p. p. m.; hence, we have as the difference of density between water made from the hydrogen of benzene and normal water only 0.5 p. p. m. This difference is so small that it can hardly be considered as significant. If it is accepted, it is possible to calculate that there is about 3% more deuterium in the hydrogen in benzene than in the hydrogen of Lake Michigan water. Such a slight difference might possibly arise in the process of producing benzene from coal or in the later purification procedures. But since the experimental error involved in the many density measurements necessary to arrive at this result may be as large or even larger than 0.5 p. p. m., we are led to the conclusion that the atomic weight of hydrogen in benzene does not differ significantly from that of the hydrogen in Lake Michigan water.

Discussion of Other Data.—A calculation of the concentration of deuterium in the other organic compounds listed in Table I would be more or less uncertain due to the fact that the exact correction to apply for the difference between the atomic weight of oxygen in air and water is unknown in each case. In some work to be reported in *Science*, it will be shown that there is a slight but nevertheless significant difference between the atomic weight of oxygen in water from Lake Michigan and from Nevada. The datum of Snow and Johnston can be corrected with some certainty since the water of Ohio is probably the same as the water of Illinois; if a correction of $-6.0\ \gamma$ is applied to their figure of $6.1\ \gamma$, there is no excess density left. This means that the atomic weight of hydrogen in Oklahoma butane is normal (within the experimental errors involved). Probably an accurate determination of the atomic weight of hydrogen in most of the other compounds listed in Table I would also show it to be normal, or at least much more nearly normal than has previously been thought.

Summary

The abundance of deuterium in benzene has been measured by burning benzene with oxygen and comparing the density of the resulting water with normal water. It is demonstrated that the atomic weight of the oxygen used in the combustion must be determined in order for the data to have any significance. Other possible sources of error such as exchange of the oxygen isotopes between carbon dioxide and water, fractionation of the oxygen isotopes during combustion, fractionation of the isotopes of water during the condensation process, etc., are shown to be negligible. When the important correction is made for the difference between the atomic weight of oxygen in water and in air, the excess density of the benzene water over that of Lake Michigan water is only 0.5 p. p. m. which is not considered to be significant. Data obtained by other workers is discussed and the conclusion is reached that the atomic weight of hydrogen in organic compounds is more nearly normal than has hitherto been suspected.

EVANSTON, ILLINOIS RECEIVED OCTOBER 31, 1935

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Relation of the Structure of Dialkyl Barbituric Acids to the Length of their Action[1]

BY H. A. SHONLE, J. H. WALDO, A. K. KELTCH AND H. W. COLES[2]

Over fifty dialkyl barbituric acids have been studied in an investigation correlating the structure to the length of action, effectiveness, depth of anesthesia, and toxicity, as determined by the intraperitoneal injection of solutions of their sodium salts in white rats.[3] During this investigation a number of new barbituric acids were prepared in order to determine the specific effect of certain desired alkyl groups. A brief pharmacological report already has appeared.[3,4]

These new barbituric acids were prepared as previously described.[5] The primary alcohols were converted into bromides, using phosphorus tribromide, or hydrobromic acid in sulfuric acid solution, while the secondary bromides were prepared by the action of dry hydrogen bromide,[6] or in a few instances by phosphorus tribromide.[7]

These alkyl bromides, after being carefully fractionated in vacuum, were condensed with an absolute alcoholic solution of sodio-ethyl ethylmalonate. The alkyl malonic esters so obtained were purified by fractional distillation under vacuum. The various alkyl ethyl malonic esters

(1) Presented at the St. Petersburg, Florida, meeting of the American Chemical Society, March 25–30, 1934.

(2) Present address: Mellon Institute, Pittsburgh, Pennsylvania.

(3) E. E. Swanson, *Proc. Soc. Exptl. Biol. Med.*, **31**, 961 (1934).

(4) 2,4-Dimethylpentylethyl, 1,4-dimethylpentylethyl, 2-ethylhexylethyl, and 1-propylbutylethyl barbituric acids were used clinically during the latter part of 1933 and the first part of 1934 by G. A. Kempf and L. G. Zerfas.

(5) H. A. Shonle, A. K. Keltch and E. E. Swanson, THIS JOURNAL, **52**, 2440 (1930).

(6) M. L. Sherrill, B. Otto and L. W. Pickett, *ibid.*, **51**, 3023 (1929); M. L. Sherrill, C. Baldwin and D. Haas, *ibid.*, **51**, 3034 (1929).

