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

THE SYNTHESIS OF HEXAHYDROPYRIMIDINES FROM 1,3-DIAMINES AND KETONES OR ALDEHYDES

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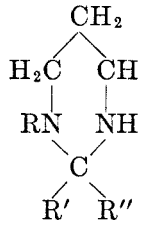
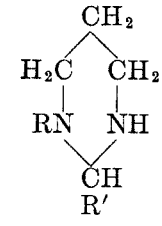
Received July 18, 1949

Previous workers (1, 2, 3, 4) have shown that 1,3-diamines will condense with aldehydes or ketones to produce hexahydropyrimidines. We have extended this earlier work by preparing a number of new compounds. Several ketones tried in this study have been found to produce good yields of the corresponding hexahydropyrimidines (I). When benzophenone, ethyl oxomalonate, quinone, and benzalacetone were substituted for the common ketones, none of the expected pyrimidines were obtained.



I

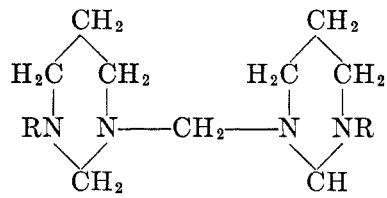


II

In some instances aldehydes give a comparable reaction (producing compounds of type II) but for some unknown reason this type of reaction is less general and less satisfactory. Thus when acetaldehyde, butyraldehyde or benzaldehyde was interacted with N-isopropyl-1,3-propanediamine, none of the expected hexahydropyrimidines was isolated.

Also, it has been demonstrated that when the aldehyde is formaldehyde *bis*-compounds (III) may form.

$$2\ RNHCH_2CH_2CH_2NH_2 + 3\ HCHO \rightarrow 3H_2O +$$



III

It has not been found possible to cause other aldehydes (for example furfural) to behave in a similar manner. Presumably in these reactions the hexahydropyrimidine of type II is first formed followed by the interaction of 2 moles of the hexahydropyrimidine and 1 mole of formaldehyde with the loss of 1 mole of water.

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EXPERIMENTAL

A. KETONES AND 1,3-DIAMINES

A number of hexahydropyrimidines were prepared using the same general procedure, which was essentially that used by Bergmann, *et al.* (4). Only one needs to be given in detail. Table I summarizes the data.

1-Isopropyl-2-methyl-2-phenylhexahydropyrimidine. A mixture of 34.8 g. (0.3 mole) of N-isopropyl-1,3-propanediamine and 36 g. (0.3 mole) of acetophenone was prepared. A little benzene was added and the mixture was heated under conditions to distill the benzene-water azeotropic mixture through a 4′ packed-column. The column was fitted with a decanter stillhead so that the benzene returned constantly to the reaction mixture. The temperature was gradually increased from 120° to 180° during a 6-hour period, resulting in the removal of 5 g. of water. Upon distillation from a modified Claisen flask at 20 mm., the product was a colorless liquid which boiled at 173–175°. Yield, 37 g. (57%).

Anal. Calc'd for $C_{14}H_{22}N_2$: C, 76.96; H, 10.16; N, 12.82; Neut. equiv., 109.12.
Found: C, 77.03; H, 10.14; N, 12.80; Neut. equiv., 110.44.

B. ALDEHYDES AND 1,3-DIAMINES

Reaction of N-isopropyl-1,3-propanediamine and formaldehyde. In one experiment, a mixture of 58 g. (0.5 mole) of N-isopropyl-1,3-propanediamine and 63 g. (0.75 mole) of 40% aqueous formaldehyde was prepared and heated under the usual conditions to remove water by distilling the benzene-water azeotropic mixture through a 4′ packed-column. By heating for 3 hours from 90 to 110°, a total of 51 g. of water was removed. The residue was distilled and separated into two main fractions. The first fraction, b.p. 74–75° at 22 mm., analyzed correctly for N-isopropylhexahydropyrimidine; yield 30%.

Anal. Calc'd for $C_7H_{16}N_2$: N, 21.85; Neut. equiv., 64.1.
Found: N, 21.41; Neut. equiv., 65.8.

The second fraction, b.p. 140–142° at 3 mm., analyzed correctly for *bis*-(3-isopropyl-1,3-diazacyclohexyl)methane (Type III); yield, 24%.

Anal. Calc'd for $C_{15}H_{32}N_4$: N, 20.85; Neut. equiv., 67.06.
Found: N, 20.34; Neut. equiv., 70.46.

In a second experiment, equimolecular quantities of N-isopropyl-1,3-propanediamine and formaldehyde were allowed to react under the conditions of the preceding experiment. Apparently some of the expected N-isopropylhexahydropyrimidine formed, but it was not sufficiently pure to give a suitable analysis.

In a third experiment, 152 g. (1.31 moles) of N-isopropyl-1,3-propanediamine was dissolved in 100 ml. of methanol. Then 2.8 moles of 40% aqueous formaldehyde was added portionwise while stirring and cooling. The temperature was maintained at 30–40°. The mixture was finally heated to 60° on a steam-bath. The methanol and other volatile constituents were removed *in vacuo* by heating to a maximum temperature of 110°. The product was distilled at 2 mm.; yield, 91 g. (70%).

Anal. Calc'd for the *bis*-compound, $C_{15}H_{32}N_4$: N, 20.85; Molecular weight, 268.
Found: N, 21.14; Molecular weight, 264.

