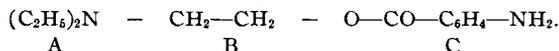


SCIENTIFIC SECTION

SOME ESTERS OF DIALKYLAMINO METHANOLS.*¹

BY E. V. LYNN AND FREDERICK V. LOFGREN.

In recent years numerous compounds have been made (1) by modifying the structure of procaine. These have been produced with the hope of discovering a better local anæsthetic and, to a less extent, in order to obtain more information about the relation between constitution and anæsthetic action. In every case the compounds had a higher molecular weight than procaine. These modifications have been produced by variations in one or more of the three units A, B and C of procaine:



In general the method of selection was more or less haphazard, which is usually the case in endeavors engendered by commercial profit, although by its means several useful anæsthetics have been manufactured. No attempt was made to proceed from simple to complex until sufficient evidence was evolved so that definite conclusions could be drawn as to the effect of structural changes on the physiological action.

The primary purpose of our investigation was to determine the effect of substitution of $-\text{CH}_2-$ for $-\text{CH}_2-\text{CH}_2-$ in position B on the procaine molecule. In the compounds prepared unit A was represented by diethylamino, di-*n*-propylamino, di-*n*-butylamino and diisooamylamino groups, while unit C was the benzoyl, *n*-aminobenzoyl, *p*-aminobenzoyl and cinnamyl groups. The present paper represents only the chemical preparation of the compounds made.

The dialkylamino methyl alcohols were first produced by the condensation of the corresponding amines with formaldehyde. These alcohols were then treated with the acyl chloride in 10 per cent sodium hydroxide solution. In all, sixteen compounds and the salts of eight of them were so made. The aminobenzoyl derivatives were prepared by reducing the corresponding nitro compounds.

The compounds produced in this manner were tested for anæsthetic properties by application to a muscle-nerve preparation and to the cornea of a rabbit. The results indicate that a number of the substances have local anæsthetic properties, although their irritant character militates against any practical employment. A subsequent paper will discuss the pharmacological experiments.

EXPERIMENTAL PART.

Di-Ethyl-Amino-Methyl-Benzoate.—Thirty grams of diethyl-aminomethyl alcohol (2) were treated with 45 grams of benzoyl chloride in the presence of an excess of 10 per cent sodium hydroxide. The mixture after cooling was extracted with ether. The liquid, remaining after evaporation of the solvent, was fractionally distilled under reduced pressure. The 22-gram fraction distilling at 150–160° C. under 16-mm. pressure was analyzed for nitrogen. The greater portion of the

* Presented to the Scientific Section, A. PH. A., Miami meeting, 1931.

¹ Submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Washington.

fraction distilled at 157–158° C. under 16-mm. pressure. The substance was a pale yellow liquid, soluble in ether, chloroform, benzene, olive oil and absolute alcohol but was insoluble in water. Attempts were made to form salts, without success.

Per cent of nitrogen: found 6.83 and 6.86; calculated for $C_{12}H_{17}NO_2$, 6.76.

Di-n-Propyl-Amino-Methyl-Benzoate.—Using the same technique as for the preceding compound, 20 grams of di-*n*-propyl-aminomethyl alcohol (2) reacting with 25 grams of benzoyl chloride gave a 14-gram fraction of a liquid which distilled at 165–173° C. under 17-mm. pressure. The greater portion of this fraction distilled at 168–171° C. under 17-mm. pressure. The compound was a pale yellow liquid soluble in ether, chloroform, benzene, olive oil and absolute alcohol but insoluble in water. Attempts at manufacturing salts were unsuccessful.

Per cent of nitrogen: found 6.26 and 6.36; calculated for $C_{14}H_{21}NO_2$, 5.95.

Di-n-Butyl-Amino-Methyl-Benzoate.—Twenty-one grams of di-*n*-butylamino-methyl alcohol (3) on benzylation with 20 grams of benzoyl chloride using the preceding technique and extracting with ether gave a 15-gram liquid fraction distilling at 180–190° C. under 17-mm. pressure. The greater portion of this liquid distilled at 187–188° C. under 17-mm. pressure. The substance was a pale, yellow liquid, soluble in ether, chloroform, benzene, olive oil and absolute alcohol but insoluble in water. No salts were obtained.

Per cent of nitrogen: found 5.33 and 5.07; calculated for $C_{16}H_{25}NO_2$, 5.32.

