDOLIN-3-YLIDENE DERIVATIVES

C. G. RICHARDS* and D. E. THURSTON†
School of Pharmacy, Portsmouth Polytechnic, Portsmouth, England

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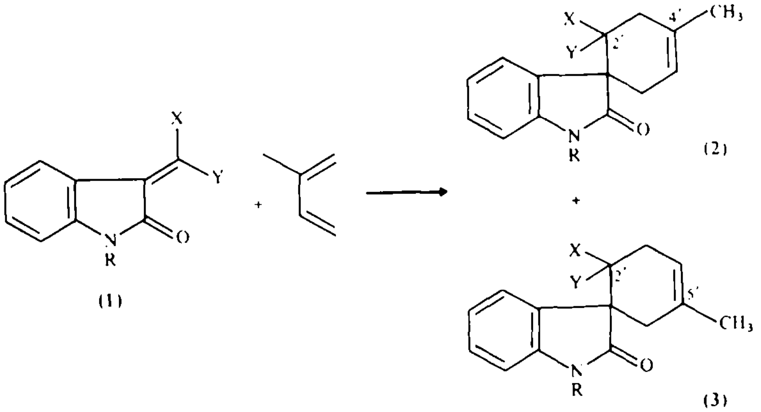
Abstract—The Diels-Alder reaction of isoprene with eight 2-oxoindoline-3-ylidene derivatives is discussed and the structure and conformation of the adducts assigned by the use of 270 MHz PMR spectroscopy. Some transformations of the adducts are also described.

The publication by Okada[1] of the results of reaction between 3 - methoxycarbonylmethylene - 2 - oxoindoline derivatives, penta - 1,3 - diene and 1 - acetoxybuta - 1,3 - diene has prompted us to report the results[2] of similar reactions between isoprene and a series of mono- and disubstituted 2 - oxoindolin - 3 - ylidene derivatives (**1a–l**) of known stereochemistry.[3,4] These findings represent a continuation of our studies[5–9] of the Diels-Alder reactivity of these compounds.

No reaction was observed when the components were heated together in various solvents but reaction in sealed tubes produced adducts from dienophiles **1a–h** (Table 2). The other compounds (**1i–l**) either did not react or produced polymers under more severe conditions.

TLC and 60 MHz PMR spectra indicated that the products after one crystallisation (with the exception of that from the methyl ketone (**1a**) which contained an isomer of unknown structure) consisted of one of the two possible adducts. However, 270 MHz PMR spectra allowed both structural and conformational analysis of the products and in three cases showed the presence of small amounts of the second isomer which were removed by further crystallisation.

The C-2′ protons of the monosubstituted adducts (**2a–d**) and adduct derivatives (**2m, 2n**) appeared as the expected doublet of doublets. However, the signals for the 3′-methylene group of the phenyl ketone (**2b**) and nitrile (**2c**) adducts appeared as broad doublets and those for the methyl ketone (**2a**) and nitro (**2d**) adducts as broad five-line multiplets which simplified to a doublet of doublets on irradiation of H2′. Modification of the 2′-substituent (**2m–p**) or the presence of a second group



	X	Y	R		X	Y	R
a	$COCH_3$	H	H	i	Cl	H	CH_3
b	COC_6H_5	H	H	j	H	OH	CH_3
c	CN	H	H	k	CO_2CH_3	OH	CH_3
d	NO_2	H	H	l	$NHCOCH_3$	H	H
e	$CO_2C_2H_5$	CN	H	m	$CONH_2$	H	H
f	CN	CN	H	n	NH_2	H	H
g	CO_2CH_3	CO_2CH_3	H	o	$CH(OH)C_6H_5$	H	H
h	$CO_2C_2H_5$	$CO_2C_2H_5$	H	p	$CH(Cl)C_6H_5$	H	H

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†Present address: The Drug Dynamics Institute, College of Pharmacy, University of Texas at Austin, Austin, TX 78712, U.S.A.

