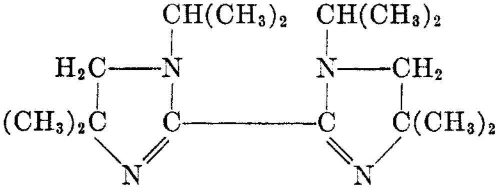
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF NEW MEXICO]

THE SYNTHESIS OF 2,3-PIPERAZINEDIONES FROM 1,2-DIAMINES AND OXALIC ESTERS

J. L. RIEBSOMER

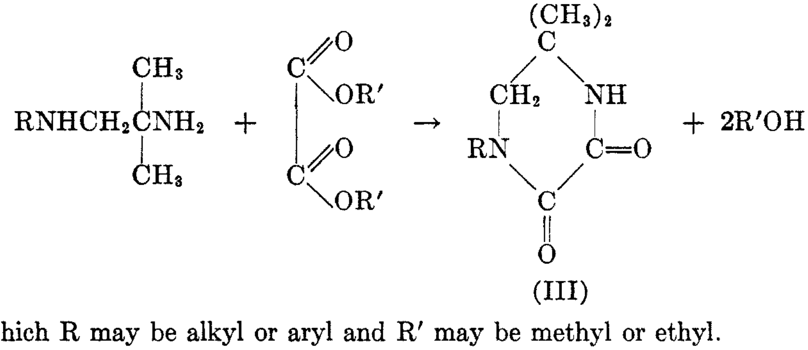
Received July 5, 1949

It has been shown previously (1) that the common dibasic acids with four or more carbon atoms per molecule react with 1,2-diamines to produce *bis*-imidazolines. These reactions were effected under substantially the same conditions as for another series of imidazolines prepared from monobasic acids and 1,2-diamines (2). But when oxalic acid was heated with N-(2-aminoisobutyl)isopropylamine the possible *bis*-imidazoline (I) did not form, but instead there was obtained a low yield of 1-isopropyl-4,4-dimethyl-2-imidazoline (II). This result suggested that one of the two carboxyl groups of the oxalic acid reacted in the usual manner to form an imidazoline and that the second carboxyl group lost carbon dioxide, thus forming (II).



(I)

In view of the relative instability of oxalic acid, it appeared that (I) might possibly be synthesized by interacting methyl oxalate with N-(2-aminoisobutyl)-isopropylamine, and splitting out methanol and water instead of water alone as in the previous imidazoline synthesis. This procedure failed to produce (I) but did give a fair yield (63%) of 5,5-dimethyl-1-isopropyl-2,3-piperazinedione. The by-product was a viscous liquid of undetermined nature. It may have been a polyamide which one might reasonably expect. This same type of reaction was tried with other 1,2-diamines and seems to be reasonably satisfactory when the diamine contains one primary and one secondary amino group. The general reaction may be formulated as follows:

