TABLE I

N^1-ALKANESULFONYLSULFANILAMIDES

Alkanesulfonyl group	Appearance	Melting range, °C.	Assay by $NaNO_2$	Assay by NaOH
Ethanesulfonyl-	Short prisms	206.5–207.5	101.0	101.0
1-Butanesulfonyl-	Plates	209.0–210.5	100.1	100.8
1-Pentanesulfonyl-	Plates	183.0–184.5	99.6	98.5
2-Ethyl-1-hexanesulfonyl-	Plates	189.0–191.0	100.5	100.0
1-Dodecanesulfonyl-	Plates	188.8–189.9	...	99.4
Cyclohexanesulfonyl-	Leaflets	230 dec.	100.0	100.3
10-*dl*-Camphorsulfonyl-	Leaflets	213.0–214.5	100.8	100.2
Phenylmethanesulfonyl-	Plates	242.0–243.5	99.8	99.4

to be complete. Dilute hydrochloric acid was added to bring the *p*H to 8–9 and the mixture was cooled to 15°. The excess N^4-acetylsulfanilamide was filtered and washed well with cold water. The mother liquor was acidified to *p*H 1 with hydrochloric acid. A sticky precipitate formed which soon crystallized to white, sandy crystals of N^4-acetyl-N^1-(1-butanesulfonyl)-sulfanilamide. A portion of the crude product was saved and purified by solution as the sodium salt, treatment with activated charcoal and reprecipitation. On attempting to recrystallize from water, partial hydrolysis of the N^4-acetyl group resulted.

The balance of the crude product was hydrolyzed with sodium hydroxide by the same procedure used for N^1-acylsulfanilamides.[3] The hydrolyzate on cooling and standing deposited coarse crystals of sodium N^1-(1-butanesulfonyl)-sulfanilamide which were salted out of solution by the excess sodium hydroxide present. The salt was twice recrystallized from concentrated aqueous solutions. Recoveries from the sodium salt mother liquors were made by acidifying to *p*H 4.0–4.5 and filtering off the free compound. This was recrystallized from water.

The other compounds listed in Table I were similarly prepared. All were assayed by the same procedures used for the N^1-acylsulfanilamides.[3] N^1-1-Dodecanesulfonylsulfanilamide was too insoluble in mineral acids to be analyzed by diazotization.

Summary

1. Sulfanilamide derivatives of the general formula, $NH_2(4)C_6H_4SO_2NHSO_2R$, were synthesized where R was alkane (2 to 12 carbons), cycloalkane and aralkane.

2. Preliminary studies in mice indicated low effectiveness of these compounds against beta-haemolytic streptococci.

BOUND BROOK, N. J. RECEIVED APRIL 9, 1940

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF MOUNT HOLYOKE COLLEGE]

Differences Observed in the Behavior of Unsaturated Hydantoins under the Action of Bromine

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Reactions involving the addition of bromine to hydantoins possessing unsaturated side chains in the C-5-position have been reported as leading to the formation of quite different classes of compounds, the character of which seems to depend upon the conditions of the experiment. For example, unsaturated hydantoins in which a bromine atom was found to have replaced a hydrogen atom in the side chain invariably were formed when benzalhydantoin, anisalhydantoin and many similar compounds,[2] dissolved in glacial acetic acid, were treated with molecular quantities of bromine

(a) $HNCONHCOC{=}CHC_6H_5 \xrightarrow{+\ Br_2} NHCONHCOC{=}CBrC_6H_5 + HBr$

In other cases[3] where reactions were carried out in chloroform or carbon tetrachloride and these solvents subsequently displaced by alcohol, saturated ethoxy-monobromo derivatives of the hydantoins were formed.

(b) $CH_3NCON(CH_3)COC{=}CHC_6H_5 \xrightarrow[+\ C_2H_5OH]{+\ Br_2} CH_3NCON(CH_3)COC(OC_2H_5)CHBrC_6H_5 + HBr$

The question naturally arises as to whether these differences are due to the nature of the unsaturated hydantoins involved, or solely to experimental conditions. In the latter case *all*

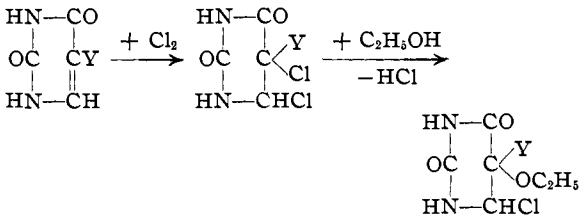
(1) Acknowledgment must be made to Dr. Dorothy A. Hahn for suggesting and coöperating in this research.

