was added. The flask was stoppered, shaken well for several minutes, and kept at room temperature for 24 hr. The solvents were removed by vacuum distillation. The remaining dark liquid was dissolved in 20 ml. of hot ethanol. Upon cooling 2.97 g. (83% yield) of a white solid was obtained, m.p. 158–160°. Upon recrystallization from ethyl acetate, the m.p. was 161–162° (lit.,[2] m.p. 161–162°).

3,4-Dihydro-3-cyclohexyl-6-benzyloxy-2*H*-1,3-benzoxazine (IIIa).—Cyclohexylamine (11.5 ml., 0.1 mole) was added dropwise with stirring to 15 ml. of 37% aqueous formaldehyde (0.2 mole) dissolved in 100 ml. of methanol at 15 to 18°. 4-Benzyloxyphenol (20 g., 0.1 mole) was added and the resulting solution kept at room temperature for 24 hr. Upon removing the solvents, a sticky white solid remained. It was treated with a mixture of 50 ml. of ether and 40 ml. of water containing 6 g. of sodium hydroxide. The ether layer was separated. The aqueous portion was further extracted with three 20-ml. portions of ether. The ether extracts were combined. The aqueous portion was acidified with dilute hydrochloric acid, and 11.8 g. of white solid, m.p. 119–121°, separated. A mixture melting point with 4-benzyloxyphenol showed no depression. The residue obtained by removal of solvent from the combined ether extracts was dissolved in 25 ml. of hot 95% ethanol. Upon cooling 11.9 g. of white solid, m.p. 66–69°, was obtained. After three recrystallizations from 95% ethanol the product melted at 69–70°; 82% yield, based upon consumed 4-benzyloxyphenol.

2-Cyclohexylaminomethyl-4-benzyloxyphenol (IVa).—To the benzoxazine IIIa (9.69 g., 0.03 mole) in 20 ml. of 95% ethanol was added 3 ml. of concentrated hydrochloric acid. The flask was warmed slowly on a water bath until 5 ml. of ethanol distilled. Then the flask was cooled and an additional 1.5 ml. of concentrated hydrochloric acid was added. The mixture was again distilled until 3 ml. of ethanol passed over. The undistilled solution gradually deposited 9.6 g. of white product, m.p. 190–197°. After three recrystallizations from 95% ethanol the *hydrochloride* melted at 203–205°.

A 4.8-g. sample of the hydrochloride was placed in a separatory funnel with 50 ml. of water. After adding 4 ml. of 2-aminoethanol with shaking, the mixture was extracted with four 25-ml. portions of ether. Evaporation of the ether left 4.6 g. brownish-white solid, m.p. 83–85°; after three recrystallizations from *t*-butyl alcohol, m.p. 85–86°. A mixture melting point with a sample prepared directly by interacting equimolar quantities of cyclohexylamine, formaldehyde, and 4-benzyloxyphenol gave no depression.

2-Cyclohexylaminomethylhydroquinone (Ia) from IVa Hydrochloride.—A 20.4-g. sample of IVa hydrochloride (0.059 mole) in 55 ml. of concentrated hydrochloric acid was refluxed for 1 hr. After cooling, an additional 30 ml. of concentrated hydrochloric acid was added and the mixture warmed under reflux for 2 hr. at 90 to 95°. The resulting light brown solid was removed by filtration, washed with six 20-ml. portions of ether, and dissolved in hot water. After cooling, 2-aminoethanol was added to the aqueous solution until no further solid (7.6 g.) separated; m.p. 169–171° after recrystallization from ethanol–petroleum ether (1:1). The melting point was not depressed by mixing with Ia prepared directly from hydroquinone. An additional 1.3 g. was obtained by adding 2-aminoethanol to the original filtrate after separation of the ether; 68% total yield.

