N-ARYLPYRROLIDONES

II. CHLOROMETHYLATION OF N-PHENYLPYRROLIDONE AND SOME TRANSFORMATIONS OF ITS CHLOROMETHYL DERIVATIVE

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The chloromethylation of N-phenylpyrrolidone proceeds at the paraposition of the benzene ring. The reactivity of the chloromethyl group in reactions with ammonium thiocyanate, potassium ethylxanthate, sodium acetate, thiourea, potassium phthalimide, urotropine, sodium thiosulfate, and potassium permanganate was investigated. A number of previously undescribed compounds, of which some were found to be active pesticides, were synthesized.

This paper is devoted to a study of the chloromethylation of N-arylpyrrolidone and the conversion of its chloromethyl derivative to various previously unknown compounds.

We have found the conditions for obtaining good yields (77%) of chloromethylated N-phenylpyrrolidone. This reaction occurs at 30-32°C in concentrated hydrochloric acid with formaldehyde and hydrogen chloride as the chloromethylating agents. The major reaction product is N-(p-chloromethylphenyl)pyrrolidone (I), the structure of which was confirmed by PMR spectroscopy* and IR spectroscopy.† Signals of the methylene groups of the pyrrolidine ring are observed in the PMR spectrum: a multiplet from the protons of the α- and β-CH_2 groups ($\delta \sim 2.35$ ppm), a triplet from the protons of the γ-CH_2 group (δ 3.82 ppm; J 7 Hz), and a singlet from the protons of the CH_2Cl group (δ 4.62 ppm). The protons of the benzene ring give a symmetrical spectrum of the AA'BB' type characteristic for para substitution, which can be interpreted as an AB spectrum [2, 3]: δ_H ortho 7.67 ppm, δ_H meta 7.37 ppm, J_{AB} 9.0 Hz.

A very intense band at 1700 cm^{-1}, which is characteristic for the stretching vibration of the C=O group, is observed in the IR spectra. The character of the absorption in the region of out-of-plane, synphase vibrations of the aromatic C–H bonds – the presence of a band of medium intensity at 845 cm^{-1} – does not contradict the conclusion of the para position of the substituents in the benzene ring that was made on the basis of an analysis of the PMR spectra.

We investigated the nucleophilic substitution of halogen in the chloromethyl group by various functional groups and also oxidized it and replaced it by an aldehyde group.

When a mixture of I and ammonium thiocyanate or of I and potassium ethylxanthate is refluxed in acetone, good yields of N-(p-thiocyanotomethylphenyl)pyrrolidone (II) or N-(p-ethylxanthatophenyl)pyrrolidone (III) can be obtained. The reaction of I with sodium acetate in glacial acetic acid to form N-(p-acetoxymethylphenyl)pyrrolidone (IV) proceeds with the same ease. N-(p-Aminomethylphenyl)pyrrolidone (V) could be synthesized by refluxing a mixture of I, potassium phthalimide, and potassium carbonate in di-

*The PMR spectrum was recorded from a 10% solution in deuteroacetone with a DA-60-GZ spectrometer with an operating frequency of 60 MHz and hexamethyldisiloxane as the internal standard.

†The IR spectra of KBr pellets were recorded with a UR-10 spectrometer. We thank A. F. Vasil'ev, V. V. Negrebetskii, and N. L. Aryutkina for recording the spectra.

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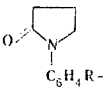
TABLE 1



Compound	R	Mp, °C	Empirical formula	Found, %					Calculated, %				
				C	H	Cl	N	S	C	H	Cl	N	S
I	CH_2Cl	90—91	$C_{11}H_{12}ClNO$	63,2	5,6	17,4	6,6	—	63,0	5,7	16,9	6,7	—
II	CH_2SCN	66—67	$C_{12}H_{12}N_2OS$	62,2	5,3	—	12,3	13,9	62,1	5,2	—	12,1	13,8
III	$CH_2SC(=S)OC_2H_5$	85—86	$C_{14}H_{17}NO_2S_2$	57,3	6,2	—	5,1	21,1	57,0	5,8	—	4,7	21,7
IV	CH_2OCOCH_3	55—56	$C_{13}H_{15}NO_3$	67,0	6,2	—	6,1	—	66,9	6,4	—	6,0	—
V	CH_2NH_2	168—169	$C_{11}H_{14}N_2O$	69,2	7,5	—	14,9	—	69,5	7,4	—	14,7	—
VI	$CH_2SC(=NH\cdot HCl)NH_2$	223 (dec.)	$C_{12}H_{15}N_3OS\cdot HCl$	50,0	5,2	12,6	14,9	11,7	50,4	5,6	12,3	14,7	11,2
VII	COOH	210	$C_{11}H_{11}NO_3$	64,1	5,2	—	7,1	—	64,4	5,4	—	6,8	—
VIII	CHO	119	$C_{11}H_{11}NO_2$	69,5	5,9	—	7,6	—	69,8	5,8	—	7,4	—
IX	CH_2SH	173—174	$C_{11}H_{13}NOS$	63,4	6,2	—	6,9	15,1	63,8	6,3	—	6,8	15,5

methylformamide with subsequent hydrolysis of the reaction product. The hydrochloride of N-(p-isothiouroniummethylphenyl)pyrrolidone (VI) was obtained by refluxing a mixture of I and thiourea in dry acetone.

