hydrochloric acid, evaporated to dryness and extracted with hot alcohol. When the alcohol portion was evaporated to dryness, no residue was obtained.

Trichloroacetylisodurene.—One-half gram of trichloroacetylisodurene was maintained at 120° with 25 cc. of a solution of 40% sodium hydroxide in a sealed tube. Close observation showed only slow changes in the oil. At the end of thirteen hours considerable brown solid was found to have formed in the now discolored oil. At the end of twenty-six hours most of the oil had become dark brown or had changed over to the solid. The oil and solid mixture was filtered, washed with water and treated with acetone. Only a slight amount of light brown residue failed to dissolve. The acetone extract was evaporated to yield a small quantity of brown oil, presumably some of the starting material. The alkali filtrate was acidified with hydrochloric acid, evaporated to dryness and extracted with hot alcohol. This extract failed to yield any 2,3,4,6-tetramethylbenzoic acid, although a very small quantity of residue was obtained.

Summary

It has been shown that acetyl derivatives of mesitylene, durene and isodurene are converted into the corresponding trihaloacetyl compounds by treatment with solutions of sodium hypohalites. The following compounds have been prepared: di-(trichloroacetyl)-mesitylene (IV), di-(tribromoacetyl)-mesitylene (VI), tribromoacetyldurene (IX), trichloroacetyldurene (VII), tribromoacetylisodurene (XII), trichloroacetylisodurene (X), di-(trichloroacetyl)-isodurene (XIII) and di-(tribromoacetyl)-isodurene (XV). Long treatment of the trihaloacetyl derivatives of durene and isodurene with hot concentrated alkali failed to cleave these compounds into the corresponding acid derivatives.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ILLINOIS, AND THE LILLY RESEARCH LABORATORIES, ELI LILLY AND CO., INDIANAPOLIS, INDIANA]

THE ANTIPYRETIC ACTION OF PARA-ACETYLAMINOPHENYLURETHANS

BY RICHARD F. B. COX, C. R. ECKLER AND R. L. SHRINER

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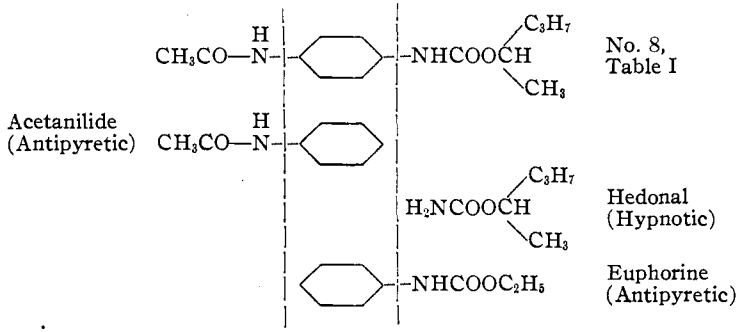
The combination in a single molecule of antipyretic, analgesic and hypnotic action would give a very useful therapeutic compound. One of the groupings which is associated with antipyretic action is the acetylaminophenyl grouping, which is present in acetanilide and phenacetin. Hypnotic activity is exhibited by certain urethans such as hedonal[1] (the urethan of pentanol-2). Some urethans, especially phenylurethan, also possess antipyretic effects. Hence it was thought that the preparation of a series of compounds combining these two groups might lead to useful substances. The present investigation was carried out on compounds of the type $CH_3CONHC_6H_4NHCOOR$ (*p*).

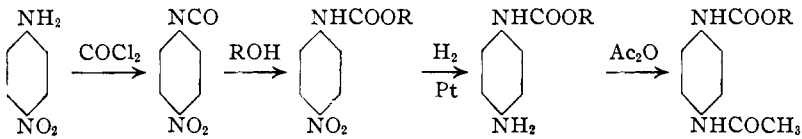
[1] Dreser, *Wiener klin. Wochenschr.*, **1899**, 1007.

The structural relationship between one of these derivatives and known compounds with their physiological action is indicated in the following formulas



By a comparison of the above formulas it will be noted that the structure at the top combines the essential functional groups of the other three and the question of the pharmacological action of such a compound is of considerable interest.

Preparation of the Compounds.—The compounds were synthesized by means of the following reactions



The *p*-nitrophenylurethans, which were prepared by means of the method previously described,[2] were reduced catalytically with hydrogen and platinum-oxide platinum black[3] in glacial acetic acid in order to avoid any hydrolysis of the urethan. After removal of the catalyst the acetic acid solution of the amine was mixed with acetic anhydride and refluxed. This yielded the acetyl derivative without isolating the amine itself. By using this procedure pure colorless crystalline compounds were obtained. They were purified by recrystallization from alcohol. Their properties and analyses are given in Table I.

Pharmacological Tests

The methods available for the determination of analgesic, antipyretic and hypnotic action have not been well worked out and leave much to be desired in regard to accuracy. No satisfactory method, other than clinical use, is available for detecting analgesic properties. However, since analgesic action usually parallels antipyretic action, a determination of the latter serves as a rough index of the former. The technique finally

[2] Shriner and Cox, THIS JOURNAL, **53**, 1601 (1931); Horne and Shriner, *ibid.*, **53**, 3186 (1931).

