Anal. Calcd. for $C_9H_{13}NBrCl$: Cl, 14.2. Found: Cl, 14.2.

N,N-Dimethyl-4-bromo-2-methylaniline was obtained in 68% yield from 4,6-dibromo-2-methylaniline and in 54% yield from 4-bromo-2-methylaniline. In the latter reaction 3 g. of tar also was obtained. The product distilled at 120–130° (20 mm.); d^{20}_{20} 1.3300; n^{20}_D 1.5660; M^{20}_D calcd. 53.4; found 52.4. It was characterized as the hydrochloride, which proved to be too hygroscopic for a melting point determination and was therefore analyzed directly.

Anal. Calcd. for $C_9H_{13}NBrCl$: Cl, 14.2. Found: Cl, 13.9.

N,N-Dimethyl-2,4-dimethylaniline was prepared in 90% yield from 6-bromo-2,4-dimethylaniline. Its picrate melted at 122.0–122.5° (121–123°).[12]

N,N-Dimethyl-2,4,6-trichloroaniline.—Under these same conditions 2,4,6-trichloroaniline was methylated without loss of chlorine. The N,N-dimethyl-2,4,6-trichloroaniline was identified by its physical properties: b. p. by Siwoloboff method 246° (247°);[10] d^{20}_{20} 1.3140; n^{20}_D 1.5660; M^{20}_D calcd. 55.6, found 55.7.

---

[12] Fichter and Müller, *Helv. Chim. Acta*, **8**, 290 (1925).

Summary

In the reductive alkylation of aromatic primary amines containing bromine in the ortho positions, one or both bromine atoms are removed when amalgamated zinc and hydrochloric acid is used as the reducing agent. With formaldehyde as the alkylating agent, substituted dimethylanilines are produced. This bromine removal is due to the activation of the bromine by the strongly positive ammonium salt ortho to it.

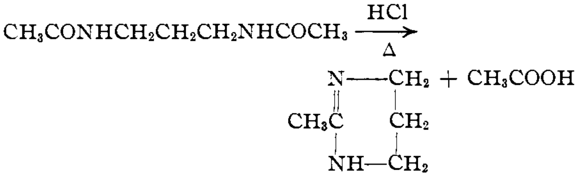
URBANA, ILLINOIS RECEIVED JUNE 3, 1940

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF SWARTHMORE COLLEGE]

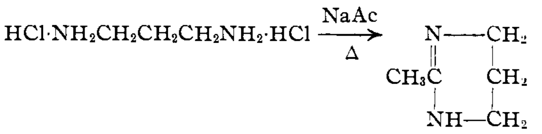
A Synthesis of Tetrahydropyrimidines

BY SAMUEL R. ASPINALL

Very little is known about the chemistry of reduced pyrimidines. An examination of the literature shows that only three derivatives of tetrahydropyrimidine have been reported and these were prepared in small yields and impure condition. Almost nothing is stated about their reactions. Hofmann,[1] in reporting the preparation of 2-methyl-3,4,5,6-tetrahydropyrimidine[2] by heating diacetyltrimethylenediamine in a stream of dry hydrogen chloride, described the compound as a dark brown oil, but recorded no yields nor physical constants of the base nor of any of its derivatives.

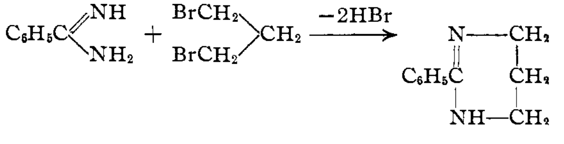


Hofmann also reported the 2-phenyl derivative but the description of the procedure and the compound was vague. Haga and Majima[3] obtained the 2-methylpyrimidine in a state of reasonable purity by fusing the hydrochloride of trimethylenediamine with sodium acetate.



Harries and Haga[4] had used the same method to prepare 2,4,6-trimethyl-3,4,5,6-tetrahydropyrimidine from 2,4-diaminopentane. This type of reaction, analogous to the preparation of 2-methyl-4,5-dihydroimidazole by fusing ethylenediamine hydrochloride with sodium acetate, is known to give very poor results.[5]

Pinner[6] reported 2-phenyl-3,4,5,6-tetrahydropyrimidine to be a minor, oily by-product when benzamidine and trimethylene dibromide were allowed to react for several weeks.



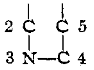
Its analysis, by means of the chloroplatinic acid salt, was very poor.

Later, Branch and Titherley[7] reported that they were unable to obtain any 2-phenyl-3,4,5,6-tetrahydropyrimidine using Hofmann's method, but a modification of Pinner's technique yielded,

---

[1] Hofmann, *Ber.*, **21**, 2336 (1888).

[2] The pyrimidine nucleus is numbered as follows:



[3] Haga and Majima, *Ber.*, **36**, 333 (1903).

[4] Harries and Haga, *ibid.*, **32**, 1191 (1899).