(2) Wheeler, Hoffman and Johnson, *J. Biol. Chem.*, **10**, 154 (1911); Wheeler and Hoffman, *Am. Chem. J.*, **45**, 376 (1911); Johnson and Wrenshall, THIS JOURNAL, **37**, 2133 (1915); Johnson and Davidson, *ibid.*, **47**, 563 (1925).

(3) Litzinger, *ibid.*, **56**, 676 (1934); Hahn, McLean and Murphy, *ibid.*, **60**, 1927 (1938).

classes of unsaturated hydantoins,[4] as represented for example by benzalhydantoin, its N-3-methyl and its N-1-N-3-dimethyl derivatives, might be assumed to be capable respectively of undergoing both types of transformation (a and b). This has now been shown to be the case.

That in each instance the final product results from a secondary reaction appears obvious because of the fact that the bromine is decolorized as rapidly as added and the reaction, which is usually complete within five minutes, is not accompanied by any apparent evolution of hydrobromic acid. Recently reactions similar to those indicated as (b) have been reported as taking place when the 2,4-diketotetrahydropyrimidines were treated first with chlorine in chloroform solution and subsequently with alcohol. In the case of unsaturated compounds of this type it was possible, moreover, to isolate primary dichloro addition products and then later under the direct action of alcohol to transform them into secondary chloroethoxy derivatives[5]



In the case of the unsaturated hydantoins under investigation the problem of isolating similar primary dibromo addition products presented serious technical difficulties because of the fact that they were extremely unstable. Nevertheless a single compound belonging to this class, namely, N - 3 - methyl - C - 5,5 - bromo - bromobenzyl-hydantoin, finally was obtained in the form of fine white needles which possessed a well-defined melting point and which was sufficiently stable to allow of a fairly satisfactory analysis. That the latter was not completely satisfactory was due to the fact that the substance is so unstable that even in solid condition it loses hydrobromic acid slowly at ordinary temperatures and on long standing passes quantitatively into the corresponding *unsaturated* mono-bromo derivative. It is insoluble in cold alcohol but, when warmed slightly, passes instantly into the corresponding *saturated* ethoxybromo derivative with the evolution of heat and hydrobromic acid. The corresponding dibromo addition product of benzalhydantoin was also separated in solid crystalline form but never in a sufficiently pure condition to justify an analysis. In the case of dimethylbenzalhydantoin all of the compounds involved in the bromination were so extremely soluble as to preclude any possibility of separating them.

That the final products formed in the transformations (a) and (b) belong to unsaturated and saturated classes of hydantoins, respectively, was confirmed by a spectrographic study, the results of which are presented in Fig. 1.[6] The pronounced differences between these two classes of hydantoin derivatives both as to intensity and region of absorption already have been established[7] and the present results agree closely with earlier reports.

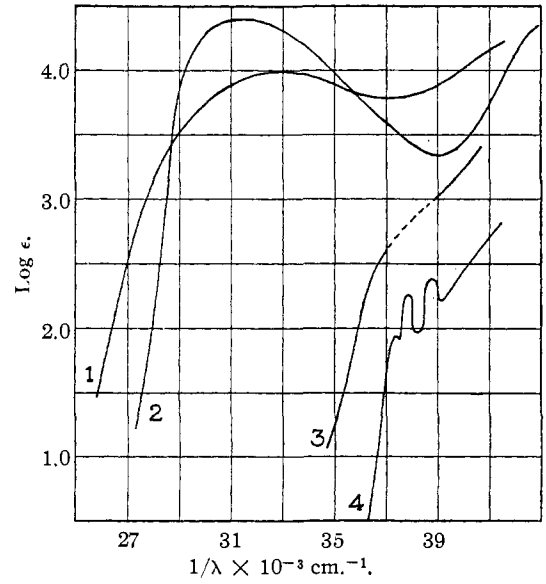


Fig. 1.—(1) Bromobenzalhydantoin; (2) benzalhydantoin; (3) C-5,5-ethoxy-bromobenzyl-hydantoin; (4) benzylhydantoin.

