

Synthesis of 2,3'-Bipyrrole. Denitrosation in the Knorr Pyrrole Synthesis¹

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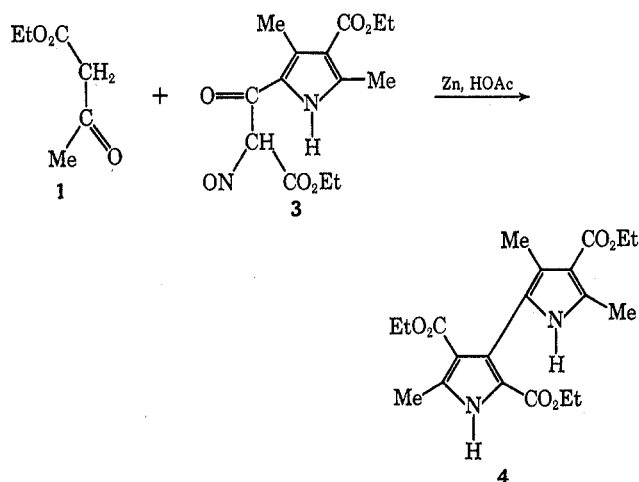
The 2,2'-bipyrrolylpyrrolylmethene metabolite, prodigiosin, has been widely investigated as a possible antimicrobial agent and has shown some antifungal³ and antimalarial⁴ activity. In a consideration of the influence of structure on activity, it was of interest to initiate a study directed at the synthesis and antimicrobial evaluation of congeneric 2,3'-bipyrrolylpyrrolylmethenes. In this communication we describe the synthesis of a 2,3'-bipyrrole and unexpected results in the frequently employed Knorr pyrrole synthesis.

In contrast with the numerous syntheses of 2,2'-bipyrroles,⁵ only one synthesis of a 2,3'-bipyrrole has been reported.⁶ In this earlier work the condensation of ethyl 2-amino-3-oxo-3-(3,4-dimethylpyrrol-2-yl)propanoate hydrochloride with ethyl acetoacetate (1) in the presence of sodium acetate and potassium acetate is described as yielding 2-(2-carboxy-4-ethoxycarbonyl-5-methylpyrrol-3-yl)-3,5-dimethylpyrrole. The condensation in this case is seen to be accompanied by hydrolysis of one of the ester groupings. An attempt by us to extend this procedure to the reaction of ethyl 2-amino-3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)propanoate hydrochloride (2) and ethyl acetoacetate was unsuccessful. Nevertheless, from the reaction of ethyl 2-nitroso-3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)propanoate (3), ethyl acetoacetate, and

zinc in acetic acid, we were able to obtain 2-(2,4-diethoxycarbonyl-5-methylpyrrol-3-yl)-3,5-dimethyl-4-ethoxycarbonylpyrrole (4) in a low yield (6%). Interestingly, a number of years ago, Knorr and Lange⁷ reported obtaining better pyrrole yields in several examples starting with aminoacetophenone hydrochloride instead of *via* the *in situ* reduction of nitrosoacetophenone, as in the usual procedure.

Because of the poor yield obtained in the otherwise successful Knorr synthesis of 4 we were led to investigate the possibility of improvement of these results through a better understanding of the influence of reaction conditions on yield. We have found, when the synthesis is attempted in a helium atmosphere instead of the usual ambient laboratory conditions, that none of 4 is formed and instead the denitrosation⁸ product, ethyl 3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)propanoate (5), is obtained in a high yield (92%). These surprising results prompted a similar comparison of the Knorr pyrrole synthesis with ethyl nitrosobenzoylacetate (6) and ethyl acetoacetate. Again, under ordinary laboratory conditions the expected 2,4-diethoxycarbonyl-5-methyl-3-phenylpyrrole (7) resulted, but, when the reaction was carried out in a helium atmosphere, ethyl cinnamate (8), the product from denitrosation, reduction, and dehydration of ethyl nitrosobenzoylacetate, was the major product, and none of 7 was detected. Finally, the zinc dust in acetic acid reduction of a mixture of ethyl nitrosoacetoacetate (9) and ethyl acetoacetate is a standard procedure for the synthesis of 2,4-diethoxycarbonyl-3,5-dimethylpyrrole (Knorr's pyrrole 10).⁹ However, when ethyl nitrosoacetoacetate alone is treated with zinc dust in acetic acid under conditions comparable to those used in the standard synthetic procedure for 10, but employing an atmosphere of argon, Knorr's pyrrole (13%) is formed directly reflecting denitrosation of some of the starting nitroso derivative. Moreover, a small amount of the denitrosated product, ethyl acetoacetate (3.9%), was also isolated from the reaction. The importance of the atmosphere (presumably oxygen) on the success of the Knorr pyrrole synthesis in the examples reported herein is clear and it appears likely that this may be a general phenomenon. The experimental evaluation of its scope and the role of the atmosphere is planned for investigation.

