[CONTRIBUTION FROM RESEARCH AND DEVELOPMENT DEPARTMENT, COMMERCIAL SOLVENTS CORPORATION]

# The Preparation of Some Hexahydropyrimidines from Nitroparaffins[1]

BY MURRAY SENKUS

Recent studies[1a,2] of the reaction of nitroparaffins with formaldehyde and amines had made available some new nitro amines. Some reactions of the 1,3-propanediamines were investigated and it was found that they will react with formaldehyde to give 5-nitrohexahydropyrimidines. For example 2-nitro-2-methyl-1,3-propanebis-(isopropylamine) and formaldehyde gave 5-nitro-1,3-diisopropyl-5-methylhexahydropyrimidine in good yield. Further work showed that 5-nitrohexahydropyrimidines could be prepared by other methods. Thus the above compound was also prepared by allowing one mole of 2-nitro-2-methyl-1,3-propanediol to react with 2 moles of isopropylamine and one mole of formaldehyde; it was also prepared by allowing one mole of nitroethane to react with 2 moles of isopropylamine and 3 moles of formaldehyde. A number of 5-nitrohexahydropyrimidines were prepared by the above methods and are reported herein.

It was also found that the 5-nitrohexahydropyrimidines can be hydrogenated readily in the presence of Raney nickel to the corresponding 5-aminohexahydropyrimidines. The new amines that were prepared are also described in the present paper.

## Experimental

### I. 5-Nitrohexahydropyrimidines

Examples of each of the three procedures which were developed for the preparation of 5-nitrohexahydropyrimidines are given below.

**Method A.** (a) **5-Nitro-1,3-diisopropyl-5-methylhexahydropyrimidine from 2-Nitro-2-methyl-1,3-propanebis-(isopropylamine) and Formaldehyde.**—To a 2-liter, round-bottom flask equipped with a stirrer and a Dean and Stark[3] moisture trap which was connected to a condenser were added 217 g. (1 mole) of 2-nitro-2-methyl-1,3-propanebis-(isopropylamine), 500 ml. of cyclohexane and 75 ml. (1 mole) of 36% (by weight) aqueous formaldehyde. The mixture was agitated and refluxed until water had ceased separating in the trap. The volume of the mixture was reduced to 400 ml. by evaporation on the steam-bath. The residue was cooled to 15° and the product was allowed to crystallize; yield was 195 g.

(b) **5-Nitro-1,3-diphenyl-5-methylhexahydropyrimidine from 2-Nitro-2-methyl-1,3-propanebis-(aniline) and Formaldehyde.**—A mixture which consisted of 570 g. (2 moles) of 2-nitro-2-methyl-1,3-propanebis-(aniline), 150 ml. (2 moles) of 36% aqueous formaldehyde and 1500 ml. of ethyl alcohol was stirred and refluxed for eight hours. Stirring was continued and the mixture was cooled slowly to 25° during which time the product crystallized. The mixture was filtered and the solid was washed with 400 ml. of ethyl alcohol. The yield of a light yellow crystalline product was 525 g.

**Method B.** (a) **5-Nitro-1,3-dibenzyl-5-methylhexahydropyrimidine from 2-Nitro-2-methyl-1,3-propanediol, Benzylamine and Formaldehyde.**—A mixture which consisted of 57 ml. (0.76 mole) of 36% (by wt.) aqueous formaldehyde, 102 g. (0.76 mole) of 2-nitro-2-methyl-1,3-propanediol, 161 g. (1.51 mole) of benzylamine and 300 ml. of methanol was refluxed for six hours. The homogeneous solution was poured into a 1-liter beaker and the product commenced to crystallize. The mixture was allowed to stand overnight and then it was filtered. The product was washed on the funnel with 200 ml. of cold (10°) methanol and dried in air; yield was 196 g.

(b) **5-Nitro-1,3-diisopropyl-5-hydroxymethylhexahydropyrimidine from Tris-(hydroxymethyl)-nitromethane, Isopropylamine and Formaldehyde.**—To 15 g. (0.1 mole) of tris-(hydroxymethyl)-nitromethane were added in the cold 12 g. (0.2 mole) of isopropylamine and 7 ml. (0.1 mole) of 36% (by weight) aqueous formaldehyde. The mixture was stirred at room temperature for thirty minutes and then was allowed to stand at 5° overnight. The mixture was filtered and the solid product was dried in the air for four hours; yield was 22 g.

