The Reaction of Indolizines with Esters of Orthoformic Acid: Synthesis of Tris-indolizine Molecular Propellers

Olof Ceder* and Mohammed Rashid Sharif

Department of Organic Chemistry, University of Gothenburg, Kemigården 4, S-41296 Gothenburg, Sweden

Received August 25, 1986

A series of tris(indolizinyl)methanes (**2**, **3**) have been prepared from esters of orthoformic acid and indolizines (**1**) substituted in the five-membered ring. The tris(indolizinyl)methanes are three-bladed molecular propellers in which the three blades are structurally identical lacking local C_2 axes. Compounds of this type are chiral and eight stereoisomeric conformations are possible.

Reaktion von Indolizinen mit Orthoameisensäureestern: Synthese von molekularen Tris-indolizin-Propellern

Aus Orthoameisensäureestern und im Fünfring substituierten Indolizinen (**1**) wird eine Serie von Tris(indolizinyl)methanen (**2**, **3**) dargestellt. Diese sind molekulare Dreiblatt-Propeller, in denen die drei Flügel bei Fehlen einer lokalen C_2-Achse strukturell identisch sind. Verbindungen dieses Typs sind chiral. Acht stereoisomere Konformationen sind möglich.

In the presence of strong acids of Lewis- or Brönstedt-type, esters of orthoformic acid form dialkoxycarbonium ions[1,2,3] which can electrophilically attack activated aromatic systems to form trisubstituted methanes. The first example of such a reaction seems to have been reported by Fischer and Körner in 1884[4a], who treated *N,N*-dimethylaniline with triethyl orthoformate and obtained the triphenylmethane compound leuco crystal violet. Later, Harley-Mason and Bu'Lock[4b] treated indole with triethyl orthoformate and obtained tris(3-indolyl)methane; the analogues from some 2- and 3-substituted indoles have also been reported[2,5,6]. A plausible mechanism for the reaction has been put forward by Pindur et al.[2a].

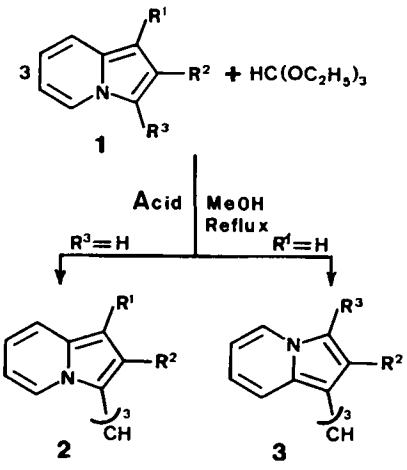
Indolizine, the isoelectronic isomer of indole, which contains a non-protonable bridgehead N-atom, can be expected to react analogously with orthoformates. In the present communication we report the preparation of a variety of tris compounds from 2- and 1,2- or 2,3-substituted indolizines and orthoformic acid esters.

The tris-indolizines belong to the class of molecular propellers, which exhibit very interesting stereochemical and dynamic properties. These phenomena have been beautifully demonstrated and claryfied by Mislow et al.[7]. Our interest is to prepare molecular propellers in which the three blades are structurally identical but lacking local C_2 axes. A compound of this type is chiral, and eight stereoisomeric propeller conformations of it are possible. They can be divided into four diastereoisomeric *dl*-pairs, two of them with C_3 and two with C_1 symmetry. To our knowledge, the stereoisomerization process of this particular type of molecular propellers has not been subjected to a detailed experimental study so far (however, cf. ref.[2b]). We are also interested in obtaining tris systems of the same type, in which each unit could be individually protonated and with the positive charges located outside the axes formed by the bond from the central carbon atom.

The theoretical prediction that indolizine should undergo electrophilic substitution preferentially at C-3 and then at C-1 has been substantiated in numerous studies[8]. Normally, a mixture of 3- and 1-substituted derivatives results and in no cases have substitutions at C-2 been observed[8].