The chloromethyl group of I is oxidized by refluxing a mixture of I and alkaline potassium permanganate to give a good yield of N-(p-carboxyphenyl)pyrrolidone (VII). N-(p-Formylphenyl)pyrrolidone (VIII) is obtained when a mixture of I and urotropin is refluxed in glacial acetic acid with subsequent hydrolysis of the reaction product. N-(p-mercaptophenyl)pyrrolidone (IX) is obtained in good yield by refluxing a mixture of I, sodium hyposulfite, and sulfuric acid in absolute alcohol. The physicochemical constants of the synthesized compounds are presented in Table 1.

The synthesized compounds were tested for biological activity. Some of them were found to be active pesticides.

EXPERIMENTAL

N-(p-Chloromethylphenyl)pyrrolidone (I). A mixture of 14 g (0.086 mole) of N-phenylpyrrolidone [1], 46 g of 30% formalin, and 400 ml of concentrated hydrochloric acid was saturated with hydrogen chloride at 30-32° for 12 h. The mixture was allowed to stand at room temperature for 24 h and was then poured into 1 liter of ice water. The resulting precipitate was removed by filtration, washed with cold water until it was neutral, and dried to give 14 g (77%) of colorless crystals from petroleum ether.

N-(p-Thiocyanatomethylphenyl)pyrrolidone (II). A 3-g (0.014 mole) sample of I was added at 40-45° to a mixture of 2 g (0.026 mole) of ammonium thiocyanate in 100 ml of dry acetone, and the mixture was refluxed for 7 h and allowed to stand overnight. The precipitated NH_4Cl was removed by filtration and washed with acetone. The filtrate was concentrated in vacuo, and the reaction product was recrystallized from petroleum ether—alcohol (1 : 1) to give 3 g (90%) of II.

N-(p-Ethylxanthatomethylphenyl)pyrrolidone (III). A mixture of 3 g (0.014 mole) of I and 2.4 g (0.015 mole) of potassium ethylxanthate in 100 ml of dry acetone was refluxed for 6 h. The mixture was cooled, and the precipitated KCl was removed by filtration and washed with acetone. The filtrate was concentrated in vacuo, and the reaction product was recrystallized from petroleum ether to give 4 g (94%) of III.

N-(p-Acetoxymethylphenyl)pyrrolidone (IV). A hot solution of 3 g (0.014 mole) of I in 20 ml of glacial acetic acid was added at 40-50° to a solution of 1.2 g (0.014 mole) of sodium acetate in 10 ml of glacial acetic acid. The mixture was refluxed for 8 h and cooled, and the precipitated NaCl was removed by filtration. The filtrate was concentrated in vacuo, and the crystalline reaction product was removed by filtration and washed with cold water until it was neutral to give 2 g (60%) of IV. The product was crystallized from aqueous alcohol.

N-(p-Aminomethylphenyl)pyrrolidone (V). A ground mixture of 6 g (0.03 mole) of potassium phthalimide and 1.5 g of potassium carbonate was added to 6 g (0.028 mole) of I in 100 ml of dimethylformamide, and the mixture was refluxed for 7 h. The solvent was removed by vacuum distillation, 100 ml of 20% hydrochloric acid was added to the residue, and the mixture was heated on a boiling-water bath for 1 h. The

mixture was cooled, and the crystalline product was removed by filtration and washed with cold absolute alcohol to give 4 g (78%) of colorless crystals (from alcohol) of V.

N-(p-Isothiouroniummethylphenyl)pyrrolidone Hydrochloride (VI). A solution of 3 g (0.014 mole) of I in 30 ml of dry acetone was added at 38-40° to a solution of 1.5 g (0.019 mole) of thiourea in 30 ml of dry acetone. The mixture was refluxed for 7 h and cooled, and the reaction product was removed by filtration, washed with absolute alcohol, and dried to give 3 g (73%) of VI. The product was crystallized from alcohol.

N-(p-Carboxyphenyl)pyrrolidone (VII). A total of 100 ml of a 1% solution of $KMnO_4$ was added at 40-50° to 3 g (0.014 mole) of I in 100 ml of 1% KOH solution, and the mixture was refluxed for 6 h and allowed to stand overnight. The mixture was heated, and the manganese dioxide was removed by filtration. The filtrate was acidified with 50 ml of concentrated hydrochloric acid, and the resulting white precipitate was removed by filtration and washed with water until it was neutral to give 2.1 g (74%) of colorless crystals [from petroleum ether–alcohol (1 : 1)].

N-(p-Formylphenyl)pyrrolidone (VIII). A solution of 3 g (0.014 mole) of I in 30 ml of glacial acetic acid was added to 6 g (0.043 mole) of urotropin in 20 ml of water, and the mixture was refluxed for 5 h. A total of 30 ml of concentrated hydrochloric acid and 200 ml of water were added to the hot solution, and the mixture was heated to the boiling point. The mixture was cooled, and the solution was extracted with ether. The ether layer was separated, washed with water, and dried. The solvent was removed in vacuo, and the residue was crystallized from absolute alcohol to give 2 g (74%) of VIII.

N-(p-Mercaptophenyl)pyrrolidone (IX). A solution of 3 g (0.014 mole) of I in 25 ml of absolute alcohol was added at 30-40° to 3 g (0.019 mole) of sodium hyposulfite in 10 ml of water. The mixture was refluxed for 1 h, 25 ml of 50% sulfuric acid was added, and the mixture was refluxed for another 2 h and allowed to stand overnight. The solution was filtered, and the filtrate was heated to 27°. The precipitated reaction product was removed by filtration and dried to give 1.35 g (50%) of IX. The product was crystallized from alcohol–petroleum ether (1 : 1).

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