The nitrosation of ethyl 3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)propanoate (11) led to two products in a ratio of *ca.* 1:1. These are evidently the oximino and nitroso derivatives,¹⁰ with the latter showing an ir absorption band at 8.28 μ corresponding to a dimer.^{10d} We were able to isolate the oximino derivative in an analytically pure form. Upon standing in ethyl acetate, it isomerized to yield a mixture like that initially obtained from the nitrosation reaction.



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Experimental Section¹¹

Ketones.—Ethyl 3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)propanoate (11)¹² and ethyl benzoylacetate¹³ were synthesized as described in the literature. The ethyl acetoacetate was a redistilled commercial product.

Nitroso Ketones.—The general procedure of Barltrop and co-workers¹⁴ using isoamyl nitrite and hydrogen chloride with the ketone was followed. A minor variation in the present work was the use of tetrahydrofuran as the solvent instead of ethyl ether. Ethyl nitrosoacetoacetate (9) (29–43%) showed bp 122–125° (2.6–3.0 mm), n_D^{25} 1.4562 (lit.¹⁵ n_D^{25} 1.4557); ethyl nitrosobenzoylacetate (6), mp 119–120° (lit.¹⁶ 120–121°).

The nitrosation of ethyl 3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)propanoate (11) led to a product (3) in high yield (95% calcd for the nitroso derivative) which was found by tlc (SilicAR TLC-7G, 5% methanol–95% chloroform) to be a ca. 1:1 mixture of two components. When the slower moving component was allowed to stand in ethyl acetate for 18 hr, it was found that two components having the same R_f values as those in the original mixture were again present. The isolation of the component with the higher R_f by fraction crystallization was unsuccessful, but the component with the lower R_f was obtained from ether in this way. The crystalline white solid melted at 146–148° dec.

Anal. Calcd for $C_{14}H_{18}N_2O_6$: C, 54.18; H, 5.84; N, 9.02. Found: C, 54.03; H, 5.72; N, 8.96.

The ir (KBr) for the higher R_f fraction showed absorption bands at 2.99 (pyrrole NH), 5.74 (side chain ester C=O), 5.95 (ring ester C=O), 6.18 (keto C=O), 8.28 μ (nitroso dimer),^{10d} the lower R_f fraction, 2.87 (oximino OH), 3.07 (pyrrole NH), 5.74 (side chain ester C=O), 5.91 (ring ester C=O), 6.21 (keto C=O), 6.68 μ (oximino C=N).¹⁷

Ethyl 2-Amino-3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)propanoate Hydrochloride (2).—A solution of 3.1 g of the mixture 3 obtained from the nitrosation of ethyl 3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)propanoate in 50 ml of 95% ethyl alcohol and 1.67 ml of 6 *N* hydrochloric acid was shaken with 0.3 g of 5% palladium-on-charcoal catalyst in an atmosphere of hydrogen (initial pressure 42 psig) in a Burgess-Parr hydrogenator. Hydrogenation stopped with the uptake of 41% of the amount of hydrogen calculated for the nitroso derivative. Removal of the catalyst followed by crystallization of the solid product from a mixture of absolute ethanol and ethyl ether, containing hydrogen chloride, gave the amine hydrochloride 2. When heated this compound starts to decompose at ca. 188°.

Anal. Calcd for $C_{14}H_{21}ClN_2O_6$: C, 50.52; H, 6.26; N, 8.41. Found: C, 50.37; H, 6.19; N, 8.59.

2-(2,4-Diethoxycarbonyl-5-methylpyrrol-3-yl)-3,5-dimethyl-4-ethoxycarbonylpyrrole (4).—Following the literature description for the synthesis of Knorr's pyrrole,⁹ a solution of 5.0 g of ethyl 2-nitroso-3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)propanoate (11) and 2.1 g of ethyl acetoacetate in 100 ml of glacial acetic acid was treated with 5.0 g of zinc dust. The mixture was stirred and heated to 70° for 50 min, and the crude product was isolated as described in the literature reference. Column chromatography of the crude reaction product (SilicAR CC-7, ethyl acetate–hexane, 1:1), decolorization of the chromatograph fraction with Norit in 95% ethyl alcohol, and crystallization from the same solvent gave 0.40 g (6%) of the bipyrrole (4), mp 168.0–168.5°. The nmr spectrum for this compound shows the following: ethyl CH_3 , δ 1.25 (pentuplet, relative intensity 9); ring CH_3 , 2.04, 2.49, 2.53 (singlets, 3 each); ethyl CH_2 , 4.23 (multiplet, 6); pyrrole NH, 8.65, 9.91 (broad singlets, 1 each).

