Some Cyclisation Reactions of 2,2′-Disubstituted-*N*-arylpyrroles

G. W. H. Cheeseman*, S. A. Eccleshall and T. Thornton

Chemistry Department, Queen Elizabeth College, University of London,
Campden Hill, London W8 7AH, England

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Tricyclic products were derived from *N*-(2-methoxycarbonylphenyl)pyrrole-2-carboxaldehyde (**2**) and *N*-(2-chloromethylphenyl)pyrrole-2-carboxaldehyde (**8**).

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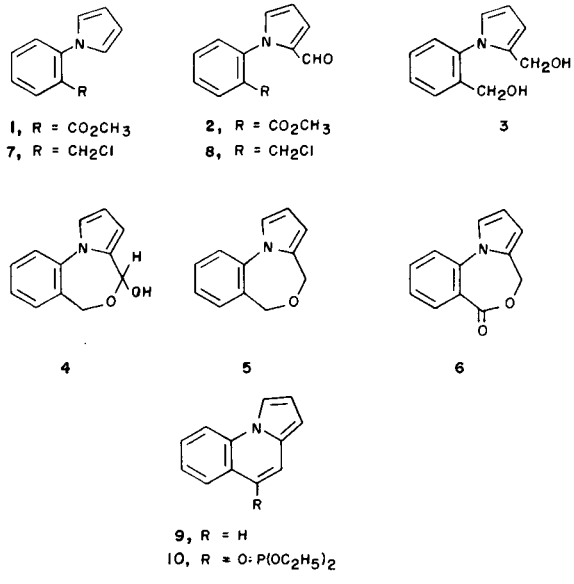
For a number of years we have investigated the cyclisation reactions of *N*-arylpyrroles [1,2] and we have been able to demonstrate the use of these compounds for the synthesis of a variety of tricyclic systems of potential biological interest. A group of Italian workers have also had a sustained interest in this area and in a recent paper [3] they reported the synthesis of some 4*H*,6*H*-pyrrolo[1,2-*a*]-[4,1]benzoxazepines, a ring system in which we had a prior interest [4].

A convenient starting material for pyrrolobenzoxazepine synthesis is *N*-(2-methoxycarbonylphenyl)pyrrole-2-carboxaldehyde (**2**), the principal product of Vilsmeier-Haack formylation of *N*-(2-methoxycarbonylphenyl)pyrrole (**1**). The nmr spectrum of the product from the formylation reaction showed however, two low field signals at δ 9.5 and 9.9 of relative intensity 5.6:1 and thus indicated that approximately 12% of the isomeric 3-carboxaldehyde had been formed. A similar percentage of 3-substituted pyrrole is obtained on Vilsmeier-Haack formylation of *N*-phenylpyrrole, bulky substituents on nitrogen, *e.g.* *t*-butyl cause substitution to occur almost entirely in the 3-position [5]. Pure *N*-(2-methoxycarbonylphenyl)pyrrole-2-carboxaldehyde (**2**) was readily isolated from the formylation product by column chromatography and crystallisation. In larger scale experiments, it was convenient to use 1,2-dichloroethane as a diluent in the reaction and to isolate the pyrrole aldehyde by vacuum distillation.

Massa, Corelli and Stefancich [3] have reported that reduction of *N*-(2 -methoxycarbonylphenyl)pyrrole-2-carboxaldehyde (**2**) with lithium aluminium hydride yields *N*-(2-hydroxymethylphenyl)-2-hydroxymethylpyrrole (**3**). We also obtained compound **3** when sodium dihydro*bis*(2-methoxyethoxy)aluminate was used as the reducing agent provided that a solution of the pyrrole was added to a solution of the reducing agent. When an *inverse* mode of addition of the reagent solutions was used, the reduction product was 4-hydroxy-4*H*,6*H*-pyrrolo[1,2-*a*][1,4]benzoxazepine (**4**). The formation of compound **4** presumably resulted from selective reduction of the ester group, followed by intramolecular cyclisation of the intermediate hydroxymethylcarboxaldehyde. *N*-(2-Hydroxymethylphenyl)-2-hydroxymethylpyrrole (**3**), previously reported to be an oil, was isolated as a crystalline solid, mp 38°. On heating compound **3** in toluene solution at 60° in the presence of phosphorus



