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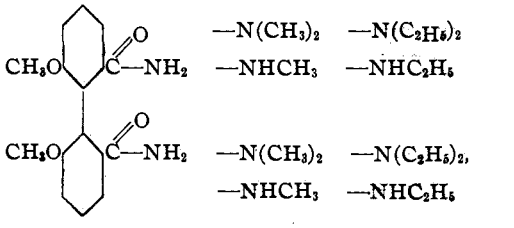
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

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).

TABLE I

SUMMARY OF RACEMIZATION EXPERIMENTS ON THE SUBSTITUTED AMIDES OF 2,2'-DIMETHOXY-6,6'-DICARBOXYDIPHENYL IN GLACIAL ACETIC ACID AT BOILING POINT OF SOLUTION

Substance	Wt. in g. made up to 20 cc.	$[\alpha]_D^{20}$ Initial reading	$[\alpha]_D^{20}$ Final reading	Time Hrs.	Time Mins.	Average K	Half-life period Hrs.	Half-life period Mins.
l-Di-amide[a]	0.0637	−64.25°	−12.9°	10	..	1.13×10^{-3}	4	26
l-Di-dimethylamide	.0519	−86.7	−23.2	7	30	1.33×10^{-3}	3	43
l-Di-diethylamide	.0607	−32.9	−14.8	22	50	2.57×10^{-4}	19	28
l-Di-monomethylamide	.0537	−50.3	−31.6	30	..	1.11×10^{-4}	45	..
l-Di-monoethylamide	.0706	−59.4	−42.5	74	30	3.22×10^{-5}	156	..

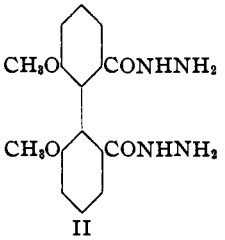
[a] The *l*-di-amide was prepared as previously described by McMahon and Adams and the rotation redetermined.

and not on the second atom from the ring as in these alkyl amides. No information is available to make possible an understanding of the structural character of an acid amide or especially an alkyl-substituted acid amide group and, therefore, merely the observed facts are being submitted.

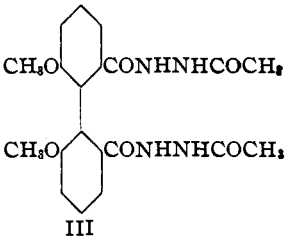
Wyckoff,[4] from crystal structure determinations of various alkyl- and dialkylamine salts, has deduced that the angle between the two methyl bonds in a dimethylamine group is tetrahedral, whereas the methyl or ethyl group in a monomethyl- or monoethylamine group is attached linearly with respect to the linkage of the nitrogen to the carbonyl group. The sphere of influence of a $-CONHCH_3$ group may, therefore, extend so far as distance from the ring is concerned, beyond that of a $-CON(CH_3)_2$ group. This linear distance may be a factor in the interference of the 6,6' groups.

One possible assumption for the different rates of racemization of various 2,2',6,6'-substituted diphenyls has been a change from one molecule to another of the distance between the two benzene rings due to the varying polarity of the substituent groups. In these acid amides it is difficult to see how polarity can play a significant role since $-CONHCH_3$, $-CONHC_2H_5$, $-CON(CH_3)_2$ and $-CON(C_2H_5)_2$ are very similar in this respect. In these compounds the effect appears more likely to rest primarily in the volume relationship of the groups.

The di-hydrazide of 2,2'-dimethoxy-6,6'-dicarboxydiphenyl (II) was also prepared.



II



III

(4) Wyckoff, *Z. Krist.*, **68**, 236 (1928); **89**, 475 (1934); *Am. J. Sci.*, **16**, 356 (1928).

The active compound, upon boiling in glacial acetic acid, increases in rotation during the first half-hour and then gradually decreases until inactive. This initial increase was due to acetylation, since the final product isolated after the experiment was completed was the *dl*-di-acetohydrazide derivative (III). The half-life period calculated on the basis of the maximum rotation as the initial reading gave a value of ten hours, which represents in a qualitative way the rate of racemization of the di-acetohydrazide. This it may be observed, is a lower value than that obtained for any of the alkylated amides with the exception of the di-dimethylamide.

