VARIATION IN PHYSIOLOGICAL ACTIVITY OF ALCOHOLS AMONG ISOMERS AND HOMOLOGS.*

BY RALPH W. HUFFERD.[1]

Exact knowledge of the comparative physiological potencies of the aliphatic alcohols is needed in the production of synthetic drugs, especially those of the anæsthetic group. A survey of the literature shows many contradictions. It seems to the writer that this confusion has come from two sources; the use of impure alcohols, and the choice of resulting conditions that do not permit of accurate observation. It is the object of the present investigation to make a new study in which special care is taken to avoid these difficulties.

EXPERIMENTAL PROCEDURE.

The alcohols were administered to guinea pigs by stomach-tube, care being taken to avoid measurable loss. The C_1, C_2 and C_3 members were diluted to 40% by volume after they had been measured. With the exception of tertiary butyl alcohol the higher alcohols were given without diluting. The animals were watched constantly for at least an hour and were then observed at 15-minute intervals until the maximum effect was past.

All pigs were of over 300-Gm. weight after 4 to 6 hours fasting without water. In a few cases longer fasting was tried but proved too severe on the animals, causing rapid loss of weight and strength. The pigs were standardized by testing their resistance to ethyl alcohol, the few that reacted abnormally being discarded.

It was first decided to determine the smallest quantities that would produce deep narcosis. This was found to be a poor condition to observe accurately. It also approached too closely to the lethal dose to permit of further use of the pigs except after a long rest. However, it was found in this attempt that guinea pigs show 5 rather well-defined stages of narcosis with most alcohols. Due to its narrow limits, one of these, the C condition, was chosen as the standard. The five stages are:

A. Sluggishness or drowsiness.

B. Loss of control of the hind legs.

C. Loss of control of the hind and fore legs to such an extent as to make locomotion impossible.

D. Narcosis from which the animal cannot be roused by holding it up by the hind legs and shaking it violently.

D+. Narcosis so deep that no reaction is produced by pinching the skin of the back between the hind shoulders, a very sensitive spot.

PURIFICATION OF ALCOHOLS.

According to the statement of the manufacturer, most of the alcohols were prepared through the Grignard reaction and were of considerable purity. Nevertheless, they were subjected to extensive fractionation, both the boiling range and the refractive index of each fraction being recorded.

All distillations were made through columns similar to the one described by Skinner and Noyes (3).

---

* Presented before the Biological Section at the 81st meeting of the American Chemical Society, Indianapolis, Ind., March 30 to April 3, 1931.

[1] De Pauw University, Greencastle, Ind.

The refractometer used is of the Abbe type and gave the values 1.3331 and 1.3718 at 20° for water and acetic acid, respectively.

All physical properties used for comparison were taken from "International Critical Tables."

Anschutz thermometers corrected to ±0.2° were used. All boiling points were corrected according to Alex. Smith's value (4) for associated liquids.

Methanol—Acetone Free. B. P. 64.5°, N_D^{20} 1.329.

Acetone-free methanol was distilled from dilute hydrochloric acid and then once from commercial quick lime and 3 times from activated lime (2). 1500 cc. of this material was redistilled, the middle fraction of 500 cc. being collected. This sample was then subjected to fractionation as shown in the following table.

Fraction.	B. P.	N_D^{20}.	Fraction.	B. P.	N_D^{20}.
1	64.5–64.7	1.3289	1	64.5–64.7	1.3287
2	64.7–64.9	1.3291	2	64.7–64.8	1.3287
3	64.9–	1.3292	3	64.8–65.0	1.3288
4	64.9–	1.3291	4	65.0–65.1	1.3287
5	64.9–65.0	1.3292	5	65.1–65.4	1.3288
6	65.0–65.1	1.3292			
7	65.1–65.3	1.3293	3 and 4 were combined for use.		

3, 4, 5 and 6 were combined and redistilled.

Methanol—Synthetic. B. P. 64.5°, N_D^{20} 1.329.

