The Influence of the Acid Radicals containing the Different Secondary Alkyls upon the Narcotic Action of Urethane.

By

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It is already known that the narcotic action of urethane is due to the ethyl radical present in the form of an ester of carbamic acid and at the same time such a radical would effect the lowering of the blood-pressure, while the amino group would exert an action upon the circulatory system and the respiratory centre, in such a way as to cause the elevation of the blood-pressure and the stimulation of the latter. Now owing to such characteristic physiological actions which may be caused by the ethyl radical on one hand and by the amino group on the other, it may be assumed that urethane is comparatively free from its disgusting by-effects.[1] Binet[2] states that the strengths of the narcotic action and poisonous effects of the homologues of urethane are dependent upon the number of carbon atoms present in the alkyl radicals, that is, more the carbon atoms present in the alkyl radicals are exhibited more the narcotic action and poisonous by-effects; the latter, however, disappear or at least decrease by the acetylation of the amino group while the narcotic action remains unchanged. Based upon the experiment with animals he has shown the relative strengths of their poisonous effects by the following scale:

$NH_2.CO.OCH_3$.....2·0	$NH_2.CO.OC_2H_5$.....4·0
$CH_3.CO.NH.CO.OCH_3$.....1·0	$CH_3.CO.NH.CO.OC_2H_5$.....1·5

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[1] Frankel, Arzneimittel Synthese, 3rd ed. pp. 488, 505; Morishuna, Arzneimittel-Lehre 4th ed. p. 271.

[2] Rev. med. Suisse Rom., 1893, 540, 628, Fränkel, Arzneimittel-Synthese, 3rd ed. p. 488.

At the suggestion of Prof. Kuhara the auther has undertaken the study of the influence of the different acid radicals containing the secondary alkyls such as R_2CH- or $RR'CH-$ upon the narcotic action of urthane, expecting that the increase of the number of carbon atoms in R and R′ may make its narcotic action more and more effective to some extent, as are seen in the substances of the veronal and sulfonal groups, simultaneously with the decrease of its poisonous effects.

From such a point of view the auther has synthesized the different acyl derivatives of urethane of the following formulas by the action of the acyl chlorides containing the different secondary alkyls upon urethane:

$$\begin{matrix} R \\ R \end{matrix}\!>\!CH.CO.NH.CO.OC_2H_5 \text{ and } \begin{matrix} R' \\ R \end{matrix}\!>\!CH.CO.NH.CO\ OC_2H_5$$

and represents them by the special names, as will be seen in the following list:

1. Diethylaceturethane, Detonal,

$$\begin{matrix} C_2H_5 \\ C_2H_5 \end{matrix}\!>\!CH.CO.NH.CO.OC_2H_5.$$

2. Ethylpropylaceturethane, Epronal,

$$\begin{matrix} C_2H_5 \\ C_3H_7 \end{matrix}\!>\!CH.CO.NH.CO.OC_2H_5.$$

3. Dipropylaceturethane, Dipronal,

$$\begin{matrix} C_3H_7 \\ C_3H_7 \end{matrix}\!>\!CH.CO.NH\ CO.OC_2H_5.$$

4. Propylbutylaceturethane, Probnal,

$$\begin{matrix} C_3H_7 \\ C_4H_9 \end{matrix}\!>\!CH.CO.NH.CO.OC_2H_5.$$

5. Dibutylaceturethane, Dibnal,

$$\begin{matrix} C_4H_9 \\ C_4H_9 \end{matrix}\!>\!CH.CO.NH.CO.OC_2H_5.$$

Further, the following substances have also been synthesized by the author for comparison with the above-mentioned narcotics:

6. Oenanthylylurethane,

$$CH_3(CH_2)_5CO.NH.CO.OC_2H_5.$$

7. N-Isoamylurethane,

$$\begin{matrix}C_2H_5\\C_2H_5\end{matrix}\!\!>\!CH.NH.CO.OC_2H_5.$$

8. α-Bromethylpropylaceturethane,

$$\begin{matrix}C_2H_5\\C_2H_5\end{matrix}\!\!>\!CBr\ CO.NH.CO.OC_2H_5.$$

Of those compounds the auther has paid an attention specially to detonal and epronal at first, with regard to their physiological actions by making experiments with frogs and rabbits in which foremostly their narcotic actions in compaiison with those of known narcotics and then their influences upon the heart, blood-vessels, respiratory centre and vagus were examined, since it is almost common that the impediments in the heart and lungs follow as the by-effects of narcotics.

As will be seen in the results of experiments executed with Rana esculenta and shown in Table V. given in the experimental part detonal seems to stand in parallel with amylene and chloral hydrates, yet to be more effective than urethane in the narcotic action, whose strength is represented in this case by the duration of sleep; epronal is still more effective being almost equal to veronal and hedonal, nevertheless its action much more prompt than that of any other narcotic in comparison.