In order to avoid substitution by the orthoester at both the 1- and 3-positions, which would lead to oligo- or polymers, we have chosen as starting materials either 1- or 3-substituted indolizines, which give tris compounds of type **2** and **3**, respectively (cf. Scheme 1). The tris compounds unsubstituted in the 1- or 3-position proved to be unstable and reacted rapidly to form blue dyes. Since the Tschitschibabin reaction was used to prepare the starting indolizines, all of them carry a 2-substituent. The nature of R^1, R^2 and R^2, R^3 were chosen to have groups giving singlets in the

Scheme 1. Tris(indolizinyl)methanes **2**, **3** prepared from indolizines **1** and triethyl orthoformate



	R^1	R^2		R^2	R^3
2a	H	CH_3	**3a**	Ph	CH_3
b	CH_3	CH_3	**b**	CH_3	CO_2CH_3
c	CH_3	Ph	**c**	CH_3	$COC_6H_4CH_3$-(2)
d	CO_2Et	CH_3			
e	CN	CH_3			

  0009–2940/87/0202–0239 $ 02.50/0

^{1}H-NMR spectra not overlapping other signals to simplify the dynamic studies and also to obtain compounds with suitable energy barriers at temperatures convenient for stereoisomerizations.

The indolizines were treated with the trialkyl orthoformate in methanol or ethanol or in some cases in chloroform solution containing catalytic amounts of sulfuric acid, *p*-toluenesulfonic acid, or phosphoryl chloride at reflux temperatures. The compounds in Scheme 1 all formed very readily, the reactions were completed in 10–60 min and the highest yields (≈90%) were obtained with *p*-toluenesulfonic acid in methanol. 2,5-Dimethylindolizine, however, failed to react and the starting material was recovered. This is probably due to the steric hindrance caused by the 5-methyl group.

The tris-indolizines are all crystalline compounds with rather high melting points and without smell. They are stable in the solid state and in solutions of hydrocarbons and alcohols, also when exposed to light. Dissolved in dichloromethane, chloroform, and other halohydrocarbons, they undergo a photochemical oxidation to blue dyes. This observation will be the subject of a separate communication.

The trimeric nature of the reaction products were ascertained from exact mass determinations by electron-impact mass spectrometry and ^{1}H- and ^{13}C-NMR spectroscopy. For one compound, tris(1,2-dimethyl-3-indolizinyl)methane (**2b**), a single-crystal X-ray-diffraction study has been performed[9]. It reveals that **2b** possesses a propeller conformation in the solid ground state with approximate C_3 symmetry and also that the central methine proton is on the opposite side of the six methyl groups.

The electron-impact mass spectra were recorded with the inlet system heated to 200°C. In all cases large molecular ion-peaks were observed. They conclusively prove the trimeric nature of the compounds.

We have already pointed out that the tris-indolizines are molecular propellers and are thus likely to display temperature dependent NMR-spectra due to the presence of several diastereoisomers in solution[7]. To support the gross structures of **2a–e** and **3a–c**, time-averaged spectra are necessary and in Table 1 ^{1}H-NMR data recorded at temperatures giving such spectra are summarized. In all cases the ^{1}H-NMR spectra display a one-proton singlet at 5.7–6.4 ppm for the central methine proton. Also, all the remaining expected signals could be identified and assigned (cf. Table 1).

These assignments of the δ values for the C-6 and C-7 protons are based on the relative order observed for the chemical-shift values in the corresponding mono-indolizines. The vicinal coupling-constant values for the protons in the indolizine rings of the tris compounds are all between 6.5 and 9.0 Hz. Broad-band decoupled and undecoupled ^{13}C-NMR spectra have been recorded for **2b** at room temperature. From the number of signals, eleven sets in both the decoupled and the undecoupled NMR spectra, it is clear that only one stereoisomer with C_3 symmetry is present at 37°C. Chemical-shift and coupling-constant values for **2b** are summarized in the Experimental section. These assignments are based on splitting-patterns and chemical-shift values reported for indolizine by Pugmire et al.[10]. Their results are supported by selective proton-decoupling experiments and by spectra of 1,3-dideuterioindolizine. Important for the structural proof of **2b** is our finding that the doublet at 34.11 ppm, assigned to the central methine carbon atom, collapses to a singlet when irradiated with the frequency assigned to the signal for the proton on the same carbon atom. This constitutes firm evidence both for the chemical-shift assignments of C-9 and for the structure of **2b**.