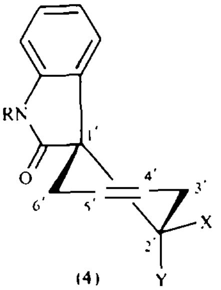
(**2e**, **3f–h**) increased the spread: $H3'_{ax}$, identified by coupling with $H2'_{ax}$ or, for isomers **3f–h**, by homoallylic coupling with the 5'-Me substituent, appeared at higher field than $H3'_{eq}$ except for the cyanoester (**2c**), amide (**2m**), alcohol (**2o**) and chloride (**2p**). This reversal may be attributed to shielding of $H3'_{eq}$ by the cyano group or the side-chain benzene ring and the use of d^5-pyridine as solvent for the amide.

The position of the Me group, at either C-4' or C-5', could be deduced from the appearance of the C-6' methylene group. The upfield arm ($H6'_{eq}$) of the widely spread doublet of doublets showed a 5 Hz coupling when the vinylic proton occurred at position 5' but did not when this position was occupied by the Me group in the adducts from compounds (**1f–h**).

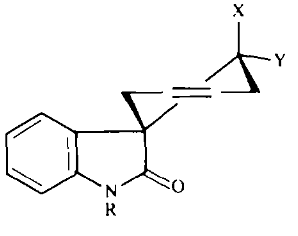
These allocations are supported by the homoallylic coupling† of ~ 2.5 Hz between the Me group and $H6'_{ax}$ in the 4'-Me adducts and $H3'_{ax}$ in the 5'-Me isomers. Spin decoupling revealed no discernable coupling between the Me group and either $H6'_{eq}$ or $H3'_{eq}$ except for the dinitrile (**3f**) in which the 5'-Me substituent was coupled to both C-3' protons. These observations are in accord with the angular dependence[10–14] of ^5J coupling.

$J3'_{eq}$-4' and $J3'_{ax}$-4' in the 5'-Me series (**3f–h**) were both found to be less than 1 Hz, similar in magnitude to the coupling between $H6'_{ax}$ and H5' in the 4'-Me adducts. The allylic coupling between H5' and C-3' protons, in the 4'-Me adducts (**2**), and between H4' and C-6', in the 5'-Me adducts (**3**), was also less than 1 Hz.

The preferred half-chair conformation (**4**) of these adducts may be established by consideration of J2'-3', as Dreiding models indicate dihedral angles of ~ 165° and 45° between $H2'_{ax}$ and $H3'_{ax}$ and $H3'_{eq}$ respectively. Karplus equates[15] these angles to J values of 9.5 and 4.5 Hz, reasonable agreement[16,17] with observed values (Table 1). The dihedral angles of 70° and 50° in the alternative conformer (**5**) imply coupling constants of 0.5 and 3.5 Hz.



(4)



(5)

The shielding of $H6'_{eq}$ by the oxoindoline CO group implicit in conformation **4** also rationalises the high field position of this proton's signal and the model suggests angles of ~ 80° and 40° between H5' and $H6'_{ax}$ and $H6'_{eq}$ giving J values[18] of < 0.5 and 6 Hz in agreement with those found. Okada suggested[1] a similar conformation for the adducts of 1,3-pentadiene and 1-acetoxybutadiene as marked shielding of the $6'_{eq}$-methyl and acetoxy groups was also observed.

The 270 MHz spectra of the adducts from three 2-oxoindolylidene derivatives (**1b**, **1g**, **1h**) showed signals for both major and minor isomers. The Me and vinyl protons of the 5'-Me isomers resonated at higher and lower field respectively than those of the 4'-Me adducts (Table 1). These differences are attributable to the juxtaposition of the 4'-position and the benzene ring in conformation **4**.