The experiments on the stoppage of the heart-beat which may be brought about by narcotics were performed by charging the solutions of the different narcotics dissolved in Ringer's solution to the extirpated hearts of Rana esculenta in the equal heights of column. The results show that detonal is least poisonous, and epronal almost equal to bromural but somewhat less poisonous than hedonal.

Moreover, the auther has conducted the experiments for the determination of the minimum and lethal doses of epronal for the rabbit. By giving 0·3 grm. of epronal to the rabbit per 1 kilog. by its weight the sedative condition followed as an effect, and by 0.5 grm. the sleep continued for an hour. By increasing doses, however, successively to 1·0, 1·5 and 2·0 grm, the rabbits fell into a deep sleep, and by 2·5 and 3·0 grm. died after 20–50 hours.

By dosing 1·5 grm. epronal per 1 kilog. rabbit the blood-pressure was observed to be 100 mm. in the mercury column, as is usually noticed in the normal rabbits, and the vagus and respiratory centre

were not influenced at all, as will be seen in the curve given in the experimental part.

According to H. H. Meyer[1] the coefficient of distribution between oil and water of the narcotic of the aliphatic series is the factor of narcotic action. The author has attempted to examine such a view with regard to detonal and epronal in comparison with some of already known narcotics by determining their coefficients of distribution, according to the method described in the experimental part, the intervals between injection and sleep and the durations of sleep. In the experiments 0·2 cc. of 0·15% solution of each narcotic per 1 grm. frog were injected, and the quantity of each was returned in term of gram-mol. per 1 grm. frog, the results of experiments being given in the following table:

TABLE I.

Narcotics.	Coefficients of distribution, (K).	Gram-mol. per 1 grm. frog.	Intervals between injection and sleep.		Durations of sleep.	
			Hr.	Min.	Hr.	Min.
Trional	4.60	124×10^{-8}	0	14	1	40
Epronal	3.30	149×10^{-8}	0	5	1	51
Detonal	1·70	161×10^{-8}	Merely in sedative condition			
Bromural	1·33	137×10^{-8}	0	15	5	30
Chloralhydrate	0.22	181×10^{-8}	Merely in sedative condition			
Urethane	0.13	337×10^{-8}	"	"	"	"
Veronal	0.119	166×10^{-8}	0	32	2	0

As seen from Table I. the coefficients of distribution do not stand in harmony with the durations of sleep, but seem to have some relation with the intervals between injection and sleep, except the case of trional, that is, higher the coefficient of distribution of narcotic more prompt its action may be.

On continuing the pharmacological study of dipronal, probnal, dibnal, oenanthylylurethane, N-isoamylurethane and α-bromethylpropylaceturea in comparison with urethane, detonal and epronal, the following results were obtained:

[1] Fränkel, Arzneimittel Synthese, 3rd ed. p. 511.

TABLE II.

Narcotics.	Chem. formulas.	Minimum doses per 1 grm. frog in aq. solution, in gram-mol.	Minimum doses per 1 grm. frog in emulsion, in gram-mol.	Strengths of narcotic action.	Ratios of strengths.	Solubilities in 100 parts water at 20°.
Urethane	$NH_2\,CO\,OC_2H_5$	1910×10^{-8}	—	10	—	—
Detonal	$(C_2H_5)_2CH.CO.NH.CO.OC_2H_5$	214×10^{-8}	5560×10^{-9}	90	9·0	0·550
Epronal	$C_2H_5(C_3H_7)CH.CO.NH.CO.OC_2H_5$	112×10^{-8}	1990×10^{-9}	170	1·9	0·150
Dipronal	$(C_3H_7)_2CH.CO.NH.CO\,OC_2H_5$	56×10^{-8}	—	340	2·0	0·040
Probnal	$C_3H_7(C_4H_9)CH\,CO.NH.CO.OC_2H_5$	39×10^{-8}	655×10^{-9}	500	1·5	0·032
Dibnal	$(C_4H_9)_2CH.CO\,NH.CO.OC_2H_5$	—	658×10^{-9}	500	1·0	0·008
Oenanthylyl-urethane	$CH_3(CH_2)_5CO\,NH.CO\,OC_2H_5$	—	2985×10^{-9}	90-170	—	0·021
N-Isoamyl-urethane	$(C_2H_5)_2CH{-}{-}NH.CO\,OC_2H_5$	200×10^{-8}	—	95	—	0·409
Adaline	$(C_2H_5)_2CBr\,CO.NH.CO\,NH_2$	34×10^{-8}	—	560	—	—
α-Bromethyl-propylacetur ea	$C_2H_5(C_3H_7)CBr\,CO\,NH.CO.NH_2$	24×10^{-8}	—	800	1·4	0·041

The strengths of narcotic action in this case have been deduced from the minimum doses of the narcotics in aqueous solution and in emulsion, as will be explained in the experimental part.