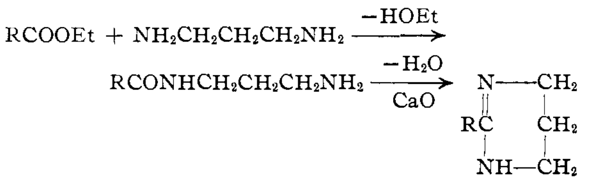
[5] Chitwood and Reid, THIS JOURNAL, **57**, 2424 (1935).

[6] Pinner, *Ber.*, **26**, 2122 (1893).

[7] Branch and Titherley, *J. Chem. Soc.*, **101**, 2342 (1912).

after a long and involved isolation procedure, the pyrimidine (as its oxalate) in 7% yield.

Since it has been shown[8] that 2-alkyl(or aryl)-4,5-dihydroimidazoles are very smoothly and efficiently produced by dehydration of monoacylethylenediamines, it was thought likely that 2-alkyl(or aryl)-3,4,5,6-tetrahydropyrimidines could be analogously produced from monoacyltrimethylenediamines. This has been found to be true.



$$RCOOEt + NH_2CH_2CH_2CH_2NH_2 \xrightarrow{-HOEt}$$

$$RCONHCH_2CH_2CH_2NH_2 \xrightarrow[CaO]{-H_2O}$$

The first step in this synthesis is the preparation of a monoacyltrimethylenediamine by interaction of an ester and trimethylenediamine.

Acetyltrimethylenediamine.—One mole (74 g.) of sodium-dried trimethylenediamine and one-third mole (29 g.) of ethyl acetate were sealed in a glass tube and heated at 100° for twelve hours. The reaction mixture was then transferred to a Claisen flask and 66 g. of low boiling material, consisting of ethanol and excess trimethylenediamine, removed under diminished pressure. When the bath temperature was increased to 165°, 26 g. of monoacetyltrimethylenediamine distilled at 130–140° (5 mm.), leaving a small residue of diacetyltrimethylenediamine. The crude monoamide on careful redistillation boiled smoothly at 130° (3 mm.); yield 23 g. (60% of the theoretical).

Acetyltrimethylenediamine, which is a pure white, strongly basic oil very soluble in water, ethanol and acetone, was converted to derivatives for characterization. It reacted violently with phenyl isocyanate to yield a crystalline urea.

$$CH_3CONHCH_2CH_2CH_2NH_2 + C_6H_5NCO \longrightarrow CH_3CONHCH_2CH_2CH_2NHCONHC_6H_5$$

1-Acetyl-3-phenylcarbonamidotrimethylenediamine precipitated immediately, with evolution of heat, when an acetone solution of acetyltrimethylenediamine (1.16 g.) was treated with one equivalent of phenyl isocyanate (1.19 g.). The white urea melted at 147° (cor.) after recrystallization from acetone.

The picrate was prepared in the usual manner in 50% ethanol–water.

The cyclization of acetyltrimethylenediamine to the tetrahydropyrimidine configuration was effected in excellent yields by means of a lime dehydration.

2-Methyl-3,4,5,6-tetrahydropyrimidine.—One-fifth of a mole (23.2 g.) of acetyltrimethylenediamine was mixed with one mole (56 g.) of finely powdered lime and heated in a sealed tube at 250° for fifteen hours.[9] 2-Methyl-3,4,5,6-tetrahydropyrimidine was extracted from the lime with absolute ethanol and distilled, after removal of the solvent, at 100–105° (6 mm.) as a pure white oil which immediately solidified; yield 17.6 g. (90%). On careful redistillation it boiled at 91° (4 mm.) and after recrystallization from ethyl acetate–petroleum ether was obtained as extremely hygroscopic white crystals melting at 75° (cor.). Repeated recrystallizations failed to remove the hygroscopic property.

2-Methyl-3,4,5,6-tetrahydropyrimidine, which is strongly basic and extremely soluble in water, ethanol and acetone, was further characterized by conversion to its picrate in the usual manner in absolute ethanol.

If it is not desired to isolate the intermediate monoacetyltrimethylenediamine, the initial acylation may be carried out at higher temperatures with consequent better yields. The product of an acetylation carried out as above, but at 150°, is a mixture of monoacetyltrimethylenediamine and 2-methyl-3,4,5,6-tetrahydropyrimidine, the latter resulting from a spontaneous dehydration of the former at the temperature of acylation. This mixture may then be subjected to a lime dehydration to give the pure pyrimidine in an over-all yield of 70%. The acetylation of trimethylenediamine also was carried out at 225° in the hope that complete dehydration of the intermediate monoacyltrimethylenediamine would be effected and thereby eliminate the necessity of the lime dehydration, but even at this high temperature only about one-third of the product was obtained in the cyclic form. The fact that a high temperature acetylation of trimethylenediamine yields a mixture of cyclic and linear bases was shown as follows.