Cyclohexylaminomethylhydroquinone (Ia) from 3-Cyclohexyl-6-benzyloxy-3,4-dihydro-2*H*-1,3-benzoxazine (IIIa).—The benzoxazine IIIa (1.0 g., 0.003 mole) and 0.5 g. of phenylhydrazine were dissolved in 15 ml. of 37% hydrochloric acid and 15 ml. of water. The mixture was heated under reflux at 75° for 5 hr. and then filtered. The resulting filtrate was extracted with ether. Upon evaporation of the ether a clear liquid remained, b.p. 179–181°/754 mm. The b.p. of benzyl chloride taken simultaneously was 180–181°. The aqueous layer was cooled to 0° and 2 ml. of 2-aminoethanol was added dropwise. The cloudy mixture was extracted with ether and upon evaporation of the ether layers 0.4 g. of a white solid was obtained, m.p. 168–170°; yield, 61%. The solid was recrystallized from methanol–benzene (19:1); m.p. and m.m.p. with an authentic sample of Ia, 172–173°.

Substitution in the Hydantoin Ring. III.[1] Halogenation[2]

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On the basis of competitive reactions between 1,5,5- and 3,5,5-trimethylhydantoins added to the study of transfer of positive halogen, it has been concluded that halogenation of the hydantoin ring, with several agents, occurs preferentially in position 3. Monohalogenation of nitrogen-unsubstituted hydantoins leads in all cases to the 1-halo derivative as a result of the intermediate formation of the 1,3-dihalo compound (isolated from various reactions) and later transfer of the halogen atom on N_3 position to another hydantoin molecule.

By substitution reactions in the hydantoin itself or in its derivatives, N-mono- and N,N′-dihalogenated compounds have been obtained corresponding to all halogen excepting fluorine.

The N-chloro derivatives, known for some time, have been obtained by utilizing different chlorinating agents: sodium hypochlorite, hypochlorous acid generated in the reaction medium starting from the former, or methyl N,N-dichlorocarbamate[3]; by passing chlorine through a water solution of the hydantoin in either neutral or alkaline medium,[4–6] and finally by transfer of halogen in reactions between hydantoins and their dihalo derivatives.[7]

The preparation and use of the bromo derivatives of a number of hydantoins were more recently described by this laboratory,[8] employing bromine in an alkaline solution of hydantoins for these preparations.

In obtaining the iodinated compounds, which were introduced as halogenating agents for the aromatic nucleus, iodine and the silver derivative of the hydantoins were employed for the N-monoiodo compounds, while for N,N′-diiodo-5,5-dimethylhydantoin, a solution of the hydantoin in alkaline aqueous medium was made to react[9] with iodine monochloride.

As regards the structure of the products which result from monohalogenation, very limited data were available in the literature which could allow a decision as to the possibilities of placing the halogen in position N_1 or N_3. Products from chlorination by means of sodium hypochlorite have been formulated as N_1 compounds, in support of which are their solubility in alkali[3]; as re-

(1) Part II, R. Jeandupeux, O. O. Orazi, and R. A. Corral, *J. Org. Chem.*, **27**, 2520 (1962).

(2) This work was supported by a grant from the Consejo Nacional de Investigaciones Científicas y Técnicas.

(3) E. Ware, *Chem. Rev.*, **46**, 403 (1950).

(4) H. Biltz and K. Slotta, *J. prakt. Chem.*, **113**, 233 (1926).

(5) A. O. Rogers, U.S. Patent 2,392,505; *Chem. Abstr.*, **40**, 2468 (1946).

(6) O. O. Orazi, J. F. Salellas, M. E. Fondovila, R. A. Corral, N. M. Mercere, and E. R. de Alvarez, *Anales asoc. quím. Arg.*, **40**, 61 (1952).

(7) P. La F. Magill, U. S. Patent 2,430,233; *Chem. Abstr.*, **42**, 2278 (1948).

(8)(a) O. O. Orazi and J. Meseri, *Anales asoc. quím. Arg.*, **37**, 192 (1949); (b) O. O. Orazi, M. E. Fondovila, and R. A. Corral, *ibid.*, **40**, 109 (1952); (c) R. A. Corral, O. O. Orazi, and J. D. Bonafede, *ibid.*, **45**, 151 (1957); and references therein quoted.

(9) R. A. Corral and O. O. Orazi, *ibid.*, **44**, 11 (1956).

gards the bromo derivatives, taking into account that the halogenation occurred on the hydantoin salified in 3, it was supposed that they were N_3 compounds,[8a] while in the iodo derivatives, the reaction of the halogen with the 3-silver derivative also led to assignment of this position for the iodine atom.[9]

This situation led us to study the problem in order to determine the orientation in the halogenation of the hydantoin ring. It should be pointed out that during the development of the present work a publication[10] occurred demonstrating the identity of the monochloro derivatives of the 5,5-dimethylhydantoin obtained by means of chlorine in the presence of a base and by transfer between the dihalo compound and the hydantoin, and giving supports in favor of position 1 for the halogen.