[3] Adams and Shriner, *ibid.*, **45**, 2171 (1923).

TABLE I

p-ACETYLAMINOPHENYLURETHANES ($CH_3CONHC_6H_4NHCOOR$ (*p*))

No.	Alkyl group (R)	M. p.	Formula	Nitrogen analyses Calcd.	Found
1	Methyl	193	$C_{10}H_{12}O_3N_2$	13.47	13.03
2	Ethyl	198	$C_{11}H_{14}O_3N_2$	12.62	12.79
3	*n*-Propyl	175	$C_{12}H_{16}O_3N_2$	11.88	11.60
4	Isopropyl	164	$C_{12}H_{16}O_3N_2$	11.88	11.48
5	*n*-Butyl	170.5	$C_{13}H_{18}O_3N_2$	11.20	11.00
6	Isobutyl	165	$C_{13}H_{18}O_3N_2$	11.20	11.10
7	*Sec.*-butyl	177	$C_{13}H_{18}O_3N_2$	11.20	11.05
8	*Sec.*-amyl	165	$C_{14}H_{20}O_3N_2$	10.61	10.22
9	*n*-Hexyl	158	$C_{15}H_{22}O_3N_2$	10.08	10.33
10	*n*-Heptyl	162	$C_{16}H_{24}O_3N_2$	9.59	9.51
11	*Sec.*-octyl	197.5	$C_{17}H_{26}O_3N_2$	9.15	8.96

adopted permitted a comparison to be made between the compounds in Table I and two well-known antipyretics, acetanilide and amidopyrin. During the same test any hypnotic action could also be noted.

The tests were made on rabbits which were starved overnight. The normal temperatures (rectal) were taken in the morning and 2 cc. of a typhoid antigen injected intramuscularly. After three or four hours, when the animals had become feverish, 0.2 g. of the compound to be tested, per kilo of body weight, was administered. Since the compounds were all insoluble and not readily wetted by water, the dry sample was mixed with powdered gum acacia and water gradually added with stirring until a thin mucilage resulted. This mixture was then washed into the stomach by means of a stomach tube. The temperatures of the rabbits were then observed at intervals for five hours. Parallel experiments were run with acetanilide and amidopyrin. Control rabbits were also observed. A portion of the data obtained is given in Table II, which shows the change in temperature at the end of three and five hours after administration of the compounds. Several rabbits were used for each compound and the values given are average figures. The individual rabbits varied somewhat from each other in their reaction to the same compound but this variation (0.1 to 0.2°) was less than the total change in temperature. The data therefore cannot be interpreted in an absolutely quantitative manner but can only serve as an indication of the relative antipyretic effect of this series of urethans as compared with acetanilide and amidopyrin.

It is interesting to note from the data in Table II that the urethans of low molecular weight and those of high molecular weight exhibited antipyretic activity while those intermediate had no favorable action. In none of the compounds prepared was the action as prompt or as extensive as that obtained with either acetanilide or amidopyrin. Careful observation of the experimental animals did not indicate that these compounds produced hypnosis or narcosis.

TABLE II

ANTIPYRETIC EFFECT OF $CH_3CONHC_6H_4NHCOOR$

Starved rabbits... 2 cc. Typhoid antigen (5 bil/a)
Urethans..... 0.20 g. per kg. body weight
Amidopyrin..... .15 g. per kg. body weight
Acetanilide..... .10 g. per kg. body weight

Urethan Alkyl group (R)	Change in temperature at the end of 3 hours, °F.	5 hours, °F.
Methyl	−0.7	−1.1
Ethyl	−1.0	−1.2
n-Propyl	−1.4	−2.1
Isopropyl	+1.1	−0.2
n-Butyl	+1.2	+ .7
Isobutyl	+0.7	+ .2
Sec.-butyl	+2.2	+1.3
Sec.-amyl	−0.5	−0.9
n-Hexyl	+ .5	−1.1
n-Heptyl	+ .1	−1.5
Amidopyrin	−3.8	−3.7
Acetanilide	−2.4	−0.4
Nothing (received antigen only)	No change (average of five)	−0.1 to −0.3 (average of five)

Summary

A series of *p*-acetylaminophenylurethans was prepared and they were tested for their antipyretic action. The compounds of low molecular weight and high molecular weight exhibited some activity but none of the compounds was as active as amidopyrin or acetanilide. No hypnotic activity was observed in any case.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

QUANTITATIVE DETERMINATION OF VITAMIN G(B_2)[1]

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Our purpose in the work here described[2] has been to develop a method whereby the responses in the weight curves of properly standardized experimental animals may become means of measuring the relative vitamin G (B_2) values of foods or of concentrates obtained in research work.

The factor here designated as vitamin G or B_2 may or may not be identical with that to which the term pellagra-preventive has been applied;

[1] Published as Contribution No. 667 from the Department of Chemistry of Columbia University.

[2] This paper is a brief summary of the work described in the privately printed dissertation submitted by Anne Bourquin in partial fulfilment of the requirements for the degree of Ph.D., Columbia University, 1929, together with the results of subsequent experience in the use of the method in the Columbia laboratories.