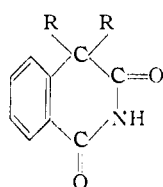


[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE WM. S. MERRELL COMPANY]

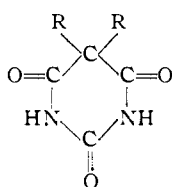
Homophthalimides as Hypnotic Agents¹BY B. R. HARRIMAN,² R. S. SHELTON, M. G. VAN CAMPEN AND M. R. WARREN

Homophthalimides were first described as hypnotics by Lumiere and Perrin³ in 1920 and 1924. These workers prepared the 4,4-diethyl, diallyl, ethyl propyl and dipropyl derivatives and reported that all but the last had hypnotic action.

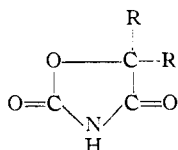
Since the —CO—NH—CO—CR₂— configuration in homophthalimide also appears in several classes of compounds possessing marked hypnotic activity, a study of substituted homophthalimides seemed an interesting.



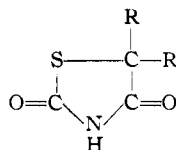
Homophthalimides



Barbiturates



2,4-Dioxo-oxazolidines



2,4-Dioxothiazolidines

The homophthalimides studied were prepared from homophthalic acid. The latter was prepared in about 65% yield by reduction of phthalonic acid⁴ with red phosphorus and iodine in phosphoric acid at 150–160°. Reduction with hydrogen in the presence of platinum, with zinc and hydrochloric acid, with zinc and acetic acid, and the Clemmensen reduction with zinc amalgam were tried and found to yield only phthalide carboxylic acid.

Homophthalic acid was converted to the imide by heating with an excess of 28% ammonium hydroxide. N-Ethyl homophthalimide was similarly prepared from 33% aqueous ethylamine. Homophthalimide dissolved in an aqueous solution of sodium carbonate or bicarbonate, but was not hydrolyzed even when heated in this solution.

A series of 4-substituted homophthalimides was prepared by refluxing an aqueous alcohol solution containing 2 moles of the appropriate alkyl halide and 2 moles of sodium bicarbonate or of sodium hydroxide per mole of homophthalimide. No reaction took place in anhydrous alcohol in the presence of sodium ethylate. Iodides were found to be the most satisfactory halides for this re-

action, except for the allyl and benzyl derivatives, for which the chlorides worked best. With ethyl, *n*-propyl, allyl, *n*-butyl, isobutyl, *n*-amyl and benzyl halides a 4,4-dialkyl derivative always resulted. With isopropyl iodide, on the other hand, only one isopropyl group could be introduced, although 4-benzyl-4-isopropyl homophthalimide was easily obtained by treatment of the isopropyl derivative with benzyl chloride. N-Ethyl homophthalimide was similarly ethylated to give N-ethyl-4,4-diethyl homophthalimide. The products were usually crystallized from ether, ligroin, or a mixture of these solvents. Yields, melting points and analyses of the compounds prepared are given in Table I.

It is interesting to note that under these conditions the imide nitrogen does not appear to undergo substitution. Homophthalimide refluxed with a three-fold excess of ethyl iodide gave only the 4,4-diethyl derivative.

TABLE I

Homophthalimide	% Yield	M. p., °C.	Analyses, %			
			Carbon		Hydrogen	
			Obs.	Calcd.	Obs.	Calcd.
N-Substituted imides						
N-Ethyl	88	104				
N-Ethyl-4,4-diethyl	55	49	73.07	73.47	7.65	7.75
4,4-Dialkyl imides						
Diethyl	57	144	71.79	71.89	7.15	6.91
Di- <i>n</i> -propyl	46	138	73.80	73.47	8.43	7.75
Diallyl	38	141	75.01	74.69	6.15	6.23
Di- <i>n</i> -butyl	52	76	74.50	74.73	8.46	8.43
Diisobutyl	3	100	74.62	74.73	8.59	8.43
Di- <i>n</i> -amyl	18	65–72	75.50	75.75	9.23	8.96
Dibenzyl	71	174	81.18	80.94	5.75	5.57
Benzyl isopropyl	47	140	77.71	77.81	6.84	6.48
4-Monoalkylimides						
Isopropyl	57	122	70.82	70.93	6.23	6.41

^a Analyses by Dr. Carl Tiedcke.

As might be expected, the N-alkyl imide was quite insoluble in neutral solvents and in alkali. Unfortunately, this is also true of the 4,4-dialkyl imides as well. For example, the 4,4-diethyl compound is quite insoluble in water, but soluble to some extent in ether, alcohol, or acetic acid. Its sodium or potassium salt is less than 1% soluble but in the presence of an appreciable excess of alkali gives a 5% solution having a pH of around 11.5.

These compounds were tested for hypnotic action by administering a suspension of the finely divided material by stomach tube to white rats. In no case was any hypnosis evident, even with the compounds reported by Lumiere and Perrin. As the size of the dose was increased from 1/4 to 1 g. per kg., toxic reactions became manifest with convulsions at the higher dosage levels. It has been concluded that compounds of this type do not have promise as hypnotic agents.

(1) Presented at the Cleveland Meeting, April, 1944.

(2) Present address: Ansco, Binghamton, New York.

(3) Lumiere and Perrin, *Compt. rend.*, **171**, 637 (1920), and *Bull. soc. chim.*, [4] **35**, 1022 (1924).

(4) Supplied by the Edwal Laboratories of Chicago.

(5) Graebe and Truempy, *Ber.*, **31**, 375 (1898).

Experimental

Homophthalic Acid.—Several 1500-g. batches of phthalonic acid were reduced to homophthalic acid by the method of Graebe and Truempy.⁵ The purified product melted at 181° and the average yield obtained was 65%.