**Method C.** (a) **5-Nitro-1,3-bis-(1-methyl-3,5-dioxacyclohexyl)-5-propylhexahydropyrimidine from 5-Amino-5-methyl-1,3-dioxane, Formaldehyde and 1-Nitrobutane.**—To 210 g. (1.8 moles) of 5-amino-5-methyl-1,3-dioxane were added 202 ml. (2.7 moles) of 36% (by weight) aqueous formaldehyde, 95 g. (0.9 mole) of 1-nitrobutane and 200 ml. of methanol. The mixture was stirred for a short time in order to make it homogeneous. The product began to crystallize from the solution after two hours at room temperature. The mixture was filtered after twenty hours. The solid was washed with cold methanol and then was dried in air; yield was 130 g.

(b) **5-Nitro-1,3-diisopropylhexahydropyrimidine from Nitromethane, Isopropylamine and Formaldehyde.**—To 120 g. (2.02 moles) of isopropylamine was added 225 ml. (3 moles) of 36% (by weight) aqueous formaldehyde in the cold. While the mixture was stirred and held at 10° by a bath, 61 g. (1 mole) of nitromethane was added dropwise. Stirring was continued for one and one-half hours and then the mixture was extracted with 1 liter of ethyl ether. The ether extract was stored over anhydrous sodium sulfate at 0° overnight. The ether solution was concentrated on the steam-bath to 400 ml. To the residue was added 1 liter of petroleum ether and the solution was again concentrated on the steam-bath, this time to 300 ml. A brown product separated from the residue at room temperature; yield was 147 g. Two recrystallizations from petroleum ether yielded a white product.

The 5-nitrohexahydropyrimidines derived from aliphatic amines are either white crystalline solids or colorless liquids; those derived from aromatic amines possess a light-yellow color. The 5-nitrohexahydropyrimidines are soluble in acetone, benzene and ether. The low molecular weight compounds are appreciably soluble in water but those with long non-polar groups on the nitrogens in the ring are insoluble in water. 5-Nitro-1,3-diisopropylhexahydropyrimidine decomposes to a tar at room temperature after several days; the other nitro compounds have shown no signs of decomposition on storage in the room for two years. They are decomposed slowly by hot mineral acids. The 5-nitrohexahydropyrimidines together with some properties and analyses are listed in Table I.

### II. 5-Aminohexahydropyrimidines

All 5-aminohexahydropyrimidines which are reported herein were prepared by the same procedure. One mole of a 5-nitrohexahydropyrimidine was hydrogenated in

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[1] Prepared for the 1946 Spring meeting of the Organic Division A. C. S. The subject matter of this paper is covered by U. S. Patents 2,391,847 and 2,387,043.

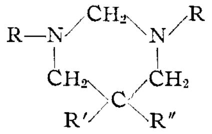
[1a] Senkus, THIS JOURNAL, **68**, 10 (1946).

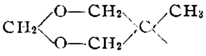
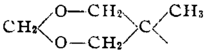
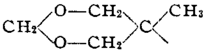
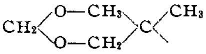
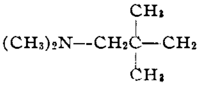
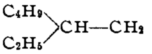
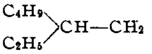
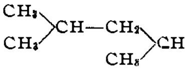
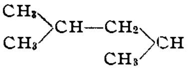
[2] Johnson, *ibid.*, 14 (1946).

[3] Dean and Stark, *Ind. Eng. Chem.*, **12**, 486 (1920).