After removal of the low boiling fraction from an acetylation carried out at high temperature the material boiling at 120–140° (5 mm.) was collected. It was a pure white oil weighing 29 g. and upon careful redistillation was divisible into 3 fractions. The first fraction, boiling at 95–96° (5 mm.), weighed 9 g. and was identified as 2-methyl-3,4,5,6-tetrahydropyrimidine by its boiling point and mixed melting points with authentic samples of the free base and its picrate. The second fraction, having a steadily rising boiling point from 100 to 130° (5 mm.), weighed 11 g. and was a mixture from which derivatives of 2-methyl-3,4,-

---

[8] Aspinall, THIS JOURNAL, **61**, 3195 (1939); A. J. Hill and Aspinall, *ibid.*, **61**, 822 (1939).

[9] The tube should be less than one-half full and placed on its side so that the expansion of the lime during hydration does not break the glass.

TABLE I

REACTION OF TRIMETHYLENEDIAMINE WITH ESTERS[a]

React. temp., °C.	Reacting ester	Reaction product	B. p. °C.	B. p. Mm.	M. p., °C., cor.	Yield, %	Nitrogen, % Calcd.	Nitrogen, % Kjeldahl I	Nitrogen, % Kjeldahl II
100	Ethyl acetate	Acetyltrimethylenediamine[b]	130	3		60	anal. only as derivs.		
150	Ethyl acetate	2-Methyl-3,4,5,6-tetrahydropyrimidine[b] and acetyltrimethylenediamine	91	4	75[c]	70[d]	28.57	28.33	28.26
150	Ethyl benzoate	2-Phenyl-3,4,5,6-tetrahydropyrimidine[b] and benzoyltrimethylenediamine	155–165	5	87[e]	70[d]	17.50 anal only as derivs.	17.46	17.65

[a] One mole of anhydrous trimethylenediamine and one-third mole of ester were heated in a glass tube for twelve hours. [b] Soluble in alcohol, acetone, and water. [c] Sealed capillary. Literature 72–74°, *Ber.*, **36**, 333 (1903). [d] Overall yield of pyrimidine after the reaction product has been subjected to lime dehydration. [e] Literature 72–78°, *J. Chem. Soc.*, **101**, 2342 (1912).

TABLE II

PHENYL UREAS

Reacting base	Phenylureido derivative	M. p., °C., cor.	Nitrogen, % Calcd.	Nitrogen, % Kjeldahl I	Nitrogen, % Kjeldahl II
Acetyltrimethylenediamine[a]	1-Acetyl-3-phenylcarbonamidotrimethylenediamine[b]	147	17.87	17.77	17.85
Benzoyltrimethylenediamine[c]	1-Benzoyl-3-phenylcarbonamidotrimethylenediamine[d]	166[e]	14.14	14.28	14.30

[a] Reaction done in acetone. [b] Recrystallized from acetone. [c] Reaction done in benzene. [d] Recrystallized from dilute ethanol. [e] The urea precipitates as a solvate and gives the correct analysis and a reproducible melting point only after drying at 100° for several hours in an Abderhalden dryer.

TABLE III

PICRATES

Reacting base	M. p., °C., cor.	Nitrogen, % Calcd.	Nitrogen, % Kjeldahl I	Nitrogen, % Kjeldahl II
Acetyltrimethylenediamine	197[a]	20.29	20.23	20.36
2-Methyl-3,4,5,6-tetrahydropyrimidine	157[b]	21.41	21.50	21.41
2-Phenyl-3,4,5,6-tetrahydropyrimidine	181[c]	18.00	18.14	18.04

[a] Formed and recrystallized in 50% ethanol. [b] Formed and recrystallized in absolute ethanol. Literature 152°, *Ber.*, **36**, 333 (1903). [c] Formed and recrystallized in absolute ethanol.

5,6-tetrahydropyrimidine and monoacetyltrimethylenediamine were isolated and identified. The third fraction, boiling at 130–131° (5 mm.) and weighing 9 g., was pure acetyltrimethylenediamine as shown by its boiling point and the mixed melting points of its derivatives with authentic samples.

The synthesis of 2-phenyl-3,4,5,6-tetrahydropyrimidine was carried out at 150° without the isolation of the intermediate monobenzoyltrimethylenediamine. Benzoylation of trimethylenediamine at 100, 150 and 250° yielded a mixture of the cyclic and linear bases which was converted to the pure pyrimidine by lime dehydration. The mixed character of the original benzoylation product was adequately shown by isolation of derivatives of both bases.

The author is indebted to Mr. Samuel M. Raymond for the preparation of the trimethylenediamine used in this study.

Summary

1. The interaction of trimethylenediamine with carboxylic acid esters has been shown to yield monoacyltrimethylenediamines.

2. A study of the ease of dehydration of monoacyltrimethylenediamines has been made.

3. A satisfactory synthesis of 2-substituted-3,4,5,6-tetrahydropyrimidines by dehydration of monoacyltrimethylenediamines has been developed.

4. The bases prepared in this study have been characterized as picrates and phenyl ureas.

SWARTHMORE, PENNA. RECEIVED MAY 9, 1940