Di-iso-Amyl-Amino-Methyl-Benzoate.—Seventeen grams of diisoomylamino-methyl alcohol (2) and 14 grams of benzoyl chloride were benzyolated as above and extracted with ether. The residue after evaporation of the ether gave, upon distillation at 16-mm. pressure, a 15-gram fraction which boiled at 190–195° C. with the greater portion boiling at 193–194° C. This fraction was analyzed. It was a yellowish liquid soluble in ether, chloroform, benzene, olive oil and absolute alcohol but insoluble in water. No salts were obtained.

Per cent of nitrogen: found 4.87 and 5.07; calculated for $C_{18}H_{29}NO_2$, 4.80.

Di-Ethyl-Amino-Methyl-Cinnamate.—Ten grams of diethylaminomethyl alcohol and 18 grams of cinnamoyl chloride were mixed together with an excess of 10 per cent sodium hydroxide solution. After the reaction had ceased and the mixture had cooled, it was extracted with ether. The residual liquid remaining after evaporation of the ether was subjected to fractional distillation under reduced pressure. The 9-gram fraction distilling at 180–195° C. under 17-mm. pressure was analyzed by determination of nitrogen. The greater portion of this fraction distilled at 190° C. under 17-mm. pressure and on cooling solidified to a white solid melting at 66–67° C. The product was insoluble in water but soluble in ether, chloroform, benzene, olive oil and absolute alcohol.

Per cent of nitrogen: found 5.94 and 6.39; calculated for $C_{14}H_{19}NO_2$, 6.00.

Sulphate.—The sulphate of this compound was obtained by adding a saturated solution of concentrated sulphuric acid in ether to an ether solution of the base. A white crystalline salt separated immediately from the mixture and was washed

several times with ether. The salt had a melting point of 121–122° C. and hydrolyzed upon addition of water.

Per cent of H₂SO₄: found 29.96; calculated for C₁₄H₁₉NO₂·H₂SO₄, 29.60.

Di-n-Propyl-Amino-Methyl-Cinnamate.—Using the same technique as in preparing the preceding compound, 10 grams of di-*n*-propylaminomethyl alcohol and 13 grams of cinnamoyl chloride upon fractional distillation under 16-mm. pressure gave a 10-gram portion distilling at 205–215° C. which upon cooling formed a white crystalline solid melting at 54° C. This compound was insoluble in water but soluble in ether, chloroform, benzene, olive oil and absolute alcohol.

Per cent of nitrogen: found 5.29 and 5.67; calculated for C₁₆H₂₃NO₂, 5.36.

Sulphate.—The sulphate of this compound was prepared as above except that the salt separated from the ether slowly. This salt was a white crystalline solid melting at 113–114° C. and apparently hydrolyzed when added to water.

Per cent of H₂SO₄: found 27.04; calculated for C₁₆H₂₃NO₂·H₂SO₄, 27.29.

Di-n-Butyl-Amino-Methyl-Cinnamate.—Fifteen grams of di-*n*-butylaminomethyl alcohol and 15 grams of cinnamoyl chloride upon benzylation as with the preceding cinnamates were extracted with ether. The residue after evaporation of the ether was distilled under reduced pressure and the fraction distilling at 210–228° C. under 14-mm. pressure was analyzed. The greater portion of this fraction distilled at 226–227° C. under 14-mm. pressure. The distillate upon cooling was an amber-colored liquid, insoluble in water but soluble in chloroform, ether, benzene, olive oil and absolute alcohol. No salts of this base were obtained.

Per cent of nitrogen: found 4.96 and 5.15; calculated for C₁₈H₂₇NO₂, 4.84.

Di-iso-Amyl-Amino-Methyl-Cinnamate.—Using the same general method as in preparing the other cinnamates, 12 grams of diisoaminomethyl alcohol and 11 grams of cinnamoyl chloride were allowed to react together. The residue remaining from the ether extraction after evaporating the ether was subjected to distillation under reduced pressure. The 11-gram fraction distilling at 210–230° C. under 11-mm. pressure was reserved for analysis. The greater portion of this distillate came over at 227–229° C. The product was a thick, amber-colored liquid soluble in ether, chloroform, benzene, olive oil and absolute alcohol but insoluble in water. No salts of this base were obtained.

Per cent of nitrogen: found 4.66 and 4.66; calculated for C₂₀H₃₁NO₂, 4.41.

