

Syntheses of 3,4-Dimethylpyrrole

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Synopsis. Treatment of *N*-sulfinyl compound with 2,3-dimethylbutadiene gives a cycloadduct which affords 3,4-dimethylpyrrole in satisfactory yields by heating in a strongly alkaline methanolic solution.

From an interest in synthesizing porphyrins, we have attempted to prepare a large amount of 3,4-dimethylpyrrole (I). Although various pyrrole syntheses have been worked out,¹⁾ 3,4-disubstituted pyrroles have been available only *via* several steps. The Knorr synthesis affords in *ca.* 50% yield ethyl 2,3,4-trimethylpyrrole-5-carboxylate which we converted into I in 20–40% yield based on Fischer's procedure.²⁾ The unsatisfactory results prompted us to find a new synthetic route to I.

Alkaline hydrolysis of 2-aryl-3,6-dihydro-4,5-dimethyl-1,2-thiazine 1-oxide gives 1-aryl-3,4-dimethylpyrrole in high yields³⁾ whereas various 2-substituted 3,6-dihydrothiazine 1-oxide exclusively yield γ,δ -unsaturated amine by acidic, neutral or even alkaline hydrolysis.⁴⁾ We have carefully investigated the alkaline hydrolysis of some derivatives of dihydrothiazine 1-oxide (III), the 2-position of which is substituted by ester groups.

The *N*-sulfinylamides (IIa R=CO₂Et,⁵⁾ IIb R=CO₂Ph, IIc R=PO(OEt)₂⁶⁾ were obtained in excellent yields by the action of thionyl chloride and dry pyridine upon the corresponding carbamate or phosphoramidate. In order to attain a good yield, thionyl chloride and pyridine should be added dropwise to a benzene solution of carbamate or phosphoramidate at the same rate. A poor yield was attained when thionyl chloride was added to a solution of urethane and pyridine.^{5b)} The *N*-sulfinyl compounds were not purified on account of the high sensitivity toward heat and moisture, as characterized by means of IR spectra. IIb crystallized on cooling. The IR spectrum exhibits bands at 1260 and 1100 cm⁻¹ characteristic of the N=S→O group^{4a)} and at 1750 cm⁻¹ due to the carbonyl group. After pyridine hydrochloride had been removed under protection from moisture, 2,3-dimethylbutadiene was added to the solution of crude *N*-sulfinylamide followed by refluxing to give the cycloadduct (III). 2-Ethoxycarbonyl (IIIa)^{5a)} and diethoxyphosphonyl (IIIc) derivatives have a high boiling point and were not purified because of reduction in yield caused by distillation. They were characterized by IR spectra. 2-Phenoxycarbonyl derivative (IIb) was purified by recrystallization from cyclohexane to give 79.5% yield of hygroscopic crystals, mp 84–86 °C, which decompose with the evolution of sulfur dioxide on being left to stand at room temperature.

When cycloadducts (III) were heated in strongly

TABLE 1. SYNTHESSES OF 3,4-DIMETHYLPYRROLE

Exp. run	R in III	Alkali ^{a)}	Mol of alkali	Solv.	Yield (%) ^{b)}
1	CO ₂ Et	NaOMe	4	MeOH	5–10
2	CO ₂ Et	KOH	8	MeOH	34–48
3	CO ₂ Et	NaOMe	7	MeOH	62
4	CO ₂ Ph	NaOH	5	MeOH	40
5	CO ₂ Ph	NaOH	5	H ₂ O	trace ^{c)}
6	CO ₂ Ph	NaOMe	7	MeOH	59
7	PO(OEt) ₂	KOH	8	EtOH–H ₂ O	22
8	PO(OEt) ₂	NaOMe	6	MeOH	27

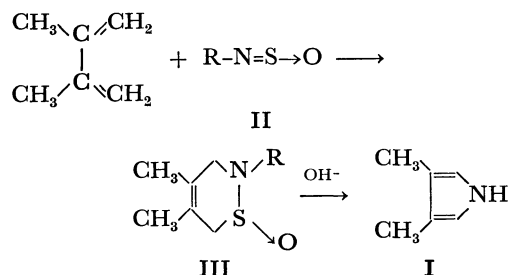
a) Alkali hydroxide; 20–30 w/w% in methanol or water. Sodium methoxide: *ca.* 10 w/w% in methanol.

b) Based on the crude cycloadduct (III) except runs 4–6 where the purified cycloadduct was used. c) Ehrlich's test was positive.

alkaline methanol, 3,4-dimethylpyrrole was formed (Table 1) although Levchenko and coworkers described the exclusive formation of γ,δ -unsaturated amine by the action of 2.5 mol sodium hydroxide on IIIa in ethanol.^{5a)} The pyrrole was isolated by steam-distillation. A dark resinous substance remained. Evolution of hydrogen sulfide and sulfur dioxide was observed on acidification of the aqueous residue. The strength of alkali played a key role for the formation of the pyrrole; when the cycloadduct were heated in aqueous alkali, the yield of the pyrrole was always smaller than in methanol (run 5, Table 1).