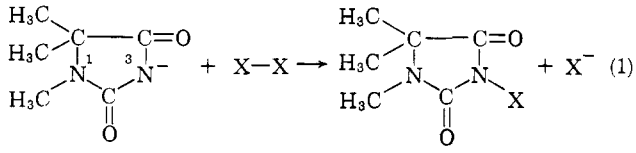
In order to determine which of the two reactive positions, N_1 or N_3, is more easily substituted in halogenation, competitive reactions of 1,5,5- and 3,5,5-trimethylhydantoins in the presence of several halogenating agents were performed (Table I).

Table I

Competitive Halogenation of 1,5,5- and 3,5,5-Trimethylhydantoin

Halogenating agent	1-Halo derivative, %	3-Halo derivative, %
1 mole NaOH + Cl_2	4	80
1 mole NaOH + Br_2	20	57
ClOH	0	97
ClONa	42	9
BrONa	81	8

The results of experiments in which the halogen reacted with an equimolecular aqueous solution of the hydantoins and alkali indicated a very high predominance of the reactivity of position 3 with respect to 1; these experimental data led us to interpret the principal reaction of the process in the following form, in which it has been taken into account that the N_3—H bond is practically the only one that becomes ionized on the basis of the dissociation constants of the N—H bonds in positions 3 and 1 (1,5,5-trimethylhydantoin pK_a 9.02; of N_1-hydrogen[11] 14 or more).

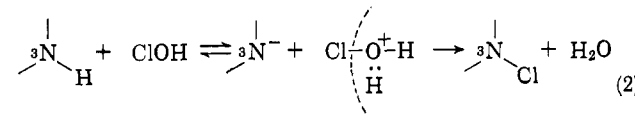


(1)

The competition using hypochlorous acid affords with practically quantitative yield only the 3-chloro derivative, and this may be formulated by the following equations; the higher acidity of the hydrogen at position 3 is presumed to be the reason for that predominance.

Protonated hypochlorous acid is indicated as the halogenating entity participating as such and/or by previous formation of Cl^+.[12]

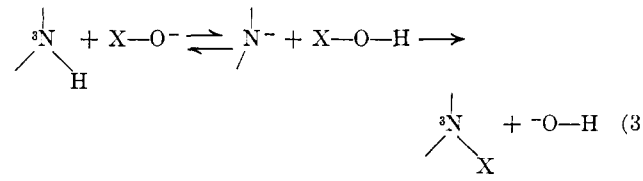
On the other hand, in the competitive reactions in which the hypohalites were employed, the 1-halo derivatives were obtained predominantly. However when the 1,5,5- and 3,5,5-trimethylhydantoins were treated



(2)

separately, sodium hypobromite gave the bromo derivative in each case (53 and 43% yield, respectively), while with sodium hypochlorite, 3-chloro-1,5,5-trimethylhydantoin (55%) was obtained; but there was no reaction with the 3,5,5-trimethylhydantoin. This last result is very striking if the corresponding competitive reactions are taken into account.

These facts may be rationalized on the supposition that the halogenation of the 1,5,5-trimethylhydantoin with hypochlorite occurs in the following way.



(3)

This accounts for the fact that the N_1-methylated hydantoin is more reactive than its 3-isomer; the failure of the latter to react is due to the low acidity of the N_1-hydrogen which is not sufficient for the formulated equilibrium to have significance. With the hypobromite on the other hand, halogenation is attained in the two positions N—H of the ring, this difference being explainable on the basis of the dissociation constants of the respective acids (ClOH, 6.5×10^{-8}; BrOH, 2×10^{-11}).

Position 3 being established as the most reactive, it follows that in the competitive reactions a transfer of the halogen of 3-halo-1,5,5-trimethylhydantoin initially formed to the 3,5,5-trimethylhydantoin occurs.