Di-Ethyl-Amino-Methyl-m-Nitro-Benzoate.—Twelve grams of diethylaminomethyl alcohol were treated with 22 grams of *m*-nitrobenzoyl chloride in the presence of an excess of 10 per cent sodium hydroxide. Upon completion of the reaction, the mixture was shaken with ether. Upon evaporation of the ether, the oily residue remaining was distilled under reduced pressure. A 10-gram product distilling between 200–207° C. under 11-mm. pressure was obtained which upon cooling formed a white crystalline solid melting at 70–72° C.

Per cent of nitrogen: found 11.90 and 11.71; calculated for C₁₂H₁₆N₂O₄, 11.11.

Di-Ethyl-Amino-Methyl-m-Amino-Benzoate.—Five grams of diethylaminomethyl-*m*-nitrobenzoate were reduced by dissolving in an excess of concentrated

hydrochloric acid and adding granulated zinc to the product. Upon completion of the reaction the solution was made distinctly alkaline with sodium hydroxide and the oily layer was removed by shaking out with ether. The oily residue left after evaporation of the ether was distilled under reduced pressure. The fraction distilling at 200–208° under 11-mm. pressure was analyzed. Upon cooling, it formed a yellow crystalline solid which melted at 75–76° C.

Per cent of nitrogen: found 13.45 and 13.39; calculated for $C_{12}H_{18}N_2O_2$, 12.61.

Monohydrochloride.—This salt was prepared by passing dry hydrogen chloride into an anhydrous ether solution of the base. The sticky white precipitate was dissolved in a small amount of absolute alcohol and white crystals separated upon the addition of purified ethyl acetate. The salt was further purified by crystallization two additional times from a mixture of alcohol and ethyl acetate. The salt was soluble in water and had a melting point of 184–185° C.

Per cent of HCl: found 14.09; calculated for $C_{12}H_{18}N_2O_2.HCl$, 14.36.

Di-n-Propyl-Amino-Methyl-m-Nitro-Benzoate.—Using the Schotten-Baumann reaction, 12 grams of di-*n*-propylaminomethyl alcohol and 17 grams of *m*-nitrobenzoyl chloride in the presence of 10 per cent sodium hydroxide solution were allowed to react together. After the reaction mixture had cooled, it was extracted with ether, the ether was evaporated and the oily liquid remaining was subjected to fractional distillation under reduced pressure. The 13-gram portion, distilling between 205–219° C. at 11-mm. pressure was reserved for analysis. It was a brownish, oily liquid, the greater portion of which boiled at 213–218° C. at 11-mm. pressure.

Per cent of nitrogen: found 10.71 and 10.66; calculated for $C_{14}H_{20}N_2O_4$, 9.99.

Di-n-Propyl-Amino-Methyl-m-Amino-Benzoate.—Five grams of di-*n*-propylaminomethyl-*m*-nitrobenzoate were reduced with hydrochloric acid and zinc. The oily liquid, which was obtained from this mixture by making alkaline with sodium hydroxide solution, extracting with ether and finally evaporating off the solvent, was distilled under reduced pressure. The 2-gram product, distilling at 205–210° C. under 9-mm. pressure was reserved for analysis. It was a brownish, oily liquid

Per cent of nitrogen: found 12.03 and 11.19; calculated for $C_{14}H_{22}N_2O_2$, 11.19.

Monohydrochloride.—This salt was prepared by passing dry hydrogen chloride into an anhydrous ether solution of the base. Yellowish white crystals were obtained by recrystallizing three times from ethyl acetate after dissolving in a small amount of absolute alcohol. The crystals which were soluble in water had a melting point of 141–142° C.

Per cent of HCl: found 13.10; calculated for $C_{14}H_{22}N_2O_2.HCl$, 12.72.

Di-n-Butyl-Amino-Methyl-m-Nitro-Benzoate.—Using a similar reaction as in preparing the other-*m*-nitrobenzoates 12 grams of di-*n*-butyl-amino-methyl alcohol were mixed with 15 grams of *m*-nitrobenzoyl chloride in the presence of 10 per cent sodium hydroxide solution. The oily liquid recovered from the ether extraction of the reaction mixture was fractionally distilled under reduced pressure. The 12 grams of product distilling at 205–230° C. under 11-mm. pressure were analyzed.

Most of this distillate came over at 227–228° C. under 11-mm. pressure. The product was a thick, brownish liquid.