A sample of synthetic methanol was distilled from activated lime after two hours refluxing and then fractionated as follows:

Fraction.	B. P.	N_D^{20}.	Fraction.	B. P.	N_D^{20}.
1	.....	1.3303	1	64.3–64.7	1.3293
2	.....	1.3305	2	64.7	1.3292
3	.....	1.3307	3	64.7–65.0	1.3293
4	.....	1.3309	4	65.0–66.0	1.3300
5	.....	1.3310	2 and 3 were combined for use.		
6	.....	1.3311			

3, 4 and 5 were combined and redistilled.

Ethyl Alcohol—100%. B. P. 78.5°, N_D^{20} 1.3617.

A middle fraction of 2 liters was cut out of a 5-liter sample of industrial alcohol. This was redistilled and the first and last 500-cc. fractions discarded. The resulting product was refluxed with commercial lime for 3 hours and distilled off on a steam-bath. The distillate was refluxed with activated lime. The process was repeated 3 times. The final distillate had a volume of about 500 cc. It was fractionated, the first and last fractions of 150 cc. each being discarded. The middle fraction was fractionated as follows:

Fraction.	B. P.	N_D^{20}.	Fraction.	B. P.	N_D^{20}.
1	78.1–78.2	1.3608	4	78.3–	1.3612
2	78.2–78.3	1.3612	5	78.3–78.4	1.3612
3	78.3–	1.3612	res.	.....	1.3612

Fractions 3 and 4 were combined for use.

Ethyl Alcohol—96%.

Industrial alcohol was distilled from lime without refluxing, and then cut into

3 equal fractions by distillation. The middle fraction was used. It has a specific gravity at 20° referred to water at 4° of 0.8013, showing it to have a purity of 96%.

n-Propyl Alcohol. B. P. 97.8, N_D^{20} 1.3854.

Fraction.	B. P.	N_D^{20}.
1	95.9	1.3838
2	95.9–96.3	1.3839
3	96.3–96.5	1.3839
4	96.5–96.7	1.3839
5	96.7–96.8	1.3840

3, 4 and 5 were combined and refluxed with activated lime.

1	–96.1	1.3840
2	96.1–96.7	1.3840
3	96.7–97.1	1.3841
4	97.1–97.3	1.3841
5	97.3–97.5	1.3841
res.	.....	....

3, 4 and 5 were combined and redistilled.

Fraction.	B. P.	N_D^{20}.
1	–96.5	1.3848
2	96.5–96.7	1.3845
3	96.7–97.2	1.3847
4	97.2–97.4	1.3847
res.	.....	....

3 and 4 were combined and redistilled.

1	97.1	1.3846
2	97.1–97.3	1.3847
3	97.3–97.5	1.3846
res.	.....	....

2 and 3 were combined for use.

Isopropyl Alcohol. B. P. 82.3, N_D^{20} 1.3776.

The middle fraction of a sample of the alcohol was refluxed with activated lime and then redistilled as follows:

Fraction.	B. P.	N_D^{20}.
1	–81.4	1.3792
2	81.4–81.9	1.3787
3	81.9–82.1	1.3790
res.	.....	....

The 3 fractions were combined and again treated with activated lime. The distillate boiled constant at 82.3° but was white. It was redistilled, yielding clear distillate as follows:

1	–82.3	1.3768
2	82.3–	1.3772
res.	.....	....

Fraction 2 was used.

n-Butyl Alcohol. B. P. 117.7, N_D^{20} 1.3991.

Fraction.	B. P.	N_D^{20}.
1	–116.8	....
2	116.8–117.8	1.3975
3	117.8–118.5	1.3977
4	118.5–118.5	1.3978
res.	.....	.....

Fraction 3 was used.

Isobutyl Alcohol. B. P. 107.3°, N_D^{20} 1.396.

Fraction.	B. P.	N_D^{20}.
1	–105.4	1.3940
2	105.4–106.0	1.3941
3	106.0–106.4	1.3942
4	106.4–106.4	1.3940

2 and 3 were combined and redistilled.

