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The preparation and intravenous anaesthetic activity of tetrahydrofuran-3-ols

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A number of tetrahydrofuran-3-ols have been prepared and examined for intravenous anaesthetic activity. The compounds studied had low intrinsic anaesthetic activity and there was an inverse relation between anaesthetic activity or toxicity and solubility in water. It was considered unlikely that compounds comparable in activity to thiopentone or methohexitone would be found in this series.

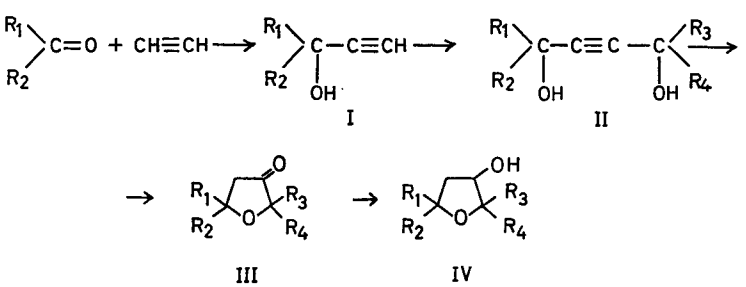
Many unrelated chemical compounds cause general anaesthesia in animals, and attempts have been made to relate their physical properties to their anaesthetic activity (Butler, 1950; Miller, Paton & Smith, 1965). From these studies it may be concluded that any anaesthetic compound must be both soluble in lipid materials and sufficiently soluble in water to enable it to reach its site of action. Thus, any anaesthetic compound could be given intravenously provided it was sufficiently soluble in water.

The general anaesthetic, diethyl ether, which is usually inhaled, can cause anaesthesia when injected intravenously in aqueous solution (Adams, 1944; Butt, Ochs & others, 1965). But diethyl ether is not very potent and only poorly soluble in water. Tetrahydrofuran (THF), the cyclic analogue of diethyl ether, also causes anaesthesia when inhaled (Stoughton & Robbins, 1936; Henderson & Smith, 1936) or injected intravenously in aqueous solution (see this paper); unlike diethyl ether, THF is very soluble in water. Accordingly, we decided to prepare a number of novel substituted derivatives of THF with the object of increasing anaesthetic activity and examining the relation between solubility in water and activity. Simple alkyl substituted THF's were insoluble in water, but the addition of a hydroxyl group to the ring overcame this problem, and resulted in the series of tetrahydrofuran-3-ols now examined.

CHEMISTRY EXPERIMENTAL

Synthetic methods

Preparation of the tetrahydrofuranols.



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The foregoing general method which was used for the synthesis of the furanols can lead to a number of isomeric forms. At the ring closure stage hydration of the triple bond takes place and this can lead, when at least one of R_1, R_2, R_3 and R_4 are different, to two position isomers where the ketone group is either in the 3 or 4 position. Reduction of the ketones to alcohols can lead to a further series of geometrical isomers.

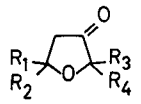
General preparative methods

Ethynyl alcohols (I). These were prepared by the literature methods.

Acetylenic diols (II). These were prepared by the general method of Dupont (1913). Most of these intermediates have been described in the literature; those that were new were generally cyclized to the furanone without purification.

Tetrahydrofuranones (III). The acetylenic diols were ring closed to the furanones (Table 1) by the general method of Dupont (1913).