Referring the table it is noticed that the increase in the number of carbon atoms of R and R′ in the acid radicals containing the secondary alkyls such as $(R_2CH)'$ or $(RR'CH)'$ would evidently exert an influence upon the narcotic action making it more and more effective, possibly reaching the maximum value at probnal or propylbutylacet-urethane, while in the higher homologues perhaps no more increase of action may take place as probnal and dibnal do not show difference in the strengths of action. Also it is seen that the same relation exists in the adaline series. The auther has synthesised α-bromethylpropyl-aceturea, which is analogous in structure with adaline but richer in carbon atoms than the latter, and then conducted their comparative experiments on the strengths of their narcotic action, in which we have observed

that just as in the case of urethane series α-bromethylpropylaceturea is much more effective than its lower homologue, adaline.

Oenanthylylurethane which contains the acid redical consisting of a primary alkyl and is isomeric with epronal, possesses a notably less narcotic action then the latter; hence the secondary alkyl must be more energetic in action than the primary.

In the case of N-isoamylurethane which differs in constitution from detonal by the lack of the carbonyl group, its narcotic action has been found to be somewhat stronger than that of detonal, but its poisonous character far more energetic than that of the latter, as noticed in the experiments on the failure of the heart. The presence of the carbonyl group, therefore, seems not to exert a remarkable influence upon the narcotic action, but evidently to decrease the poisonous character of the substance.

The solubilities of the urethane derivatives of the homologous series containing the acid radicals consisting of the secondary alkyl groups seem to have an intimate relation with the narcotic action, that is, the narcotic action may be inversely propartional to the solubility with the exception of dibnal. Moreovere, in such substances of the homologous series, their action upon the heart becomes more and more effective as their narcotic action increases.

EXPERIMENTAL PART.

I. Synthesis of the Different Acylurethanes and Some Allied Compounds.

1. *Diethylaceturethane* (*Detonal*),

$$\begin{matrix} C_2H_5 \\ C_2H_5 \end{matrix}\!\!>\!CH.CO.NH.CO.OC_2H_5.$$

For preparing this substance a mixture of diethylacetyl chloride, $(C_2H_5)_2$ CH.COCl,[1] from diethylacetic acid[2] and urethane was heated in a flask provided with an inverted condenser over a water bath for an hour. The product, when cooled, was treated with a dilute solution of sodium carbonate and filtered, and the residue was washed with cold water and then made to crystallize from alcohol. Detonal consists of colourless

[1] Ber. D. chem. Ges, **23**, 189.

[2] Lieb. Ann., **204**, 141.

needle-shaped crystals which fuse at 88°, and is somewhat volatile. It is soluble in 190 parts of water but easily in alcohol, ether, chloroform and benzene. It decomposes by heating with a solution of an alkali evolving ammonia, and then by treating the product with an acid an oil separates out with the evolution of carbon dioxide. The analysis of the substance gave the following results:

I 0·2331 grm. substance gave 0·4785 grm. CO_2 and 0·1885 grm. H_2O.
II 0·1534 ,, ,, ,, 0·3999 ,, ,, ,, 0·1245 ,, ,,
III 0·2451 ,, ,, ,, 16·1 cc. N at 13° and 771 mm.
VI 0·1483 ,, ,, ,, 9·5 cc. ,, 15° ,, 774 mm.

	Calculated for $C_9H_{17}NO_3$.	Found.			
		I	II	III	IV
Carbon	57·75	57·15	57·73	—	—
Hydrogen	9·07	9·09	9·01	—	—
Nitrogen	7·49	—	—	7·92	7·66

With an expectation to convert detonal into more soluble form, the auther has attempted to prepare its sodium compound which is possible to be formed in its enol form, by treating detonal dissolved in alcohol with alcoholic sodium ethylate, but efforts ended in vain. From the product of reaction, however, there separated out after 24 hours colourless crystals which were repeatedly washed with alcohol and ether, and dried over sulphuric acid. The substance partly decomposes at 70°, and its aqueous solution evolves carbon dioxide by the addition of hydrochloric acid or simply by boiling, and gives the iodoform reaction. The substance must, therefore, be sodium ethylcarbonate, as is confirmed by the following analytical results:

I 0·1081 grm. substance gave 0·1287 grm. CO_2 and 0·0413 grm. H_2O.
II 0·3066 ,, ,, ,, 0·1981 ,, Na_2SO_4.

	Calculated for $C_3H_5O_3Na$.	Found.	
		I	II
Carbon	32·14	32·47	—
Hydrogen	4·46	4·28	—
Sodium	20·53	—	20·95

The mother liqueur from the crystals of sodium ethylcarbonate was evaparated to dryness, and the residue subjected to sublimation, by which process colourless needle-shaped crystals melting at 112° were

deposited. By heating the crystals with a solution of an alkali ammonia was found to be liberated and by acidifing the product of reaction we got an oily substance; hence the crystals ought to be diethylacetamide and the oil diethylacetic acid. The analysis of the crystals gave the following results:

I 0·1074grm substance gave 0·2457grm. CO_2 and 0·1070grm. H_2O
II 0·1058 „ „ „ 0·2437 „ „ „ 0·1031 „ „
III 0·1045 „ „ „ 11 cc. N at 17° and 761·8 mm.