pentoxide, 4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepine (**5**) was formed. We confirmed that sodium borohydride reaction of *N*-(2-methoxycarbonylphenyl)pyrrole-2-carboxaldehyde (**2**) in ethanol, at room temperature gave 6-oxo-4*H*-pyrrolo-[1,2-*a*][4,1]benzoxazepine (**6**) [3]. In this case selective reduction of the aldehyde group must have occurred prior to cyclisation. An analogous lactonisation occurs in the biphenyl series, but 2-hydroxymethyl-2′-methoxycarbonylbiphenyl was heated to 150° in order to effect cyclisation [6].

In the course of this work, we also investigated the Vilsmeier-Haack formylation of *N*-(2-chloromethylphenyl)-pyrrole (**7**) [7]. When the reaction was carried out in boiling 1,2-dichloroethane, a 70% yield of the 2-carboxaldehyde (**8**) was obtained. However formylation in *N*,*N*-dimethylformamide at 0° gave a 40% yield of a 1:1 mixture of the 2- and 3-aldehydes, from which both pure isomers were isolated.

Analogy with a recently published indole synthesis [8], suggested that compound **8** might function as a precursor of pyrrolo[1,2-*a*]quinoline (**9**). Accordingly we treated the chloromethyl aldehyde **8** with triethyl phosphite (it was unreactive to triphenylphosphine) and then reacted the intermediate phosphonate with sodium ethoxide. The major product formed by this process was not the expected pyrroloquinoline **9**, which was only isolated in trace amounts, but the 5-diethoxyphosphoryl derivative **10**.

EXPERIMENTAL

The ir spectra of solids were taken as Nujol mulls and liquids as thin films between sodium chloride discs. The nmr spectra were measured at 60 MHz in deuteriochloroform on either a Perkin Elmer R 12B or a Brücker WP60 spectrometer. Mass spectral measurements were recorded on a Kratos MS 25 machine equipped with a DS 50 S data system. Column chromatography was carried out using Merck 7734 silica gel.

N-(2-Methoxycarbonylphenyl)pyrrole-2-carboxaldehyde (**2**).

This was prepared by essentially the same method as described by Massa, Corelli and Stefancich [3]. Alternatively when the reaction was carried out as described in the preparation of the carboxaldehyde **8** below, and the product was isolated by vacuum distillation, the yield was 74%. The distillate (bp 158-159°/1.0 mm) solidified on standing and was purified by crystallisation from diethyl ether to give a sample of the carboxaldehyde, mp 62° (lit [3] 53-55°); ir 1720 cm^{-1} (C=O); nmr: δ 3.6 (s, 3H, CH_3), 6.4 (dd, 1H, β-pyrrolic), 6.95 (dd, 1H, β-pyrrolic), 7.1-8.0 (m, 5H, α-pyrrolic and benzenoid), 9.5 (s, 1H, CHO); ms: 229 (M^+).

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.47; H, 4.83; N, 6.31.

4-Hydroxy-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepine (**4**).

To a solution of *N*-(2-methoxycarbonylphenyl)pyrrole-2-carboxaldehyde (**2**) (4.13 g, 0.018 mole) in dry toluene (50 ml) was added, dropwise, over 1 hour, a solution of sodium dihydro*bis*(2-methoxyethoxy)aluminate (70% w/w in toluene 10 ml) in dry toluene (50 ml). Stirring was continued at room temperature, under nitrogen, for 2 hours and then aqueous sodium hydroxide (20% w/v) was cautiously added until no further reaction occurred. The aqueous layer was separated off and extracted with toluene. The combined organic layers were washed with saturated sodium chloride solution, dried (anhydrous magnesium sulphate), evaporated and the residue vacuum distilled. The product (0.93 g, 26%) had bp 112-114°/0.7 mm; ir: 3400 cm^{-1} (O-H); nmr: δ 2.8 (b, 1H, OH), 4.4 (s, 2H, CH_2), 6.2 (dd, 1H, β-pyrrolic), 6.8 (dd, 1H, β-pyrrolic, 7.1-7.6 (m, 6H, α-pyrrolic, methine, benzenoid); ms: 201 (M^+).