This transfer was supposed to result from the alkalinity produced in the course of the reaction and in concordance with that, experiments with 3-chloro- or 3-bromo-1,5,5-trimethylhydantoin and 3,5,5-trimethylhydantoin in the presence of an equivalent of sodium hydroxide gave as a result the disappearance of the starting 3-halo derivative and the isolation with good yield of the 1-isomer. It is pertinent to mention that no significant transfer occurs when an equivalent of sodium salt of the 1,5,5-trimethylhydantoin (Table II) is used as the base.

In the other two processes of halogenation the 3-halo compound is obtained very predominantly because, reactions 1 and 2 having occurred, a neutral medium remains, in which there is no important transference of halogen (Table II).

From the foregoing discussion it may be concluded that *in the halogenation with all the agents examined herein (halogen, hypohalous acid, and hypohalite), the N_3 position is by far the most reactive.* From this conclusion and the indicated transfer, it could be anticipated that the monohalo derivatives of nitrogen-unsubstituted hydantoins obtained from halogen and the hydantoin salt (equation 1) and from hypohalous acid (equation 2) would be 3-halo derivatives (kinetic control) whilst with hypohalites, 1-halo compounds would be obtained (thermodynamic control).

This is in contradiction to the evidence in the case of the chlorinated substances[10]; on the other hand, it pro-

(10) R. C. Petterson and U. Grzeskowiak, *J. Org. Chem.*, **24**, 1414 (1959).
(11) L. W. Pickett and M. McLean, *J. Am. Chem. Soc.*, **61**, 423 (1939).
(12) P. B. D. De La Mare, E. D. Hughes, and C. A. Vernon, *Research*, **3**, 192 (1950); D. H. Derbyshire and W. A. Waters, *J. Chem. Soc.*, 73 (1951).

TABLE II

TRANSFER OF POSITIVE HALOGEN

Donor (DMH[a] deriv.)	Acceptor	Conditions	1-halo deriv., %	Recovered donor, %
1,3-Dichloro	DMH	Acetone; 5°; 12 hr.	100	
1,3-Dibromo	DMH	Acetone; 5°; 12 hr.	100	
1,3-Diiodo	DMH	Acetone; 5°; 12 hr.	100	
1,3-Dibromo	DMH (10% excess)	Water; 0°; 10 hr.	83	0
3-Chloro-1-methyl	3-Methyl-DMH	Water; 0°; 30 min. (or acetone; 12 hr.)	0	92
3-Chloro-1-methyl	3-Methyl-DMH	Water; 0°; 30 min. + 1 equiv. NaOH	59	5
3-Chloro-1-methyl	3-Methyl-DMH	1 equiv. NaOH + 1 equiv. 1,5,5-trimethyl-DMH	10	43
3-Chloro-1-methyl	3-Methyl-DMH	Benzene; 80°; 4 hr.	26	74
3-Bromo-1-methyl	3-Methyl-DMH	Water; 0°; 30 min.	18	74
3-Bromo-1-methyl	3-Methyl-DMH	Water + 1 equiv. NaOH	50	0

[a] DMH: 5,5-dimethylhydantoin.

vides for the possibility of obtaining N-monohalohydantoin isomers using different halogenating agents.

To examine these problems, a direct comparison was made, which showed the identity of all the N-monochloro-5,5-dimethylhydantoin obtained by chlorination of the sodium or silver salt of the parent hydantoin, and also those that resulted from the use of hypochlorous acid or sodium hypochlorite; likewise the bromo derivatives prepared by the analogous methods were identical. This result compelled the reexamination of the structure of these compounds.

The acetylation of the N-monobromo-5,5-dimethylhydantoin did not permit conclusions to be drawn with respect to the placing of the halogen atom. The resulting acetyl derivative, different from the 1-acetyl-3-bromo-5,5-dimethylhydantoin, was debrominated by reaction with 2-ethoxynaphthalene giving a monoacetyl 5,5-dimethylhydantoin which was shown to be identical with the one assumed[13] as the 3-acetyl-5,5-dimethylhydantoin or more preferably as the 2-enol 5,5-dimethylhydantoin acetate. Only the former alternative would define the halogen position in the starting substance, since the 2-enol structure could arise either from N_1- or N_3-bromo-5,5-dimethylhydantoin.