It may be noted in passing that the bromo-ethoxy addition products are compounds of phar-

(4) Compare Seikel, THIS JOURNAL, **59**, 436 (1937).

(5) Johnson and Sprague, *ibid.*, **59**, 2436–2439 (1937). It is interesting to note that ethylene linkages in both pyrimidines and hydantoins react under analogous conditions to form similar types of halogen-alkoxy addition products. This is perhaps remarkable in view of the fact that the double bond is incorporated in the ring structure in one case and in the side chain in the other. It should be added however that the kinetics of reactions of this kind have not as yet been completely elucidated [Bartlett and Tarbell, *ibid.*, **58**, 466 (1936)].

(6) Grateful acknowledgment is due Dr. Hildegard Stücklen for directing this work. The curves were plotted by Doris R. Seeger in partial fulfilment of the requirements for a B.A. degree with honors, June, 1939. In the case of 3 it may be added that a dotted line is used to indicate narrow bands due to the presence of the phenyl group although the exact positions could not be measured because of the diffuseness of the bands.

(7) Hahn and Evans, THIS JOURNAL, **50**, 809 (1928); Hahn and Dyer, *ibid.*, **52**, 2505 (1930); Hahn, McLean and Murphy, *ibid.*, **60**, 1928 (1938).

macological interest because of their relation as 5,5-disubstituted hydantoins to sodium diphenylhydantoin[8] and C-5,5-phenyl-ethylhydantoin.[9] The latter, due to their anticonvulsant and other therapeutic effects, are, as is well known, finding application in medicine in the treatment of epilepsy and related disorders. In this connection attention may be called to the marked decrease in toxicity that results from the substitution of methyl for hydrogen in the N-3- and N-1-N-3 positions in the hydantoin ring, as shown in the table,[10] where the figures represent the minimum lethal dose administered orally to mice:

$HN\overline{CONHCOC}(OC_2H_5)CHBrC_6H_5$	3.0 mg./M.
$HN\overline{CON(CH_3)COC}(OC_2H_5)CHBrC_6H_5$	80.0 mg./M.
$CH_3N\overline{CON(CH_3)COC}(OC_2H_5)CHBrC_6H_5$	120.0 mg./M.

These figures are especially significant in view of the fact that 12.0 mg./M. represents the minimum lethal dose of sodium diphenylhydantoin. None of the other possible physiological effects of the above bromoethoxyhydantoins have as yet been investigated.

Experimental

The N-3-methyl-C-5-benzalhydantoin[11] and N-1,N-3-dimethyl-C-5 benzalhydantoin[12] used in all of the following experiments were obtained by methods previously developed in this Laboratory. In preparing the corresponding unsaturated bromo derivatives the method used in the case of benzalhydantoin as reported by Wheeler, Hoffman and Johnson,[2] was followed.

N-3-Methyl-C-5-bromobenzalhydantoin, m. p. 173–173.5°, was obtained by adding bromine (4.5 g.) slowly to a suspension of N-3-methyl-benzalhydantoin (5.0 g.) in glacial acetic acid (25 cc.). The bromine was decolorized as rapidly as added and, on heating, copious fumes of hydrobromic acid were evolved. The clear solution, when evaporated to 15 cc. over a steam-bath and then set aside to crystallize, deposited 4.28 g. of a product, m. p. 160–166°, which was purified by recrystallization from alcohol.

Anal. Calcd. for $C_{11}H_9O_2N_2Br$: C, 46.99; H, 3.23; N, 9.97; Br, 28.43. Found: C, 46.79; H, 3.29; N, 10.00; Br, 28.50.

The substance is only slightly soluble in cold (1.0 g. in 100 cc.) but more soluble in boiling alcohol (10.0 g. in 100 cc.). Treated with hydrogen iodide and red phosphorus, it passed quantitatively into N-3-methylbenzylhydantoin which was identified by comparision with an analyzed specimen, m. p. 140–141°.[13]

N-1,N-3-dimethyl-C-5-bromobenzalhydantoin, m. p. 122–123°, was obtained and purified in a manner analogous to that described above.[14]

Anal. Calcd. for $C_{12}H_{11}O_2N_2Br$: C, 48.81; H, 3.76; N, 9.50; Br, 27.08. Found: C, 48.82; H, 3.94; N, 9.57; Br, 27.45.