(7) C. M. Hsueh and C. S. Marvel, *ibid.*, **50**, 855 (1928).

were then refluxed for about eighteen hours with urea in the presence of an alcohol solution of sodium ethylate to form the corresponding alkyl ethyl barbituric acids. After precipitation the

TABLE I

	Alkyl substituent	Bromide B. p., °C.	Mm.	n_D	T, °C.	Alkyl ethyl ethylmalonate B. p., °C.	Mm.	n_D	T, °C.
1	2,4-Dimethylpentyl[a,b,c]	65–66	27	1.4485	25	140–141	10.0	1.4343	25
2	1,4-Dimethylpentyl[b,c,d]	67–72	40	1.4435	22	133–134	7.5	1.4351	25
3	1-Propylbutyl[e]	75–75.5	38	1.4478	25	110–111	3.0	1.4376	25
4	1,3-Dimethylpentyl[b,c,f]	67–71	40	1.4460	20	126–127	4.0	1.4366	25
5	4-Methylheptyl[a,c,g]	73–74	16	1.4578	25	115–116	1.0	1.4398	20
6	2,4-Dimethylhexyl[a,c,g]	76–81	22	1.4648	23	107–109	1.0	1.4412	20
7	2-Ethylhexyl[b,c,h]	93–98	40	1.4542	20	127–130	4.0	1.4393	24
8	4-Methylpentyl[a,g]	55–60	29	1.4494	25	108	2.0	1.4347	28
9	5-Methyl-2-ethylhexyl[c,g,i]	84–92	20	1.4555	20	125–128	1.0	1.4412	20
10	3-Methyl-2-ethylhexyl[c,g,i]	88–92	20	1.4617	20	120–123	2.5	1.4451	20
11	2-Methylpentyl[a,g]	51–53	25	1.4484	26.5	103–105	2.0	1.4392	28
12	1,3-Dimethylbutyl[b,c,j,k]	61–63	71	1.4400	25	97.5–99	3.0	1.4353	25
13	2-Ethylbutyl[h,l]	143–144	760	1.4490	25	167	30.0	1.4360	25

[a] Alcohol obtained through courtesy of du Pont de Nemours & Co. [G. D. Graves, *Ind. Eng. Chem.*, **23**, 1381 (1931)]. Boiling points as follows: (1) 159.65–159.9°; (5) 181–183°; (6) 172–175°; (8) 147.5°; (11) 146.5°. When the barbituric acid was prepared from alcohol number 6, it was obvious that some discrepancy existed between the assigned and the actual structure of this alcohol. [b] The bromide prepared by the aqueous $HBr-H_2SO_4$ method and the PBr_3 method were identical. [c] This bromide had not been described previously. [d] Alcohol prepared from iso-amyl bromide and acetaldehyde by Grignard reaction. [e] The bromides prepared by PBr_3 and dry HBr were identical and free from isomers. [f] Alcohol prepared from 2-methylbutyl bromide and acetaldehyde by Grignard reaction. [g] Bromide prepared by PBr_3. [h] Alcohol obtained through courtesy of Carbide and Carbon Chemicals Corp. Boiling points as follows: (7) 184.6°; (12) 148.9°; (13) 147–147.6°. [i] Alcohol obtained through courtesy of Dr. H. Adkins [R. Connor and H. Adkins, THIS JOURNAL, **54**, 4678 (1932)]. [j] This alcohol was also prepared from isobutyl bromide and acetaldehyde by the Grignard reaction. [k] T. T. Chu and C. S. Marvel [THIS JOURNAL, **53**, 4449 (1931)] describe the bromide of this alcohol. [l] E. Fourneau and J. Matti [*J. pharm. chim.*, [8] **14**, 513 (1931)] describe this bromide as boiling at 141–144° and the 2-ethylbutylethyl ethylmalonate as boiling at 158° at 27 mm. Our bromide was prepared with dry HBr with no evidence of isomer formation.

TABLE II

	Alkyl ethyl barbituric acid	M. p., °C.[b]	% Nitrogen[i] Calcd.	Found		M. A. D. mg./kg.	M. L. D. mg./kg.	Av. duration of symptoms of surviving rats, min.
1	2,4-Dimethylpentyl[a]	124.8–125	11.02	10.94	10.96	70	140	63
2	1,4-Dimethylpentyl[b]	136–136.6	11.02	11.06	11.07	80	240	66
3	1-Propylbutyl[b,c]	129–131.5	11.02	11.01	10.90	30	65	75
4	1,3-Dimethylpentyl	126–127	11.02	11.11	11.18	70	200	102
5	4-Methylheptyl	77–79	10.44	10.49	10.58	80	230	115
6	2,4-Dimethylhexyl[d]	105–115	10.44	10.54	10.60	80	230	132
7	2-Ethylhexyl[e]	116–116.5	10.44	10.28	10.40	80	230	154
8	4-Methylpentyl[f]	108–110	11.67	11.50	11.62	70	180	155
9	5-Methyl-2-ethylhexyl	134.8–135.6	9.93	9.96	10.13	140	340	158
10	2-Methylpentyl	151–154	11.67	11.77	11.55	70	180	225
11	3-Methyl-2-ethylhexyl	150–152	9.93	10.00	10.04	160	400	255
12	1,3-Dimethylbutyl	173.5–174.5	11.67	11.69	11.50	Convulsions	10	...
13	2-Ethylbutyl[g]	134–134.5	11.67	11.55	11.81	80	170	284
	Iso-amyl (control)	154–155	...	.....		85	200	225