	Calculated for $C_6H_{13}NO$.	Found.		
		I	II	III
Carbon	62·62	62·38	62·81	—
Hydrogen	11·30	11·21	10·92	—
Nitrogen	12·17	—	—	12·33

The decomposition of detonal by sodium ethylate, therefore, would be represented as follows:

$$\begin{matrix} C_2H_5 \\ C_2H_5 \end{matrix}\!\!>\!CH.CO.NH.CO.OC_2H_5 + HONa \longrightarrow$$

$$\begin{matrix} C_2H_5 \\ C_2H_5 \end{matrix}\!\!>\!CH.CO.NH_2. + NaO.CO.OC_2H_5.$$

2. *Ethylpropylacetylurethane* (*Epronal*),

$$\begin{matrix} C_2H_5 \\ C_3H_7 \end{matrix}\!\!>\!CH.CO.NH.CO.OC_2H_5.$$

Epronal was obtained from urethane and ethylpropylacetyl chloride from ethylpropylacetic acid prepared according to the statement by Schukowski.[1] The process was almost wholly analogous with the preparation of detonal. Epronal consists of colourless needle-shaped crystals which fuse at 72°. It is soluble in 700 parts of cold water, but readily in alcohol, ether, chloroform and benzene. Its chemical behaviours are similar to those of detonal. The analysis of the substance gave the following values for carbon, hydrogen and nitrogen:

I 0·1810grm. substance gave 0·3944grm. CO_2 and 0·1525grm H_2O.
II 0·1703 „ „ „ 0·3903 „ „ „ 0·1513 „ „

[1] Ber. D. chem. Ges., R. **21**, 57.

III 0.1712 „ „ „ 12·5 cc. N at 12° and 760·3 mm.
IV 0·1967 „ „ „ 12.7 cc. „ „ 13° „ 760.3 mm.

	Calculated for $C_{10}H_{19}NO_3$	Found.			
		I	II	III	IV
Carbon	59.70	59.42	59·30	—	—
Hydrogen	9.45	9.51	9·96	—	—
Nitrogen	6·97	—	—	7.37	7·44

3. *Dipropylacetylurethane*, (*Dipronal*),

$$\begin{matrix} C_3H_7 \\ C_3H_7 \end{matrix}\!\!>\!CH.CO.NH.CO.OC_2H_5.$$

This substance was prepared from urethane and dipropylacetyl chloride from dipropylacetic acid obtained by following Schukowski's[1] method. It crystallizes in colourless needles melting at 88–89°. It is soluble in 2500 parts of water at 20°, but readily in alcohol, ether, chloroform and benzene. Its chemical behaviours are similar to those of detonal and epronal. The analysis of the substance gave the following results:

I 0·1526 grm. substance gave 0·3441 grm. CO_2 and 0·1357 grm. H_2O.
II 0·1218 „ „ „ 6·6 cc. N at 12° and 764 mm.

	Calculated for $C_{11}H_{21}NO_3$.	Found.	
		I	II
Carbon	61·40	61·49	—
Hydrogen	9·77	9·97	—
Nitrogen	6·51	—	6·61

4. *Propylbutylacetylurethane* (*Probnal*),

$$\begin{matrix} C_3H_7 \\ C_4H_9 \end{matrix}\!\!>\!CH.CO.NH.CO.OC_2H_5.$$

This substance was prepared from urethane and propylbutylacetyl chloride from propylbutylacetic acid obtained according to Schukowski's method.[2] It crystallizes in colourless needles melting at 69–70°. The

[1] Ber, D. chem. Ges., R. **21**, 57.
[2] *Ibid.*

substance dissolves in 3125 parts of water at 20°, while it is easily soluble in alcohol, ether, chloroform and benzene. Its chemical behaviours resemble those of dipronal. The analysis gave the following results:

I 0·1255 grm. substance gave 0·2866 grm. CO_2 and 0·1142 grm. H_2O.
II 0·1316 „ „ „ 6·9 cc. N at 11° and 763 mm.