The compound is very soluble in acetic acid and alcohol. Treated with hydrogen iodide and red phosphorus, it was transformed into N-1,N-3-dimethylbenzylhydantoin which was identified by comparison with an analyzed specimen, m. p. 86.5–87°.[11]

The method previously reported by Hahn, McLean and Murphy[3] was again applied in the preparation of C-5,5-ethoxy-bromobenzylhydantoin and of the corresponding N-3-methyl derivative although, due to the relative insolubility in carbon tetrachloride of the compounds taking part in both of these reactions, certain experimental difficulties were encountered. However, when care was taken to avoid the formation of any least trace of hydrobromic acid prior to the introduction into the reaction mixture of a relatively large volume of absolute alcohol, yields of more than 90% of each of the above products were obtained.

$N\overline{HCONHCOC}(OC_2H_5)CHBrC_6H_5$, **C-5,5-Ethoxy-bromobenzyl-hydantoin**, m. p. 202.5–203°, was prepared by adding a molecular quantity of bromine (17.2 g. diluted to 25 cc.) at 0° and under constant stirring, to benzalhydantoin, m. p. 218–219°, suspended in carbon tetrachloride (20.0 g. in 300 cc.). The reaction, which was complete in a few minutes, was accompanied by the transformation of the yellow crystals of benzalhydantoin into a precipitate of fine white crystals, the bromine being decolorized rapidly with no perceptible formation of hydrobromic acid. When, however, 300 cc. of absolute alcohol was added to the mixture and heat applied, hydrobromic acid was evolved in large quantities and a perfectly clear colorless solution was formed.[15] The latter was then alternately concentrated and treated with additional quantities of absolute alcohol until the carbon tetrachloride and last traces of hydrobromic acid had been largely eliminated, when upon cooling a white crystalline compound was deposited. Successive precipitates obtained from filtrates, all melting between 199 and 202°, were combined (31.9 g.) and purified by recrystallization from boiling absolute alcohol.[16]

(8) Merritt and Putnam, *Arch. Neurol. Psychiatry*, **42**, 1053 (1939).

(9) Pilcher and Gerstenberger, *Am. J. Diseases Children*, **40**, 1239 (1930).

(10) The biochemical investigation of ten gram specimens of these compounds, which were prepared in this Laboratory, was very kindly undertaken by Dr. Oliver Kamm, of the Research and Biological Laboratories of Parke, Davis and Company.

(11) Litzinger, THIS JOURNAL, **56**, 673 (1934).

(12) Hahn and Evans, *ibid.*, **50**, 817 (1928).

(13) For the electrolytic dissociation constant of this compound, compare Pickett and McLean, *ibid.*, **61**, 424 (1939).

(14) It is significant that the unsaturated monobromo derivatives can be recrystallized unchanged from alcohol and even from alcoholic solutions of hydrogen bromide. Great care must nevertbeless be exercised in their preparation to avoid the presence of any trace of alcohol since otherwise mixtures are obtained which are very difficult to separate.

(15) In cases where hydrobromic acid was given off *before* the alcohol had been added, the product was found to be contaminated by the presence of a considerable quantity of bromobenzalhydantoin. Since the latter can be separated only with the greatest difficulty, care must be taken to avoid its formation which is always attended by the evolution of hydrogen bromide.

(16) The solubilities of the ethoxybromo derivatives of (a) benzal- and (b) methylbenzal-hydantoins in 100 cc. of absolute alcohol are respectively (a) 2.84 g. at 20° and 13.64 g. at the temperature of the boiling solvent; (b) 0.64 g. and 5.73 g. under the same conditions.

Anal. Calcd. for $C_{12}H_{13}O_3N_2Br$: C, 46.02; H, 4.18; Br, 25.52. Found: C, 46.09; H, 4.28; Br, 26.31.