TABLE I

SOME HEXAHYDROPYRIMIDINES OF THE TYPE



| R | R′ | R″ | M. p. °C. | B. p. °C. | B. p. Mm. | $n^{20}_D$ | $d^{20}_{20}$ | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $C_6H_5CH_2$ | $CH_3$ | $NO_2$ | 113.5 | | | | | | | | | 12.91 | 12.48 |
| $C_6H_5CH_2$ | $CH_3$ | $NH_2$ | | 178 | 0.6 | 1.5659 | 1.0484 | | | | | 14.23 | 14.15 |
| $C_6H_5CH_2$ | $CH_3$ | $N{=}CH_2$ | | 196 | 0.8 | 1.5628 | 1.0610 | | | | | 13.67 | 13.46 |
| $C_6H_5CH_2$ | $C_2H_5$ | $NO_2$ | 93.7 | | | | | | | | | 12.38 | 12.41 |
| $C_6H_5CH_2$ | $C_3H_7$ | $NO_2$ | 113.0 | | | | | | | | | 11.89 | 11.80 |
| $C_6H_5CH_2$ | $C_3H_7$ | $NH_2$ | | 178 | 0.3 | 1.5554 | 1.0304 | | | | | 12.99 | 12.91 |
|  | $CH_3$ | $NO_2$ | 151.8 | | | | | 52.15 | 52.02 | 7.88 | 7.66 | | |
|  | $CH_3$ | $NH_2$ | | 175 | 0.3 | 1.4891 | 1.1028 | | | | | 13.32 | 13.26 |
|  | $C_3H_7$ | $NO_2$ | 94.4 | | | | | | | | | 11.25 | 11.18 |
|  | $C_3H_7$ | $NH_2$ | | 169 | 0.3 | 1.4968 | 1.1050 | | | | | 12.24 | 12.25 |
| $(CH_2OH)(CH_3)_2C$ | $CH_3$ | $NO_2$ | 124.0 | | | | | 53.95 | 53.68 | 9.41 | 9.06 | | |
| $(CH_2OH)(CH_3)_2C$ | $CH_3$ | $NH_2$ | | 162 | 0.4 | 1.4923 | 1.0544 | | | | | 16.20 | 16.01 |
| $(C_4H_9)_2NCH_2CH_2CH_2$ | $CH_3$ | $NH_2$ | | 230 | 0.7 | 1.4724 | 0.8892 | | | | | 15.44 | 15.40 |
|  $(CH_3)_2N-CH_2C(CH_3)_2-CH_2$ | $CH_3$ | $NH_2$ | | 162 | 0.4 | 1.4767 | 0.9261 | | | | | 20.50 | 19.72 |
| $C_{18}H_{37}$ | $C_2H_5$ | $NO_2$ | 45.8 | | | | | | | | | 6.33 | 6.45 |
| $C_{18}H_{17}$ | $C_2H_5$ | $NH_2$ | 33.2 | | | | | | | | | 6.63 | 6.39 |
| $(C_6H_{13})(CH_3)CH$ | $CH_3$ | $NH_2$ | | 167 | 0.5 | 1.4622 | 0.8648 | | | | | 12.37 | 12.44 |
| $(C_6H_{13})(CH_3)CH$ | $C_2H_5$ | $NH_2$ | | 160 | 0.2 | 1.4669 | 0.8801 | | | | | 11.88 | 11.70 |
|  $(C_4H_9)(C_2H_5)CH-CH_2$ | $CH_3$ | $NH_2$ | | 160 | 0.4 | 1.4668 | 0.8889 | | | | | 12.37 | 12.42 |
|  $(C_4H_9)(C_2H_5)CH-CH_2$ | $C_2H_5$ | $NH_2$ | | 140 | 0.3 | 1.4686 | 0.8832 | | | | | 11.88 | 11.57 |
|  $(CH_3)_2CH-CH_2(CH_3)CH$ | $CH_3$ | $NH_2$ | | 120 | 1.0 | 1.4556 | 0.8610 | | | | | 14.82 | 14.53 |
|  $(CH_3)_2CH-CH_2(CH_3)CH$ | $C_2H_5$ | $NH_2$ | | 122 | 0.4 | 1.4626 | 0.8735 | | | | | 14.12 | 13.73 |
| $(CH_3)_2CH$ | $CH_2OH$ | $NO_2$ | 137.0 | | | | | 53.85 | 54.29 | 9.45 | 9.10 | | |
| $(CH_3)_2CH$ | $CH_2OH$ | $NH_2$ | | 111 | 0.4 | 1.4845 | 1.0136 | | | | | 19.51 | 19.22 |
| $(CH_3)_2CH$ | $CH_3$ | $NO_2$ | 40.9 | | | | | 57.61 | 58.09 | 10.11 | 9.79 | | |
| $(CH_3)_2CH$ | $CH_3$ | $NH_2$ | | 100 | 10 | 1.4577 | 0.8828 | | | | | 21.08 | 21.02 |
| $(CH_3)_2CH$ | H | $NO_2$ | 77.0 | | | | | 55.78 | 56.34 | 9.83 | 9.65 | | |
| $(CH_3)_2CH$ | H | $NH_2$ | | 105 | 10 | 1.4569 | 0.8794 | | | | | 22.68 | 22.71 |
| $CH_3$ | $CH_2OH$ | $NO_2$ | 121.0 | | | | | 44.43 | 44.57 | 7.99 | 7.94 | | |
| $CH_3$ | $CH_3$ | $NO_2$ | 48.6 | | | | | 48.53 | 48.97 | 8.73 | 8.33 | | |
| $CH_3$ | $CH_3$ | $NH_2$ | | 69 | 10 | 1.4704 | 0.9039 | | | | | 29.34 | 29.37 |
| $CH_3$ | $C_2H_5$ | $NO_2$ | 38.5 | | | | | 51.31 | 51.21 | 9.15 | 8.88 | | |
| $CH_3$ | $C_6H_5$ | $NO_2$ | 97.4 | | | | | 61.25 | 61.18 | 7.28 | 7.16 | | |
| $C_6H_5$ | $CH_3$ | $NO_2$ | 68.2 | | | | | 68.66 | 68.51 | 6.44 | 6.28 | | |
| $C_6H_5$ | $CH_3$ | $NH_2$ | | 180 | 0.1 | 1.4905 | 1.0998 | | | | | 15.72 | 15.69 |
| $p$-$CH_3$-$C_6H_4$ | $CH_3$ | $NO_2$ | 113.2 | | | | | | | | | 12.91 | 12.50 |
| $p$-$CH_3$-$C_6H_4$ | $CH_3$ | $NH_2$ | | 190 | 0.2 | 1.5965 | 1.0707 | | | | | 14.22 | 14.20 |