Table 1. ^{1}H-NMR chemical shifts (ppm) for protons in the tris-indolizines **2a–3c**

	2a	**2b**	**2c**	**2d**	**2e**	**3a**	**3b**	**3c**
H1	6.15	–	–	–	–	–	–	–
H5	7.41	7.30	7.14	8.29	7.74	7.58	9.5	10.10
H6	6.44	6.23	6.05	6.59	6.75	6.25	6.4	6.78
H7	6.73	6.53	6.44	7.03	7.15	6.38	6.6	6.85
H8	7.35	7.10	7.00	7.27	7.29	7.03	6.6	6.47
9-CH	6.04	6.06	6.22	6.33	6.06	5.78	6.20	5.93
1-CH_3	–	1.32	2.03	[a]	–	–	–	–
2-CH_3	1.17	2.21	–	1.89	1.34	–	2.23	2.21
3-CH_3	–	–	–	–	–	2.19	[b]	[c]
Phenyl protons	–	–	6.62 and 6.94	–	–	6.51 and 6.95	–	7.15, 7.18 and 7.27
Temp.	−40	37	37	90	−40	37	20	37°C

[a] Methyl and methylene protons in the ethyl ester group, 1.34 and 4.35 ppm, respectively. – [b] Methyl ester protons, 3.85 ppm. – [c] Methyl protons in the toluoyl group, 1.34 ppm.

Financial support from the *Swedish Natural Science Research Council* is gratefully acknowledged. We thank Mr. *R. Torberntsson* for NMR-spectral measurements.

Experimental

NMR spectra: Bruker WH 270 spectrometer, CD_2Cl_2 as solvent, TMS as internal reference. – UV and visible spectra: In ethanol, Cary-Varian Model 210 spectrophotometer. – IR spectra: KBr, Perkin-Elmer Model IR 197 spectrophotometer. – Mass spectra: GEC-AEI 902 mass spectrometer, Department of Medical Biochemistry, University of Gothenburg. – Thin-layer chromatography: Silica Gel 60 F 254 (Merck) or aluminium oxide DC-card ALF 2 (0.2 mm; Merck). Colourless spots were visualized with short-wave ultraviolet light. – Column chromatography: Silica Gel (0.063–0.2 mm; Merck) or aluminium oxide, Type 507 C (neutral, 100–125 mesh; Merck).

2-Methyl-, 1,5-dimethylpyridine (Fluka, puriss), and chloroacetone (Fluka; 95%, practical), starting materials for the preparation of the simple indolizines, were used without purification. Bromoacetone was prepared as described by Levene[11]. Literature procedures were followed for the synthesis of 2-methyl-[12], 1,2-dimethyl-[13], 1-methyl-2-phenyl-[14], 1-cyano-2-methyl-[15], 3-methyl-2-phenylindolizine[14], ethyl 2-methyl-1-indolizinecarboxylate[16], and 2-methyl-3-indolizinecarbonyl chloride[16]. The ^{1}H-NMR data for the tris-indolizines are recorded in Table 1.