$\overline{NHCON(CH_3)COC(OC_2H_5)CHBrC_6H_5}$, **N-3-Methyl-C-5,5-ethoxy-bromobenzyl-hydantoin**, m. p. 179–180°, was prepared under exactly the same conditions as those described above and obtained in approximately the same percentage yields. It was, however, also prepared by treating N-3-methyl-C-5,5-bromo-bromobenzyl-hydantoin directly with absolute alcohol, a reaction which will be described in more detail later. In both cases the product was purified by recrystallization from boiling absolute alcohol.[16]

Anal. Calcd. for $C_{13}H_{15}O_3N_2Br$: C, 47.71; H, 4.62; N, 8.57; Br, 24.42. Found: C, 47.71, 47.80; H, 4.62, 4.55; N, 8.59; Br, 24.37.

It will have been noted that the addition of bromine to both benzalhydantoin and N-3-methylbenzalhydantoin was accompanied by the formation of a voluminous white crystalline precipitate. This was thought to represent a primary dibromo addition product, but the fact that in each case it was practically as insoluble in carbon tetrachloride as the unsaturated hydantoin from which it was formed, made its separation from small unacted-upon quantities of the latter extremely difficult. In the case of benzalhydantoin this addition product was never obtained in a sufficiently pure condition to justify its analysis although a white crystalline compound was finally separated mechanically. The latter melted at 178–182° with an evolution of gas, formed a colorless solid on cooling and melted again at about 235°. This is interesting in view of the fact that bromobenzalhydantoin was reported by Wheeler, Hoffman and Johnson[2] as melting at 239–240°.

$\overline{NHCON(CH_3)COCBrCHBrC_6H_5}$, **N-3-Methyl-C-5,5-bromo-bromobenzyl-hydantoin**, m. p. 153–154° to a clear liquid prior to the evolution of gas, was prepared by treating 20 g. of N-3-methylbenzalhydantoin suspended in 300 cc. of boiling carbon tetrachloride with one equivalent of bromine. Within a few minutes the color had become pale orange and there was a heavy precipitate of very fine white needles which was filtered and washed free from bromine (27.0 g.). The precipitate was then suspended in cold carbon tetrachloride, and unchanged methylbenzalhydantoin which floated on the surface was removed by repeated decantations.

Anal. Calcd. for $C_{11}H_{10}O_2N_2Br_2$: C, 36.50; H, 2.78; Br, 44.15. Found: C, 36.82; H, 2.82; Br, 41.75. The same specimen analyzed two months later was found to have sustained a further loss of hydrobromic acid that made the amount practically quantitative.

Anal. Calcd. for $C_{11}H_9O_2N_2Br$: Br, 28.43. Found: Br, 28.67.

The compound is in fact so unstable that it loses hydrobromic acid slowly at room temperature, and when heated in an oven at 105° it passes quantitatively into N-3-methyl-C-5-bromobenzalhydantoin, m. p. 173–173.5°. It is almost insoluble in cold absolute alcohol but dissolves on warming to form a pale yellow solution. The latter suffers an almost immediate discharge of color accompanied by the evolution of hydrobromic acid and the separation of N-3-methyl-C-5,5-ethoxy-bromobenzyl-hydantoin, m. p. 179–180°.

Spectrographic measurements were made by the method developed by Stücklen[17] for use with a hydrogen lamp as the light source. Each compound was dissolved in absolute alcohol which had been especially purified for spectrographic use. A Hilger quartz spectrograph (E 36) was employed, and photographs were made on Eastman no. 40 plates. Although curves were plotted for the corresponding derivatives of both benzal- and methylbenzal-hydantoins, the latter corresponded so closely with the former that it has not been thought necessary to reproduce them.

Summary

The preparation under the action of bromine of C-5,5-bromoethoxy derivatives of both benzal- and N-3-methylbenzalhydantoins has been described and certain of their biochemical properties noted. In the case of N-3-methylbenzalhydantoin interest centers in the fact that a primary dibromo addition product was isolated which when warmed with absolute alcohol decomposed to give the corresponding bromo-ethoxy derivative but which when heated alone, passed quantitatively into N-3-methyl-C-5-bromobenzalhydantoin.

SOUTH HADLEY, MASS. RECEIVED APRIL 12, 1940

(17) Stücklen. *J. Opt. Soc. Am.*, **29**. 37 (1939).