(11) Melting points were determined with a Fisher-Johns apparatus and are uncorrected; ir spectra, Beckman IR-5; nmr spectrum, Varian HA-100, in $CDCl_3$ using the TMS lock signal; vpc, Model A-100-C and A-700 Aerographs, Wilkens Instrument Co., using columns from the same company. Elemental analyses are by the Berkeley Analytical Laboratory.

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Anal. Calcd for $C_{20}H_{26}N_2O_6$: C, 61.52; H, 6.71; N, 7.17. Found: C, 61.31; H, 6.69; N, 7.30.

2,4-Diethoxycarbonyl-5-methyl-3-phenylpyrrole (7).—Essentially the procedure used for the synthesis of the bipyrrole was followed using 2.2 g of ethyl nitrosobenzoylacetate, 1.3 g of ethyl acetoacetate, 30 ml of glacial acetic acid, and 2.0 g of zinc dust. The reaction mixture was held at 100–110° for 45 min in this synthesis. The product, mp 124–126°, isolated directly from the reaction mixture, weighed 2.0 g (67%). A sample recrystallized from cyclohexane–benzene and three times from 95% ethyl alcohol melted at 127.0–128.0° (lit.¹⁸ 117–119°).

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.87; H, 6.43; N, 4.59.

Denitrosation of Nitroso Ketones. (a) **Ethyl Nitrosoacetoacetate (9).**—Fifty grams of zinc dust was added portionwise to a stirred solution of 12.3 g of the nitroso derivative in 200 ml of glacial acetic acid. During this period the temperature was held to a maximum of 70° and, after all of the zinc had been added, the mixture was stirred and refluxed for 1 hr. The reaction system was maintained in an atmosphere of argon during the entire operation. The white solid that separated, 2.4 g (13%), when the reaction mixture was poured into water, was shown to be 2,4-dimethyl-3,5-diethoxycarbonylpyrrole (10) by its mp 132–134° (lit.⁹ 136–137°) and a comparison of its infrared spectrum with that of an authentic sample. The aqueous phase from which 10 had separated was neutralized with sodium bicarbonate and extracted with ether. After drying the extract with magnesium sulfate and evaporating the solvent, an oil remained. This was shown by vpc analysis (Carbowax 20M) to contain ethyl acetoacetate (1) (3.9%).

(b) **Ethyl Nitrosobenzoylacetate (6).**—A mixture of 1.1 g of the nitroso compound and 0.65 g of ethyl acetoacetate in 45 ml of glacial acetic acid was treated with 15.3 g of zinc dust as in the preceding experiment. However, in this case the reaction mixture was held at 70° for 10 min after addition of all of the zinc and was not heated further. Also, the reaction was conducted in an atmosphere of helium. The work-up was the same as in the above example and 0.76 g of an oil was obtained. Vpc analysis (diethylene glycol succinate) showed the presence of four components. Ethyl cinnamate (8), the major component, and ethyl acetoacetate were identified by "spiking." The cinnamate ester was also isolated and identified by comparison of its ir spectrum with that of an authentic sample.

(c) **Ethyl 2-Nitroso-3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)propanoate (3).**—The reaction was carried out as in the above example using 5.0 g of 3, 2.1 g of ethyl acetoacetate, 100 ml of glacial acetic acid, and 13.5 g of zinc dust. A reaction temperature of 100–110° was used. The bulk of the solvent was evaporated at reduced pressure, the remaining acetic acid was neutralized with aqueous sodium bicarbonate, and the crude product was extracted with ethyl ether. Column chromatography (SilicAR CC-7, ethyl acetate–hexane) yielded 4.17 g (92%) of ethyl 3-oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)propanoate (11), mp 143° (lit.¹² 140.5–142°), having an ir spectrum identical with that of an authentic sample.

Registry No.—2, 24744-71-6; 3, 24744-72-7; 4, 24744-73-8; 7, 3651-13-6; 9, 24744-75-0.

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Selective Photocoupling of Perfluorodiacyl Fluorides

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Photolysis of monofunctional perfluoroacyl fluorides has been described as a route to nonfunctional fluorocarbons¹ and fluorocarbon ethers.² However, irradiation

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