Experimental

***l*-2,2'-Dimethoxy-6,6'-dicarboxydiphenyl.**—2,2'-Dimethoxy-6,6'-dicarboxydiphenyl, m. p. 295–297° (McMahon and Adams, 293–294°; Kenner and Turner, 288–290°) was prepared as described by McMahon and Adams.[5] It was resolved by means of quinine, the observed m. p. of the less soluble salt being 175–177° (corr.) and rotation $[\alpha]^{20}D$ +119° (McMahon and Adams, m. p. 178–179°, $[\alpha]^{20}D$ +111°; Kenner and Turner, $[\alpha]^{20}D$ +126°).[6]

A mixture of 3 g. of the less soluble salt and 40 cc. of 5% sodium hydroxide was ground in a mortar for thirty minutes. The mixture was extracted with four 15-cc. portions of cold chloroform. The alkaline solution was completely freed from chloroform by blowing air through it and acidified with 6 *N* hydrochloric acid. The *l*-acid precipitated as a white spongy mass which was filtered, washed with water and dried; m. p. 291–293°; $[\alpha]^{20}D$ −114°.

Di-dimethylamide of *l*- and *dl*-2,2'-Dimethoxy-6,6'-dicarboxydiphenyl.—A mixture of 0.2 g. of racemic acid and 2 cc. of thionyl chloride was refluxed for a half hour. The excess thionyl chloride was removed *in vacuo*, the acid chloride dissolved in 6 cc. of dry benzene and dimethylamine slowly bubbled in for five minutes. The precipitated dimethylamine hydrochloride was filtered and the amide obtained from the benzene solution by evaporation. It was purified from a mixture of petroleum ether and ethyl acetate forming white needles, m. p. 175–176° (corr.).

Anal. Calcd. for $C_{20}H_{24}O_4N_2$: N, 7.87. Found: N, 8.00.

(5) McMahon and Adams, THIS JOURNAL, **55**, 709 (1933).

(6) Kenner and Turner, *J. Chem. Soc.*, 2340 (1928).

The corresponding *l*-acid amide was obtained in a similar manner except that the reaction between the *l*-2,2′-dimethoxy-6,6′-dicarboxydiphenyl and thionyl chloride was carried out for one hour at room temperature, the thionyl chloride removed *in vacuo* and the product converted to the amide as described previously. From ethyl acetate and petroleum ether, it formed white needles, m. p. 133° (corr.).

Rotation. 0.0337 g. made up to 10 cc. in absolute methyl alcohol at 20° gave α_D −0.63; l = 2; $[\alpha]^{20}D$ −93.5°. The product after racemization had a m. p. 174–175°.

Anal. Calcd. for $C_{20}H_{24}O_4N_2$: C, 67.33; H, 6.73; N, 7.87. Found: C, 67.38; H, 6.68; N, 7.86.

Di-diethylamide of *l*-2,2′-Dimethoxy-6,6′-dicarboxydiphenyl.—The preparation was similar to that of the dimethylamide of the *l*-acid, using 2 cc. of diethylamine. The product was purified from petroleum ether forming white needles, m. p. 125–126° (corr.).

Rotation. 0.0341 g. made up to 10 cc. in absolute methyl alcohol at 20° gave α_D −0.59°, l = 2; $[\alpha]^{20}D$ −86.5°.

Anal. Calcd. for $C_{24}H_{32}O_4N_2$: N, 6.80. Found: N, 6.82.

Di-monomethylamide of *l*-2,2′-Dimethoxy-6,6′-dicarboxydiphenyl.—The procedure at the beginning was similar to that for the di-dimethylamide. The amide, however, separates in the benzene solution. As a consequence, the benzene mixture, after the addition of the dimethylamine, was shaken with water to dissolve dimethylamine hydrochloride and the amide filtered off. It was purified from dilute methyl alcohol, forming colorless needles, m. p. 268–270° (corr.).

Rotation. 0.0287 g. made up to 10 cc. of absolute methyl alcohol at 20° gave α_D −0.51, l = 2; $[\alpha]^{20}D$ −88.9°.

Anal. Calcd. for $C_{18}H_{20}O_4N_2$: N, 8.54. Found: N, 8.60.

Di-monoethylamide of *l*-2,2′-Dimethoxy-6,6′-dicarboxydiphenyl.—Prepared like the di-monomethylamide using 2 cc. of ethylamine, the product was purified from alcohol and benzene. It formed colorless needles, m. p. 233° (corr.).