Per cent of nitrogen: found 9.55 and 9.32; calculated for $C_{16}H_{24}N_2O_4$, 9.09.

Di-n-Butyl-Amino-Methyl-m-Amino-Benzoate.—This compound was manufactured as the other *m*-aminobenzoates by reduction of 5 grams di-*n*-butylamino-methyl-*m*-nitrobenzoate with hydrochloric acid and zinc, extraction of the alkaline reaction mixture with ether and fractional distillation of the oily liquid remaining after evaporation of the ether. The 2-gram fraction boiling between 215–220° C. under 10-mm. pressure was analyzed. The product was a thick, brownish liquid.

Per cent of nitrogen: found 10.26 and 9.92; calculated for $C_{16}H_{26}N_2O_2$, 10.06.

Monohydrochloride.—This salt was prepared from the base in the usual manner. It was recrystallized three times from ethyl acetate after dissolving in a small amount of absolute alcohol. The yellowish white salt had a melting point of 159–160° C. It was soluble in water.

Per cent of HCl: found 11.81; calculated for $C_{16}H_{26}N_2O_2 \cdot HCl$, 11.58.

Di-iso-Amyl-Amino-Methyl-m-Nitro-Benzoate.—Twelve grams of diisoamylaminomethyl alcohol and 12 grams of *m*-nitrobenzoyl chloride were mixed together with an excess of 10 per cent sodium hydroxide solution. The reaction mixture was extracted with ether and the oily residue remaining after evaporation of the ether was fractionally distilled. The 8-gram fraction distilling at 220–234° C. under 11-mm. pressure was reserved for analysis. The product was a viscid brown liquid; the greater portion of which distilled at 230–233° C. under 11-mm. pressure.

Per cent of nitrogen: found 8.71 and 8.75; calculated for $C_{18}H_{28}N_2O_4$, 8.33.

Di-iso-Amyl-Amino-Methyl-m-Amino-Benzoate.—Five grams of diisoamylaminomethyl-*m*-nitrobenzoate were reduced with hydrochloric acid and zinc. The reaction mixture after making alkaline with sodium hydroxide solution was extracted with ether, the solvent evaporated and the oily residue was distilled under reduced pressure. The 2-gram portion distilling between 220–233° C. under 10-mm. pressure was analyzed. This substance was a thick, brownish liquid.

Per cent of nitrogen: found 8.95 and 8.92; calculated for $C_{18}H_{30}N_2O_2$, 9.14.

Monohydrochloride.—The salt was obtained by passing dry hydrogen chloride into an anhydrous ether solution of the diisoamylaminomethyl-*p*-aminobenzoate. The precipitate was purified by recrystallizing three times from ethyl acetate after dissolving in a small amount of absolute alcohol. The salt was in the form of nearly white granules which melted at 178–180° C. It was soluble in water but apparently hydrolyzed.

Per cent of HCl: found 11.07; calculated for $C_{18}H_{30}N_2O_2 \cdot HCl$, 10.64.

Di-Ethyl-Amino-Methyl-p-Nitro-Benzoate.—Ten grams of diethylaminomethyl alcohol were mixed with 18 grams of *p*-nitrobenzoyl chloride in presence of an excess of 10 per cent sodium hydroxide solution. The reaction mixture after cooling was extracted with ether and subsequently the solvent was removed by evaporation. The oily residue was distilled under reduced pressure. The 10-gram fraction boiling

at 200–211° C. under 10-mm. pressure was analyzed. At room temperature this product solidified forming a yellow crystalline mass melting at 62–63° C.

Per cent of nitrogen: found 11.62 and 11.84; calculated for $C_{12}H_{16}N_2O_4$, 11.11.

Di-Ethyl-Amino-Methyl-p-Amino-Benzoate.—Five grams of diethylamino-methyl-*p*-nitrobenzoate were reduced with hydrochloric acid and zinc. After reaction had ceased the mixture was made distinctly alkaline with sodium hydroxide and extracted with chloroform. The chloroform was evaporated leaving an oily liquid which was distilled under reduced pressure. The 2-gram portion distilling at 200–215° C. was analyzed. It solidified at room temperature to form a yellow crystalline solid with a melting point of 121–122° C.

Per cent of nitrogen: found 13.03 and 13.17; calculated for $C_{12}H_{18}N_2O_2$, 12.61.