Fraction.	B. P.	N_D^{20}.
1	107.1	1.3937
2	107.1–107.2	1.3938
res.	.....	....

Fraction 2 was used.

sec.-Butyl Alcohol. B. P. 99.5°, N_D^{20} 1.397.

Fraction.	B. P.	N_D^{20}.
1	–98.5	1.3964
2	98.5–98.9	1.3963
3	98.9–99.3	1.3964
res.	.....	....

Fraction 3 was used.

tert.-Butyl Alcohol. B. P. 82.8°, N_D^{20} 1.387, M. P. 25°.

Fraction.	B. P.	N_D^{20}.
1	–81.1	1.3860
2	81.1–81.9	1.3867
res.	.....	....

Fraction 2 was refluxed with activated lime and distilled.

Fraction.	B. P.		
1	81.1	1.3863	m. p. 20°
2	81.1–81.4	1.3867	m. p. 23°
res.	.....	....	m. p. 18°

Fraction 2 was used.

n-Amyl Alcohol. B. P. 137.9°, N_D^{13} 1.414, $N^{14}{}_D{}^{6}$ 1.4096.

Fraction.	B. P.	N_{20}^{D}.
1	–137.3	1.4087
2	137.3–137.8	1.4087
3	137.8	1.4089

Fraction.	B. P.	N_D^{20}.
4	137.8	1.4089
5	137.8–138.3	1.4088
res. (1/3)	.....	....

Fractions 4 and 5 were combined for use.

Isoamyl Alcohol. B. P. 130.5°, N_D^{20} 1.4075.

Fraction.	B. P.	N_D^{20}.
1	–130.8	1.4058
2	130.8–131.5	1.4060

Fraction.	B. P.	N_D^{20}.
3	131.5–131.6	1.4060
res.	.....	1.4060

Fraction 3 was used.

sec.-Amyl Alcohol (methyl *n*-propyl carbinol). B. P. 119.5°, N_D^{20} 1.4072.

Fraction.	B. P.	N_D^{20}.
1	–118.8	1.4058
2	118.8–119.8	1.4064
3	119.8–120.0	1.4063
4	120.0–120.2	1.4063
5	120.2–121.3	1.4063
res.	.....	....

2, 3, 4 and 5 were combined and redistilled.

Fraction.	B. P.	N_D^{20}.
1	115.8–117.8	1.4057
2	117.8–119.3	1.4058
3	119.3–120.0	1.4063
4	120.0–120.3	1.4064
res.	.....	1.4073

3 and 4 were combined for use.

tert.-Amyl Alcohol (dimethyl ethyl carbinol). B. P. 101.8°, N_D^{20} 1.406.

Fraction.	B. P.	N_D^{20}.
1	– 99.7	1.4030
2	99.7–100.7	1.4037

Fraction.	B. P.	N_D^{20}.
3	100.7–101.5	1.4038
res.	.....	1.4038

Fraction 3 was used.

n-Hexyl Alcohol. B. P. 155.8.

Fraction.	B. P.	N_D^{20}.
1	–151.8	....
2	151.8–152.8	1.4145
3	152.8–153.3	1.4152
4	153.3–154.3	1.4156
5	154.3–155	1.4157
6	155 –155.8	1.4158
7	155.8–156.5	1.4160
res.	.....	1.4171

3, 4, 5 and 6 were combined and redistilled.

Fraction.	B. P.	N_D^{20}.
1	–150.8	1.4140
2	150.8–153.8	1.4152
3	153.8–155.8	1.4158
res.	.....	1.4160

2 and 3 were combined and redistilled.

1	–153.8	1.4143
2	153.8–154.8	1.4163
res.	.....	1.4163

Fraction 2 was used.

sec.-Hexyl Alcohol (methyl *n*-butyl carbinol). B. P. 131.9°, N_D^{20} 1.411.

