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THE IDENTIFICATION OF SOME HYPNOTICS OF THE BARBITURIC ACID SERIES.

BY GEORGE W. HARGREAVES AND H. W. NIXON.

Barbituric acid derivatives due to their wide-spread use as hynotics have become of increased importance in analytical work of a toxicological or pharmaceutical nature.

Numerous qualitative tests have been proposed for barbital and other individual members of this group but no reaction has been applied to a whole series of these compounds. In most cases, only a few derivatives have been investigated. It is necessary to know in using a qualitative test whether it is specific for the substance being tested or whether it may be simulated by some related compound. For this investigation, samples of most of the widely used barbituric acid derivatives were obtained.

After a comprehensive survey of the literature, a number of reactions were selected which might provide a scheme for the detection and positive identification of any member of the group studied. It will be seen from the table of results that this purpose has been accomplished.

EXPERIMENTAL.

Solubility Tests.—The free acids are only sparingly soluble in water but readily dissolve in 5% sodium carbonate or hydroxide. The ethyl isopropyl derivative is used in the form of the calcium salt (Ipral) and is readily soluble in water. Others commonly employed in the form of their sodium salts are the diethyl; phenyl ethyl; ethyl, *l*-methyl butyl (Nembutal) and ethyl isoamyl (Sodium Amytal) barbituric

acids. Acidification of the aqueous solutions of these salts yields a precipitate of the free acid unless the solutions are very highly diluted.

Melting Points.—A variation in melting points was found in the literature for several of these compounds. Recently, Fischer and Kofler (1) have shown that barbital can exist in three modifications. Allyl, isopropyl barbituric acid (2) can exist in two forms.

Para-Nitrobenzyl Derivatives.—Lyons and Dox (3) have used *p*-nitrobenzyl chloride for the identification of barbituric acid derivatives. In addition to those prepared by them, the *p*-nitrobenzyl derivatives of ethyl, *l*-methyl butyl; ethyl, cyclohexenyl; and allyl, isopropyl barbituric acid were prepared.

0.5 Gm. of substance and 0.25 Gm. of sodium carbonate are dissolved in 5 cc. of water, 0.85 Gm. of *p*-nitrobenzyl chloride in 10 cc. of alcohol is added and the mixture refluxed about an hour. If the derivative precipitates during the reaction it is filtered hot. If no precipitate forms, the sample is cooled. If still no precipitate forms, hot water is added until a cloudiness results. Recrystallize from alcohol.

Permanganate Test.—0.05 Gm. of substance is dissolved in 5 cc. of 5% Na_2CO_3 and 5 drops of 0.1*N* permanganate is added. This reaction serves to distinguish "Dial," "Phanadorn" and allyl, isopropyl barbituric acid, and can also be used for the quantitative determination of these substances.

Precipitation Tests.—For these reactions, saturated solutions of the free acids were used. 5-cc. portions of these solutions were tested with 1 cc. of the reagent, then followed by an excess. The precipitants employed were:

Mercuric Nitrate T.S. Mercuric Sulphate T.S. Saturated Aqueous Solution of Mercuric Chloride. Results are given in the table.

COLOR REACTIONS.

Concentrated Sulphuric Acid.—0.1-Gm. samples were treated with a few drops of conc. H_2SO_4. No coloration was observed except in the case of Phanadorn which gave a distinct reaction. This reaction is very sensitive with Phanadorn, a good test being obtained with as small a quantity as one mg.

Formalin Sulphuric Acid (4).—0.01-Gm. samples were treated with 1 cc. of 10% formaldehyde and 4 cc. of conc. H_2SO_4 and observed after standing two minutes at room temperature and were then heated a minute on the water-bath. Results are given in the table.

Nitrite Sulphuric Acid (5).—0.1-Gm. samples were treated with 1 cc. of conc. H_2SO_4 and 2 drops of a 2% sodium nitrite solution and observed first cold and then after heating on the water-bath.

TABLE OF RESULTS.

	B. Acid.	M. p. ° C. Uncorr.	M. p. of Nitrobenzyl Derivative.	Permanganate Test.
1	Diethyl (Barbital)	190–191	192	Negative
2	Ethyl isopropyl (Ipral)	200–203	160	.....
3	Ethyl, *n*-butyl (Neonal)	126–128	146	.....
4	Ethyl, *l*-methyl butyl (Nembutal)	129–130	142	.....
5	Ethyl isoamyl (Amytal)	154–156	138	.....
6	Ethyl phenyl (Luminal)	172–174	182	.....
7	Ethyl cyclohexenyl (Phanodorn)	171–174	195	Positive
8	Allyl isopropyl	138.5–140.5	191	.....
9	Diallyl (Dial)	170–171	190	.....

	$HgSO_4$.	$Hg(NO_3)_2$.	$HgCl_2$.	Conc. H_2SO_4.
1	Precipitate soluble in excess	Precipitate soluble in excess	Negative	No color
2	.....	.....	Slight	.....
3	.....	.....	Positive	.....
4	.....	.....	.....	.....
5	.....	.....	Negative	.....
6	.....	.....	Positive	.....
7	.....	.....	.....	Orange red
8	.....	.....	Negative	No color
9	.....	.....	.....	.....

	Formalin Sulphuric.	Nitrite Sulphuric. Cold.	Hot.		Formalin Sulphuric.	Nitrite Sulphuric. Cold.	Hot.
1	Slight yellow	No color	No color	6	Dark red	Yellow	Yellow
2	.....	...	...	7	Red brown when heated, green fluorescence	Same as with H_2SO_4	Same as with H_2SO_4
3	.....	...	...	8	Negative	Negative	Negative
4	.....	...	...	9	Light yellow, greenish on heating, slight fluorescence	Slight yellow	Red
5	Greenish yellow on heating	...	...				

MICROCHEMICAL REACTIONS.

For one interested in supplementing these tests with microchemical reactions the following references are suggested:

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DISINFECTANTS IN MINERAL WATER BOTTLES.

The Medical Superintendent Officer of Health of Belfast has received a deputation from mineral water merchants in the city, who drew attention to the practice of utilizing mineral water bottles to hold disinfectants. In support of this contention they had produced mineral water bottles bearing the label, "Carbolic Acid," and the name of the vendor firm.