	Calculated for $C_{12}H_{23}NO_3$.	Found.	
		I	II
Carbon	62·88	62·29	—
Hydrogen	10·05	10·20	—
Nitrogen	6·11	—	6·28

5. *Dibutylacetuiethane (Dibnal),*

$$\begin{matrix} C_4H_9 \\ C_4H_9 \end{matrix}\!\!>\!CH.CO.NH.CO.OC_2H_5.$$

This substance was obtained from uiethane and dibutylacetyl chloride from dibutylacetic acid by the method analogous to those of the preceding acylurethanes It crystallizes in colouiless needles melting at 44°. The substance dissolves in 12500 parts of water, while it is readily soluble in alcohol, ether, chloroform and benzene. Its chemical characters are similar to those of probnal. The analytical results are as follows:

I 0·1232 grm. substance gave 0·2895 grm. C_2O and 0·1150 grm. H_2O.
II 0·1341 „ „ „ 6·6 cc. N at 13° and 764 mm.

	Calculated for $C_{13}H_{25}NO_3$.	Found.	
		I	II
Carbon	64·20	64·08	—
Hydrogen	10·29	10·46	—
Nitrogen	5·76	—	5·86

6. *Oenanthylylurethane,*

$$CH_3.(CH_2)_5.CO.NH.CO.OC_2H_5.$$

This substance was obtained from urethane and Oenanthylyl chloride from oenanthylic acid prepared by oxidizing castor oil with nitiic acid. Oenanthylylurethane crystallizes in colourless thin plates melting at 67°,

and dissolves in 4762 parts of water. It is readily soluble in alcohol, ether, benzene and chloroform. The analysis of the substance gave the following results:

I 0·1217 grm. substance gave 0·2640 grm. CO_2 and 0·1038 grm. H_2O.
II 0·1348 „ „ „ 8·1 cc. N at 11° and 761 mm.

	Calculated for $C_{10}H_{19}NO_3$.	Found.	
		I	II
Carbon	59·70	59·16	—
Hydrogen	9·45	9·57	—
Nitrogen	6·97	—	7·18

7. *N-Isoamylurethane,*

$$\begin{matrix} C_2H_5 \\ C_2H_5 \end{matrix}\!\!>\!CH.NH.CO.OC_2H_5.$$

The substance was prepared according to the method given by Lengfeld and Stieglitz,[1] which is based upon the Beckmann rearragement of acidbromamide by the action of sodium alcoholate. In this case diethylacetamide and sodium ethylate were used. It is a colourless fragrant oil boiling at 155° (460 mm.) and its 1 part dissolves in 244 parts of water at 20°. Its analysis gave the following values:

I 0·1230 grm. substance gave 0·2686 grm. CO_2 and 0·1200 grm. H_2O.
II 0·1414 „ „ „ 10·3 cc. N at 12° and 763 mm.

	Calculated for $C_8H_{17}NO_2$.	Found.	
		I	II
Carbon	60·38	59·55	—
Hydrogen	10·69	10·93	—
Nitrogen	8·81	—	9·05

8. *α-Bromethylpropylaceturea,*

$$\begin{matrix} C_2H_5 \\ C_3H_7 \end{matrix}\!\!>\!CBr.CO.NH.CO.NH_2.$$

This compound was prepared by the action of α-bromethylpropylacetylbromide upon urea. It crystallizes in colourless needles, which

[1] Amer. Chem. J. **15**, 504; **16**, 370.

fuse at 97° in the state of opacity but clearly at 105°. Its 1 part dissolves in 2439 parts of water at 20°. It is, however, readily soluble in alcohol, ether, benzene and chloroform. The analysis gave the following results:

I 0·1405 grm. substance gave 0·1969 grm. CO_2 and 0.0772 grm. H_2O.
II 0·0957 „ „ „ 9·5 cc. N at 10° and 763 mm.
III 0·1211 „ „ „ 0·0892 grm. AgBr.

	Calculated for $C_8H_{13}N_2O_2Br$.	Found.		
		I	II	III
Carbon	38·25	38·22	—	—
Hydrogen	5·98	6·16	—	—
Nitrogen	11·15	—	11·64	—
Bromine	31·87	—	—	31·35

II. The Coefficients of Distribution.

The determination of the coefficients of distribution between oil and water was performed at 17–20° using those two substances as solvents. Olive oil (Ph. J. III), as selected in this case, was rectified by shaking with a dilute solution of sodium carbonate, and then by separating an oily layer with sodium chloride which was washed with water until the alkaline reaction disappears.

A certain quantity of a narcotic was dissolved in olive oil so rectified, to which equal quantity of water was added, and the mixture shaked for 24 hours. Having allowed the latter to stand for 2 days, the aqueous layer was separated, and then saturated with hydrochloric acid by passing its current. The aqueous solution, so saturated, was heated in a sealed tube at 130° for 5 hours. Now the contents of the tube were evaparated in order to drive out a greater part of hydrochloric acid, then diluted with water and neutralized, again diluting to a certain definite volume. Having taken a definite quantity of such a solution, the quantity of ammonia was determined by mean of Nessler's solution with the aid of a colorimeter. From the amount of ammonia thus found the quantity of the narcotic dissolved in the aqueous part can be calculated. Denoting the quantity of the narcotic dissolved in water

by W and that of the same first taken by S we can get its coefficient of distribution by the formula,

$$K=\frac{S-W}{W}$$

In the case of the non-valatilie narcotic, however, we can directly determine the amount in an aqueous solution by evaporating to dryness. The results of experiments will be given in the following table:

TABLE III.