Fraction.	B. P.	N_D^{20}.	Fraction.	B. P.	N_D^{20}.
1	–138.8	1.4148	3	139.3–139.5	1.4150
2	138.8–139.3	1.4148	res.	.....	1.4148

Fraction 3 was used.

tert.-Hexyl Alcohol (dimethyl *n*-propyl carbinol). B. P. 123°.

Fraction.	B. P.	N_D^{20}.	Fraction.	B. P.	N_D^{20}.
1	–122.8	1.4079	2	122.8–123.8	1.4087

Fraction 2 was used.

n-Heptyl Alcohol. B. P. 175.8°, N_D^{20} 1.425.

Fraction.	B. P.	N_D^{20}.	Fraction.	B. P.	N_D^{20}.
1	–174.4	1.4207	res.	.....	....
2	174.4–174.9	1.4212	Fraction 2 was used.		

sec.-Heptyl Alcohol (di *n*-propyl carbinol). B. P. 155.4°, N_D^{20} 1.421.

Fraction.	B. P.	N_D^{20}.	Fraction.	B. P.	N_D^{20}.
1	–153.8	1.4130	3	155.3–156.3	1.4150
2	153.8–155.3	1.4145	res.	.....	....

Fraction 3 was used.

n-Octyl Alcohol. B. P. 194°, N_D^{20} 1.430.

Fraction.	B. P.	N_D^{20}.	Fraction.	B. P.	N_D^{20}.
1	–189.9	1.4273	4	192.9–193.1	1.4290
2	189.9–191.9	1.4290	res.	.....	1.4295
3	191.9–192.9	1.4290	Fraction 4 was used.		

n-Nonyl Alcohol. B. P. 215°, N_D^{20} 1.4338.

Fraction.	B. P./28 mm.	N_D^{20}.	Fraction.	B. P./28 mm.	N_D^{20}.
1	–112	1.4320	1	116–117	1.4326
2	112–113	1.4325	res.	.....	1.4329
res.	.....	1.4338	Fraction 1 was used.		

Fraction 2 was redistilled.

1	–113	1.4315	3	115–118	1.4328
2	113–115	1.4324	res.	.....	1.4343

Fraction 3 was redistilled.

EXPERIMENTAL RESULTS.

Mols./100 Grams.

No Effect.	A.	B.	C.	D.	D+.	Killed.
Methanol-Acetone Free.						
(9)	(21)	(22)	(7)	(2)	(1)	(4)
Max. 0.0087	0.0126	0.0176	0.0186	0.0357	0.0225	0.0357
Min. 0.0064	0.0079	0.0092	0.0156	0.0357	....	0.0157
Av.	0.0099	0.0136	0.0173	0.0357	....	....
Methanol-Synthetic.						
(2)		(8)	(5)	(4)		(2)
Max. 0.0161	....	0.0163	0.0186	0.0363	....	0.0363
Min. 0.0129	....	0.0099	0.0129	0.0129	....	0.0186
Av.	....	0.0129	0.0148	0.0208	....	....
Ethyl Alcohol—100%.						
	(3)	(9)	(14)	(4)	(3)	(2)
Max.	0.0076	0.0086	0.0092	0.0094	0.0144	0.0128
Min.	0.0067	0.0067	0.0067	0.0092	0.0128	0.0128
Av.	0.0070	0.0071	0.0084	0.0093	0.0133	....

Ethyl Alcohol—96%.

	(2)	(3)	(10)	(5)	(9)		
Max.	0.0032	0.0047	0.0081	0.0087	0.0089	....	....
Min.	0.0031	0.0042	0.0038	0.0047	0.0064	....	....
Av.	....	0.0045	0.0052	0.0070	0.0077	....	....

n-Propyl Alcohol.

		(5)	(3)	(8)	(4)		(4)
Max.	....	0.00228	0.00335	0.00402	0.00402	....	0.00402
Min.	....	0.00174	0.00268	0.00268	0.00268	....	0.00335
Av.	....	0.00201	0.00295	0.00322	0.00322	...	....

Isopropyl Alcohol.