approximately 500 ml. of methanol in the presence of Raney nickel catalyst at 75 to 100° and a pressure of 1000 lb. per sq. in. The mixture was filtered and the filtrate was distilled at atmospheric pressure through a one-foot Vigreux column to remove the methanol. The product was isolated by rectification of the residue at reduced pressure.

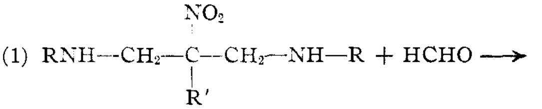
The 5-aminohexahydropyrimidines which were prepared are colorless liquids. The lower members in this series and those which contain hydrophilic groups on the ring nitrogens are soluble in water. The higher members are insoluble in water. All of the compounds which were prepared are soluble in petroleum ether, methanol and benzene. The lower members possess a pyridine-like odor which becomes less pronounced with increase in molecular weight. Their thermal stability is good since there was no observable decomposition of any of these compounds during their distillation *in vacuo*. The 5-aminohexahydropyrimidines which were prepared together with some properties and analyses are listed in Table I.

No debenzylation occurred during the hydrogenation of any of the 5-nitro-1,3-dibenzylhexahydropyrimidines. Further attempts were made to debenzylate 5-amino-1,3-dibenzyl-5-methylhexahydropyrimidine by hydrogenating it in methanol in presence of palladized charcoal at a pressure of 1500 lb. per sq. inch and temperatures of 75, 100 and 150°, but with no success. The stability of the nitrogen to benzyl group linkage during these hydrogenations is noteworthy in view of reported debenzylations of compounds like 2-benzylamino-2-methyl-1-propanol[4] and benzylethylmethylamine.[5]

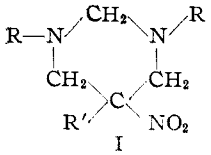
5-Amino-1,3-dibenzyl-5-methylhexahydropyrimidine was allowed to react with aqueous formaldehyde in an attempt to prepare a derivative of this compound. Distillation of this reaction mixture gave 5-methyl-5-methyleneimino-1,3-dibenzylhexahydropyrimidine. Some properties of this compound are listed in Table I.