Similarly, 3-methylpyrrole was obtained in 13% overall yield when isoprene was used instead of dimethylbutadiene. The poor yield of the pyrrole in this case should results from less sufficient cycloaddition.

Attempts to isolate 2-unsubstituted 3,6-dihydrothiazine 1-oxide (III; R=H) by the reaction of IIb with such weaker bases as ammonia and aniline were unsuccessful.



IIa and IIIa; R=CO₂Et, IIb and IIIb; R=CO₂Ph, IIc and IIIc; R=PO(OEt)₂.

Experimental

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Materials. Benzene was dried over sodium wire, and pyridine over potassium hydroxide. Thionyl chloride

was distilled just before use.

3,4-Dimethylpyrrole (Starting From Ethyl Carbamate). In a 1 l round-bottomed flask, equipped with a mechanical stirrer, a reflux condenser attached with a calcium chloride tube, and two 100 ml dropping funnels, were placed 27.1 g ethyl carbamate and 150 ml dry benzene. Pyridine and thionyl chloride were added dropwise at the same rate with efficient stirring and cooling with cold water. After the mixture was further stirred for one hour at room temperature, 25.0 g 2,3-dimethylbutadiene was added in one portion. The mixture was heated under mild refluxing and stirring and then allowed to stand overnight. After voluminous pyridine hydrochloride was filtered and washed with benzene, the filtrates were evaporated under reduced pressure to afford an oily residue of crude 2-ethoxycarbonyl-3,6-dihydro-4,5-dimethyl-1,2-thiazine 1-oxide, $\nu_{\max}$ (neat); 1725, 1317, 1250, 1100 cm^{-1} . To the residue was added 135 g potassium hydroxide dissolved in 300 ml methanol, and the dark colored mixture was refluxed 2 h. The solvent was distilled under ordinary pressure, and the reaction mixture was steam-distilled to give an oily substance which was extracted repeatedly with ether. The extracts were dried over anhydrous potassium carbonate, and the solvent was removed. Vacuum distillation of the oily residue gave 13.77 g 3,4-dimethylpyrrole of bp₂₅ 67–70 °C (lit, bp₁₄ 65.5–66 °C).⁷⁾ The yield was 47.7% based on ethyl carbamate.

2-Phenoxycarbonyl-3,6-dihydro-4,5-dimethyl-1,2-thiazine 1-Oxide. After 30.0 g phenyl carbamate was treated with 35.1 ml pyridine and 15.1 ml thionyl chloride in 250 ml benzene in the same manner as above, pyridine hydrochloride was filtered off and washed with dry benzene. To the combined benzene solutions was added 19.8 g 2,3-dimethylbutadiene, and the mixture was refluxed for 1 h after being left standing overnight. The solvent was removed by vacuum distillation to afford crystalline residue which was recrystallized from cyclohexane. The 1,2-thiazine 1-oxide weighed 46.1 g (79.6% based on phenyl carbamate) and melted at 84–86 °C. $\nu_{\max}$ (KBr); 1745, 1342, 1211, 1080 cm^{-1} . Found: C, 58.84; H, 6.14; N, 5.26%. Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_3\text{S}$: C, 58.84; H, 5.69; N, 5.28%. The crystals decomposed gradually with evolution of sulfur dioxide. Treatment of this compound with alkali yielded 3,4-dimethylpyrrole as shown in Table 1.

Phenyl *N*-sulfinylcarbamate was isolated when the benzene solution was removed *in vacuo* under protection from moisture, after the reaction of phenyl carbamate with thionyl chloride

in the presence of pyridine. The new *N*-sulfinyl derivative crystallized on cooling in a refrigerator, showing characteristic IR bands at 1260 and 1100 cm^{-1} due to $\text{N}=\text{S}\rightarrow\text{O}$ groups.^{4a)}

3-Methylpyrrole. In the same way as mentioned above, crude ethyl *N*-sulfinylcarbamate, obtained by the reaction of 30.0 g ethyl carbamate with 40.0 g thionyl chloride and 26.5 g pyridine, was treated with 28.0 g isoprene. The mixture was refluxed for 3 h. After pyridine hydrochloride had been removed by filtration, the salt was washed with benzene. The benzene was distilled *in vacuo* to afford an oily residue which was heated with 130 g potassium hydroxide in 300 ml methanol for 3 h. The solvent was distilled off, and the residue was steam-distilled. The distillate was extracted with ether, and the solvent was distilled off after the ether had been dried with potassium carbonate. Distillation of the residue gave 6.60 g crude 3-methylpyrrole which was purified by redistillation: 3.93 g (13% based on ethyl carbamate), bp 140–145 °C (lit,^{2a)} bp 142–143 °C).

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