Narcotics.	Narcotics taken in gram.	Water taken in gram.	Olive oil taken in gram.	Narcotics in gram transferred to water.	K.
Epronal	0 10	30	30	0 0229	3·300
„	0 10	30	30	0 0228	3·400
Detonal	0 10	30	30	0 0361	1 800
„	0 70	80	80	0 2607	1·700
Urethane	1 00	30	30	0 8834	0 132
Veronal	0 10	50	50	0 0900	0 111
„	0 15	50	50	0 1340	0 119
Trional	0·15	40	40	0 0145	4 600

III. The Relative Strengths of the Narcotic Action.

The auther had to represent in the experiments (1) and (2) the strength of the narcotic action of a substance by the length of time in which the frog (Rana esculenta) can not release from the dorsal position with its own power.

The following tables show the mean values obtained for the different narcotics, arranged according to the concentration of solutions, having been deduced from the experimental results.

(1) The different narcotics each in 0·00025 grm. per 1 grm. frog were injected in the different concentrations:

TABLE IV.

Narcotics.	Concentration of solutions in %.	Intervals between injection and sleep.		Intervals between injection and the stoppage of respiration.		Durations of sleep.		Durations of the cessation of respiration.		Intervals between awaking and recovery.	
		Hr.	Min.	Hr.	Min.	Hr.	Min.	Hr.	Min	Hr.	Min.
Veronal	0·50	0	20	0	20	4	19	4	19	3	30
Hedonal	0·80	0	9	0	19	3	33	3	19	2	0
Epronal	0·15	0	16	0	25	0	56	0	26	0	40
Detonal	0 50	Released from the dorsal position with difficulty									

(2) The different narcotics each in 0·0003 grm. per 1 grm. frog were injected in the same concentration:

TABLE V.

Narcotics.	Concentration of solutions in %.	Intervals between injection and sleep.		Intervals between injection and the stoppage of respiration.		Durations of sleep.		Durations of the cessation of respiration.		Intervals between awaking and recovery.	
		Hr.	Min.	Hr.	Min.	Hr.	Min.	Hr.	Min.	Hr.	Min.
Veronal	0 15	0	32	0	32	2	0	2	0	5	30
Hedonal	„	0	7	0	7	1	55	1	55	2	0
Epronal	„	0	5	0	5	1	51	1	51	2	30
Bromural	„	0	15	0	15	5	30	5	30	3	0
Trional	„	0	14	0	14	1	14	1	14	1	20
Chloralhydrate	„	Released from the dorsal position with difficulty									
Amylenhydrate	„	„		„		„		„		without „	
Detonal	„	„		„		„		„		„	

When the injection of 0·00075 grm. of detonal per 1 grm. frog was executed the values shown in Table VI were obtained:

TABLE VI.

Narcotic.	Interval between injection and sleep.		Interval between injection and stoppage of respiration.		Duration of sleep.		Duration of the cessation of respiration.		Interval between awaking and recovery.	
	Hr.	Min.	Hr.	Min.	Hr.	Min.	Hr.	Min.	Hr.	Min.
Detonal	0	9	0	9	2	10	1	21	0	43

(3) The experiments were still further continued with the higher homologous acylurethanes and some allied compounds together with urethane, detonal and epronal in the manner described in the previous experiments, but in the case of the substances which do not dissolve in water in such a degree as to cause the narcotic action, they were injected in the state of emulsion with 4% gum arabic.

The present experiments were performed in December 1915, while the pervious ones in June the same year. The results of experiments will be given in the following table:

TABLE VII.

Narcotics.	Minimum doses per 1 grm. frog in aq. solution,		Minimum doses per 1 grm. frog in emulsion,		Strengths of narcotic action.
	in grm.	in gram-mol.	in grm.	in gram mol.	
Urethane	0.001700	1910×10^{-8}	—	—	10
Detonal	0.000400	214×10^{-8}	0.001040	5560×10^{-9}	90
Epronal	0.000225	112×10^{-8}	0.000400	1990×10^{-9}	170
Dipronal	0.000120	56×10^{-8}	—	—	340
Probnal	0.000090	39×10^{-8}	0.000150	655×10^{-9}	500
Dibnal	—	—	0.000160	656×10^{-9}	500
Oenanthylylurethane	—	—	0.000600	2985×10^{-9}	90–170
N-Isoamylurethane	0.000320	200×10^{-8}	—	—	95
Adaline	0.000080	34×10^{-8}	—	—	560
α-Bromethyl-propylaceturea	0.000060	24×10^{-8}	—	—	800

In this case the strengths of the narcotic action of the different substances with the exception of dibnal and oenanthylylurethane, as

given in the table, have been deduced by dividing the minimum dose of urethane in aqueous solution by that of each narcotic in the same and then multiplying the quotient by 10 so as to take that of urethane as 10× unit. The minimum doses of dibnal and oenanthylylurethane, however, on account of their feeble solubilities in water, have been determined in the state of emulsion, and also those of detonal and epronal in the same for comparison. Since the minimum doses of probnal and dibnal are almost equal in the state of emulsion, the strength of the narcotic action of dibnal may be assumed as almost equal to that of probnal, consequently as 500. That of oenanthylylurethane in emulsion lying between the values of detonal and epronal, the strength of its narcotic action ought to lie between 90 and 170.