Tris(2-methyl-3-indolizinyl)methane (**2a**): To a stirred solution of 4.00 g (31.3 mmol) of 2-methylindolizine and 1.54 g (10.4 mmol) of triethyl orthoformate in 35 ml of absolute methanol, one drop of

conc. sulfuric acid was added. The solution, which immediately turned dark-blue, was kept at 86°C for 1 h, when crystals started to separate. On cooling, more crystals were formed; these were collected by filtration, washed first with methanol/isopropylalcohol and then with ether. Purification by chromatography on alumina (EtOAc used as eluant) gave 2.96 g (72%) of **2a** as white crystals, m.p. 193°C. Thin-layer chromatography (Al_2O_3; EtOAc/MeOH, 9:1) revealed the presence of only one spot, R_f = 0.66. When the same procedure was repeated using catalytic amounts of $POCl_3$ or of *p*-toluenesulfonic acid the yields of **2a** were 58 and 77%, respectively. – MS (EI; 70 eV): M^+ 403.2045; calcd. for $C_{28}H_{25}N_3$ 403.2048.

Tris(1,2-dimethyl-3-indolizinyl)methane (**2b**): Preparation as described for **2a** with 2.00 g (13.8 mmol) of 1,2-dimethylindolizine and 0.68 g (4.5 mmol) of triethyl orthoformate in 25 ml of absolute methanol. The solution turned dark-green on addition of sulfuric acid. The greenish crystals which formed were recrystallized from benzene/methanol to give 1.70 g (83%) of **2b** as colourless, long needles, m.p. 210–212°C. Thin-layer chromatography (Al_2O_3; EtOAc/MeOH, 8:2). With $POCl_3$ or *p*-toluenesulfonic acid, the yields of **2b** were 64 and 90%, respectively. – UV (ethanol): λ_{max} (log ε) = 252 nm (2.36), 240 (2.28), 290 (1.40), 308 (1.43), and 360 (1.17). – MS (EI; 70 eV): M^+ 445.2518; calcd. for $C_{31}H_{31}N_3$ 445.2517. – ^{13}C NMR: Singlets: δ = 107.5 (C-1), 144.4 (C-2), 127.3 (C-3), 129.7 (C-8a). Doublets (δ/*J* in Hz): 121.2/167.5 (C-5), 109.6/153.5 (C-6), 114.2/160.6 (C-7), 116.6/162.8 (C-8), 34.11/117.3 (C-9). Quartets: 126.2 (1-CH_3), 125.7 (2-CH_3).

Tris(1-methyl-2-phenyl-3-indolizinyl)methane (**2c**): As described for **2a** with 1.70 g (8.2 mmol) of 1-methyl-2-phenylindolizine and 0.41 g (2.7 mmol) of triethyl orthoformate. The solution turned dark-blue on addition of one drop of sulfuric acid. The bluish crystals were washed several times with isopropyl alcohol. Greenish crystals, yield 1.53 g (89%), m.p. 174–176°C, TLC: R_f = 0.85 (EtOAc). When $POCl_3$ was used instead of sulfuric acid the yield of **2c** was 65%. – UV (ethanol): λ_{max} (log ε) = 255 nm (2.17), 353 (1.51). – MS (EI; 70 eV): M^+ 631.2988; calcd. for $C_{46}H_{37}N_3$ 631.2987.

Tris[1-(ethoxycarbonyl)-2-methyl-3-indolizinyl]methane (**2d**): As described for **2a** with 5.00 g (24.6 mmol) of ethyl 2-methyl-1-indolizinecarboxylate and 1.21 g (8.2 mmol) of triethyl orthoformate in 25 ml of methanol. The solution turned blue on addition of one drop of sulfuric acid. The white crystals that precipitated were dissolved in ethyl acetate and filtered through a silica gel column. The filtrate was evaporated to dryness and the residue chromatographed on the same absorbent using ether as the eluant. The white-violet crystals of **2d**, 4.00 g (79%), were sublimed at 270°C/10 Torr to give white crystals, m.p. 183–184°C. – MS (EI; 70 eV): M^+ 619.2682; calcd. for $C_{37}H_{37}N_3O_6$ 619.2682.