The amide (**2m**) was prepared by treatment[19] of the nitrile (**2c**) with alkaline peroxide but Hoffman transformation to the amine failed. This compound (**2n**) was obtained by Zn/acid reduction of the nitro compound (**2d**) after failure of catalytic and aluminium amalgam reduction.[20,21] All attempts to prepare a spirocyclohexanone by a Nef reaction[22,23] or variations[24–27] returned only the nitro adduct (**2d**). This behaviour contrasted with the formation[28] of a stable nitronic acid by the analogous 2' - nitro - 2 - oxoindoline - 3 - spiro - 3' - bicyclo[2,2,1] - hex - 5' - ene. Oxidation of the amine (**2n**) by Corey's method[29] involving 3,5 - di - t - butyl - 1,2 - benzoquinone or via the N-chloroamine[30–32] and imine[33,34] was also unsuccessful.

The phenyl ketone (**2b**) was transformed to the alcohol (**2o**) and chloride (**2p**) by standard reactions but dehydration or dehydrochlorination did not succeed.

EXPERIMENTAL

IR spectra were obtained from Nujol mulls on a Perkin-Elmer 257 spectrometer and are recorded in cm^{-1}. PMR spectra were recorded in $CDCl_3$, unless otherwise specified, using a Bruker WH270 spectrometer; resonances are recorded in ppm downfield from TMS as internal standard. Empirical analyses were performed by the School of Pharmacy, University of London. M.ps were recorded on a Gallenkamp apparatus and are uncorrected. TLC was carried out using 0.25 mm Merck Kieselgel GF_{254} (Type 60) plates with EtOAc-light petroleum (2 : 1) as eluant. Light petroleum refers to the fraction of boiling range 60–80°.

Reaction of 2-oxoindolin-3-ylidene derivatives with isoprene

The dienophile and isoprene (2.5 molar excess) in $CHCl_3$ containing hydroquinone were heated under N_2 in a sealed glass tube which was then cooled in ice for 1 hr before opening. The volatile material was removed *in vacuo* from the mixture, the residual solid or oil triturated with EtOAc-light petroleum (2 ; 1) and the product collected, washed and dried. All adducts were crystallised from EtOAc-light petroleum, decolourising with charcoal when necessary. The results of typical runs are recorded in Table 2.

Reaction of 2-oxoindolin-3-ylideneacetone with isoprene

A suspension of **1a** (12.5 g; 0.0668 mole), isoprene (11.38 g; 0.167 mole) and hydroquinone (150 mg) in dry $CHCl_3$ (70 ml) were heated under N_2 in a sealed glass tube at 145–155° for 29 hr. The usual work-up afforded a mixture of two compounds (6.67 g, 39%), m.p. 193–195°, 1.40 g of which was separated by column chromatography on silica gel (BDH 60–120 mesh; 320 g) using EtOAc as eluant. The *adduct* **2a** (0.27 g) m.p. 232–235° was crystallised from EtOAc–light petroleum to give the analytical sample, m.p. 244–245°. (Found: C, 74.98; H, 6.82; N, 5.37, $C_{16}H_{17}NO_2$ requires: C, 75.27; H, 6.71; N, 5.49%). The slower running *isomer* (0.91 g) m.p. 209–210° gave the analytical sample, m.p. 210–211°, on crystallisation from acetone/light petroleum. Found: C, 75.18; H, 6.79; N, 5.47%. IR 3170, 1715, 1670. PMR ($CDCl_3/d^6$-DMSO) 9.56 (NH, s), 2.78 (CH_3, s), 1.29 (d, J 7 Hz), 2.16 (s), 1.97 (m), 1.56 (m).

The amide (2m)

H_2O_2 (8 ml; 30%) was added dropwise over 1 min to a stirred soln of **2c** (0.35 g; 1.47 mmole) and NaOH (2 ml; 20%) in EtOH (20 ml). The mixture was heated slowly to 40° and maintained at this temp for 2 hr. Removal of the EtOH *in vacuo* and filtration of the aqueous sludge gave the *amide* **2m** (0.27 g; 72%), m.p. 305–309°. Three crystallisations from EtOH gave the analytical sample, m.p. 313–314°. (Found: C, 70.22; H, 6.35; N, 10.91, $C_{15}H_{16}N_2O_2$ requires: C, 70.29; H, 6.29; N, 10.93%).

