The Stereochemistry of 2-Oxoindolin-3-ylidene Derivatives

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The stereochemistry of a number of functionally-substituted 2-oxoindolin-3-ylidene derivatives has been established by a study of pmr and ir spectroscopy. These compounds have been shown to exist as one isomer with the exception of the substituted acetonitriles.

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The stereochemistry of 2-oxoindolin-3-ylidene derivatives has, until recently, received little attention with the majority of interest directed toward the alkylidene and arylidene 2-oxoindolines (1-6). Apart from the assignment (7) of stereochemistry to the enol (**1v**), the first attempts to elucidate the configuration of functionally substituted 2-oxoindolin-3-ylidene derivatives were made by Jones and Rae (8), and Autrey and Tahk (9) using the marked deshielding of the C-4 proton by the *cis* C-1′ substituent in the pmr spectrum of the E-isomers. We have extended their studies to determine the stereochemistry of 2-oxoindolin-3-ylidene derivatives required for the assignment of structure to the adducts formed by these compounds in the Diels-Alder reaction (10,11). During the course of this work, the use of this technique was reported to establish the configuration of three 2-oxoindolin-3-ylideneacetates (12), including **1m**, and of 2-oxoindolin-3-ylidenemercaptoacetic acid (13) and some related compounds.

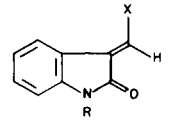
A number of derivatives carrying a hydrogen atom at C-1′, with the exception of the nitriles (**1d,1g**) and the amine (**1t**), were found to be exclusively E-isomers. The related glyoxylic esters were shown to have the Z-configuration so confirming and extending Autrey's prediction (9) that all monosubstituted 2-oxoindolin-3-ylidene derivatives which have a carbonyl group β to C-3 (C-1′) will be found to be *trans* isomers.

The H-4 doublets of the two phenyl ketones **1a** and **1b** are obscured by other aromatic protons, but their presence, and so the E-configuration, may be inferred. The ketone **1a** shows a broad multiplet of three protons, H-4 and the two protons *ortho* to the carbonyl group (acetophenone 2.09 τ); the downfield multiplet of the ketone **1b** also includes the C-7 proton, deshielded by the *N*-acetyl group. These results confirm those derived by chemical means (15) and reported as probable from the positions of the C-1′ proton resonances (25).

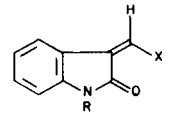
The deshielded doublets of the chloro- compounds (**1p-1r**) provide a third example of pronounced long-range deshielding by chlorine. The previous shifts have been reported (26-28) for two other systems which maintain the hydrogen and chlorine atoms in a similar spatial relationship (26,29), about 2.3 Å apart (estimated from Büchi models for **1p-1r**).

The two nitriles (**1d,1e**) are of interest as another example of 2-oxoindolin-3-ylidene derivatives which exist as an E,Z-pair. Autrey prepared (9) the acids **2a** and **2b**, and aldehydes **3a** and **3b**, and Sawayama recently described (13) the acids **4a** and **4b**. The E-nitrile was prepared by Pietra's method (30) and the Z-nitrile, detected in the reaction mixture by thin-layer chromatography, was isolated by fractional crystallisation and preparative high-performance liquid chromatography. The existence of the Z-isomer presumably derives from the small size and linearity of the cyanide moiety which minimises interactions with the 2-indolinone carbonyl group in the conformations discussed (9) by Autrey; however, the Z-nitrile slowly isomerises in dimethylsulphoxide solution.

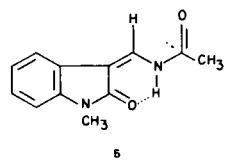
These minimal interactions result in the ready isomerisation of the E-nitrile (**1d**) on acetylation; the resulting mixture was inseparable by crystallisation, preparative thin layer or column chromatography. A small sample of E-1-acetylnitrile (**1g**) was isolated by high-performance liquid chromatography, the Z-isomer reisomerised too rapidly for spectra of the pure compound to be obtained.