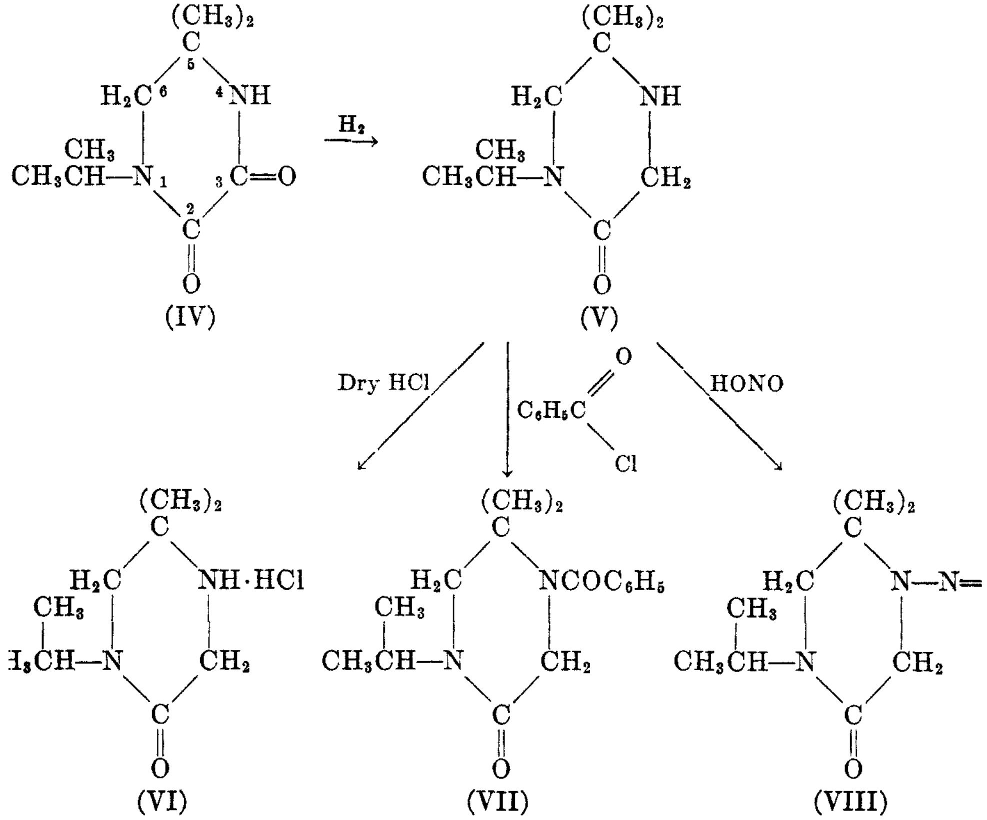


(III)

in which R may be alkyl or aryl and R′ may be methyl or ethyl.

The piperazinediones of type (III) were all colorless solids with relatively high melting points. They were insoluble in ether and usually soluble in water, giving substantially neutral solutions. These facts would be expected of materials of this structure.

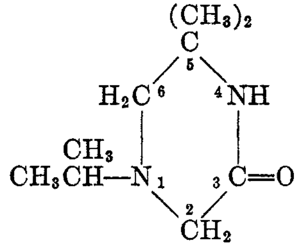
The proof of structure of compounds of type (III) is based upon the method of synthesis and upon the products formed by their reduction (either catalytically or by use of the Clemmensen method) and by a study of the reduced products. The structure determination can be described using (IV) as an example.



(IV) (V)

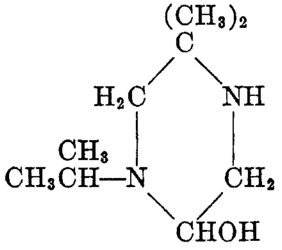
(VI) (VII) (VIII)

Compound (IV) reduced smoothly to (V) which was a colorless liquid, b.p. 151–153°/20, with a distinct amine odor. It titrated as a monoacid base; formed a monobenzoyl derivative which was neutral to bromophenol blue; and formed a monohydrochloride and the nitroso derivative (VIII) which it should do as a secondary amine. The possibility that (IV) had reduced to the isomeric compound (Va) was considered, but the evidence seems clearly against it. Compound (Va) might boil at about the same temperature as (V). It should give the same neutral equivalent and form a monohydrochloride. But since N^4 (formula Va) is essentially like that in an amide, one would not expect it to form a benzoyl or nitroso derivative. Even if it did, these derivatives should be basic in character because of the tertiary amino-nitrogen, N^1. Since the monobenzoyl derivative was neutral in character and for the other reasons indicated, (Va) cannot be considered a possibility.



(Va)

Some of the analytical data for (V) could be explained on the assumption that it was (Vb) since it differs in composition from (V) by only two atoms of



(Vb)

hydrogen. If this were the correct structure, it should form a dibenzoyl derivative, a dihydrochloride and titrate as a diacid base which, as indicated above, did not prove to be the case.

EXPERIMENTAL

The 2,3-*piperazinediones* were all prepared using substantially the same procedure. One example will be given in detail.