Monohydrochloride.—This salt was prepared by passing dry hydrogen chloride into an absolute ether solution of the base. The salt was purified by crystallization from purified ethyl acetate after dissolving in a little absolute alcohol. It was a white crystalline solid, soluble in water and melting at 189–190° C.

Per cent of HCl: found 13.85; calculated for $C_{12}H_{18}N_2O_2.HCl$, 14.09.

Di-n-Propyl-Amino-Methyl-p-Nitro-Benzoate.—Using the same technique as in preparing the corresponding diethylamino compound, 17 grams of di-*n*-propylaminomethyl alcohol and 25 grams of *p*-nitrobenzoyl chloride were permitted to react together. The oily liquid obtained from the ether extraction was distilled under diminished pressure. The 11-gram portion distilling at 210–233° C. under 17-mm. pressure was reserved for analysis. It was a yellowish white solid at room temperature melting at 37–39° C.

Per cent of nitrogen: found 10.21 and 10.11; calculated for $C_{14}H_{20}N_2O_4$, 9.99.

Di-n-Propyl-Amino-Methyl-p-Amino-Benzoate.—Five grams of di-*n*-propylaminomethyl-*p*-nitrobenzoate were reduced as in the preceding compounds. The base was extracted from the reaction mixture with ether. The oily residue from the ether was distilled under reduced pressure. The 2-gram fraction, distilling at 215–220° C. under 9-mm. pressure, was reserved for analysis. At room temperature it solidified to form a yellowish white crystalline mass melting at 75–76° C.

Per cent of nitrogen: found 11.37 and 10.90; calculated for $C_{14}H_{22}N_2O_2$, 11.19.

Monohydrochloride.—This salt was obtained in the usual manner. It was purified three times by recrystallization from ethyl acetate after dissolving in absolute alcohol. The yellowish white crystals were soluble in water and had a melting point of 152–153° C.

Per cent of HCl: found 13.02; calculated for $C_{14}H_{22}N_2O_2.HCl$, 12.72.

Di-n-Butyl-Amino-Methyl-p-Nitro-Benzoate.—Twelve grams of di-*n*-butylaminomethyl alcohol and 15 grams of *p*-nitrobenzoyl chloride were allowed to react in the usual manner. The reaction mixture was extracted with ether and the thick liquid recovered from the solvent was fractionally distilled under reduced pressure. The 6-gram fraction distilling at 210–235° C., under 11-mm. pressure was reserved. It was a thick, brownish liquid the greater part distilling at 230–234° C. under 11-mm. pressure.

Per cent of nitrogen: found 9.38 and 9.16; calculated for $C_{16}H_{24}N_2O_4$, 9.09.

Di-n-Butyl-Amino-Methyl-p-Amino-Benzoate.—Five grams of the di-*n*-butylaminomethyl-*p*-nitrobenzoate were reduced in the usual manner and extracted from the reaction mixture with chloroform and ether. The oily liquid residue recovered from the solvent was distilled under reduced pressure. The 1-gram fraction distilling between 210–228° C. under 9-mm. pressure was reserved and analyzed. It was a thick, brownish liquid.

Per cent of nitrogen: found 9.94 and 9.62; calculated for $C_{16}H_{26}N_2O_2$, 10.06.

Monohydrochloride.—This salt was obtained in the usual manner. It was recrystallized three times from ethyl acetate and absolute alcohol. It was a white crystalline substance with a melting point of 136–137° C. It was soluble in water but apparently was hydrolyzed very easily.

Per cent of HCl; found 11.98; calculated for $C_{16}H_{26}N_2O_2.HCl$, 11.58.

Di-iso-Amyl-Amino-Methyl-p-Nitro-Benzoate.—Twelve grams of diisoamylaminomethyl alcohol and 12 grams of *p*-nitrobenzoyl chloride were allowed to react as before. The oily residue from the ether extraction of the reaction mixture was distilled under reduced pressure. The 6-gram portion distilling at 220–235° C. under 8-mm. pressure was reserved for analysis. The greater portion of this fraction distilled at 232–233° C. under 8-mm. pressure. It formed a solid crystalline mass which melted at 52–54° C.

Per cent of nitrogen: found 8.38 and 8.67; calculated for $C_{18}H_{28}N_2O_4$, 8.33.