2a, R = CH_2Ph; X = CO_2H
3a, R = CH_2Ph; X = CHO
4a, R = H; X = CO_2H



2b, R = CH_2Ph; X = CO_2H
3b, R = CH_2Ph; X = CHO
4b, R = H; X = CO_2H



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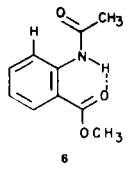
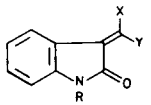


6

The configuration of the amine (**1t**) was deduced from its infrared spectrum and the structure of its N_b-acetyl derivative. The lactam carbonyl band of the amine appears, irrespective of dilution, at 1670 cm^{-1} in nujol and chloroform, indicating intramolecular hydrogen bonding possible only in the Z-isomer. The carbonyl bands of the 2-oxoindolin-3-ylidene derivatives which are capable of similar hydrogen bonding (**1h-1j,1v**) fall in the range 1650-1675 cm^{-1}, whereas the others absorb between 1710 and 1745 cm^{-1}.

The pmr spectrum of the N_b-acetyl derivative (**1u**) indicates the structure (5). The downfield position of the NH resonance at -0.95 τ derives from its involvement in intramolecular bonding. The consequent coplanarity

Table I



Compound	R	X	Y	H-4 (a)	δ τ	H-1′	Solvent	Other Features	ν CO cm^{-1}
1a(14)	H	COPh	H	1.83 (b)	-----	2.08	deuteriochloroform/trifluoroacetic acid		1714
				1.87 (b)		2.07	deuteriochloroform/DMSO-d_6		
1b(15)	$COCH_3$	COPh	H	1.74 (c)	-----	2.10	deuteriochloroform		1743
1c	$COCH_3$	$COCH_3$	H	1.37	1.28	2.82	deuteriochloroform	H-7, 1.70; δ τ 0.95	1744
1d	H	CN	H	1.90	0.76	3.57	deuteriochloroform/trifluoroacetic acid		1721
				2.06	0.71	3.64	deuteriochloroform/DMSO-d_6		
1e	H	H	CN	-----	-----	3.22	deuteriochloroform/DMSO-d_6		-----
1f	H	CN	CN	2.08	0.60	-----	DMSO-d_6		1710
1g	$COCH_3$	CN	H	1.85	0.78	3.69	deuteriochloroform	H-7, 1.72;	1752
				1.94 (d)	-----	3.37	deuteriochloroform/DMSO-d_6	δ τ 0.91	
1h(16)	H	$CO_2C_2H_5$	OH	1.89	0.98	---	deuteriochloroform/DMSO-d_6	OH, -1.08; NH, -1.30	1660
1i(17)	CH_3	$CO_2C_2H_5$	OH	1.67	1.12	-----	deuteriochloroform	OH, -3.80	1659
				1.86	1.06		deuteriochloroform/DMSO-d_6	OH, -1.39	
1j	CH_3	CO_2CH_3	OH	1.86	1.02	-----	deuteriochloroform/DMSO-d_6	OH, -1.79	1650
1k(18)	H	$CO_2C_2H_5$	H	1.49	1.29	3.28	deuteriochloroform/DMSO-d_6		1715
1l	CH_3	$CO_2C_2H_5$	H	1.45	1.29	3.20	deuteriochloroform/DMSO-d_6		1712
1m	CH_3	CO_2CH_3	H	1.44	1.43	3.09	deuteriochloroform		1710
1n	$COCH_3$	$CO_2C_2H_5$	H	1.25	1.37	3.09	deuteriochloroform	H-7, 1.67; δ τ 0.95	1745
1o(19)	H	$CONH_2$	H	1.40	1.44	3.03	DMSO-d_6		1710
1p(20)	H	Cl	H	2.01	0.79	2.42	deuteriochloroform/trifluoroacetic acid		1710
1q(21)	CH_3	Cl	H	2.07	0.92	2.59	deuteriochloroform		1712
1r(22)	H	Cl	Cl	2.03	0.77	-----	deuteriochloroform/trifluoroacetic acid		1711
				2.10	0.74		DMSO-d_6		
1s	H	NO_2	H	1.80	1.03	2.38	deuteriochloroform/DMSO-d_6		1715
1t(23)	CH_3	H	NH_2	-----	-----	2.95	deuteriochloroform		1670
1u	CH_3	H	$NHCOCH_3$	-----	-----	1.96 (d)	deuteriochloroform	NH, -0.95 (e)	1670
1v(7)	CH_3	H	OH	-----	-----	2.00	deuteriochloroform/DMSO-d_6		1675

(a) This proton appears as a doublet (J ~ 7.5 Hz) with further splitting, sometimes clearly discernable, of ~ 1.8 Hz. (b) Three-proton multiplet. (c) Four-proton multiplet. (d) Two-proton multiplet. (e) Doublet (J = 11 Hz).

and proximity of the amide carbonyl to the vinyl hydrogen atom results in its appearance as a deshielded doublet at 1.96 τ (J = 11 Hz) which reduces to a singlet on deuteration. These results agree well with those reported by Gribble and Bousquet (31) for *o*-substituted amides such as (6), NH at -1.0, H-6 at 1.25 τ.