Table 1. *The chemical characteristics of some tetrahydrofuran-3-ones.* Analyses for C and H are within the usual limits



R_1	R_2 (R_4 = H)	R_3	b.p. °C/mm Hg	Formula
Me	H	Pent	104–110/10	$C_{10}H_{18}O_2$
Et	Et	Et	120–130/80	$C_8H_{14}O_2$
Me	isoBu	H	85–89/10	$C_9H_{16}O_2$
Me	Pr	H	70–73/10	$C_8H_{14}O_2$
Me	H	Bu	98–102/16	*
Pr	Pr	H	95–98/10	$C_{10}H_{18}O_2$
Pr^i	Pr^i	H	85–90/10	$C_{10}H_{18}O_2$
Me	Nonyl	H	150–154/8	$C_{14}H_{16}O_2$
Me	Me	Et	99–103/90	*
Et	Et	Me	75–80/21	$C_9H_{16}O_2$
Me	Et	Me	105–110/50	$C_9H_{16}O_2$
Me	Me	Pr	67–71/10	$C_9H_{16}O_2$
Me	Me	Pr^i	64/10	$C_9H_{16}O_2$
Et	Et	Et	96–101/18	$C_{10}H_{18}O_2$
Me	Me	Bu	84/9	$C_{10}H_{18}O_2$
Me	Et	Pr	214–218/760	$C_{10}H_{18}O_2$
Et	Pr	Me	98–111/20	$C_{10}H_{18}O_2$
Me	Pr	Et	95–98/17	$C_{10}H_{18}O_2$
Spirocyclopentyl		Me		*
Et	Et	Me (R_4 = Me)	100–110/20	*

* Used without purification.

Tetrahydrofuranols (IV). Most of the tetrahydrofuranols were prepared by hydrogenation of the corresponding tetrahydrofuranone in ethanol in the presence of a suitable catalyst.

3-*Ethyl*-2,2,5-*trimethyl-tetrahydrofuran*-3-*ol* (19) was prepared by the action of ethyl magnesium bromide on 2,2,5-trimethyl-tetrahydrofuran-3-one.

2,2-*Diethyl*-5-*methyl-tetrahydrofuran*-3,4-*diol* (27). 2,2-Diethyl-5-methyl-tetrahydrofuran-3-one was brominated at steam bath temperature with 4 mol of bromine. The reaction mixture was steam distilled to give a heavy oil. The crude distillate, 4,4-dibromo-2,2-diethyl-5-methyl-tetrahydrofuran-3-one, was refluxed until complete solution was obtained. This solution was extracted with ether to give 3-ethyl-2,2,5-trimethyl-tetrahydrofuran-3,4-dione, b.p. 140–144°/15 mm. Found: C, 62·8; H, 8·3. $C_9H_{14}O_3$ requires C, 63·5; H, 8·2. The tetrahydrofuran-3,4-dione was catalytically reduced to give the diol (27).

3-Ethynyl-2,2,5,5-tetramethyl-tetrahydrofuran-3-ol (42). 2,2,5,5-Tetramethyl tetrahydrofuran-3-one was reacted with ethynyl magnesium bromide to give the corresponding furan-3-ol (42).

2,2,5,5-Tetramethyl-tetrahydro-3-hydroxy-3-furanyl methyl ketone (43). 3-Ethynyl-2,2,5,5-tetramethyl-tetrahydrofuran-3-ol was hydrated by the method of Dupont (1913) to give the corresponding methyl ketone (43).

Solubility in water. Solubility in water was determined at room temperature (20–24°).

Partition coefficients. These were determined in carbon tetrachloride-water at room temperature (20–24°).

PHARMACOLOGY EXPERIMENTAL

Intravenous anaesthetic activity in mice

The technique adopted was similar to that used by Wirth & Hoffmeister (1965) in the rabbit.

Anaesthesia was assessed in mice by observing the loss of the righting reflex, the fore and hind limb toe pinch reflexes and the corneal reflex. Anaesthesia was defined as the loss of all these reflexes. The time taken for each reflex to return was noted during the experiment. Side-effects were also noted and scored.

All compounds were dissolved in distilled water and used immediately. Injections were given into a lateral tail vein in a volume of 0·2 ml/20 g of mouse. Using 10 mice per dose level, the dose which caused anaesthesia in 50% of mice injected (AD50), and the dose which killed 50% of mice injected (LD50) within 2 h was determined. The figures were calculated using the method of Litchfield & Wilcoxon (1949). The therapeutic index was defined as the ratio of the LD50 to the AD50.