Di-iso-Amyl-Amino-Methyl-p-Amino-Benzoate.—Five grams of diisoamylaminomethyl-*p*-nitrobenzoate were reduced as before and extracted from the reaction mixture with ether. The oily residue recovered from the solvent was distilled under diminished pressure. The 2-gram fraction distilling at 220–235° C. under 10-mm. pressure was analyzed. It was a viscid, brown liquid.

Per cent of nitrogen: found 9.03; calculated for $C_{18}H_{30}N_2O_2$, 9.14.

Monohydrochloride.—This salt was manufactured in the same manner as the preceding salts. It was recrystallized five times from ethyl acetate and absolute alcohol. The salt was in the form of nearly white granules. It was soluble in water but apparently hydrolyzed immediately.

Per cent of HCl: found 11.26; calculated for $C_{18}H_{30}N_2O_2.HCl$, 10.64.

SUMMARY.

1. The following series of esters have been prepared and their physical properties studied: di-ethyl-amino-methyl-benzoate, di-*n*-propyl-amino-methyl-benzoate, di-*n*-butyl-amino-methyl-benzoate and di-iso-amyl-amino-methyl-benzoate.

2. A second, third and fourth series of esters consisting of the *m*-amino-benzoates, *p*-amino-benzoates and cinnamates of the corresponding di-alkyl-amino-methanols were also prepared and studied. Soluble salts of most of these were obtained.

3. These esters were studied pharmacologically as to their local anæsthetic properties which will be reported in a subsequent paper.

REFERENCES.

- (1) Fränkel, "Arzneimittel Synthese," 6th Edition, pages 348-391; McElvain, *J. Am. Chem. Soc.*, 46 (1924), 1721; *Ibid.*, 48 (1926), 2179; *Ibid.*, 48 (1926), 2239; *Ibid.*, 49 (1927), 2835; McElvain and co-workers, *Ibid.*, 46 (1924), 1221; *Ibid.*, 49 (1927), 2862; *Ibid.*, 50 (1928), 3348; *Ibid.*, 51 (1929), 922; *Ibid.*, 51 (1929), 887; *Ibid.*, 52 (1930), 1633; Gilman and Pickens, *Ibid.*, 47 (1925), 245; Gilman, Heckert and McCracken, *Ibid.*, 50 (1928), 437; Adams and co-workers, *Ibid.*, 48 (1926), 1758; *Ibid.*, 49 (1927), 1303; *Ibid.*, 49 (1927), 1307; Jones and Major, *Ibid.*, 49 (1927), 1527; Marvel and Sandborn, *Ibid.*, 50 (1928), 563; Marvel and Shelton, *Ibid.*, 51 (1929), 915; Blicke and Blake, *Ibid.*, 52 (1930), 235; Bolyard, *Ibid.*, 52 (1930), 1030; Hartung and Munch, *Ibid.*, 51 (1930), 2570.
- (2) Henry, *Ber.*, 28 (1895), 851.
- (3) This was prepared by using the method of Henry, *Ber.*, 28 (1895), 851. Specific gravity at 20° C., 0.8526.

TOXICITY OF METHANOL.

BY RALPH W. HUFFERD.

A total of 77 white rats were given very pure¹ methanol and ethanol by stomach-tube. Concentrations of 40-50% by volume were administered.

Toxicity was studied for single doses and for doses repeated once and twice at intervals of one day.

ETHANOL.

Mols./100 Gm.	Cc./100 Gm.	One Dose.		Two Doses.		Three Doses.	
		Killed.	Lived.	Killed.	Lived.	Killed.	Lived.
0.022	1.3	...	1
0.021	1.25	1
0.018	1.07	5
0.014	0.84	1	1	...
0.013	0.75	2	...	2	3	1	1
0.01	0.6	2	...	1	2

METHANOL.

0.036	1.47	1
0.031	1.25	5	4
0.025	1.00	3	5	1	1
0.019	0.75	2	...	5	1
0.016	0.66	5	5
0.012	0.5	8	1	2
0.01	0.4	1	4

All of the rats that did not die regained strength and weight rapidly, giving every appearance of being normal.

Irritation of the eyes was observed only in the case of some of the animals that finally died.

From these data it would appear that very pure methanol is slightly less toxic for rats than is pure ethanol even in repeated doses.

DE PAUW UNIVERSITY,
GREENCASTLE, IND.

¹ Methods of purification and tests for purity are described in another paper to be printed in THIS JOURNAL.