The shift (8) of the H-4 doublet from the mid-point of the aromatic multiplet (δ τ, Table I) gives a measure of the deshielding produced by each substituent.

EXPERIMENTAL

Pmr spectra were obtained using a Varian EM 360 spectrometer; chemical shifts are quoted in τ units. Ir spectra were recorded (in cm^{-1}) on Perkin-Elmer 257 and 377 spectrometers. Pre-coated silica gel (Merck GF_{254} Type 60) plates were used for tlc with 1:2 ethyl acetate/light petroleum as eluant. Light petroleum refers to the fraction b.p. 60-80°. All melting points are uncorrected. Elemental analyses were performed by G. Crouch, School of Pharmacy, University of London.

E-1-Acetyl-2-oxoindolin-3-ylideneacetone (**1c**).

E-2-Oxoindolin-3-ylideneacetone (32) (500 mg.) and anhydrous sodium acetate (500 mg.) in acetic anhydride (10 ml.) were heated on a steam bath for 30 minutes. The mixture was cooled, poured into ice-water (150 ml.) and the ketone (**1c**) (210 mg., 31%) was collected, m.p. 128-129°. An analytical sample was recrystallised from light petroleum, m.p. 129.5-130°; ir (nujol): 1744, 1710, 1610.

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.23; H, 4.79; N, 5.92.

E- and Z-2-Oxoindolin-3-ylideneacetonitrile (**1d** and **e**).

Z-2-Oxoindolin-3-ylidenecyanoacetic acid (33) (4.3 g.) was heated under reflux in pyridine (10 ml.) for 1.5 hours and cooled. Glacial acetic acid (25 ml.) was added and the solution was poured into water (250 ml.) to give the crude nitriles (2.50 g.), m.p. 184-185°. Two crystallisations from ethyl acetate/light petroleum followed by one from methanol gave the E-nitrile (**1d**), m.p. 202-203°. Pietra (30) reports m.p. 193-194°. A sample from the **mother** liquor of the first recrystallisation was chromatographed on a 20 cm x 1 cm I.D. stainless-steel column packed with Partisil 10 μ (Jones Chromatography) using 10% ethyl acetate in cyclohexane as eluant at a flow rate of 4 ml./minute from a Type 6000M solvent delivery system (Waters Assoc.) to yield almost pure Z-nitrile (80 mg.). Crystallisation from ethyl acetate/light petroleum gave the Z-nitrile (**1e**) (40 mg.), m.p. 170-171°. The DMSO-d_6 solution of this compound slowly deposited crystals of **1d**, m.p. 202-203° over a period of two weeks.

E- and Z-1-Acetyl-2-oxoindolin-3-ylideneacetonitrile.

E-2-Oxoindolin-3-ylideneacetonitrile (500 mg.) and anhydrous sodium acetate (500 mg.) in acetic anhydride (10 ml.) were heated on a steam bath for 30 minutes. The mixture was cooled, poured into ice-water (100 ml.) and the mixture of nitriles (600 mg., 96%), m.p. 146-147° collected. An analytical sample was recrystallised from ethyl acetate/light petroleum, m.p. 150-150.5°; ir (nujol): 2210, 1750, 1707, 1600.

Anal. Calcd. for $C_{12}H_8N_2O_2$: C, 67.91; H, 3.80; N, 13.20. Found: C, 67.90; H, 3.90; N, 13.10.

A sample of the crude mixture was chromatographed as above to give the E-1-acetyl nitrile (**1g**) (15 mg.), m.p. 152-153°.

Z-Methyl 1-Methyl-2-oxoindolinyl-3-glyoxylate (**1j**).

1-Methyl-2-oxoindolinone (29.4 g.), dimethyl oxalate (23.6 g.) and sodium methoxide (from sodium (6.9 g.)) in methanol (300 ml.) were heated under reflux for 8 hours. The solution was concentrated to one-third volume, acidified, and the ester (**1j**) (40.9 g., 90%), m.p. 104-108° isolated with chloroform. Two crystallisations from methanol gave the analytical sample, m.p. 109.5-110°; ir (nujol): 1734, 1650, 1608.