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.87; H, 5.47; N, 7.01.

N-(2-Hydroxymethylphenyl)-2-hydroxymethylpyrrole (**3**).

A solution of *N*-(2-methoxycarbonylphenyl)pyrrole-2-carboxaldehyde (**2**) (4.58 g, 0.02 mole) in dry toluene (20 ml) was added dropwise to a stirred, and ice-cooled solution of sodium dihydro*bis*(2-methoxyethoxy)aluminate (20 ml of a 70% w/w solution in toluene) in dry toluene (20 ml). The reaction mixture was stirred for a further 1.5 hours and then aqueous sodium hydroxide (10% w/v, 20 ml) was cautiously added. The aqueous layer was separated off and extracted with toluene. The combined organic layers were washed with saturated sodium chloride solution, dried (anhydrous sodium sulphate) and evaporated. The residue was purified by passage through a silica column and elution with a 2:1 mixture of toluene and ethyl acetate. The viscous oil (1.9 g, 47%) obtained after removal of solvent, solidified on standing to give white crystals, mp 38°; ir: 3320 cm^{-1} (O-H); nmr: δ 3.3-4.0 (b, 2H, O-H, deuterium oxide exchangeable), 4.2 (s, 4H, 2 × CH_2), 6.3 (m, 2H, β-pyrrolic), 6.7 (dd, 1H, α-pyrrolic), 7.2-7.6 (m, 4H, benzenoid); ms: 203 (M^+) and 185.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.70; H, 6.48; N, 6.56.

4*H*,6*H*-Pyrrolo[1,2-*a*][4,1]benzoxazepine (**5**).

A mixture of *N*-(2-hydroxymethylphenyl)-2-hydroxymethylpyrrole (**3**) (1.9 g, 0.006 mole), dry toluene (60 ml) and phosphorus pentoxide (1.5 g, 0.01 mole) was heated at 60° for 30 minutes. After cooling, the toluene layer was decanted, washed with sodium hydrogen carbonate solution, and dried (anhydrous sodium sulphate). The oily residue obtained after removal of solvent, was purified by passage through a silica column. Elution with toluene gave 4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepine (0.9 g) as an oil; nmr: δ 4.4 (s, 4H, 2 × CH_2), 6.3 (m, 2H, β-pyrrolic), 7.0 (dd, 1H, α-pyrrolic), 7.3 (m, 4H, benzenoid); ms: 185 (M^+) and 156.

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.63; H, 6.19; N, 7.55.

6-Oxo-4*H*-pyrrolo[1,2-*a*][4,1]benzoxazepine (**6**).

This was prepared by the method described in the literature [3]. The product had mp 111-112° (lit [3] 101-102°); ir: 1715 cm^{-1} (C=O); nmr: δ 5.0 (s, 2H, CH_2), 6.3 (m, 2H, β-pyrrolic), 7.1 (dd, 1H, α-pyrrolic), 7.4-7.95 (m, 4H, benzenoid); ms: 199 (M^+) and 154.

Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.30; H, 4.58; N, 6.91.

N-(2-Chloromethylphenyl)pyrrole-2-carboxaldehyde (**8**).