IV. The Failure of the Heart.

The experiments were conducted in June 1915, according to the usual method by using the extirpated hearts of Rana esculenta. The narcotics were dissolved in Ringer's solution, and the rates of action upon the heart compared in the concentrations of 0·15, 0·12 and 0·09% solutions of each substance, noticing the duration of the heart-beat in minutes and seconds until its stoppage took place after the charge of the narcotics.

Solution in 0·15%.

TABLE VIII.

Narcotics.	Number of experiments.	Durations of the heart-beat.	
		Min.	Sec.
Epronal	I	2	0
	II	1	0
Hedonal	I	0	50
	II	0	20

Narcotics.	Number of experiments.	Durations of the heart-beat.	
		Min.	Sec.
Trional	I	More than 30	Heart-beat in normal condition.
	II	„ „ „	
	III	„ „ „	
Bromural	I	12	0
	II	5	0
	III	6	0
Amylenhydrate	I	More than 30	0
	II	„ „ „	0
Chloralhydrate	I	13	0
	II	27	0
	III	—	—
Veronal	I	20	
	II	23	
	III	30	
	IV	32	
Detonal	I	More than 30	Heart-beat in normal condition.
	II	„ „ „	
	III	„ „ „	

Solution in 0·12%.

TABLE IX.

Narcotic.	Number of experiments.	Durations of the heart-beat.	
		Min.	Sec.
Hedonal	I	0	40
	II	7	0

Narcotic.	Number of experiments.	Durations of the heart-beat.	
		Min.	Sec
Epronal	I	More than 30	
	II	4	0
	III	5	0
	IV	4	0
	V	7	0

Solution in 0·09%.

TABLE X.

Narcotics.	Number of experiments.	Durations of the heart-beat.	
		Min.	Sec.
Epronal	I	25	0
	II	More than 30	0
	III	„ „ „	0
	IV	„ „ „	0
	V	„ „ „	0
	VI	„ „ „	0
Hedonal	I	More than 30	0
	II	„ „ „	0
	III	22	0
Bromural	I	More than 30	0
	II	„ „ „	0
	III	25	0

The results of the experiment performed in December 1915, with the higher homologous acylurethanes and some allied compounds together with urethane, detonal and epronal will be given in the following table :

TABLE XI.

Narcotics.	Number of experiments.	Concentration in grm.-mol. in 1 liter Ringer's solution.	Durations of the heart-beat.	
			Min.	Sec.
Urethane	I	0·2240	2	10
	II	„	1	30
	III	„	2	0
	IV	0·2020	5	25
	V	„	7	15
	VI	„	6	11
Detonal		0 0270	Five experiments were carried out. In each the heart-beat continued more than 30 minutes although weak.	
Epronal	I	0 00746	2	40
	II	„	3	15
	III	„	0	30
	IV	0·00447	4	0
	V	„	7	20
	VI	„	6	50
Dipronal		0 00180	Four experiments were carried out. In each the heart-beat continued more than 30 minutes although weak	
Probnal	I	0 00130	4	40
	II	„	4	33
	III	„	7	11
	IV	„	6	45
Dibnal		0 00020	Three experiments were carried out. In each no noticeable change was observed.	
Oenanthylyl-urethane		0 00045	Three experiments were carried out. In each no noticeable change was observed.	
N-Isoamyl-urethane	I	0 00470	5	20
	II	„	4	31
	III	„	7	12
	IV	0·00315	22	11
	V	„	24	34
	IV	„	11	20

Narcotics.	Number of experiments.	Concentration in grm.-mol. in 1 liter Ringer's solution.	Durations of the heart-beat.	
			Min.	Sec.
Adaline	I	0 00086	Three experiments were carried out In each no noticeable change was observed	
α-bromethyl-propylaceturea	I	0 00081	Three experiments were carried out In each no noticeable change was observed.	

V. The Maximum and Lethal Doses of Epronal for the Rabbit.

(1) Epronal, 0·3 grm. per 1 kilog. rabbit was charged to the stomach in the form of 3% emulsion.