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 62.03; H, 4.81; N, 5.72.

Methyl α-Hydroxy-1-methyl-2-oxoindolinyl-3-acetate.

The ester **1j** (15.0 g.) in methanol (300 ml.) was hydrogenated at 80 p.s.i. over 10% palladised charcoal (500 mg.). Removal of catalyst and solvent afforded the hydroxyester (12.2 g., 86%), m.p. 134-135°. An analytical sample was obtained by two crystallisations from benzene/light petroleum, m.p. 137-138°; ir (nujol): 3320, 1698, 1608.

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.23; H, 5.67; N, 6.00.

E-Methyl 1-Methyl-2-oxoindolin-3-ylideneacetate (**1m**).

The hydroxyester (11.2 g.) was heated in methanol (100 ml.) containing concentrated hydrochloric acid (5 ml.) at 60° for 20 minutes. The ester (**1m**) (5.83 g., 56%), m.p. 136-137°, separated on cooling. An analytical sample was recrystallised from methanol, m.p. 136-137°. Tacconi (12) reports m.p. 140-141°; ir (nujol): 1710, 1600.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.09; H, 5.18; N, 6.63.

Ethyl α-Hydroxy-1-methyl-2-oxoindolinyl-3-acetate.

Z-Ethyl 1-methyl-2-oxoindolinyl-3-glyoxylate (17) (19.0 g.) in ethanol (250 ml.) was hydrogenated over Adams' catalyst (500 mg.). Removal of catalyst and solvent gave the acetate (16.0 g., 83%), m.p. 120-121°. Recrystallisation from ethyl acetate/light petroleum gave the analytical sample, m.p. 121-121.5°; ir (nujol): 3328, 1701, 1605.

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.24; H, 6.07; N, 5.62. Found: C, 62.48; H, 6.12; N, 5.59.

E-Ethyl 1-Methyl-2-oxoindolin-3-ylideneacetate (**1l**).

The hydroxyester (14.0 g.) was kept at 20° in glacial acetic acid (100 ml.) containing concentrated sulfuric acid (4 ml.) for 3 hours. Addition of water (300 ml.) gave the ester (**1l**) (7.2 g., 55%), m.p. 83-85°. Two crystallisations from aqueous ethanol gave the analytical sample, m.p. 85-85.5°; ir (nujol): 1712, 1600.

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.11; H, 5.56; N, 5.96.

E-Ethyl 1-Acetyl-2-oxoindolin-3-ylideneacetate (**1n**) (35).

Ethyl α-hydroxy-2-oxoindolinyl-3-acetate (18) (500 mg.) and anhydrous sodium acetate (500 mg.) were heated under reflux in acetic anhydride (25 ml.) for 8 hours. The cooled mixture was poured into water (200 ml.) and the ester (**1n**) (510 mg., 93%), m.p. 87-89° collected. Two crystallisations from ethanol gave the analytical sample, m.p. 88.5-89°; ir (nujol): 1745, 1719, 1710; (chloroform): 1745, 1712.

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.86; H, 5.01; N, 5.37.

Compound **1n** was also obtained, in lower yield, by acetylation of **1k**.

E-2-Oxoindolin-3-ylidenenitromethane (**1s**) (34).

Triethylamine (4.04 g.) in methanol (10 ml.) was rapidly added to a vigorously stirred solution of 3-chloro-3-nitromethyl-2-oxoindoline (2) (9.06 g.) in methanol (60 ml.). The immediate

addition of water (180 ml.) gave the nitro compound (**1s**) (7.65 g., 95%), m.p. 158-160° dec. An analytical sample was recrystallised from methanol, m.p. 159-160° dec.; ir (nujol): 3190, 3090, 1715, 1610, 1510, 1335.

Anal. Calcd. for $C_9H_6N_2O_3$: C, 56.84; H, 3.18; N, 14.73. Found: C, 57.04; H, 3.09; N, 14.61.

Z-3-Acetamidomethylene-1-methyl-2-oxoindoline.

The amine **1t** (5.0 g.) and acetic anhydride (60 ml.) were heated under reflux in pyridine (25 ml.) for 1.5 hours. The amide **1u** (4.51 g., 72%), m.p. 183-184° crystallised on cooling. An analytical sample, m.p. 186.5-187° was obtained by three crystallisations from ethanol; ir (chloroform): 3280, 1710, 1680, 1630. Positions were unaffected by concentration.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.56; H, 5.41; N, 12.81.

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