Tris(1-cyano-2-methyl-3-indolizinyl)methane (**2e**): As described for **2a** with 2.00 g (12.8 mmol) of 1-cyano-2-methylindolizine and 0.63 g (4.3 mmol) of triethyl orthoformate. The solution turned green on addition of one drop of sulfuric acid. The yellow crystals of **2e**, 1.60 g (78%), were purified on alumina using ether as the eluant and then recrystallized from methanol/ethyl acetate to give white-yellowish crystals, m.p. 187–193°C. – UV (ethanol): λ_{max} (log ε) = 410 nm (1.74), 305 (1.95), 253 (2.13), 240 (2.04). – IR (KBr): 2210 cm^{-1} (C≡N). – MS (EI; 70 eV): M^+ 478.1900; calcd. for $C_{31}H_{22}N_6$ 478.1905.

Tris(3-methyl-2-phenyl-1-indolizinyl)methane (**3a**): To a stirred solution of 2.10 g (10.1 mmol) of 3-methyl-2-phenylindolizine in 30 ml of methanol 0.50 g (3.4 mmol) of triethyl orthoformate was added; the solution turned to dark-green on addition of one drop of sulfuric acid. Crystals started to separate after keeping the mixture for 1 h at 86°C. The solid was collected by filtration, washed with petroleum ether (light) and acetone and then dried to give 1.30 g (61%) of **3a** as white crystals, m.p. 268°C. With $POCl_3$ the yield of **3a** was 47%. – MS (EI; 70 eV): M^+ 631.2987; calcd. for $C_{46}H_{37}N_3$ 631.2987.

Tris[2-methyl-3-(methoxycarbonyl)-1-indolizinyl]methane (**3b**)

a) *Methyl 2-Methyl-3-indolizinecarboxylate* was prepared following the procedure of Jones and Stanyer[17]. A solution of 3.00 g (15.5 mmol) of 2-methyl-3-indolizinecarbonyl chloride in 30 ml of absol. methanol was refluxed for 25 min. The red solution formed was evaporated to dryness under reduced pressure. The oily residue was neutralized with 10% aqueous sodium hydrogen carbonate and extracted with ether. The extracts were dried ($MgSO_4$) and evaporated to dryness. The oil which remained crystallized directly when triturated with a few drops of methanol. Fine yellow-greenish crystals, m.p. 90–92°C, were isolated. Yield 2.40 g (82%).

b) Compound **3b** was prepared as described for **3a** with 2.00 g (12.3 mmol) of methyl 2-methyl-3-indolizinecarboxylate in 30 ml of methanol and 0.61 g (4.1 mmol) of triethyl orthoformate. When a few drops of sulfuric acid were added the solution turned blue. The mixture was refluxed for 35 min and then cooled with ice. A light-violet precipitate formed which was separated by filtration and chromatographed on silica gel (EtOAc) to give 1.70 g (84%) of **3b** as a white powder, m.p. 220–227°C. – MS (EI; 70 eV): M^+ 577.2180; calcd. for $C_{34}H_{31}N_3O_6$ 577.2212.

Tris[2-methyl-3-(2-methylbenzoyl)-1-indolizinyl]methane (**3c**)

a) *Synthesis of 2-Methyl-3-(2-methylbenzoyl)indolizine:* To a solution of 3.00 g (23.4 mmol) of sublimed 2-methylindolizine in 12 ml of benzene 3.50 g (22.7 mmol) of 2-methylbenzoyl chloride was added and left overnight. The reaction mixture was neutralized with aqueous sodium hydroxide and then extracted with chloroform. Evaporation of the dried ($MgSO_4$) extracts to dryness gave a green oil. It was dissolved in ether and passed over a short column of alumina. When the eluates were evaporated to dryness an oily yellow product remained. It crystallized on addition of a few drops of petroleum ether to give 4.10 g (72%), m.p. 64–67°C.

b) Compound **3c** was prepared as described for **3a** with 2.50 g (10.0 mmol) of 2-methyl-3-(2-methylbenzoyl)indolizine and 0.49 g (3.3 mmol) of triethyl orthoformate in 5 ml of methanol. The solution turned dark-violet when a drop of sulfuric acid was added. It was kept at 70°C for 10 min and was then cooled. The precipitate formed was separated by filtration, washed with methanol, and dried. Yield 1.50 g (59%) of **3c**, m.p. >350°C (dec.). – MS (EI; 70 eV): M^+ 757.3304; calcd. for $C_{52}H_{43}N_3O_3$ 757.3279.