		(8)	(4)	(7)	(4)		
Max.	....	0.00353	0.00353	0.00484	0.00524	....	....
Min.	....	0.00151	0.00262	0.00288	0.00327	....	....
Av.	....	0.00249	0.00302	0.00393	0.00434	....	....

n-Butyl Alcohol.

		(3)	(3)	(7)	(9)		
Max.	....	0.00085	0.00093	0.00109	0.00131	....	....
Min.	....	0.00077	0.00052	0.00069	0.00085	....	....
Av.	....	0.00082	0.00073	0.00089	0.00102	...	....

Isobutyl Alcohol.

		(3)	(7)	(3)	(4)		
Max.	....	0.00108	0.00119	0.00108	0.00130	....	....
Min.	....	0.00069	0.00057	0.00108	0.00097	....	....
Av.	....	0.00087	0.00099	0.00108	0.00114	....	....

sec.-Butyl Alcohol.

		(5)	(10)	(9)	(6)		
Max.	....	0.00095	0.0012	0.00131	0.00131	....	....
Min.	....	0.00051	0.00069	0.00076	0.00093	....	....
Av.	....	0.00077	0.00096	0.00093	0.00114	....	....

tert.-Butyl Alcohol.

		(11)	(5)	(6)	(6)		
Max.	....	0.00133	0.0016	0.00195	0.00195	....	....
Min.	....	0.00064	0.00091	0.00149	0.00128	....	....
Av.	....	0.00096	0.00126	0.00176	0.00182	....	....

n-Amyl Alcohol.

	(1)	(3)	(5)	(2)	(7)		
Max.	0.00056	0.00065	0.00070	0.00067	0.00074	....	....
Min.	.....	0.00060	0.00065	0.00067	0.00065	....	....
Av.	.....	0.00062	0.00067	0.00067	0.00069	....	....

Isoamyl Alcohol.

	(1)	(2)	(2)	(2)	(7)		
Max.	0.00055	0.00065	0.00060	0.00065	0.00074	....	....
Min.	.....	0.00055	0.00060	0.00060	0.00046	....	....
Av.	.....	0.00060	0.00060	0.00063	0.00067	...	....

sec.-Amyl Alcohol.

		(9)	(3)	(6)	(12)		
Max.	.....	0.00046	0.00051	0.00055	0.00055	....	....
Min.	.....	0.00018	0.00046	0.00046	0.00037	....	....
Av.	.....	0.00034	0.00049	0.00052	0.00045	....	....

tert.-Amyl Alcohol.

		(3)	(2)	(9)	(5)		
Max.	.....	0.00037	0.00046	0.00056	0.00060	....	....
Min.	.....	0.00037	0.00046	0.00037	0.00042	....	....
Av.	.....	0.00037	0.00046	0.00046	0.00051	....	....

n-Hexyl Alcohol.

	(4)	(2)			(3)	(3)	
Max.	0.00068	0.00080	.....	.....	0.00080	0.00080	....
Min.	0.00064	0.00068	.....	.....	0.00068	0.00072	....
Av.	.....	0.00074	.....	.....	0.00076	0.00075	....

sec.-Hexyl Alcohol.

	(1)			(4)	(4)	(1)	
Max.	0.00041	.....	.....	0.00051	0.00051	0.00041	....
Min.	.....	.....	.....	0.00033	0.00041	.....	....
Av.	.....	.....	.....	0.00039	0.00043	.....	....

tert.-Hexyl Alcohol.

	(1)		(1)	(6)	(8)	(2)	(1)
Max.	0.00020	.....	0.00020	0.00027	0.00032	0.00030	0.00020
Min.	.....	.....	.....	0.00020	0.00024	0.00020	.....
Av.	.....	.....	.....	0.00025	0.00028	0.00025	.....

n-Heptyl Alcohol.

	(5)	(3)		(1)	(1)	(2)	(3)
Max.	0.00106	0.00106	.....	0.00106	0.00151	0.00106	0.00141
Min.	0.00042	0.00071	.....	.....	.....	0.00106	0.00106
Av.	.....	0.00085	.....	.....	.....	0.00106	.....

sec.-Heptyl Alcohol.

