A CHLORAL DERIVATIVE OF LEVULINIC ACID.

BY HAROLD W. COLES.*

INTRODUCTION.

While searching for a substitute for chloral as a hypnotic, Hanriot and Richet (1) at first studied the chloralides and, in particular, the lactic chloralide. Contrary to their anticipations, however, the lactic chloralide did not have any hypnotic powers and caused serious organic troubles in the animals. The chloraloses were then investigated, and alpha-chloralose gave excellent results (2).

The sleep produced by the chloralose does not resemble that produced by chloral, for the reflexes are neither abolished nor diminished, and indeed are increased. It is a substance much more active than chloral, and six hundred mg. per Kg. body weight does not cause death in the dog. Yet, while chloralose is a considerable step ahead itself in being more active and less toxic, and while it compares favorably (3) with other hypnotics, it is still lacking in several respects.

The alpha-chloralose, although much more soluble than the beta-isomer, is still only slightly soluble in water and has a disagreeable bitter taste. It is often unreliable in its effects. Frequently no hypnosis occurs under fatal doses, and some observers have reported transitory by-effects as trembling, spasms, epileptoid or cataleptoid attacks, dizziness, hallucinations and delirium.

Probably some of the uncertainty of the chloralose action is due to the fact that it still retains unchanged its aldehyde group.[1] It occurred to the author that chloral joined to a substance with an acid group might combine both stability and solubility since a sodium salt could be made. Levulinic acid suggested itself as the proper compound to join to the chloral since it offered a promise of being available commercially and inexpensively (4). Furthermore, the chloral-levulinic acid permits the pharmacological study of a different type of chloral linkage, being joined to the levulinic acid, carbon to carbon, through a double bond, while in the chloralides (chloraloses) the chloral is attached through oxygen (5).

The chloral-levulinic acid was prepared and also a number of its derivatives for identification purposes. The chloral-levulinic acid, although the chloral portion made up fifty-three per cent of the entire molecule, had no hypnotic activity. This surprising result will be discussed later in this paper.

The chloral derivative of levulinic acid should not be confused with the levulochloraloses already described (6) as those compounds are chloral derivatives of levulose, the sugar.

EXPERIMENTAL.

Condensation of Chloral with Levulinic Acid.[2]—A number of different condensing agents were tried before a suitable one was found. Gaseous hydrochloric acid (7) resulted in a very small yield and the product was difficult to obtain in a pure condition. The use of anhydrous calcium sulfate (Drierite) (8) in a sealed tube with a few drops of sulfuric acid gave a nicely crystalline compound which, on analysis, revealed a much too high percentage of chlorine.

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[1] It reduces Fehling's solution on boiling and forms a hydrazine, although in Meyer-Jacobson, Vol. 1, page 930, the general statement is made that the chloraloses do not reduce Fehling's solution.

[2] Courtesy of Dr. G. J. Cox, Mellon Institute.

The reaction was carried out at 115–120° for 5 hours. Long needles, melting at 135° (U. S. P. corr.), giving a smoky luminous flame, and a Beilstein test for halogen were obtained. The crystals are soluble in all alcohols, chloroform, ether, benzene, xylene, acetone, amyl acetate, petroleum benzin; insoluble in hot and cold water, sodium bicarbonate; difficultly soluble in hot sodium hydroxide. No red color was produced with concentrated sulfuric acid (9). Analysis: C, 26.57%; H, 2.20%; Cl, 53.29%. Calculated for monochloral-levulinic acid: C, 34%; H, 3.2; Cl, 43.34%. The compound gave a phenylhydrazine derivative containing 4.15% nitrogen (micro-Dumas). Calculated percentage nitrogen for a derivative of monochloral-levulinic acid is 8.34%. It is believed to be a dimol derivative.

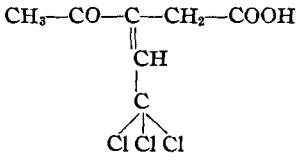
Esters of levulinic acid can be prepared in excellent yields with Drierite present to remove the water as rapidly as it is formed. This esterification was not exhaustively studied for optimum yields.

