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Synthesis of Some 1-Substituted 3-Carbalkoxy-4-piperidone Hydrochlorides

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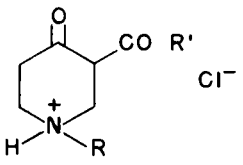
Synthesis of 1-substituted 3-carbethoxy-4-piperidone hydrochlorides (I, R' = C_2H_5) has been reported (1, 2).



I

We wish to report the synthesis of several new piperidone hydrochlorides of structure I. The synthesis consisted essentially of two steps: 1. addition of a primary amine to an alkyl acrylate (3) and 2. Cyclization of the two to one adduct with sodium in xylene (4). The piperidones were isolated as hydrochlorides.

$$RNH_2 + 2CH_2{=}CHCO_2R' \longrightarrow$$

$$RN(CH_2CH_2CO_2R')_2 \xrightarrow[\text{then HCl}]{\text{Na}} I$$

The table presents the results of these syntheses.

EXPERIMENTAL

All of the piperidone hydrochlorides were prepared by the same general procedure. Experimental details for the synthesis of 1-allyl-3-carbethoxy-4-piperidone hydrochloride are given below.

Bis(2-Carbethoxyethyl)allylamine.

To a solution of 17.1 g. (0.3 mole) of allylamine in 66 ml. of absolute alcohol was added slowly 84.1 g. (0.84 mole) of ethyl acrylate. The solution was kept in an ice bath during addition. After addition was complete the reaction solution was allowed to stand for four days. Solvent and excess ethyl acrylate were stripped under vacuum. The amount of the first distillation cut was negligible. This cut was presumably the secondary amine formed by one to one addition. The second distillation cut, bis(2-carbethoxyethyl)allylamine, amounted to 77 g. (0.3 mole) and had the following properties: b.p. 185-190° at 4 mm., n_D^{27}, 1.4496.

1-Allyl-3-carbethoxy-4-piperidone Hydrochloride.

To 77 g. (0.3 mole) of the above product was added 6.9 g. (0.3 mole) of granular sodium in 79 g. of xylene. A vigorous reaction occurred without heating. When the reaction subsided the mixture was refluxed one hour. The reaction solution was cooled and poured on 300 g. of ice. The water layer was extracted with ether to remove uncyclized reactant. The water solution was acidified with 12 *M* hydrochloric acid at 0°. After making the solution alkaline to litmus with solid potassium carbonate, it was extracted with ether until the ether extract gave a weak ferric chloride test. The combined ether extracts were concentrated to 200 ml. and dried over magnesium sulfate. Dry hydrogen chloride was passed into the ether solution to precipitate the piperidone as the hydrochloride. The piperidone hydrochloride was recrystallized from absolute ethanol-isopropyl ether.

REFERENCES

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TABLE

1-Substituted 3-Carbalkoxy-4-piperidone Hydrochlorides

R	R'	% Yield (a)	M. p. °C (b)	Carbon (c) Calcd.	Carbon (c) Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found
Allyl	Methyl	78	146-147	51.40	51.58	6.90	6.85	15.17	15.28
Allyl	Ethyl	72	149-150	53.34	52.87	7.32	7.41	14.31	14.41
n-Propyl	Methyl	75	155-156	50.96	50.76	7.70	7.92	15.04	15.18
Isopropyl	Methyl	5.4 (d)	147-148	50.96	50.70	7.70	7.76	15.04	15.14
n-Butyl	Methyl	42	135-136	52.91	53.00	8.07	8.06	14.19	14.20
Benzyl	Methyl	51	173-174	59.26	59.51	6.39	6.59	12.49	12.40
2-Phenethyl	Methyl	46	170-171	60.50	60.17	6.77	7.06	11.90	11.90

(a) Yield based on the amount of amine added to the alkyl acrylate. (b) Melting points are corrected. All compounds decomposed above 170°. (c) Carbon and hydrogen analyses were made by Weiler and Strauss Microanalytical Laboratory. (d) The yield of crude oily product was 19%.