Rotation. 0.0372 g. made up to 10 cc. of absolute methyl alcohol at 20° gave α_D −63°; l = 2; $[\alpha]^{20}D$ −84.7°.

Anal. Calcd. for $C_{20}H_{24}O_4N_2$: N, 7.87. Found: N, 8.02.

Dihydrazide of *l*-2,2′-Dimethoxy-6,6′-dicarboxydiphenyl.—The acid chloride was treated with 10 cc. of absolute methyl alcohol and warmed slightly. After standing one hour, the methyl alcohol was evaporated and the crystalline ester was obtained. The ester was then refluxed with 15 cc. of 50% aqueous hydrazine solution for forty-five minutes. At the end of that time the oil had disappeared. Upon concentration to a small volume and on cooling, the product precipitated. The crude hydrazide was purified by recrystallization from 15 per cent. aqueous hydrazine solution. It formed white needles, m. p. 263–265° (corr.).

Rotation. 0.0296 g. made up to 10 cc. in absolute methyl alcohol gave α_D −0.30°, l = 2; $[\alpha]^{20}D$ −50.67°. 0.0610 g. made up to 20 cc. in glacial acetic acid gave α_D −0.51°, l = 2; $[\alpha]^{20}D$ −83.5°.

Anal. Calcd. for $C_{16}H_{15}O_4N_4$: N, 16.98. Found: N, 17.12.

The corresponding racemic hydrazine was prepared in a similar manner from the *dl*-acid chloride, methyl alcohol and hydrazine. The product was much more soluble in organic solvents than the active hydrazide. It was purified from a mixture of benzene and alcohol, fine white needles, m. p. 254–255° (corr.).

Anal. Calcd. for $C_{16}H_{18}O_4N_4$: N, 16.98. Found: N, 16.93.

***dl*-Di-acetohydrazide of *l*-2,2′-Dimethoxy-6,6′-dicarboxydiphenyl.**—The diaceto derivative was formed by boiling 0.075 g. of racemic hydrazide with 20 cc. of glacial acetic acid for one hour. Upon cooling, the product separated and was purified from glacial acetic acid; fine crystalline powder, m. p. 284–286° (corr.).

Anal. Calcd. for $C_{20}H_{22}O_6N_4$: N, 13.5. Found: N, 13.27.

The active hydrazide required fifteen hours of boiling for completion of the formation of the diaceto derivative: white crystalline powder, m. p. 284–286° (corr.).

Anal. Calcd. for $C_{20}H_{22}O_6N_4$: N, 13.5. Found: N, 13.4.

Racemization Experiments

The active compounds were all racemized in boiling glacial acetic acid and sufficient readings taken to determine half-life periods. The results are given in Table I.

The data on the active dihydrazide of *l*-2,2′-dimethoxy-6,6′-dicarboxydiphenyl are as follows: first reading, −83.5°; after thirty minutes, −171°; after two hours, −150°; after four hours and forty minutes, −129.5°; after ten hours and fifteen minutes, −90°; in three days, 0°.

Upon isolation after the experiment was completed, the product proved to have a melting point of 284–286° and to be identical with the racemic diaceto compound formed from *dl*-dihydrazide.

Summary

1. The rate of racemization of a series of alkyl amides of 2,2′-dimethoxy-6,6′-dicarboxydiphenyl in glacial acetic acid was determined. The order of rates was as follows: $-\overset{O}{\overset{\|}{C}}-NH_2$ and $-\overset{O}{\overset{\|}{C}}-N(CH_3)_2 > -\overset{O}{\overset{\|}{C}}-N(C_2H_5)_2 > -\overset{O}{\overset{\|}{C}}-NHCH_3 > -\overset{O}{\overset{\|}{C}}-NHC_2H_5$.

2. The active di-hydrazide derivative under similar conditions became acetylated and showed simultaneously an increase in rotation. The di-acetohydrazide then racemized showing a rate less than that of the $-\overset{O}{\overset{\|}{C}}-N(CH_3)_2$ and greater than that of the $-\overset{O}{\overset{\|}{C}}-N(C_2H_5)_2$.

URBANA, ILLINOIS RECEIVED JANUARY 27, 1936