[Contribution from the Daniel Sieff Research Institute]

CONDENSATION OF HETEROCYCLIC AMINES WITH DICARBOXYLIC ACID ANHYDRIDES

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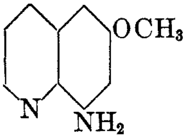
Heterocyclic chemotherapeuticals which bear amino groups are commonly introduced into the body as cations. However, as the p_H of the blood and of the majority of living cells lies between 7.0 and 7.5, it is to be anticipated that the free bases are circulating in the body fluids. It is, therefore, of interest to convert such amines into derivatives, which under "natural" circumstances appear as anions. It is known (1), *e.g.*, that cationic detergents are powerful inhibitors of bacterial growth, whereas anionic detergents show only a weak action in some exceptional cases.

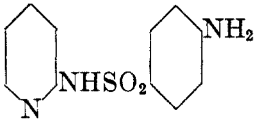
As model experiments, we studied the condensation of 6-methoxy-8-aminoquinoline (I) and sulfapyridine (II) with succinic, maleic, and phthalic anhydrides, in order to see if the presence of the tertiary nitrogen atom in the hetero nucleus would interfere with the condensation reactions of the aromatic amino group and change the rules which are usually accepted for these condensations. Maleic anhydride especially has the ability to form acid salts with the tertiary nitrogen of the quinoline system (2). Two main factors generally determine the trend of the reaction between amines and anhydrides: temperature, and relative amounts of the components, whereas the reaction time is of minor importance. For example, phthalic anhydride and aniline in equimolar mixture yield below 100° the acid amide, whereas above this point the anil is formed. However, when the amount of amine is increased, the diamide prevails more and more (3). These results, however, change from one compound to another; Morgan and Walton (4) have shown that a mixture of one mole of atoxyl with two moles of succinic anhydride give at 180° exclusively the succinamidoarsanilic acid; only at 240° does cyclization to the imide derivative occur. From an equimolar mixture of the two reactants, appreciable amounts of the diamide can be isolated. On the other hand, it was reported by Sanna (5) that *p*-iodoaniline in boiling benzene yields the succinanilic acid after short reaction times, and the anil by prolonged heating.

In the experiments to be described here, the following observations have been made. An equimolar mixture of I with succinic anhydride below 100° yields the acid amide (III) quantitatively. Above 100°, with or with-out solvent, a mixture of the diamide (IV) and the anil (V) is obtained; increasing the amount of the anhydride to five moles gives only V. With maleic anhydride, only low temperature condensation is possible, leading to VI, whose structure is proved by the fact that diazomethane methylates the free carboxyl and adds to the double bond (VII). If the acid were linked to the tertiary nitrogen, dimethyl pyrazolinedicarboxylate would have resulted (2). On the other hand, we obtained with phthalic anhydride under all conditions, even at room temperature, exclusively the imide (VIII). The acid amide (IX), which is formed from VIII by alkaline hydrolysis, reverts to the imide at the melting point (70°), or by boiling in dilute alcohol.

With sulfapyridine the following behavior has been observed. In the condensation with succinic anhydride, 100° again appears to be the limit between formation of the acid amide (X) or the anil (XI); the molar relation of the two components, however, exerts no influence, because the diamide was never obtained. It is somewhat surprising that XI is even hydrolyzed by soda. With maleic anhydride, the acid XII is the sole reaction product, even at 190°. It may be recalled that Miller and co-workers (6) found a similar behavior of sulfanilamide towards these two anhydrides. In the



I



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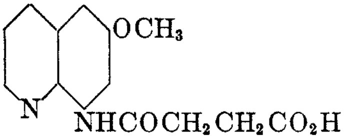

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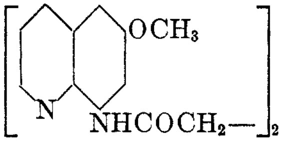

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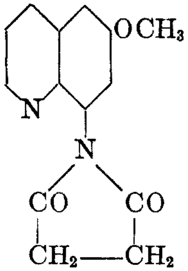

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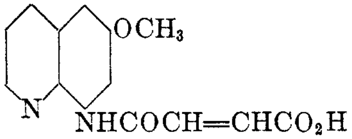

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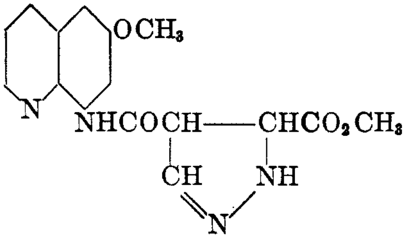

