Anal. Calcd. for $C_8H_8 \cdot AgNO_3$: C, 34.81; H, 2.92; Ag, 39.1. Found: C, 34.54; H, 3.00; Ag, 39.7.

When this adduct was placed in a bath at 170° rising at 2° per minute, cycloöctatetraene was lost, and the residual solid melted with decomposition at 173 ± 0.5°.

(c) When the complexes of formula $C_8H_8 \cdot AgNO_3$ or $2C_8H_8 \cdot AgNO_3$ were recrystallized from 20% aqueous silver nitrate, or from ethanol, a third compound was formed. The pale green crystalline product obtained after three recrystallizations from 15 parts of hot absolute ethanol, after drying at 30 mm. for twelve hours over calcium chloride and cycloöctatetraene saturated with paraffin, melted at 173–174° when placed in a bath at 170° rising at 2° per minute. There was no detectable prior loss of cycloöctatetraene.

Anal. Calcd. for $2C_8H_8 \cdot 3AgNO_3$: C, 26.70; H, 2.25; Ag, 45.10. Found: C, 26.73; H, 2.59; Ag, 45.51.

When the complex $C_8H_8 \cdot AgNO_3$ was evacuated to 0.1 mm. at room temperature, it lost cycloöctatetraene rapidly until a composition approximating $2C_8H_8 \cdot 3AgNO_3$ was reached. Continued evacuation at 70–85° resulted in virtually complete removal of unchanged cycloöctatetraene.

Both the complexes $C_8H_8 \cdot AgNO_3$ and $2C_8H_8 \cdot AgNO_3$ suffered partial decomposition when dissolved in water. A portion of the cycloöctatetraene could be recovered by steam distillation or by ether extraction of the solutions. A better recovery of cycloöctatetraene was effected by pouring the aqueous solution of complexes into cold concentrated ammonium hydroxide.

When 30.5 g. of the $2C_8H_8 \cdot 3AgNO_3$ complex was dissolved in 100 ml. of water, 25 g. of sodium chloride in 100 ml. of water was added, and the mixture steam distilled, 7.85 g. (90%) of cycloöctatetraene, $n^{25}D$ 1.5348, m. p. −4.5 to −3.5°, was recovered. Infrared absorption spectra, utilizing the characteristic absorption band of styrene at 11.01 μ, indicated the product to be virtually free from styrene. The starting material had contained 0.5% of styrene.

Summary

The reaction of cycloöctatetraene with two equivalents of sodium in liquid ammonia, followed by addition of ammonium chloride, has been found to yield a mixture of 1,3,6- and 1,3,5-cycloöctatrienes, from which the 1,3,6-isomer has been separated in 94–96% purity by fractional distillation. Treatment of the mixture of isomers with potassium *t*-butoxide resulted in rearrangement of the unconjugated to the conjugated isomer, and this procedure provides a convenient synthesis for 1,3,5-cycloöctatriene.

1,3,5-Cycloöctatriene has been found to rearrange on heating to an isomer with lower refractive index and a nearly identical ultraviolet absorption spectrum, which is not 1,3,6-cycloöctatriene, and may be either a stereoisomer or a bridged structural isomer.

Three crystalline addition compounds of cycloöctatetraene with silver nitrate have been prepared, and a crystalline adduct of silver nitrate with 1,3,5-cycloöctatriene. These addition compounds have proved to be useful as derivatives and for purification of the hydrocarbons, which can be regenerated from them.

CAMBRIDGE, MASSACHUSETTS

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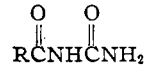
[CONTRIBUTION FROM ABBOTT LABORATORIES]

Anticonvulsant Drugs. III. Some Allophanates

BY M. A. SPIELMAN, J. D. BARNES AND W. J. CLOSE

An earlier communication[1] described the synthesis of some acylureas (I) which were tested for their anticonvulsant activity. Each known anticonvulsant drug contains in its molecule a lipophilic and a hydrophilic component, and in the acylureas the hydrophilic part is the carbonylurea fragment $-CONHCONH_2$. With the idea



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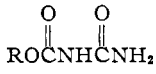

II

of modifying the latter, an oxygen atom may be intercalated at the point of junction, and the resulting products are allophanates (II) which offer an interesting field for exploration in the search for drugs against epilepsy.

The esters of allophanic acid have been known for more than a century[2] but their pharmacological characteristics have been little examined except that a few have been tested as hypnotics.[3] Of these, *t*-amyl allophanate was found to be of some interest, although it has never become established in clinical use.