[a] May also be prepared from 2,4-dimethylpentylethyl ethyl cyanoacetate, b. p. 128° at 3–4 mm., $n^{25}D$ 1.4352. [b] U. S. Patent 1,996,629. [c] May also be prepared by condensing 1-propylbutylethyl cyanoacetate (b. p. 123–125°, at 3 mm., $n^{25}D$ 1.4347) with ethyl bromide, which gives 1-propyl-butylethyl ethylcyanoacetate, b. p. 131° at 2–3 mm., $n^{25}D$ 1.4387. [d] Another fraction was obtained which melted at 97–100°. It was impossible to obtain a sharp melting point. [e] May also be prepared from 2-ethylhexyl ethyl ethylcyanoacetate, b. p., 152–153° at 4 mm., $n^{20}D$ 1.4391. [f] When methylpentanol-1 was prepared from iso-butyl bromide and ethylene oxide or from iso-amyl bromide and formaldehyde by the Grignard reaction, the 4-methylpentyl ethyl barbituric acid obtained melted at 176–178°. The actual structure of the two compounds is being further investigated. [g] E. Forneau and J. Matti [*J. pharm. chim.*, [8] **14** 513 (1931)] give a melting point of 125° for this barbituric acid, and D. Bovet, *ibid.*, p. 523, reports the M. E. D. as 0.0275 mg. per g. and the M. L. D. as 0.100 mg. per g. when injected into rats. [h] Anschütz thermometer readings. [i] Micro Dumas run by W. J. Doran.

barbituric acids were purified by recrystallization from dilute alcohol.

The pure alkyl ethyl barbituric acids were converted into their sodium salts by the addition of a 50% solution of sodium hydroxide to an alcoholic solution of the barbituric acid, after which the alcohol was removed by vacuum distillation.

Table I gives some of the physical constants of the various alkyl bromides and alkyl ethyl malonic esters used. Table II gives the melting points and the percentage of nitrogen of the corresponding barbituric acids and also the minimum anesthetic and minimum lethal doses in mg. per kg. when these barbituric acids were injected into white rats in the form of solutions of their sodium salts. The average duration of symptoms is given in minutes.

From the pharmacological data, it is to be noted that the actual amount of the alkyl ethyl barbituric acid required to produce anesthesia had no direct bearing on the length of action, nor does the molecular weight of the alkyl group determine the length of action. In some instances the presence of a secondary alkyl group confers a briefer action than does the primary straight or branched chain isomer. Pharmacological differences of the isomeric barbituric acids in many instances are greater than is noted when homologous barbituric acids are compared. 1-3-Dimethylbutylethyl barbituric acid produced convulsions and had no hypnotic or anesthetic effect even in the sub-lethal doses. We know of no explanation for this phenomena. All of the other isomeric hexyl derivatives which have been studied have shown a normal anesthetic action.

We wish to thank Mr. E. E. Swanson and Mr. W. E. Fry for the pharmacological assays and Mr. Wilbur J. Doran for the determination of nitrogen in the barbituric acids.

Summary

1. The preparation of a number of new alkyl bromides and new dialkyl malonic esters has been described.

2. The preparation of a number of new alkyl ethyl barbituric acids has been described and their pharmacologic action summarized.

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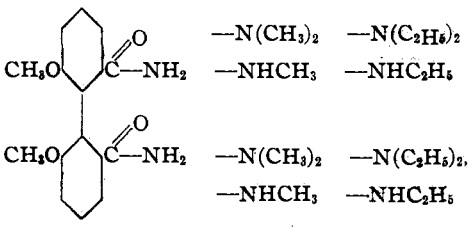
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Relative Rates of Racemization of Substituted Diamides of 2,2′-Dimethoxy-6,6′-dicarboxydiphenyl. XLII[1]

BY CHI YI HSING[2] AND ROGER ADAMS

A study of the effect upon rates of racemization of diphenyl molecules of groups attached to the atoms in the 2,2′,6,6′ positions of the ring has been continued.[3] A series of alkyl-substituted amides of 2,2′-dimethoxy-6,6′-dicarboxydiphenyl has been prepared.



These substances may be racemized by boiling in glacial acetic acid solution and comparison of rates determined under these conditions. The results are given in Table I.

Although the experimental error in the determination of the rates of racemization in boiling glacial acetic acid is large and much greater than that which occurs when compounds may be racemized at relatively low temperatures, it is far less than would be necessary to cause any change in order of half-life periods of the substances studied, with the possible exception of the di-amide and di-dimethylamide.

It is to be especially noted that the monosubstituted amides are far more stable than the unsubstituted or the disubstituted. This is not what had been anticipated from results of study of other types of diphenyls. However, most of the compounds used in previous investigations had substituents on the atom directly attached to the ring

(1) The preceding paper in this series is, Hanford and Adams, THIS JOURNAL, **57**, 1592 (1935).

(2) Part of a thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

(3) Stanley, McMahon and Adams, THIS JOURNAL, **55**, 706 (1933); Kleiderer and Adams, *ibid.*, **55**, 4219 (1933); Yuan and Adams, *Chem. Rev.*, **12**, 261 (1933); Li and Adams, THIS JOURNAL, **57**, 1565 (1935).