1'° 20$^{min.}$ P.M. Dosed; respiration counted 92.
1'° 40^{min} P.M. Shut the eyes in the sedative condition, but moved to and fro.
2'° 50$^{min.}$ P.M. Shut the eyes, but walked by persuation.
3'° 50$^{min.}$ P.M. As it was, but in a somewhat healthy condition.

(2) Epronal, 0·5 grm. per 1 kilog. rabbit.

1'° 25$^{min.}$ P.M. Dosed; respiration counted 70.
1'° 45$^{min.}$ P.M. Fell into a deep sleep; respiration counted 55.
2'° 35$^{min.}$ P.M. Scented around, but the paralyzed hind legs did not allow to walk; continued the sleep further.
3'° 35$^{min.}$ P.M. Shut the eyes, but walked by persuation; respiration counted 60.
4'° 0$^{min.}$ P.M. In healthy condition.

(3) Epronal, 1·0 grm. per 1 kilog. rabbit.

1'° 30$^{min.}$ P.M. Dosed; respiration counted 71.
1'° 40^{min} P.M. Shut the eyes, but walked to and fro.
1'° 50$^{min.}$ P.M. Fell into a sleep; respiration counted 60.
2'° 15^{min} P.M. Moved; but continued the sleep.
2'° 30$^{min.}$ P.M. The paralyzed hind legs did not allow to get up and fell into the sleep again; respiration counted 55.

2'° 53^{min} P.M.	The rattling sound in trachea and the wriggle of intestine were noticed.
4'° 20^{min} P.M.	Continued the sleep; respiration counted 55.
5'° 20$^{min.}$ P.M.	Could not get up by the paralysis of hind legs but became sensible; respiration counted 55.
The next day.	Recovered.

(4) Epronal, 1·5 grm. per 1 kilog. rabbit.

11'° 5$^{min.}$ A.M.	Dosed; respiration counted 80.
11'° 15$^{min.}$ A.M.	Fell into a deep sleep.
11'° 50$^{min.}$ A.M.	The hind legs paralyzed; respiration counted 60.
1'° 40$^{min.}$ P.M.	Continued the sleep; respiration counted 60.
3'° 30$^{min.}$ P.M.	As it was.
4'° 40$^{min.}$ P.M.	Continued the sleep; the wriggle of intestine was noticed.
5'° 0^{min} P.M.	Respiration counted 48.
6'° 0$^{min.}$ P.M.	Continued the sleep; respiration counted 55.
The next day.	Recovered.

(5) Epronal, 2·0 grm. per 1 kilog. rabbit.

11'° 10$^{min.}$ A.M.	Dosed; respiration counted 70.
11'° 17$^{min.}$ A.M.	Fell into a deep sleep; respiration counted 57.
11'° 40$^{min.}$ A.M.	The hind leges paralyzed; respiration counted 50.
12'° 15$^{min.}$ P.M.	Continued the sleep; respiration counted 47.
3'° 30$^{min.}$ P.M.	Endeavoured to get up but in vain; respiration counted 32.
4'° 0$^{min.}$ P.M.	The wriggle of intestine was observed.
5'° 0$^{min.}$ P.M.	Continued the sleep; respiration counted 33.
6'° 0$^{min.}$ P.M.	As it was.
The next day.	Recovered.

(6) Epronal, 2·5 grm. per 1 kilog. rabbit.

10'° 0$^{min.}$ A.M.	Dosed; respiration counted 90.
10'° 20$^{min.}$ A.M.	Fell into a sleep; respiration counted 60.
12'° 0$^{min.}$ A.M.	The wriggle of intestine was observed; respiration counted 50.

5'° 0min. A.M.	Continued the deep sleep; respiration counted 40.
The next day.	Continued the sleep all the day; respiration counted 35–40.
At noon the day after next.	Became sensible and took some food.
4'° 0min. P.M.	Moved to and fro with paralyzed hind legs.
The next day succeeding.	Died.

(7) Epronal, 3·0 grm. per 1 kilog. rabbit.

3'° 0min. P.M.	Dosed; respiration counted 80.
3'° 20min. P.M.	Fell into a sleep.
4'° 0min. P.M.	Continued the sleep; respiration counted 60.
6'° 0min. P.M.	Continued the sleep; respiration counted 50.
At noon the day after next.	Died.

VI. The Influence of Epronal upon the Blood-pressure, Vagus and Respiratory Centre.

In about an hour after dosing 1·5 grm. epronal per 1 kilog. rabbit, a rabbit fell into a sleep. The blood-pressure, then observed, was found to be almost constantly 100 mm. in the mercury column as is usually noticed in the normal rabbit; by giving stimulation to the vagus or an obstruction to respiration the degradation of the blood-pressure took place as shown in the curve given at the end of this article. Such facts show that the vagus and the respiratory centre would not be influenced at all.

In conclusion, I beg to offer my best thanks to Professors Kuhara and Morishima for their valuable suggestions and guidance in carrying out this research.

The Blood-Pressure Curve.