It was found that freshly fused sodium acetate was the best condensing agent (9). One mole equivalent of pure levulinic acid, one mole equivalent of freshly distilled chloral and one mole equivalent of freshly fused sodium acetate were mixed together and placed on a water-bath under a reflux condenser. The mixture became cloudy, darkened in color and became quite viscous. After four hours it was allowed to cool, then poured into distilled water. The supernatant liquid was decanted from the black syrup and the syrup washed repeatedly with distilled water. The dark syrup was then dissolved in about ten volumes of absolute alcohol, decolorized as much as possible with Norite, and the alcoholic filtrate reduced to a small volume. On standing, long needles separated out which were filtered off, washed repeatedly with a cold alcohol-water mixture (1:1) and dried at 80°. These crystals (best yield—30 per cent) have a melting point[1] of 113.5° C. and analyzed as follows:

Calculated for $C_7H_7O_3Cl_3$: Cl, 43.34%
Found:[2] (Parr Bomb method) Cl, 43.32%.

The crystals are quite insoluble in water, but are readily soluble in most organic solvents, glacial acetic acid and aqueous alkaline solutions. Cold dilute potassium permanganate is rapidly decolorized. Rapid decomposition takes place on vacuum distillation. The dry sodium salt tends to absorb moisture, and dissolves readily in water to give a neutral reaction. The chloral-levulinic acid does not produce the intense red color in concentrated sulfuric acid reported by Erdmann (9) for the benzylidene levulinic acid.

The compound is assigned the structure



on the basis of the literature records for analogous compounds (7, 9, 10). The proof advanced by earlier workers for beta-condensation under these conditions is questioned, and is being studied in connection with another problem.

The beta-chloral-levulinic acid gave a Beilstein test for halogen.[3] A compound of unknown structure was isolated from the condensation side-products, separating out of a glacial acid solution of impure chloral-levulinic acid.[4]

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[1] All melting points are corrected for stem exposure.

[2] Analyses by Mr. Saul Gottlieb, Columbia University.

[3] Levulinic acid, highly purified, also gave a Beilstein test for halogen, although there was insufficient halogen present to produce even a cloudiness with silver nitrate. Levulinic acid and its ethyl ester decolorize potassium permanganate in alkaline and neutral solution.

[4] Long, white needles, melting at 155.5–156°. Analysis revealed C, 26.70%, H, 2.17% and Cl, 54.30%. It is probably a compound containing two chloral residues. Calculated for one such substance ($C_9H_8O_4Cl_6$): C, 27.5%; H, 2.05%; Cl, 54.16%.

Bromination of Beta-Chloral-Levulinic Acid.—A satisfactory crystalline dibromide derivative has not yet been obtained. When finely powdered beta-chloral-levulinic acid is exposed to bromine vapor in a desiccator, fifty per cent excess bromine over that required for formation of a dibromide is absorbed, and the crystalline material becomes liquid. On exposure to the air, most of the excess bromine is given off, but no crystalline material could be isolated.

Derivatives of Beta-Chloral-Levulinic Acid.—These derivatives, the physical characteristics of which are given in the table, were prepared by the usual methods with the exception of the oxime where the suggestion of Bryant and Smith (11) as to the use of pyridine was followed.

TABLE OF DERIVATIVES.

Derivative.	Color.	M. P.	Nitrogen Per Cent (Micro-Dumas). Calculated.	Found.
p-Nitrophenylhydrazone	White	182°	11.03	11.29
Semicarbazone[1,2]	White	205.5–206°	13.88	13.63
p-Bromophenylhydrazone	White	161°	6.74	6.59
β-Naphthylhydrazone	Pinkish	188–189°	7.27	7.50
Phenylhydrazone	White	174.5°	8.35	8.12
Oxime[1,2]	White	103–104°	5.37	5.35
Thio-semicarbazone	White	177–177.5°	13.19	13.01

[1] Soluble in all alcohols, ketones, dioxan, chloroform, amyl acetate, benzene, dibutyl phthalate, hot water; insoluble in pentene-2, petroleum benzin.

[2] Soluble in concentrated sulfuric acid without color production.

DISCUSSION.

Beta-chloral-levulinic acid administered orally to rats, either as the free acid or soluble sodium salt, did not show any hypnotic activity in doses of 1500 mg. per Kg. weight of animal.[1] No toxic effect was noticed. This surprising lack of activity is probably due to the stability of the substance (no chloroform is produced on boiling with alkaline solutions) and to the inability of the rat to hydrolyze off the chloral residue. It is not believed likely that the condensation of the chloral group with levulinic acid in the alpha- or gamma-position would result in a compound any more satisfactory, as these types of derivatives are likewise stable.