Preparation of 5,5-dimethyl-1-isopropyl-2,3-piperazinedione (IV). A mixture of 65 g. (0.5 mole) of N-(2-aminoisobutyl)isopropylamine and 59 g. (0.5 mole) of dimethyl oxalate was heated under conditions to distill the methanol produced from the reaction through a 4′-packed column. The temperature of the reaction flask was slowly increased during a period of 4 hours to a maximum of 180°. A total of 30 g. (0.94 mole) of methanol was thus removed. Upon cooling, the product solidified and upon crystallization from acetone melted at 203°. Yield 58 g. (63%). The solvent was removed from the filtrate and the residue found to be a viscous oil. The nature of this residue was not determined.

Table I gives a summary of the 2,3-piperazinediones prepared by this method.

Reduction of 5,5-dimethyl-1-isopropyl-2,3-piperazinedione (IV) to *5,5-dimethyl-1-isopropyl-2-keto-1,4-hexahydrodiazine* (V). This reduction was carried out by two methods. A. *Catalytic reduction.* To a solution containing 89 g. of (IV) in 800 ml. of methanol was added 10 g. of Raney nickel and hydrogenation was carried out for 19 hours at 200° and at 2000 p.s.i. The product was filtered, 0.9 g. of platinum black was added and hydrogenation was continued 7 more hours at 200° and 2000 p.s.i. The platinum black was removed and the

TABLE I

2,3-PIPERAZINEDIONES

AMINE USED	PRODUCT	FORMULA	M.P., °C.	YIELD, %	ANALYSES					
					Calc'd			Found		
					C	H	N	C	H	N
N-(2-Aminoisobutyl)isopropylamine	5,5-Dimethyl-1-isopropyl-2,3-piperazinedione	$C_9H_{16}N_2O_2$	203	63	58.65	8.76	15.26	58.35	8.64	15.00
N-(2-Aminoisobutyl)-*n*-butylamine	1-*n*-Butyl-5,5-dimethyl-2,3-piperazinedione	$C_{10}H_{18}N_2O_2$	118	50	60.55	9.15	—	59.76	9.20	—
N-(2-Aminoisobutyl)-*sec*-butylamine	1-*sec*-Butyl-5,5-dimethyl-2,3-piperazinedione	$C_{10}H_{18}N_2O_2$	210–212	34	—	—	14.26	—	—	14.14
N-(2-Aminoisobutyl)aniline	5,5-Dimethyl-1-phenyl-2,3-piperazinedione	$C_{12}H_{14}N_2O_2$	194–196	53	66.00	6.44	—	65.70	6.36	—
N-(2-Aminoisobutyl)-*p*-toluidine	5,5-Dimethyl-1-*p*-tolyl-2,3-piperazinedione	$C_{13}H_{16}N_2O_2$	246–247	26	—	—	12.07	—	—	12.04

methanol was evaporated, leaving a residue with an amine odor. Upon distillation, the only distinct fraction boiled at 152–153°/20; yield 18.6 g. (23%).

Anal. Calc'd for (V) $C_9H_{18}N_2O$: C, 63.48; H, 10.66.
Found: C, 63.84; H, 10.79.

B. *Clemmensen reduction.* A mixture of 100 g. of mossy zinc, 8 g. of mercuric chloride, 5 ml. of conc'd hydrochloric acid, and 125 ml. of water was stirred 5 minutes. The aqueous solution was decanted and to the amalgamated zinc was added 75 ml. of water, 100 ml. of conc'd hydrochloric acid, and 36.8 g. (0.2 moles) of (IV). This mixture was refluxed 9 hours. The solution was decanted from the unused zinc and potassium hydroxide was added in excess. This alkaline solution was extracted with ether, the ether extract was dried over solid potassium hydroxide, and distilled; b.p. 130–131°/4, yield 17 g. (50%).

Anal. Calc'd for (V) $C_9H_{18}N_2O$: N, 16.45; neut. equiv., 170.14.
Found: N, 16.32; neut. equiv., 172.79.