Several procedures for the preparation of allophanates have been published[2,4] but we found that when small amounts were desired, the method of choice was that of passing cyanic acid vapor into an alcohol without solvent. Alcohols in limited amount were diluted with dry ether. Like others[5] we observed that significant amounts of carbamates were formed in the reaction and often led to reduced yields. Preparation of allophanates by acidifying a solution or suspension of potassium cyanate in an alcohol[4] gave erratic results; from 3-methyl-2-butanol, for example, we isolated only the carbamate.

(1) Spielman, Geiszler and Close, THIS JOURNAL, **70**, 4189 (1948).

(2) A history of allophanates and a bibliography of preparative methods are given by Bougault and Leboucq, *Bull. soc. chim.*, [4] **47**, 594 (1930).

(3) Fraenkel, "Arzneimittelsynthese," Julius Springer, Berlin, 1927, p. 525; German Patent 226,228; Remfry, *J. Chem. Soc.*, **99**, 625 (1911).

(4) Werner and Gray, *Proc. Roy. Soc. Dublin*, **24**, 209 (1947); German Patent 248,164; Davis and Blanchard, THIS JOURNAL, **51**, 1809 (1929).

(5) Béhal, *Compt. rend.*, **168**, 945 (1919); German Patent 120,864.

TABLE I

ALLOPHANATE ANTICONVULSANTS, ROCONHCONH$_2$

R	M. p., °C.	Formula	Nitrogen, % Calcd.	Found	Anticonvulsant potency Electroshock	Metrazol
$ClCH_2CH_2$–	179–182[a]				0	0
iso-C_3H_7–	184–185[b]				+	0
iso-C_4H_9–	179–180[b]				0	0
s-C_4H_9–	159–160[b]				++	+
t-C_4H_9–	189–190[b]				+	++
n-C_5H_{11}–	158–159	$C_7H_{14}N_2O_3$	16.1	16.1	0	0
iso-C_5H_{11}–	161–162[c]				0	0
s-C_5H_{11}–	157–158[b]				+	0
$(C_2H_5)_2CH$–	171–172[d]	$C_7H_{14}N_2O_3$	16.1	16.1	++	+
iso-$C_3H_7CH(CH_3)$–	169–170	$C_7H_{14}N_2O_3$	16.1	16.1	0	±
t-C_5H_{11}–	166–168[e]	$C_7H_{14}N_2O_3$	16.1	16.2	++	++
n-$C_4H_9CH(CH_3)$–	170–171[b]				++	0
$C_2H_5CH(CH_3)CH_2$–	149–150	$C_7H_{14}N_2O_3$	16.1	16.4	++	0
iso-$C_4H_9CH(CH_3)$–	162–163[b]				0	0
$(C_2H_5)_2CHCH_2$–	156–158	$C_8H_{16}N_2O_3$	14.9	14.8	0	0
n-$C_3H_7CH(CH_3)CH_2$–	150–151	$C_8H_{16}N_2O_3$	14.9	15.0	0	0
iso-$C_3H_7CH(C_2H_5)$–	185–186[d]	$C_8H_{16}N_2O_3$	14.9	15.1	0	++
$(C_2H_5)_2C(CH_3)$–	153–154[a]				++	++
cyclo-C_6H_{11}–	173[b]				0	0
iso-$C_4H_9CH(C_2H_5)$–	185–187	$C_9H_{18}N_2O_3$	13.8	14.1	0	0
s-$C_4H_9CH(C_2H_5)$–	172–174	$C_9H_{18}N_2O_3$	13.8	13.5	0	++
n-$C_5H_{11}CH(CH_3)$–	148–150	$C_9H_{18}N_2O_3$	13.8	13.7	0	0
iso-$C_4H_9CH(CH_3)CH_2$–	116–117	$C_9H_{18}N_2O_3$	13.8	13.6	0	0
$(C_2H_5)_3C$–	173–174[f]	$C_9H_{18}N_2O_3$	13.8	14.0	0	++
CH_2=$CHCH_2C(CH_3)(C_2H_5)$–	132–135	$C_9H_{16}N_2O_3$	14.0	14.0	++	+
$C_6H_5CH_2$–	182–183[g]				++	0
iso-$C_3H_7C(C_2H_5)_2$–	140–141 dec.	$C_{10}H_{20}N_2O_3$	12.9	13.1	0	++
iso-$C_4H_9C(C_2H_5)_2$–	148–150[b]				0	0
$C_6H_5CH_2CH_2$–	186–188[h]				+	0
$C_6H_5CH(CH_3)$–	185–186[b]				+	++
$C_6H_5CH(C_2H_5)$–	149–150	$C_{11}H_{14}N_2O_3$	12.6	12.7	++	+++
$C_6H_5C(CH_3)_2$–	124–126 dec.	$C_{11}H_{14}N_2O_3$	12.6	12.7	±	+
$C_6H_5C(C_2H_5)_2$–	151–152 dec.	$C_{13}H_{18}N_2O_3$	11.2	11.2	0	0
$C_6H_5(CH_2$=$CHCH_2)C(CH_3)$–	139–143 dec.	$C_{13}H_{16}N_2O_3$	11.3	11.2	0	±
$(C_6H_5)_2CH$–	181–182 dec.	$C_{15}H_{14}N_2O_3$	10.4	10.3	0	0
$(CH_3)_2C(COOC_2H_5)$–	125–126	$C_8H_{14}N_2O_5$	12.8	12.9	0	±