N-isopropyl-2-(2′-furyl)hexahydropyrimidine. A mixture was prepared containing 58 g. (0.5 mole) of N-isopropyl-1,3-propanediamine and 48 g. (0.5 mole) of furfural. Much heat was evolved and the mixture was cooled externally to prevent the temperature exceeding 50°. Benzene was added and the mixture was heated under the usual conditions to remove water. The temperature was increased during a 5-hour period to a maximum of 160°, thus removing 8.5 g. of water. The product which distilled at 122–123° at 5 mm. weighed 62 g. (64%).

Anal. Calc'd for $C_{11}H_{18}N_2O$: C, 67.98; H, 9.34; N, 14.42; Neut. equiv., 97.08.
Found: C, 67.98; H, 9.53; N, 14.23; Neut. equiv., 91.69.

N-(β-Hydroxyethyl)hexahydropyrimidine. To 206 g. (1.745 moles) of N-(β-hydroxyethyl)-1,3-propanediamine was added 100 ml. of methanol. To this mixture was added 1.7

TABLE I

HEXAHYDROPYRIMIDINES OF TYPE I FROM KETONES AND 1,3-DIAMINES

AMINE USED	KETONE USED	FORMULA	B.P., °C.	MM.	YIELD, %	ANALYSES							
						C		H		N		Neut. Equiv.	
						Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found
N-Isopropyl-1,3-propanediamine	Acetophenone	$C_{14}H_{22}N_2$	173–175	20	57	76.96	77.03	10.16	10.14	12.82	12.80	109.12	110.44
N-Isopropyl-1,3-propanediamine	Ethyl methyl ketone	$C_{10}H_{22}N_2$	104–107	20	61	70.50	70.49	13.03	13.03	16.39	16.36	85.11	86.81
N-2-Ethylhexyl-1,3-propanediamine	Acetophenone	$C_{19}H_{32}N_2$	183–185	4	82	—	—	—	—	9.71	9.38	144.16	151.22
N-2-Ethylhexyl-1,3-propanediamine	Acetone	$C_{14}H_{30}N_2$	115–120	3	78	—	—	—	—	12.33	12.90	113.14	109.18
N,N-Dibutyl-4-aza-1,7-heptanediamine	Acetone	$C_{17}H_{37}N_3$	160–165	4	73	—	—	—	—	14.83	15.79	94.4	89.7
N,N-Dibutyl-4-aza-1,7-heptanediamine	Acetophenone	$C_{22}H_{39}N_3$	205–208	3	75	—	—	—	—	12.16	11.83	115.1	119.02

moles of 40% aqueous formaldehyde with stirring and cooling so that the temperature remained at 45–50°. This mixture was finally heated ½ hour on a steam-bath. The methanol and other volatile constituents were distilled *in vacuo* up to a pot temperature of 120°. The product which distilled at 137–140° at 17 mm. weighed 209 g. (92%).

Anal. Calc'd for $C_6H_{14}N_2O$: N, 21.43; Molecular weight, 130.1; Neut. equiv., 65.
Found: N, 21.23; Molecular weight, 113; Neut. equiv., 66.5.

When furfural was substituted for formaldehyde in the above reaction in an attempt to produce N-(β-hydroxyethyl-2-α-furyl)hexahydropyrimidine, only a black tar was formed.

N-(2-ethylhexyl)hexahydropyrimidine. To 233 g. (1.28 moles) of N-(2-ethylhexyl)propanediamine was added one mole of aqueous 40% formaldehyde with stirring and cooling so that the temperature was maintained at 45–50°. After the reaction was complete, the more volatile constituents were distilled *in vacuo* up to a pot temperature of 130°. The remainder of the product was fractionated at 10 mm. The main fraction boiled at 120–121° and weighed 194 g. (98%).

Anal. Calc'd for $C_{12}H_{26}N_2$: N, 14.40; Molecular weight, 198.
Found: N, 14.14; Molecular weight, 214.

Bis-3-(3'-dibutylaminopropyl)-1,3-diazacyclohexylmethane. To 243 g. (1.0 mole) of N,N-dibutyl-4-aza-1,7-heptanediamine was added 200 ml. of methanol. To this mixture was added portionwise 2 moles of aqueous 40% formaldehyde while stirring and cooling to maintain the temperature at 40–50°. After about 75% of the formaldehyde was added, two layers formed. The mixture was finally heated for a few minutes with steam. The methanol and other volatile constituents were removed *in vacuo* up to a pot temperature of 130°. Upon distillation, 230 g. (88%) of the expected product was obtained.

Anal. Calc'd for $C_{31}H_{66}N_6$: N, 16.09; Molecular weight, 522.
Found: N, 15.61; Molecular weight, 508.

A number of these new hexahydropyridmidines have been tested as insect repellents, but none have been found effective.

ACKNOWLEDGMENT

The authors are pleased to express their appreciation to the research laboratories of Commercial Solvents Corporation for generous support of this work.

SUMMARY

1. Ketones react with 1,3-diamines to give good yields of hexahydropyrimidines.

2. Some aldehydes likewise produce hexahydropyrimidines in good yields, but this type of reaction is less satisfactory.

3. In some instances, when formaldehyde reacts with 1,3-diamines, it has been shown that *bis*-1,3-diazacyclohexylmethanes may be produced.

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