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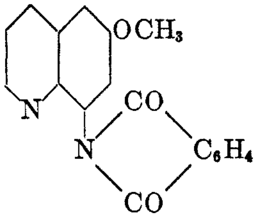
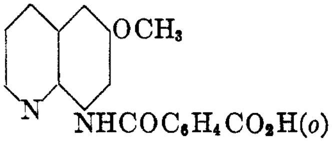
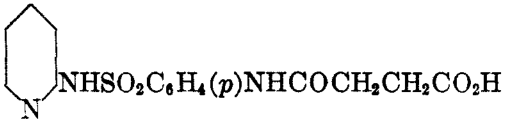


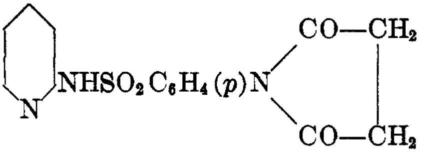
VIII



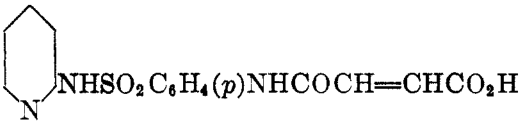
IX



X



XI



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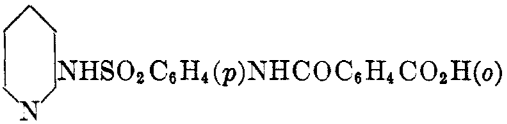
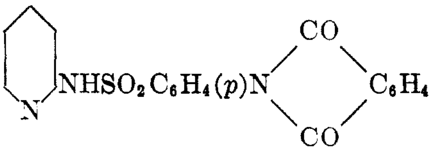


XIII



XIV

reaction with II, phthalic anhydride behaves like succinic anhydride; the acid XIII, however, shows the same melting point as the imide XIV. Apparently conversion of XIII into XIV occurs below the melting point of the former.

The results of this investigation are summarized in Table I. The solubility of the various new compounds in hydrochloric acid or acetic acid shows no regularity, as can be seen from Table II.

TABLE I

	SUCCINIC ANHYDRIDE	MALEIC ANHYDRIDE	PHTHALIC ANHYDRIDE
Base I			
Below 100°.............	Acid amide	Acid amide	Imide
Above 100°.............	Imide (and diamide)	No result	Imide
Base II			
Below 100°.............	Acid amide	Acid amide	Acid amide
Above 100°.............	Imide	Acid amide	Imide

TABLE II

SOLUBILITIES OF THE CONDENSATION PRODUCTS IN HYDROCHLORIC ACID AND ACETIC ACID

FORMULA NO.	CONC'D HCl	DIL. HC	GLACIAL ACETIC ACID	DIL. ACETIC ACID
III	insoluble	insoluble	soluble	insoluble
V	insoluble	insoluble	insoluble	soluble
VI	soluble on heating	(suspension ?)	soluble	soluble
IX	dissolves in the first moment and precipitates immediately		soluble	insoluble
VIII	soluble	insoluble	insoluble	insoluble
X	insoluble	insoluble	soluble	(soluble ?)
XI	soluble	insoluble	insoluble	insoluble
XII	soluble	(insoluble ?)	insoluble	insoluble
XIII	soluble	insoluble	insoluble	insoluble
XIV	insoluble	insoluble	insoluble	insoluble
IV	insoluble	insoluble		

EXPERIMENTAL

I. *Condensation reactions of 6-methoxy-8-aminoquinoline* (I)

(a) The amine did not react with succinic acid (2 moles) in boiling dioxane.

(b) I (1.75 g.) and succinic anhydride (1 g., 1 equiv.) were boiled for 3 hours in benzene (50 cc.). While still hot, the solution deposited a brown precipitate, which was soluble in cold soda. From ethanol, short yellow needles, m.p. 151° (decomp.) were obtained. The substance (III) is also soluble in much water and crystallizes from it unchanged; yield, 2.6 g.

Anal. Calc'd for $C_{14}H_{14}N_2O_4$: C, 61.3; H, 5.1.
Found: C, 60.7; H, 5.3.

The *methyl ester* was prepared with diazomethane; m.p. 127–128° (from benzene).

Anal. Calc'd for $C_{15}H_{16}N_2O_4$: N, 9.7. Found: N, 9.9.

(c) I (1.75 g.) and succinic anhydride (1 g.) were thoroughly mixed and heated to 120° for 2 hours. The mixture was washed with hot water, and the residue boiled with butyl acetate. From this solvent, the imide V crystallized in quadrangular, nearly colorless blocks, m.p. 178°; yield, 1 g.

Anal. Calc'd for $C_{14}H_{12}N_2O_3$: C, 65.6; H, 4.7; N, 10.9.
Found: C, 65.3; H, 5.1; N, 11.2.

The second substance, which is insoluble in butyl acetate, was recrystallized from pyridine; m.p. 258°, yield 1.2 g. (IV).

Anal. Calc'd for $C_{24}H_{22}N_4O_4$: C, 67.0; H, 5.1; N, 13.0.
Found: C, 67.0; H, 5.1; N, 13.0.