[a] Grandière, *Bull. soc. chim.*, [4] **35**, 187 (1924). [b] Reference 8. [c] Davis and Blanchard, THIS JOURNAL, **51**, 1809 (1929). [d] Béhal[8] gives 179°. [e] Béhal[8] gives 152° and a similar figure is reported by Remfry.[3] [f] Mavrodin, *Compt. rend.*, **192**, 363 (1931), gives 182–183°; Grandière, ref. *a*, gives 156°. [g] Bougault and Leboucq[2] record 191.5°; Traube's figure, *Ber.*, **22**, 1573 (1889), is in agreement with ours. [h] Béhal[8] also reports 186°; Bougault and Leboucq give 197.5°.

We are indebted to Dr. G. M. Everett and Dr. R. K. Richards for evaluation of our compounds which were tested for their ability to suppress or modify convulsive seizures provoked in mice by electroshock or by injection of Metrazol (pentamethylenetetrazole). Graded, oral doses of the allophanates were given, usually 200, 400 and 800 mg. per kg., and their low toxicity was evident in the virtual absence of any effects except depression. The scale of activity is expressed as follows: +++, complete protection without symptoms; ++, protection at levels which produce side effects such as depression, ataxia, etc.; +, partial protection with symptoms.

Table I summarizes our results. Analytical data are given for those compounds which are new and for those whose melting points differ enough from literature values to create doubt concerning identity. References to previous preparations are given in the footnotes.

Allophanates derived from primary alcohols are usually inactive unless the chain is branched. Benzyl allophanate, however, gave fair protection against electroshock at the rather high dose level of 800 mg. per kg. Secondary and tertiary allophanates, particularly those with highly branched systems, protect against either electroshock or Metrazol and sometimes against both. They are moderately hypnotic, however, as might have been inferred from the earlier literature. None of our compounds was considered worthy of clinical trial. It is interesting that those lipophilic groups (R in I and II) which appeared best in the acylureas were, in general, also best in the allophanate series. A disappointing exception is the benzyl radical which is very effective

in phenacetylurea but is much less so in benzyl allophanate.

Experimental Part[6]

All alcohols used in this work were purchased from commercial sources or were prepared by published methods. None is new.

Cyanic acid was generated by subliming cyanuric acid from a 25-cc. flask connected by a glass joint to a Pyrex tube heated to dull redness in an electric combustion furnace. The exit end of the tube was bent downward to lead the effluent gases into a 50-cc. flask containing the alcohol. A gentle current of carbon dioxide was used to prevent accidental sucking back.

In a typical run, 5 g. of cyanuric acid was placed in the generator and 10–15 cc. of the alcohol in the receiver which was clamped in a pan of cold water. When less than 5 cc. of alcohol was available, 10 cc. of dry ether was used as solvent. The cyanuric acid was heated with a free flame, and the carbon dioxide was adjusted so that one bubble per second appeared. Sublimation of the bulk of the cyanuric acid required about fifteen minutes. The receiver was removed, stoppered and left to itself for twenty-four hours.[7] When the reaction was at an end as evidenced by disappearance of the acrid odor of cyanic acid, the allophanate was separated by filtration and washed with a little ether. It was purified to constant melting point by crystallization from an ethanol solution previously treated with carbon to aid in removal of a trace of cyanuric acid. Yields were usually 2–4 g. Carbamates, formed as by-products, account, in part, for the small yields.[5,8]

A single example of the potassium cyanate method is representative. To 25 g. of glacial acetic acid and 15 g. of *t*-amyl alcohol was added portion-wise with stirring 8.1 g. of potassium cyanate. The temperature rose to 50° and gradually subsided. After the mixture had stood several hours, it was diluted with water and extracted with ether. The ether was washed with water and evaporated on the steam-bath. The residue after crystallization from ethanol yielded 0.9 g. of *t*-amyl allophanate; m. p. and mixed m. p. 166–168°.