Freshly distilled phosphoryl chloride (1.97 g, 0.013 mole) was added dropwise, with stirring at 0°, to *N,N*-dimethylformamide (1.02 g, 0.014 mole). The mixture was stirred at room temperature for 10 minutes and then diluted with 1,2-dichloroethane (20 ml). After cooling to 5°, a solution of *N*-(2-chloromethylphenyl)pyrrole (**7**) (2.04 g, 0.011 mole) in 1,2-dichloroethane (20 ml) was added with stirring. The temperature was maintained at 5° during the addition and then the reaction mixture was heated under reflux for 1 hour. After cooling, a solution of hydrated sodium acetate (8.92 g, 0.066 mole) in water (50 ml) was added and the mixture heated under reflux for 20 minutes and then cooled. The organic layer was separated and the aqueous layer extracted with diethyl ether (4 × 25 ml). The combined organic layers were washed with saturated aqueous sodium carbonate solution, treated with charcoal, dried (anhydrous magnesium sulphate) and evaporated. Vacuum distillation of the residue gave the product (1.63 g, 70%) as a colourless oil (bp 139-140°/0.2 mm) which readily crystallised. A sample recrystallised from methanol had mp 84°; ir: 1650 cm^{-1} (C=O); nmr: δ 4.2 (s, 2H, CH_2), 6.5 (dd, 1H, β-pyrrolic), 7.0-7.5 (m, 6H, β-pyrrolic, α-pyrrolic and benzenoid), 9.5 (s, 1H, CHO); ms: 219/221 (M^+).

Anal. Calcd. for $C_{12}H_{10}ClNO$: C, 65.59; H, 4.59; N, 6.38. Found: C, 65.17; H, 4.55; N, 6.32.

In an experiment carried out in *N,N*-dimethylformamide as solvent and at 0°, the crude product was dissolved in chloroform and the solution filtered through a column of silica. Elution with ethyl acetate:toluene (1:16) gave first *N*-(2-chloromethylphenyl)pyrrole-2-carboxaldehyde (**8**) (20%) and then the isomeric 3-carboxaldehyde (19%), mp 66-67°, after crystallisation from light petroleum bp 60-80°; ir: 1670 cm^{-1} (C=O); nmr: δ 4.4 (s, 2H, CH_2), 6.8 (dd, 1H, β-pyrrolic), 6.9-7.6 (m, 6H, β-pyrrolic, α-pyrrolic and benzenoid), 9.9 (s, 1H, CHO); ms: 219/221 (M^+).

Anal. Calcd. for $C_{12}H_{10}ClNO$: C, 65.59; H, 4.59; N, 6.38. Found: C, 65.45; H, 4.60; N, 6.43.

Cyclisation of *N*-(2-Chloromethylphenyl)pyrrole-2-carboxaldehyde (**8**).

A mixture of triethyl phosphite (2.5 g, 0.015 mole) and the chloromethylcarboxaldehyde (**8**) (1.65 g, 0.0075 mole) was stirred and heated under nitrogen at 165-170° for 2 hours. After cooling, sodium ethoxide (1.0 g, 0.015 mole) was added and the mixture stirred under nitrogen at room temperature for 30 minutes. Water (25 ml) was then added and the product extracted into diethyl ether. The ether extracts were washed with saturated sodium chloride solution, dried (anhydrous sodium sulphate) and evaporated. The residue was chromatographed on a silica gel column using 1:1 toluene-ethyl acetate as the eluting solvent. The first fraction probably contained pyrrolo[1,2-*a*]quinoline (**9**) in trace amounts; ms: 167 (M^+). The second fraction, on evaporation, yielded 5-diethoxyphosphorylpyrrolo[1,2-*a*]quinoline (**10**) (1.7 g, 75%), mp 76-78°, after crystallisation from cyclohexane; ir: 1250 cm^{-1} (P=O); nmr: δ 1.3 (t, 6H, 2 × CH_3), 4.1 (m, 4H, 2 × CH_2), 6.8-8.4 (m, 8H, H-4, pyrrolic and benzenoid); ms: 303 (M^+) and 166 (M^+-$C_4H_{10}O_3P$).

Anal. Calcd. for $C_{16}H_{18}NO_3P$: C, 63.36; H, 5.98; N, 4.62. Found: C, 62.94; H, 5.99; N, 4.53.

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