The results were analysed using a PDP.8 computer. Regression lines were calculated using a least squares fit assuming the relation between the data would be expressed by a polynomial equation of the form

$$Y = X(0) + X(2)x + X(2)x^2 \ldots + X(m)x^m$$

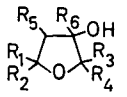
for powers 0 to 7. Using the coefficients determined for each equation, the variance of the points about each line was calculated for each power. The variances were then compared for significant diminution in size.

RESULTS

The anaesthetic activity (AD50), acute intravenous toxicity (LD50) and therapeutic index of each compound were determined in mice. The results have been summarized in Table 2. Data on diethyl ether, THF and two barbiturate intravenous anaesthetics, methohexitone and thiopentone, have been included for comparison purposes.

Most of the compounds prepared possessed anaesthetic activity and some, 5, 9 and 18, were found to have particularly high therapeutic indexes in comparison with thiopentone and methohexitone. However, the tetrahydrofuran-3-ols were much less active than the barbiturate anaesthetics. All the compounds examined induced anaesthesia very rapidly. Often the animal lost its righting reflex before the injection was completed. Induction was usually accompanied by convulsive side-effects which varied in severity from compound to compound (Table 2). Recovery from anaesthesia was also rapid; most animals recovered their righting reflex within 15

Table 2. *The chemical characteristics and intravenous anaesthetic activity in the mouse of some tetrahydrofuran-3-ols.* Data on diethyl ether, tetrahydrofuran, methohexitone and thiopentone are included for comparison purposes. T.I. = therapeutic index, S.E. = side-effects, Sol. = solubility in water (%). Analyses for C and H are within the usual limits