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†This coupling appeared as line-broadening in the compounds **2m**, **2o** and **2p**.

Table 1. PMR and IR parameters for the Diels–Alder adducts and related compounds

	H4' or H5'	$H2'_{ax}$	J		$H6'_{ax}$	$H6'_{eq}$	J		$H3'_{eq}$	$H3'_{ax}$	J	CH_3	NH	Others	Minor Isomer		Infra red		
			$2'_{ax}$-$3'_{ax}$	$2'_{ax}$-$3'_{eq}$			$6'_{ax}$-$6'_{eq}$	$6'_{eq}$-5'			$3'_{ax}$-$3'_{eq}$				CH_3	H4' or H5'	NH-	CO	Others
2a	5.44	3.33	11.0	6.5	2.61	1.90	17.5	5.0	2.42 (a)	2.34 (a)	17.5	1.84	7.65	$C\underline{H}_3CO$– 2.06	-	-	3350	1700	$COCH_3$ 1725
2b	5.47	4.20	10.0	8.0	2.73	1.97	17.0	5.5	2.45 (b)	-	-	1.79	7.87	-	1.71	5.56	3150	1705	PhCO 1690
2c	5.49	3.23	9.5	8.0	2.63	2.09	17.0	5.0	2.53 (b)	-	-	1.81	7.92	-	-	-	3380	1720	CN 2240
2d	5.41	5.08	10.5	7.5	2.73	2.11	17.0	5.0	2.95 (a)	2.86 (a)	17.5	1.86	7.92	-	-	-	3165	1725	NO_2 1540, 1380
2e	5.55	-	-	-	3.04	2.11	17.0	4.5	2.72	3.02	17.5	1.88	8.49	CH_2 CH_3 3.99 1.08	-	-	3360	1705	CN CO_2Et 2240 1742
3f	5.53	-	-	-	2.67	2.38	18.0	-	3.22	2.93	17.5	1.81	8.15	-	-	-	3190	1715	CN 2250
3g	5.52	-	-	-	2.90	1.84	16.0	-	2.89	2.70	17.5	1.70	7.65	CH_3 CH_3 3.69 3.42	1.84	5.44	3170	1710	CO_2Me 1752, 1728
3h	5.52	-	-	-	2.91	1.86	16.0	-	2.91	2.76	18.0	1.69	7.76	CH_2 CH_3 3.88 1.00 4.16 1.22	1.84	5.44	3170	1715	CO_2Et 1750, 1735
(c) 2m	5.36	3.57	11.0	6.0	2.90	2.03	16.5	5.5	2.53	2.99	17.5	1.71	8.56	-	-	-	3300	1710	$CONH_2$ 1670, 3465, 3355
2n	5.41	3.41	10.5	6.0	2.71	2.05	16.5	5.5	2.36	2.04	17.5	1.79	8.12	-	-	-	3210	1700	NH_2 3370, 3280
(d) 2o	5.35	2.61	12.0	5.0	2.70	1.94	16.5	5.5	1.83	2.47	17.5	1.73	-	$PhC\underline{H}$– 4.70($\overline{J}$ 2Hz)	-	-	3260	1690	OH 3400
2p	5.36	2.85	10.5	5.5	2.63	1.88	17.0	5.5	2.30	2.46	17.5	1.77	7.83	$PhC\underline{H}$– 4.68($\overline{J}$ 5Hz)	-	-	3160	1710	-