Preparation of the hydrochloride of (V). The hydrochloride was prepared from samples of (V) obtained by each of the reduction methods. The properties were identical for both preparations. Two g. of (V) was dissolved in dry ether and treated with dry hydrogen chloride. A white solid formed and the ether was decanted. The solid was crystallized from ethanol; yield 1.5 g., m.p. 192°.

Anal. Calc'd for $C_9H_{19}ClN_2O$: N, 13.55; Cl, 17.18.
Found: N, 13.46; Cl, 17.32.

Preparation of the benzoyl derivative of (V). To 2 g. of (V) was added 5 ml. of water and 4 g. of benzoyl chloride. The mixture was agitated while 20 ml. of 20% aqueous sodium hydroxide was added portionwise. A white solid formed which, upon crystallization from 90% ethanol, melted at 152–153°; yield 1.6 g.

Anal. Calc'd for $C_{16}H_{22}N_2O_2$: N, 10.21. Found: N, 10.15.

This benzoyl derivative was neutral in character.

Preparation of 5,5-dimethyl-1-isopropyl-2-keto-4-nitroso-1,4-hexahydrodiazine. To 4.5 g. (0.0265 mole) of (V) was added 4.4 ml. (0.053 mole) of conc'd hydrochloric acid in 5 ml. of water. This mixture was cooled to 0° and an aqueous solution of sodium nitrite was added slowly with stirring. The temperature was maintained at 0–5°. An oil separated which crystallized upon standing, and was purified by recrystallization from ethanol; m.p. 115°, yield 3.9 g. (75%).

Anal. Calc'd for $C_9H_{17}N_3O_2$: N, 21.09. Found: N, 21.00.

Reduction of 1-n-butyl-5,5-dimethyl-2,3-piperazinedione (IX) *to 1-n-butyl-5,5-dimethyl-2-keto-1,4-hexahydrodiazine* (X). The Clemmensen reduction of 0.2 mole of (IX) was carried out as described for (IV) above. The product (X) boiled at 155–157°/6; yield 11.4 g. (31%).

Anal. Calc'd for (X) $C_{10}H_{20}N_2O$: N, 15,20; neut. equiv., 184.16.
Found: N, 15.07; neut. equiv., 185.53.

The *hydrochloride* of (X) was prepared by the usual method; m.p. 127–129°.

Anal. Calc'd for $C_{10}H_{21}ClN_2O$: N, 12.58; Cl, 15.93.
Found: N, 12.46; Cl, 16.17.

Reduction of 1-sec-butyl-5,5-dimethyl-2,3-piperazinedione (XI) *to 5,5-dimethyl-2-keto-1-sec-butyl-1,4-hexahydrodiazine* (XII). The Clemmensen reduction of 0.2 mole of (XI) was carried out as described for (IV) above. The product (XII) boiled at 140–141°/6, yield 8.5 g. (23%).

Anal. Calc'd for (XII) $C_{10}H_{20}N_2O$: N, 15.20; neut. equiv., 184.16.
Found: N, 14.87; neut. equiv., 187.75.

The *hydrochloride* of (XII) was prepared by the usual method; m.p. 175–176°.

Anal. Calc'd for $C_{10}H_{21}ClN_2O$: N, 12.58; Cl, 15.93.
Found: N, 12.64; Cl, 16.16.

Attempts were made to reduce 5,5-dimethyl-1-phenyl-2,3-piperazinedione and 5,5-dimethyl-1-*p*-tolyl-2,3-piperazinedione by the Clemmensen method, but none of the expected products were obtained. The reduced material possessed an amine odor, but the yields were low and attempts at purification failed.

Acknowledgment. The author is pleased to express his appreciation to Commercial Solvents Corporation for generous support of this study.

SUMMARY

1. Oxalic esters react with 1,2-diamines to produce 2,3-piperazinediones. Five examples have been described.

2. These piperazinediones can be reduced to 2-keto-1,4-hexahydrodiazines.

ALBUQUERQUE, NEW MEXICO

REFERENCES

(1) RIEBSOMER, publication in process.

(2) RIEBSOMER, *J. Am. Chem. Soc.*, **70,** 1629 (1948).