At 180°, the reaction gave the same results. When 5 equivalents of succinic anhydride was used at 120°, only the imide V could be isolated; yield, 1.5 g.

The imide was hydrolyzed by 5% sodium hydroxide on the steam-bath within 15 minutes. On acidifying with acetic acid, the product III of m.p. 150° was precipitated.

(d) I and maleic anhydride yielded only tarry products, when heated to 120° or boiled in xylene solution.

(e) I (1.75 g.) and maleic anhydride (1 g.) were gently heated on the water-bath in benzene solution (50 cc.). After a few minutes, a yellow mass crystallized; this substance (VI) crystallized from alcohol in brick-red needles; m.p. 225° (decomp.), yield, 2.6 g.

Anal. Calc'd for $C_{14}H_{12}N_2O_4 + H_2O$: N, 9.7. Found: N, 9.5.

The reaction product of the acid VI with diazomethane was recrystallized from methanol, m.p. 160–162° (VII).

Anal. Calc'd for $C_{16}H_{16}N_4O_4$: N, 17.1. Found: N, 17.2.

(f) I (1.75 g.) and phthalic anhydride (1.5 g., 1 equiv.) were dissolved at room temperature in 10 cc. of dioxane. After some hours, the reaction product (VIII) settled out; the same result was obtained in boiling dioxane; yield, quantitative. After recrystallization from dioxane, the m.p. was 261°.

Anal. Calc'd for $C_{18}H_{12}N_2O_3$: N, 9.2. Found: N, 9.1.

The imide VIII is insoluble in soda; in 10% sodium hydroxide, however, it dissolves in a few minutes. From this solution, the free acid IX can be precipitated at 0° by dilute acetic acid; yield, nearly quantitative. When dissolved in hot dilute alcohol, it regenerated the imide. The acid IX melts at about 70°, but immediately solidifies and shows then the m.p. 260° of the imide.

Anal. Calc'd for $C_{18}H_{14}N_2O_4$: C, 67.1; H, 4.3; N, 8.7.
Found: C, 67.4; H, 4.2; N, 8.7.

II. *Condensation reactions of sulfapyridine* (II)

(a) II (1.25 g.) and succinic anhydride (0.5 g., 1 equiv.) in dioxane (30 cc.) were heated on a water-bath for 3 hours. The solvent was evaporated *in vacuo*, the residue dissolved in cold soda, and precipitated with dilute hydrochloric acid. After recrystallization from ethanol, it showed the m.p. 145° (X); yield, 1.4 g.

Anal. Calc'd for $C_{15}H_{15}N_3O_5S$: N, 12.0. Found: N, 11.8.

(b) II (2.5 g.) and succinic anhydride (1 g.) were heated for 2 hours at 140°. The mixture was extracted with boiling water and the residue recrystallized from 40% acetic acid or pyridine; yield, 3.1 g., needles, m.p. 288–290° (XI). The imide is hydrolyzed immediately by cold sodium hydroxide or by warm soda solution to the acid X.

Anal. Calc'd for $C_{15}H_{13}N_3O_4S$: N, 12.7. Found: N, 12.5.

(c) II (2.5 g.) and maleic anhydride (1 g.) were heated on a steam-bath in dioxane (60 cc.). After half an hour, a yellow precipitate appeared (XII); yield, 3 g. From nitrobenzene, a brown powder was obtained, m.p. 208°.

Anal. Calc'd for $C_{15}H_{13}N_3O_5S$: N, 12.1. Found: N, 12.1.

When a mixture of the two reactants was melted at 120° or at 190°, the acid XII was also the sole reaction product. The acid is stable even at 205°.

(d) II (2.5 g.) and phthalic anhydride (1.5 g.) were boiled in dioxane (50 cc.) for one-half hour, after which the reaction product (XIII) settled out. The acid was purified by dissolving in cold soda and precipitating with dilute acetic acid at 0°. The m.p., 276°, is identical with that of the imide (XIV). For analysis, the substance was dried at room temperature; yield, quantitative.

Anal. Calc'd for $C_{19}H_{15}N_3O_5S + H_2O$: C, 54.9; H, 4.1; N, 10.1.
Found: C, 55.1; H, 4.2; N, 10.1, 10.2.

(e) II (1.25 g.) and phthalic anhydride (0.75 g.) were heated to 190° for 2 hours. The gray mass was then triturated with cold soda and recrystallized from pyridine; m.p. 276°, yield, 1.7 g.

Anal. Calc'd for $C_{19}H_{13}N_3O_4S$: N, 11.1. Found: N, 10.8.

Hydrolysis of the imide is easily effected by cold sodium hydroxide.

We wish to thank Dr. L. Haskelberg of this Institute for a gift of the quinoline base used in these experiments.

REHOVOTH, PALESTINE.

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