(a) By irradiation at $H2'_{ax}$

(b) This doublet collapses to a singlet on irradiation at $H2'_{ax}$

(c) d^5-pyridine

(d) $CDCl_3/D_2O$

Table 2. Reaction of 2-oxoindolin-3-ylidene derivatives with isoprene

Dienophile g; mole	Hydroquinone mg	Solvent ml	Reaction Conditions °/hr	Initial Weight g	mp	Yield %	Number of crystallisations for analysis	mp	Formula	Analysis Found Required C	H	N
1b; 20.00; 0.0802	250	70	140–50/24	18.32	203–208	72	4	220–221	$C_{21}H_{19}NO_2$	79.20 79.47	6.09 6.03	4.40 4.41
1c; 20.00; 0.118	250	70	115–25/24	20.21	190–195	72	3	202–203	$C_{15}H_{14}N_2O$	75.18 75.60	5.92 5.92	11.57 11.76
1d; 12.00; 0.0631	300	40	85–95/118	5.70	207–210	35	3	214–215	$C_{14}H_{14}N_2O_3$	65.22 65.10	5.62 5.46	10.75 10.85
1e; 20.00; 0.0826	250	70	130–150/24	21.04	176–179	82	3	184–185	$C_{18}H_{18}N_2O_3$	69.60 69.66	5.96 5.85	9.02 9.03
1f; 30.00; 0.154	500	120	135–45/24	26.05	193–195	64	5	200–201	$C_{16}H_{13}N_3O$	72.51 72.98	5.01 4.98	15.87 15.96
1g; 15.00; 0.0574	200	60	115–125/24	14.07	169–175	74	2	187–188	$C_{18}H_{19}NO_5$	65.81 65.64	5.94 5.82	4.16 4.25
1h; 19.00; 0.0657	250	70	135–145/29	8.94	193–196	38	5	200–201	$C_{20}H_{23}NO_5$	67.10 67.20	6.54 6.50	3.85 3.92

The amine (**2n**)

Zn dust (10 g) was added in 1 g portions over a period of 1 hr to a vigorously stirred soln of **2d** (3.0 g; 11.6 mmole) in MeOH (500 ml) containing conc HCl (40 ml) and water (100 ml); the temp of the mixture was kept below 20°. The mixture was stirred for an additional hr and allowed to stand for 15 hr. After filtration and removal of MeOH *in vacuo*, the aqueous residue was made alkaline with NaOH (20%); isolation with CH_2Cl_2 afforded the *amine* **2n** (1.34 g; 51%), m.p. 167–169°. One crystallisation from EtOAc gave the analytical sample, m.p. 168–169°. (Found: C, 73.70; H, 7.03; N, 12.37. $C_{14}H_{16}N_2O$ requires: C, 73.65; H, 7.06; N, 12.27%).

The benzyl alcohol (**2o**)

The ketone **2b** (6.5 g; 20.5 mmole) in dry EtOH (500 ml) was heated under reflux for $1\frac{1}{2}$ hr with $NaBH_4$ (1.0 g; 26.4 mmole). After removal of the solvent and trituration of the residue with water (20 ml), the *alcohol* **2o** (6.35 g; 97%) m.p. 209–210° was collected, washed with water and dried. The analytical sample was obtained by four crystallisations from EtOAc-light petroleum, m.p. 228–229°. (Found: C, 79.62; H, 6.75; N, 4.51. $C_{21}H_{21}NO_2$ requires: C, 78.97; H, 6.63; N, 4.39%).

The chloride (**2p**)

$SOCl_2$ (0.4 g; 3.36 mmole) was added dropwise over 15 min to a vigorously stirred soln of **2o** (0.8 g; 2.50 mmole) in dry pyridine (5 ml) at 0°. The stirring was continued for 1 hr, water (5 ml) added and the soln acidified with conc HCl. The *chloride* **2p** (0.71 g; 84%), m.p. 174–175° was isolated with ether, three crystallisations from light petroleum (b.p. 80–100°) gave the analytical sample, m.p. 175–176°. (Found: C, 73.97; H, 6.22; N, 3.90; Cl, 9.59. $C_{21}H_{20}NOCl$ requires: C, 74.65; H, 5.96; N, 4.15; Cl, 10.49%).