CAS Registry Numbers

2a: 65592-75-8 / **2b**: 105969-32-2 / **2c**: 105944-55-6 / **2d**: 105944-56-7 / **2e**: 105944-57-8 / **3a**: 105944-58-9 / **3b**: 105944-59-0 / **3c**: 105944-61-4 / ethyl 2-methyl-1-indolizinecarboxylate: 31108-60-8 / 1-cyano-2-methylindolizine: 3243-04-7 / 2-methyl-3-indolizinecarbonyl chloride: 70601-77-3 / methyl 2-methyl-3-indolizinecarboxylate: 105944-60-3 / 2-methyl-3-(2-methylbenzoyl)indolizine: 105944-62-5 / 2-methylindolizine: 768-18-3 / 1,2-dimethylindolizine: 1125-77-5 / 1-methyl-2-phenylindolizine: 1019-12-1 / 3-methyl-2-phenylindolizine: 6028-82-6 / triethyl orthoformate: 122-51-0

[1] E. H. Cordes in *The Chemistry of Carboxylic Acids and Esters*, Ed. S. Patai, p. 623, Interscience Publishers, London 1969.
[2] [2a] E. Akgün, U. Pindur, J. Müller, *J. Heterocycl. Chem.* **20** (1983) 1303. – [2b] U. Pindur, *J. Heterocycl. Chem.* **19** (1982) 1371.

[3] R. A. McClelland, P. W. K. Lam, *Can. J. Chem.* **62** (1984) 1068.
[4] [4a] O. Fischer, G. Körner, *Ber. Dtsch. Chem. Ges.* **17** (1884) 99. – [4b] J. Harley-Mason, J. D. Bu'Lock, *Biochem. J.* **51** (1952) 430.
[5] H. v. Dobeneck, H. Prietzel, *Hoppe-Seylers Z. Physiol. Chem.* **299** (1955) 214.
[6] O. S. Wolfbeis, *Monatsh. Chem.* **112** (1981) 369.
[7] K. Mislow, D. Gust, P. Finochario, R. J. Boettcher, *Fortschr. Chem. Forsch.* **47** (1974) 1.
[8] [8a] F. J. Swinbourne, J. H. Hunt, G. Klinkert, *Adv. Heterocycl. Chem.* **23** (1978) 103. – [8b] W. Flitsch in *Comprehensive Heterocyclic Chemistry*, Eds. C. W. Bird, G. W. Cheeseman, Vol. 3, Chapter 4, Pergamon Press, Oxford, 1984.
[9] O. Ceder, M. R. Sharif, L. Andersen, submitted for publication (*Chem. Ber.*).
[10] R. J. Pugmire, M. J. Robins, D. M. Grant, R. K. Robins, *J. Am. Chem. Soc.* **93** (1971) 1887.
[11] P. A. Levene, *Org. Synth., Coll. Vol.* **II** (1944) 88.
[12] D. O. Holland, J. H. C. Nayler, *J. Chem. Soc.* **1955**, 1657.
[13] E. D. Rossiter, J. E. Saxton, *J. Chem. Soc.* **1953**, 3654.
[14] M. Fraser, S. McKenzie, D. H. Reid, *J. Chem. Soc. B*, **1966**, 44.
[15] J. Hurst, T. Melton, D. G. Wibberley, *J. Chem. Soc.* **1965**, 2948.
[16] D. O. Holland, J. H. C. Nayler, *J. Chem. Soc.* **1955**, 1503.
[17] G. Jones, J. Stanyer, *J. Chem. Soc. C*, **1969**, 901.

[201/86]