	(3)	(1)	(1)	(1)	(3)	(2)	
Max.	0.00056	0.00044	0.00032	0.00035	0.00056	0.00046	.....
Min.	0.00035	.....	.....	.....	0.00035	0.00035	.....
Av.	.....	.....	.....	.....	0.00046	0.00040	.....

n-Octyl Alcohol.

	(10)						
Max.	0.0016	.....	.....	.....	.....	.....	.....
Min.	0.0005	.....	.....	.....	.....	.....	.....

n-Nonyl Alcohol.

	(9)						
Max.	0.0014	.....	.....	.....	.....	.....	.....
Min.	0.0005	.....	.....	.....	.....	.....	.....

Average values compared with ethyl alcohol = 1.

DISCUSSION OF RESULTS.

The choice of ethyl alcohol as a standard for comparison is based on the great consistence of the results that it gave and the fact that it contains a carbon to carbon linkage, thus giving it closer relationship to the higher homologs than is possessed by methanol.

The discrepancy existing between 96% and 100% ethyl alcohol is not explained but is in accord with the observations of Atkinson (1).

The differences shown by the two samples of methanol probably have little or no significance.

As has been stated, of all of the conditions the C permits of most accurate observation. However, the B gives values very closely paralleling those of C.

The values obtained seem to be sufficiently definite to place the alcohols in their respective positions with considerable confidence. It was never possible to obtain either the B or C condition with *n*-hexyl alcohol but values calculated from the A and D values indicate clearly that the drop in activity among the normal homologs starts with it.

The data seem to explain why there have been so many differences of opinion expressed as to variation among isomers. The order of increasing strength among the butyl alcohols is reversed by the amyl isomers.

The drop in narcotic power of the normal homologs is very great. In the single case of the heptyl member it appears to be accompanied by marked increase in toxicity. Doses of *n*-octyl and *n*-nonyl equivalent to one and a half times the C dose of *n*-butyl alcohol in no instance had any visible effect.

An interesting observation in connection with tertiary butyl alcohol is its powerful inebriating effect. For several hours after recovering sufficiently from the C and D conditions to be on their feet the pigs will run wildly and unsteadily when disturbed.

The extent to which most of the samples had to be purified to yield successive fractions of constant boiling point and refractive index leaves little question but that workers who did not carefully purify their alcohols (many of them did not) have worked with very impure materials.

ACKNOWLEDGMENT.

Acknowledgment is made to Edgar M. Adams for assistance in the experimental work of the problem.

LITERATURE CITED.

(1) Atkinson, JOUR. A. PH. A., 17 (1928), 28.
(2) Danner and Hildebrand, *J. Am. Chem. Soc.*, 44 (1922), 2826.
(3) Skinner and Noyes, *Ibid.*, 39 (1917), 2718.
(4) Smith and Menzies, *Ibid.*, 32 (1910), 907.

PHARMACEUTICAL ETHICS IN THE MIDDLE AGES.

Pharmaceutical ethics was a reality in the Middle Ages, and he who infringed it was held severely to account. The distinction between physician and pharmacist was sharply drawn and no encroachment on the part of one profession on the prerogatives of the other was permitted. A curious oath dating from the fourteenth century, which all who were licensed as apothecaries were obliged to take, read as follows: "I swear not to malign any of my former masters, physicians, pharmacists or others, whoever they may be; to uphold, as far as in me lies, the honor, glory, ornament and majesty of medicine; not to disclose to idiots and ingrates their secrets and mysteries; to do nothing rashly, without the counsel of physicians or in the hope of gain; to disown and to avoid like the plague the disreputable and entirely pernicious methods of practice now followed by charlatans, empirics and dabblers in alchemy, to the great disgrace of the magistrates who tolerate them. May the Lord prosper me as I observe these conditions."—From *The Pharmaceutical Journal of New Zealand.*