SUMMARY.

1. A new derivative of levulinic acid, namely, chloral-levulinic acid, has been prepared.

2. Chloral-levulinic acid, in relatively large quantities, is non-toxic and non-hypnotic when given orally to rats.

3. Seven nitrogen derivatives of chloral-levulinic acid are described for purposes of identification.

The author wishes to thank Dr. George D. Beal, Assistant Director of Mellon Institute, for his advice during the progress of this work.

REFERENCES.

(1) Hanriot and Richet, *Compt. rend.*, 116, 63 (1892).
(2) Hanriot and Richet, *Bull. soc. chim.* (3), 9, 947 (1893).
(3) Willcox, *Lancet*, 225, 1425 (1933).
(4) Cox and Dodds, *Ind. Eng. Chem.*, 25, 967 (1933).
(5) Coles, Goodhue and Hixon, *J. Am. Chem. Soc.*, 51, 519 (1929); Freudenberg and Vajda, *Ibid.*, 59, 1955 (1937).

[1] The author is indebted to Mr. H. A. Holaday and associates of the E. R. Squibb & Sons Biological Laboratories, New Brunswick, N. J., for these tests.

(6) Hanriot, *Ann. chim. phys.*, 18, 466 (1909); Hanriot and Richet, *Compt. rend.*, 122, 1127 (1896).

(7) Sen and Roy, *J. Indian Chem. Soc.*, 7, 404 (1930).

(8) Hammond, St. Petersburg Amer. Chem. Soc. Meeting (March 1934).

(9) Erdmann, *Ber.*, 18, 3441 (1885).

(10) Borsche, *Ibid.*, 47, 1108 (1914); 48, 842 (1915); Kehrer and Kleberg, *Ibid.*, 26, 345 (1893); Erdmann, *Ibid.*, 21, 635 (1888); 24, 3201 (1891); Ludwig and Kehrer, *Ibid.*, 24, 2776 (1891); Erlenmeyer, *Ibid.*, 23, 74 (1890); Erdmann, *Ann.*, 254, 182, 197, 218 (1889); 258, 129 (1900).

(11) Bryant and Smith, *J. Am. Chem. Soc.*, 57, 57 (1935). See also Bachmann and Boatner, *Ibid.*, 58, 2097 (1936); Gulati and Ray, *Current Science*, 5, 75 (1936); Cook, Hewett and Lawrence, *J. Chem. Soc.* (London), 71 (1936).

THE PRESENT STATUS OF ACONITE RESEARCH.*

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The fundamental problem in aconite research is to find an aconite or aconites that can be depended upon to yield a definite alkaloidal entity. This short paper is intended as a progress report and to show the pressing need for some important problems to be solved. In the Index Kewensis approximately 524 species of aconites are listed. How many of these types are correctly named remains to be seen. The mere publication of the species in the Kew Index does not indicate that such a species of plant is valid, although it may be an aconite type. Our U. S. P. definitions should be more precise. Over thirty types of napellus have been investigated and all would fit into the category of this genus, but preliminary tests show that much variation is present both from the morphological and chemical standpoint. From amorphous aconitine a colleague of mine has isolated a type of ephedrine alkaloid. Other breakdown products are now being investigated by this worker. Such research throws new light upon the structure of the aconitine molecule and the need for basic research in this group. Microchemical tests which will show the type of chemical present without growing huge amounts of the plant are greatly needed.

The problem of knowing just what you have with such a heterogeneous group of plants remains unanswered at present. The taxonomist merely gives his opinion. All the strains of aconites that yield aconitine should be grown. This work is now being carried on and there are over a hundred types in cultivation. Twice this number was once under cultivation but the inability to secure funds for this research resulted in a great loss. Each desirable strain is then propagated clonally by means of daughter tubers. The conception of the clone seems to have been overlooked in pharmaceutical investigations of drug plants. In this way a series of plants are grown until enough have been obtained to give material sufficient for an adequate chemical investigation. A hundred pounds of dried root material would give ap-aproximately a half pound of crude alkaloid for both chemical and pharmacological investigation. It would take about 1000 plants for this work. Naturally such a problem is slow work, takes much land and many hands to cultivate, and much bookkeeping for records. By this method we are certain of the source of the plant. Its chemical characters will not fluctuate. We have established a unit for future

* Presented before the Scientific Section, A. PH. A., New York meeting, 1937.

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