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REFERENCES

[1] K. Okada, H. Sakuma, M. Kondo and S. Inoue, *Chem. Lett.* **3**, 213 (1979).
[2] D. E. Thurston, Ph.D. Thesis, Portsmouth Polytechnic (1980).
[3] D. R. Long, C. G. Richards and M. S. F. Ross, *J. Heterocyclic Chem.* **15**, 633 (1978).
[4] G. Jones and W. J. Rae, *Tetrahedron* **22**, 3021 (1966).
[5] M. S. F. Ross, Ph.D. Thesis, University of London (1971).
[6] C. G. Richards and M. S. F. Ross, *Tetrahedron Letters* 4391 (1968).
[7] D. R. Long, Ph.D. Thesis, Portsmouth Polytechnic (1975).
[8] C. N. Herring, Ph.D. Thesis, Portsmouth Polytechnic (1973).
[9] N. Raeburn, Ph.D. Thesis, Portsmouth Polytechnic (1978).
[10] M. Karplus, *J. Chem. Phys.* **33**, 1842 (1960).
[11] S. Sternhell, *Rev. Pure and Appl. Chem.* **14**, 15 (1964).
[12] C. N. Banwell and N. Sheppard, *Disc. Faraday Soc.* **34**, 115 (1962).
[13] C. Cimarusti and J. Wolinsky, *J. Org. Chem.* **31**, 4118 (1966).
[14] R. J. Abraham, H. Gottschalck, H. Paulsen and W. A. Thomas, *J. Chem. Soc.* 6268 (1965).
[15] M. Karplus, *J. Chem. Phys.* **30**, 11 (1959).
[16] M. Karplus, *J. Am. Chem. Soc.* **85**, 2870 (1963).
[17] R. J. Abraham and K. G. R. Pachler, *Mol. Phys.* **7**, 165 (1963).
[18] G. V. Smith and H. Krilof, *J. Am. Chem. Soc.* **85**, 2016 (1963).
[19] Vogel, *Textbook of Practical Organic Chemistry* (4th Edn). Longmans, London (1978).
[20] E. J. Corey, N. H. Anderson, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas and R. E. K. Winter, *J. Am. Chem. Soc.* **90**, 3245 (1968).
[21] E. J. Corey, I. Vlattas, N. H. Anderson and K. Harding, *Ibid.* **90**, 3247 (1968).
[22] E. E. van Tamelen and R. J. Thiede, *Ibid.* **74**, 2615 (1952).

[23] N. Kornblum and R. A. Brown, *Ibid.* **87**, 1742 (1965).

[24] E. Keinan and Y. Mazur, *Ibid.* **99**, 3861 (1977).

[25] J. E. McMurry, J. Melton and H. Padgett, *J. Org. Chem.* **39**, 259 (1974).

[26] A. K. Mehrotra, D. Ranganathan and S. Ranganathan, *J. Am. Chem. Soc.* **96**, 5261 (1974).

[27] N. Kornblum and P. A. Wade, *J. Org. Chem.* **38**, 1418 (1973).

[28] D. R. Long and C. G. Richards, *Tetrahedron Letters* 1603 (1975).

[29] E. J. Corey and K. Achiwa, *J. Am. Chem. Soc.* **91**, 1429 (1969).

[30] H. Ruschig, W. Fritsch, J. Schmidt-Thome and W. Haede, *Chem. Ber.* **88**, 883 (1955).

[31] D. T. Sawyer and M. J. Gibian, *Tetrahedron* **35**, 1471 (1979).

[32] F. E. Scully Jnr. and R. C. Davis, *J. Org. Chem.* **43**, 1467 (1978).

[33] W. E. Bachmann, M. P. Cava and A. S. Dreiding, *J. Am. Chem. Soc.* **76**, 5554 (1954).

[34] J. Schmidt-Thome, *Chem. Ber.* **88**, 895 (1955).