[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF FLORIDA]

Derivatives of Piperazine. I

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Several series of syntheses involving piperazine have been undertaken in this Laboratory. They have very largely been inspired by the physiological possibilities presented by the types of chemical linkage involved. Pharmacological and clinical tests are being carried out at the present time and the results will be published at a later date. A search of the literature reveals no syntheses involving these groups.

Nine new compounds of piperazine are reported in this paper. Piperazine hexahydrate reacts with phenylacetyl chloride, hydrocinnamyl chloride, and anisoyl chloride, respectively, in the ratio of one molecule of base to two molecules of acyl halide. Two molecules of hydrogen chloride are eliminated in the reaction. An amide linkage is produced in which the acyl radicals are attached to the piperazine ring by direct union of carbonyl imino groups of the piperazine ring by means of the same type of piperazonium linkage mentioned above. Piperazine hexahydrate reacts with malonic acid and diethylmalonic acid in molar proportions to form compounds in which the linkage is between one carboxyl group of the dibasic acid and one imino group of piperazine. The other carboxyl group and imino group are unattached.

These condensations have been effected in anhydrous ether solution. Compounds 4, 5 and 6 (Table I), however, are obtained in better yield when alcohol is the solvent. These derivatives are hydrolyzed by refluxing in hydrochloric acid solution. The piperazine dihydrochloride thus obtained is converted into the hexahydrate by dry distillation with potassium hydroxide and identified by means of physical constants and derivatives. The appropriate organic acids recovered during the hydrolysis are likewise identified. Although these new derivatives are prepared from piperazine hexahydrate, none of them contain water of crystallization.

TABLE I

YIELDS, PROPERTIES AND COMPOSITION OF PIPERAZINE DERIVATIVES

	Compound	Yield, %	M. p., °C., corr.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	1,4-Diphenylacetylpiperazine	65	150–151	74.49	6.88	8.69	74.41	7.08	8.55
2	1,4-Dihydrocinnamylpiperazine	61	122.5–123	75.38	7.48	7.98	75.60	7.63	7.80
3	1,4-Dianisoylpiperazine	50	192.5–193.5	67.80	6.22	7.91	67.79	6.33	8.01
4	1,4-Piperazonium diphenylacetate	80	146.5–147.5	67.00	7.31	7.82	66.96	7.44	7.88
5	1,4-Piperazonium dihydrocinnamate	85	150.5–151.5	68.35	7.76	7.25	68.73	8.14	7.29
6	1,4-Piperazonium dianisoate	90	172–174	61.50	6.71	7.18	61.90	7.08	7.25
7	1-Piperazonium acid malonate	90	180 (dec.)	44.18	7.66	14.73	44.15	7.56	14.76
8	1-Piperazonium acid diethyl (C, C') malonate	85	80–81	53.62	9.00	11.38	53.76	9.05	11.17
9	1,4-Piperazonium dimonoethyl-malonate	78	144	47.97	7.48	8.00	48.23	7.43	8.03

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Summary

1. Methods have been described for the preparation of derivatives of piperazine with monobasic aromatic acids and the corresponding acyl halides, and with alpha-omega dicarboxylic acids.

2. These compounds are being studied for physiological effects.

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carbon to the trivalent nitrogen atoms. When the acids corresponding to the aforementioned acyl halides are condensed with piperazine a different type of linkage is obtained. The reactants combine again in the ratio of one molecule of base to two molecules of acid, giving the salt in which nitrogen exhibits a valence of five. Hence these compounds may be named as substituted piperazonium compounds, just as addition compounds of ammonia in which the nitrogen atom is pentavalent are known as ammonium compounds. When mono-ethyl malonate and piperazine hexahydrate are condensed a product results which is composed of two molecules of the ester and one molecule of piperazine. The ester is joined to the

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