No.	R_1	R_2	R_3 ($R_4=R_5=R_6=H$)	b.p. °C/mm Hg	Formula	AD50	LD50	T.I.	S.E.	Sol.
	Diethyl ether					202	440	2·2	+	7
	Tetrahydrofuran					607	759	1·2	++	100
	Thiopentone sodium					54·5	68·0	1·2	+	>10
	Methohexitone					17·0	36·5	2·1	+	>10
1	H	H	H	Wynberg, 1958		3850	3850	1·0	+++	100
2[1]	H	H	H	Hanschke, 1955		1340	1760	1·3	+++	20
3	Me	H	H	Curtis & others, 1962		2400	4150	1·7	+++	20
4	H	H	Me	96–97/25	$C_5H_{10}O_2$	4000	4360	1·1	+++	>10
5	Me	H	Me	185/760	$C_6H_{12}O_2$	550	1750	3·2	++	20
6	Me	H	Pent	74–75/0·06	$C_{10}H_{20}O_2$	54	64	1·2	++++	0·2
7	Pr	H	Pr	118–121/15	$C_{10}H_{20}O_2$	69	75	1·1	+++	0·2
8	Me	Me	H	Colonge & others, 1958		900	1460	1·6	+++	10
9	Me	Et	H	Colonge & others, 1958		305	890	2·9	+++	10
10	Et	Et	H	95–98/11	$C_8H_{16}O_2$	185	310	1·7	+++	2
11	Me	Bu[i]	H	109/9	$C_9H_{18}O_2$	175	175	1·0	+	1
12	Me	Pr	H	103–104/10	$C_8H_{16}O_2$	224	318	1·4	++	2
13	Me	Bu	H	117–119/20	$C_9H_{18}O_2$	77	138	1·8	++	0·4
14	Spirocyclohexyl		H	Colonge & others, 1958		225	360	1·6	++	2
15	Pr	Pr	H	121/10	$C_{10}H_{20}O_2$	84	124	1·5	++	1
16	Pr[i]	Pr[i]	H	118/10	$C_{10}H_{20}O_2$	138	138	1·0	+	1
17	Me	Nonyl	H	110/0·1	$C_{14}H_{28}O_2$	188	188	1·0	+	*
18	Me	Me	Me	82–83/30	$C_7H_{14}O_2$	650	1900	2·9	+	>25
19[14]	Me	H	Me	55–62/0·15	$C_7H_{14}O_2$	387	620	1·6	++	7
20	Me	Me	Et	80–88/11	$C_8H_{16}O_2$	625	1530	2·4	++	5
21	Me	Et	Me	117–119/38	$C_8H_{16}O_2$	340	920	2·7	++	100
22	Et	Et	Me	103/5	$C_9H_{18}O_2$	177	220	1·2	+	0·5
23[2]	Et	H	Et	120/35	$C_9H_{18}O_2$	204	385	1·9	+	2
24	Me	Me	Pr	92–95/6	$C_9H_{18}O_2$	130	300	2·3	+	2
25	Me	Me	Pr[i]	90/12	$C_9H_{18}O_2$	190	292	1·5	++	5
26	Me	Pr	Me	102/10	$C_9H_{18}O_2$	180	225	1·4	++	3
27[3]	Et	Et	Me	86–90/0·2	$C_9H_{18}O_2$	470	530	1·4	+	20
28	Et	Et	Et	99–103/9	$C_{10}H_{20}O_2$	116	186	1·6	+	1
29	Me	Me	Bu	101/10	$C_{10}H_{20}O_2$	99	137	1·4	+++	0·5
30	Me	Et	Pr	108/8	$C_{10}H_{20}O_2$	130	175	1·3	++++	1
31	Et	Pr	Me	115–119/22	$C_{10}H_{20}O_2$	195	235	1·2	++	*
32	Me	Pr	Et	114/19	$C_{10}H_{20}O_2$	130	240	1·8	+	1
33	Spirocyclopentyl		Me	117–120/8	$C_9H_{16}O_2$	330	490	1·5	++	20
34[4]	Me	Me	Me	Korbitsyna & others, 1960		720	1250	1·7	+	10
35[5]	Me	Me	Me	Heuberger & Owen, 1952		5000	5000	1·0	+	10
36[6]	Me	Me	Me	m.p. 207–209°	$C_9H_{17}O_3$	4000	4000	1·0	++	10
37[7]	Me	Me	Me	Sulzbacher & Bergmann, 1953		746	1030	1·4	+++	10
38[8]	Me	Me	Me	m.p. 131–135°	$C_7H_{16}O_2$	3230	3230	1·0	+	2
39[9]	Me	Me	Me	m.p. 80–84°	$C_9H_{18}O_2$	480	480	1·0	+	1
40[10]	Et	Et	Me	110–115/10	$C_{10}H_{20}O_2$	125	145	1·2	+++	0·5
41[11]	Me	Et	Me	Dupont, 1913		133	250	1·9	+	2
42[12]	Me	Me	Me	m.p. 86–88°	$C_{10}H_{16}O_2$	220	410	1·8	+	2
43[13]	Me	Me	Me	m.p. 46–52°	$C_{10}H_{18}O_3$	390	715	1·8	+	5
44[14]	Me	Me	Me	Sulzbacher & Bergmann, 1953		300	300	1·0	++++	7
45[15]	Et	Et	Et	128-129/16	$C_{12}H_{24}O_2$	58	82	1·4	++	0·3
46[16]	Spirocyclohexyl			Korbitsyna & others, 1960		2·5	2·5	1·0	+++	0·7

* Dissolved in 10% Cremophor E.L.

† = No side-effects. + = ataxia, slight tremors. ++ = slight convulsions, marked ataxia on recovery. +++ = convulsions, marked ataxia on recovery. ++++ = severe convulsions, rigidity and gross ataxia on recovery.