Homophthalimide.—One kilogram (5.55 moles) of homophthalic acid and 1100 ml. (ca. 16.5 moles) of 28% ammonium hydroxide were placed in a flask. The water and ammonia were distilled until the salt solidified, then the heating was continued, using a soft flame, until all the salt had decomposed to the imide, which was obtained as a dark orange viscous liquid. The imide was recrystallized from acetic acid. The product melted at 230–233°, and was obtained in 83% yield.

N-Ethyl Homophthalimide.—One hundred and eighty grams (1.0 mole) of homophthalic acid and 405 g. (3.0 moles) of 33% aqueous monoethylamine were treated as in the preparation of homophthalimide.

4,4-Diethyl Homophthalimide.—A solution of 38.4 g. (0.96 mole) of sodium hydroxide in 100 ml. of water was added to a suspension of 77.5 g. (0.48 mole) of homophthalimide in 700 ml. of alcohol. After solution was complete, 150 g. (0.96 mole) of ethyl iodide was added and the mixture was refluxed for one-half hour and allowed to stand overnight. The solution was evaporated to incipient cloudiness. On cooling crystals were obtained; m. p. 130–138°. When the filtrate was evaporated, the liquid separated into two layers, the lower of which was an aqueous solution of sodium iodide. The upper layer was evaporated to dryness and the residue combined with the first crop of crystals. This mixture was recrystallized from alcohol, then treated with charcoal in ether. The product was precipitated by the addition of petroleum ether.

N-Ethyl-4,4-diethyl Homophthalimide.—Fifty grams (0.264 mole) of N-ethyl homophthalimide suspended in 300 ml. of alcohol was mixed with a solution of 21.6 g.

(0.54 mole) of sodium hydroxide in 50 ml. of water. To this was added 82.8 g. (0.53 mole) of ethyl iodide and the mixture was refluxed eight hours. Then the alcohol was distilled and the residue diluted with water. The precipitated oil slowly crystallized. The product was collected by filtration, treated with charcoal in ether, and reprecipitated as white crystals by the addition of petroleum ether.

4,4-Dibenzyl Homophthalimide.—Fifty grams (0.31 mole) of homophthalimide suspended in 500 ml. of alcohol, 52.3 g. (0.62 mole) of sodium bicarbonate dissolved in 500 ml. of water, and 78.7 g. (0.62 mole) of benzyl chloride were refluxed together for sixteen hours, at the end of which time a considerable quantity of crystals had separated. These were collected by filtration, dissolved in hot methanol and reprecipitated by the addition of water. The precipitate was collected by filtration and treated with charcoal in ether. The other compounds listed in Table I were obtained by one or another of the methods just described.

Summary

A series of 4,4-dialkyl derivatives of homophthalimide has been prepared and tested orally for hypnotic activity. No activity was found in any of the compounds in this group, which included the diethyl, di-*n*-propyl, diallyl, di-*n*-butyl, di-*i*-butyl, di-*n*-amyl, dibenzyl, and *i*-propyl benzyl derivatives. The N-ethyl, N-ethyl-4,4-diethyl and 4-*i*-propyl derivatives of homophthalimide also have no apparent hypnotic activity.

CINCINNATI, OHIO

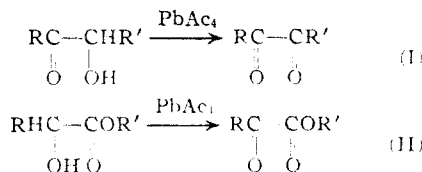
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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BANTING INSTITUTE, UNIVERSITY OF TORONTO]

A New Method of Preparing Phenylglyoxylic Acid and its Methyl Ester

BY ERICH BAER AND MORRIS KATES¹

α -Keto alcohols are readily oxidized to the corresponding α -diketones by means of lead tetracetate (L.T.A.):² The oxidation of the tetracetate alcohol is obviously facilitated by the presence of the carbonyl group in α -position. The similar, although not quite identical arrangement of groups existing in esters of α -hydroxy acids suggested the extension of reaction I to this class of compounds.



A preliminary investigation to test the feasibility of reaction II was carried out using as substrates the methyl esters of α -hydroxypalmitic acid, lactic acid and mandelic acid. The oxida-

tion of the α -hydroxypalmitic acid ester in glacial acetic acid, benzene and cyclohexane did not proceed as anticipated. Attempts to isolate α -keto palmitic acid ester from the oxidation product were unsuccessful. Somewhat more encouraging were the results of the oxidation of lactic acid methyl ester with L.T.A. in boiling benzene, cyclohexane or dioxane. In these solvents the pyruvic acid methyl ester was formed to the extent of 28, 11 and 9%, respectively. Only traces of the keto ester were produced in boiling acetic acid or ethyl acetate. The oxidation of mandelic acid methyl ester in boiling benzene, however, proceeded fully as expected and forms the basis of a new method for the practical preparation of phenylglyoxylic acid and its ester.

The synthesis is carried out according to the following sequence of reactions: mandelic acid \rightarrow mandelic acid methyl ester \rightarrow phenylglyoxylic acid methyl ester \rightarrow phenylglyoxylic acid. Calculated on the basis of mandelic acid the over-all yield of phenylglyoxylic acid methyl ester is 74% and that of phenylglyoxylic acid 67%.

The results of the present investigation show that an α -hydroxy acid in the form of its ester

(1) This paper forms part of a thesis submitted to the Department of Chemistry of the University of Toronto by M. Kates in partial fulfillment of the requirements for the degree of Bachelor of Arts, May, 1945.

(2) E. Baer, THIS JOURNAL, 62, 1597 (1940).