### Summary

The preparation of a number of 5-nitrohexahydropyrimidines by one or more of the three following procedures is described:

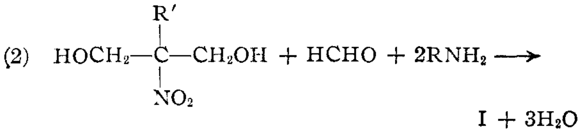


(1) $RNH-CH_2-\overset{NO_2}{\underset{R'}{C}}-CH_2-NH-R + HCHO \longrightarrow$



+ $H_2O$

I



(2) $HOCH_2-\overset{R'}{\underset{NO_2}{C}}-CH_2OH + HCHO + 2RNH_2 \longrightarrow I + 3H_2O$

(3) $R'CH_2NO_2 + 2RNH_2 + 3HCHO \longrightarrow I + 3H_2O$

The hydrogenation of some of the 5-nitrohexahydropyrimidines to the corresponding 5-aminohexahydropyrimidines is also reported.

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(4) Senkus, THIS JOURNAL, **67**, 1515 (1945).

(5) Baltzly and Buck, *ibid.*, **63**, 1964 (1941).

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[CONTRIBUTION FROM THE STAMFORD RESEARCH LABORATORIES OF THE AMERICAN CYANAMID COMPANY]

# The Preparation of DDT Using Hydrogen Fluoride as the Condensing Agent

BY J. H. SIMONS,[1] J. C. BACON, C. W. BRADLEY,[2] J. T. CASSADAY, E. I. HOEGBERG AND PAUL TARRANT

Hydrogen fluoride has been found to be a good condensing agent for a number of different reactions catalyzed by reagents such as sulfuric acid or aluminum chloride.[3] It was hoped that one of the particular advantages of the use of hydrogen fluoride in the preparation of DDT would be the elimination of side reactions usually encountered in the use of the other catalysts. For example, in a recent article Haller[4] states that thirteen impurities are present in technical DDT made by condensing chloral and chlorobenzene in the presence of sulfuric acid. Four of these compounds are formed directly in side reactions involving the sulfuric acid.

As soon as sufficient information was available from the early experiments to show the possibilities of the condensation, the scale of the experiments was increased and the conditions of the reaction and the nature of the product were examined more accurately. Table I shows the various conditions under which the reaction was run and the results obtained.

### Discussion

The results show that a large excess of chlorobenzene did not alter the reaction appreciably. A very great excess of hydrogen fluoride is necessary to complete the condensation, and lower temperatures with slower reaction rates are desirable.

Preliminary work in the laboratory and pilot plant on the production of chloral from alcohol indicated a probable yield of about 75%. On the basis of the alcohol used in the preparation of the chloral and chloral alcoholate, respectively, the yield of refined DDT was 58% in both cases. These results indicate that it might be advantageous to use crude chloral alcoholate as the starting material, thus eliminating the conversion to chloral. The quality of the product from the condensation of crude chloral alcoholate with chlorobenzene needs further investigation.

**Investigations on the By-products and Impurities.**—An investigation of the oily by-products was undertaken in an attempt to clarify the course of the reaction and to determine the probable impurities in the product.

The residual oil isolated during purification of the crude DDT, as described in the experimental section, probably contained some of the by-products obtained in the sulfuric acid process[4] as well as certain fluorine derivatives. In an effort to identify one of the more probable fluorine derivatives, a sample of 2-trichloro-1-*p*-chlorophenylethanol[5] was treated with hydrogen fluoride. A 50% yield of product, b. p. 94.5 to 96.5° at 1.5 mm., $n^{25}D$ 1.5463, was obtained which had the same physical properties as a material isolated from the by-product oils both by direct fractionation and steam distillation. Analysis of the latter material for fluorine and chlorine agrees closely with that for 2-trichloro-1-*p*-chlorophenyl-1-fluorethane ($CCl_3CHFC_6H_4Cl$). *Anal.* Calcd. for $C_8H_5Cl_4F$: Cl, 54.16; F, 7.26; mol. wt., 262. Found: Cl, 54.77, 54.96; F, 6.54; mol. wt., 262.

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(2) Deceased.

(3) Simons and Archer, THIS JOURNAL, **60**, 2953 (1938).

(4) Haller, *et al.*, *ibid.*, **67**, 1591 (1945).

(5) Prepared by the method given in British Patent 460,647; see also J. W. Howard, THIS JOURNAL, **57**, 2317 (1935).