Attempting to decide between these possibilities, the method based on the absorption in the infrared carbonyl region recently used for several N_3-acetylhydantoins[14] was tried. Band multiplicities appearing in the spectra (in Nujol and in 0.1% dichloromethane solution) of the monoacetyl-5,5-dimethylhydantoin and its parent bromo compound as well as in some of the 5,5-dimethylhydantoin derivatives chosen as models, precluded unequivocal assignments.

By methylation it was possible to determine whether in N-monochloro- or in N-monobromo-5,5-dimethylhydantoin the halogen occupies position 1; this was achieved by preparing the sodium salts of both substances with sodium hydride, followed by treatment with dimethyl sulfate, which led to the corresponding 1-halo-3,5,5-trimethylhydantoins.

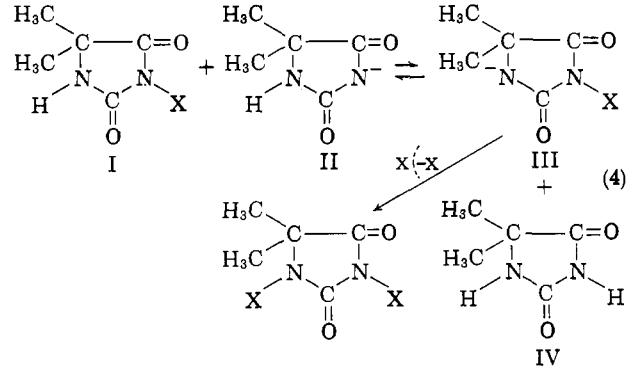
Analogous experiments on the N-monoiodo-5,5-dimethylhydantoin[9] did not succeed owing to decomposition of the iodinated derivative under the conditions used; notwithstanding, taking into account that the method of preparation is the same as that leading to the 1-chloro and 1-bromo derivatives, it may be inferred that this is also the position of the iodine atom.

As was shown above, the 3-halo compounds transfer the halogen atom little or not at all in the reaction media in which free halogen or hypohalous acid were used; in consequence this form of transfer is not a significant factor in the formation of the 1-halo compounds.

An illuminating finding was the isolation of the 1,3-dihalo compounds as reaction intermediates in the preparation of 1-monohalo derivatives; the last can result by transfer of the halogen atom on N_3 to another hydantoin molecule.

According to the literature[7] and other data given here (Table II) the reaction of dihalo hydantoins with an N-unsubstituted hydantoin giving 1-monohalo derivatives, occurs with great facility. This reaction, in acetone as a solvent as described in the Experimental, represents the best method for obtaining 1-monohalo (Cl, Br, I) hydantoins.

The intermediate formation of dihalo compounds during the preparation of 1-monohalo compounds starting from the hydantoin sodium or silver salt, may be outlined as follows (compound I formed according to equation 1).



An equilibrium analogous to 4 (anion formation at position 1) was discarded in considering the competitive reactions 1 and 2; these led almost exclusively to the 3-halo derivative, the percentage found of the 1-isomer being concordant with that expected on the basis of the transfer shown in Table II. To consider such an equilibrium here to account for the intermediate formation of the 1,3-dihalo compounds comes from supposing that the presence of the halogen atom in position 3 (compound I) increases the acidity of N_1-hydrogen by its electron withdrawal ability.

Although a direct measurement can not be made of this effect because the 3-halo derivatives are not available, an approximate value may be obtained from determining the variation of the acidity of the N_3-hydrogen by introduction of halogen in position 1. In the literature[10] it was indicated that 1-chloro-5,5-dimethyl-

(13) M. R. Salmon and A. Z. Kozlowki, *J. Am. Chem. Soc.*, **67**, 2270 (1945).

(14) J. Derkosch, *Monatsh. Chem.*, **92**, 361 (1961).

hydantoin is very strongly acidic when considering that it is a hydantoin, and our measurements indicate that the halogen in this situation increases the acidity of the parent substance nearly 100 times (pK_a 9.03 and 7.17 for 5,5-dimethylhydantoin and its 1-chloro derivative, respectively).

Similarly, the course of the formation of the dihalohydantoin using hypochlorous acid may be envisaged following the initial formation of the 3-chloro derivative according to equation 2.