(6) Microanalyses by E. F. Shelberg and staff. Melting points are uncorrected.

(7) It should be emphasized that the reaction of cyanuric acid with alcohols is not always rapid. α-Phenylethanol, for example, required several days; simple alcohols, however, usually react so rapidly that the mixture becomes hot.

Summary

Some esters of allophanic acid have been prepared and tested for anticonvulsant activity. The most active compounds are those derived from secondary and tertiary alcohols of 5–7 carbon atoms. The allophanates are mild hypnotics.

(8) Béhal, *Bull. soc. chim.*, [4] **25**, 475 (1919).

NORTH CHICAGO, ILLINOIS RECEIVED NOVEMBER 2, 1949

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY OF THE NATIONAL RESEARCH COUNCIL]

The Biogenesis of Alkaloids. I. The Isolation of N-Methyltyramine from Barley[1]

BY SAM KIRKWOOD AND LÉO MARION

During a study of the route of synthesis of the alkaloid hordenine (N-dimethyltyramine) in barley roots it was discovered that certain strains produce N-methyltyramine and not hordenine. N-Methyltyramine has never been isolated previously from a natural source although Winterstein produced it by the action of putrefactive bacteria on the alkaloid surinamine (N-methyltyrosine).[2]

The biogenesis of hordenine has been investigated by Raoul who attempted to demonstrate that the alkaloid arose from the decarboxylation of tyrosine coupled with a methylation of the resulting tyramine by formaldehyde. Persistent attempts to gain evidence for this route failed.[3] The isolation of N-methyltyramine indicates that the plant synthesizes this substance and hordenine by the methylation of tyramine through a mechanism similar to that known to exist in certain molds and in animals. Horowitz, Bonner and Houlahan have shown, by a study of mutants induced by ultraviolet irradiation, that the mold *Neurospora crassa* synthesizes choline by an enzymatic stepwise methylation of ethanolamine.[4] It is known that the animal can perform this same synthesis if it has available a supply of labile methyl groups.[5] There is some evidence in the literature that a similar stepwise enzymatic process is used by the plant in the N-methylation of alkaloids. Thus N-methylethanolamine and N-dimethylethanolamine, the two intermediates in the synthesis of choline by *N. crassa* and by animals, occur as esters in alkaloids.[6,7] This suggests that both these substances are produced by a stepwise methylation entirely analogous to that in *N. crassa* except that the plants concerned can stop the process at intermediate stages. Similarly in *Trichocereus candicans B.* and *R.* the alkaloids candicine (β-(4-hydroxyphenyl)-ethyltrimethylammonium hydroxide) and hordenine occur together.[8] This again suggests a stepwise methylation of tyramine, the plant being able to stop at both stages.

The following barleys have been found to produce N-methyltyramine: Montcalm, Olli, Sanalta and O.A.C. 21. All attempts to isolate hordenine from them have failed and it is presumed that they produce only N-methyltyramine. This points to a biochemical difference in these strains similar to that produced in *N. crassa* by ultraviolet

(1) Published as National Research Council Bull. No. 2131.

(2) Winterstein, *Z. physiol. Chem.*, **105**, 20 (1919).

(3) Raoul, *Ann. fermentations*, **3**, 129 (1937); **3**, 193 (1937); **3**, 385 (1937).

(4) Horowitz, Bonner and Houlahan, *J. Biol. Chem.*, **159**, 145 (1945); Horowitz, *ibid.*, **162**, 413 (1946).

(5) Stetten, *ibid.*, **140**, 143 (1941); du Vigneaud, Chandler, Simmonds, Noyer and Cohn, *ibid.*, **164**, 603 (1946).

(6) Faltis and Holzinger, *Ber.*, **72**, 1443 (1939).

(7) Blount, Openshaw and Todd, *J. Chem. Soc.*, 286 (1940).

(8) Reti, *Compt. rend. soc. biol.*, **114**, 811 (1933).