[1] R_5=Me. [2] R_4=Me. [3] R_3=OH. [4] R_4=Me. [5] R_4=Me, R_5=OH. [6] R_4=Me, R_5=$CONH_2$, R_6=OH. [7] $R_4=R_6$=Me. [8] R_4=Me, R_5=CH_2OH. [9] $R_4=R_5$=Me. [10] R_4=Me. [11] R_4=Et. [12] R_4=Me, R_6=$-C\equiv CH$. [13] R_4=Me, R_6=COMe. [14] R_4=Me, R_6=Et. [15] R_4=Et. [16] R_4=spirohexyl.

min and appeared normal 30–45 min later. Animals which had received lethal doses of these compounds died of respiratory failure. However, there was no indication that anaesthesia was due to anoxia when sub-lethal doses were administered.

A number of these compounds were examined in the rabbit, cat or monkey but in all species side-effects, similar to those seen in the mouse, were observed.

The partition coefficients (carbon tetrachloride–water) of ether and tetrahydrofuran were 11·0 and 3·0 respectively. Tetrahydrofuran, despite its high solubility in water, had a partition coefficient approximately one third that of ether.

DISCUSSION

It is generally accepted that a suitable balance of lipophilic and hydrophilic properties is essential for any compound to cause anaesthesia. THF appeared to fulfil this requirement as it was both soluble in carbon tetrachloride and water and had a reasonably high partition coefficient in the system carbon tetrachloride–water. We therefore hoped that alkyl substituted derivatives of tetrahydrofuran would have more anaesthetic activity than the parent compound whilst retaining high solubility in water.

In the series of tetrahydrofuran-3-ols examined, there was an inverse relation between solubility in water and anaesthetic activity (AD50) (Fig. 1A) or toxicity

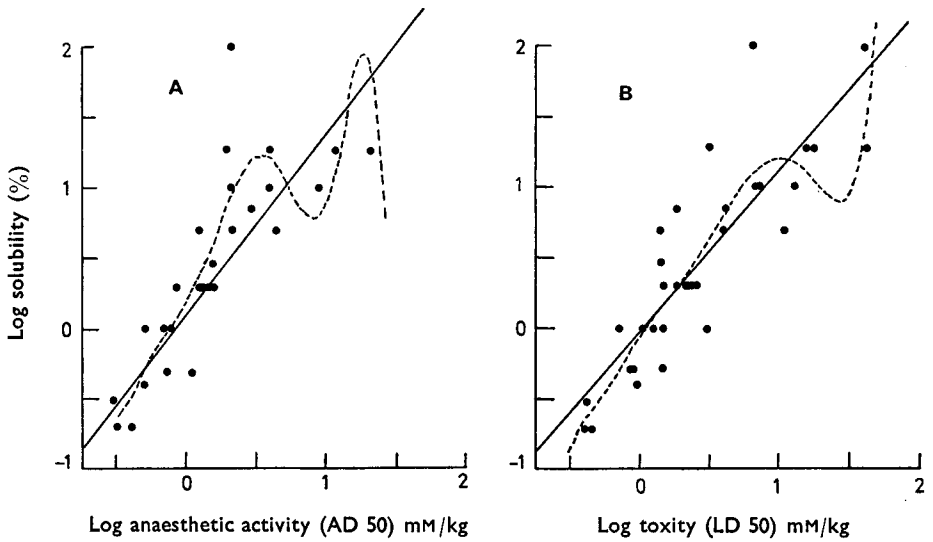


FIG. 1. A. Log anaesthetic activity (AD50) versus log per cent solubility in water. The solid line represents the normal regression line and is of unit slope. The broken line represents the regression line calculated for a 7th power polynomial equation. The variance about the normal regression line was not significantly reduced by including higher powers.

B. As above except that log toxicity (LD50) is plotted against log solubility in water. The solid line is of unit slope.

(LD50) (Fig. 1B). Similar findings have been reported for paraffin hydrocarbons (Fuhner, 1921) and a series of ethers (Cone, Forman & Krantz, 1941) though Miller & others (1965) found no such relation among the compounds they investigated. A regression line of the form

$$Y = X(0) + X(1)x$$

gave a line with a variance which was not significantly reduced by including higher powers of x. Thus if it is assumed that the thermodynamic activity of each compound is proportional to its solubility in water, then the tetrahydrofuran-3-ols adhere quite closely to Ferguson's principle (Ferguson, 1939). But this in no way precludes any

relations between activity and lipid solubility (Meyer, 1937), or solubility in organic solvents (Miller & others, 1965), or surface activity (Butler, 1950) or some other physical property. However, it does suggest that the tetrahydrofuran-3-ols cause anaesthesia in a non-specific manner. An investigation of the anaesthetic activity of the configurational isomers of some of the 2,5-disubstituted derivatives would confirm this conclusion.

Further analysis of the data obtained from this series showed that there was no relation between therapeutic index and solubility in water or anaesthetic activity.

In view of the low intrinsic anaesthetic activity of the tetrahydrofuran-3-ols and the inverse relation between activity and solubility in water, we concluded that it was unlikely that compounds comparable in activity to thiopentone or methohexitone would be found in this series.

REFERENCES

ADAMS, R. C. (1944). *Intravenous Anaesthesia*, pp. 54–64, New York: Paul B. Hoeber Inc.

BUTLER, T. C. (1950). *Pharmac. Rev.*, **2**, 121–160.

BUTT, H., OCHS, I., LYONS, J. & DELGARDO, G. (1965). *Anesth. Analg. curr. Res.*, **44**, 186–189.

COLONGE, J., FALCOTET, R. & GAUMONT, R. (1958). *Bull. Soc. chim. Fr.*, 211–218.

CONE, N. M., FORMAN, S. E. & KRANTZ, J. C. (1941). *Proc. Soc. exp. Biol. Med.*, **48**, 461–463.

CURTIS, R. F., HASSALL, C. H. & WEATHERSTON, J. (1962). *J. chem. Soc.*, 4225–4231.

DUPONT, G. (1913). *Annls Chim. phys.*, **30**, 485–587.

FERGUSON, J. (1939). *Proc. R. Soc. B.*, **127**, 387–404.

FUHNER, H. (1921). *Biochem. Z.*, **115**, 235–261.

HANSCHKE, E. (1955). *Chem. Ber.*, **88**, 1053–1061.

HENDERSON, V. E. & SMITH, A. H. R. (1936). *J. Pharmac. exp. Ther.*, **57**, 394–398.

HEUBERGER, O. & OWEN, L. N. (1952). *J. chem. Soc.*, 910–914.

KORBITSYNA, I. K., CH'EN-LEH, YIN, YUR'EV & YU, K. (1960). *Zh. obshch. Khim.*, **30**, 2214–2218.

LITCHFIELD, J. T. & WILCOXON, F. (1949). *J. Pharmac. exp. Ther.*, **96**, 99–113.

MEYER, K. H. (1937). *Trans. Faraday Soc.*, **33**, 1062–1064.

MILLER, K. W., PATON, W. D. M. & SMITH, E. B. (1965). *Nature, Lond.*, **206**, 574–577.

STOUGHTON, R. W. & ROBBINS, B. H. (1936). *J. Pharmac. exp. Ther.*, **58**, 171–173.

SULZBACHER, M. & BERGMANN, E. D. (1953). *J. Am. chem. Soc.*, **75**, 3859.

WIRTH, W. & HOFFMEISTER, F. (1965). In: *Die intravenose Kurznarkose mit dem neuen Phenoxyessigsaurederivat Propanidid* (Epontol). Editors: Horatz, K., Frey, R. and Zindler, M., p. 17. Berlin: Springer.

WYNBERG, H. (1958). *J. Am. chem. Soc.*, **80**, 364–366.