Although in this paper the mechanism of the halogen transfer from N_3 to N_1 position (Table II) is not studied, a reasonable explanation why these reactions occur resides in the electrophilic nature of the halogen which is best satisfied in this last position; in the dihalo compound the halogen atom at position 1 decreases to an even greater extent the already lower electronic density in position 3.

Experimental[15]

Competitive Halogenation (Table I).—When using the free halogen, the reactions were carried out as follows: To an aqueous solution of 0.0011 mole of 1,5,5- and 3,5,5-trimethylhydantoins with 0.001 mole sodium hydroxide in 2.5 ml. of water, 0.001 mole of halogen (bromine or chlorine) was added while stirring and keeping in an ice bath. From the solution, crystals began to separate very soon; after 5 min. from the addition of halogen the product was filtered and washed with small portions of ice-cooled water.

The experiments with sodium hypohalites were performed in the same way using an equal total volume and adding to the aqueous solution of the hydantoins in neutral medium, a solution containing 0.001 mole of sodium hypochlorite or hypobromite (filtration after 30 min.). The latter was prepared in the refrigerator according to Dehn[16] employing for 0.01 mole of bromine, 0.022 mole of sodium hydroxide in 15 ml. of water; it was analyzed as indicated in the literature.[17] The hypochlorite was obtained in the usual way, using chlorine and sodium hydroxide in stoichiometric quantities and the contents of hypochlorite and chlorate were analyzed.[18]

Other competitive chlorinations, but with a titrateda queous solution of hypochlorous acid[18] as halogenating agent, were made similarly to the foregoing reactions.

The filtered reaction products were dried at 25° *in vacuo*, and their halogen content was consistent with the calculated values for halo-trimethylhydantoins.

The composition of the brominated products was determined by dehalogenation with an excess water solution of sodium sulfite, followed by evaporation to dryness and sublimation (up to 130°/25 μ). The sublimed material was chromatographed through 100 times its weight of alumina (Woelm, pH 10, activity II); the eluate with ethyl ether–chloroform (1:1) gave 3,5,5-trimethylhydantoin identified by melting point and mixed melting point; subsequent fractions by means of a higher proportion of chloroform, chloroform alone and chloroform–absolute ethanol (9:1) afforded the 1,5,5-trimethylhydantoin, identified as the preceding one.

The chlorinated products were fractionated taking advantage of the very great differential solubility between the 1-chloro- and 3-chloro-derivatives in hexane. Extractions with a small volume of hot solvent furnished the 1-chloro-3,5,5-trimethylhydantoin (soluble) and the 3-chloro-1,5,5-trimethylhydantoin (unextracted) which were identified by melting point and mixture melting point.

The halogenation methods as described above were also applied for the preparation of the following compounds.

1-Chloro-3,5,5-trimethylhydantoin was prepared by halogenation of the parent hydantoin with chlorine in the presence of one equivalent of alkali or with hypochlorous acid (yields 75 and 71%, respectively; m.p. 88–90°); the analytical sample melted at 90–91° (from hexane).

Anal. Calcd. for $C_6H_9N_2O_2Cl$: Cl, 20.07. Found: Cl, 20.18.

An attempted preparation using sodium hypochlorite was unsuccessful.

3-Chloro-1,5,5-trimethylhydantoin.—Applying the three foregoing methods, yields of 93, 96, and 55%, respectively, were obtained; m.p. 158–162° raised to 160–162° by recrystallization from benzene.

Anal. Calcd. for $C_6H_9N_2O_2Cl$: Cl, 20.07. Found: Cl, 19.82.

1-Bromo-3,5,5- and 3-Bromo-1,5,5-trimethylhydantoin.—Their preparations are already described in the literature[19] with bromine and alkali; here, with sodium hypobromite the yields were 53 and 43%, respectively.

N-Monohalo-5,5-dimethylhydantoins.—(a) The preparations in aqueous medium employing the sodium derivative of the hydantoin were carried out according to the methods described previously for the bromo derivative[8] (but using 10% excess of the hydantoin) as well as for the chlorinated one.[5,6]

(b) Treatment of 5,5-dimethylhydantoin with sodium hypochlorite or hypobromite rendered a solution (*cf.* ref. 1). By acidification (pH 6.6) of the chilled and stirred solution from hypochlorite with dilute hydrochloric acid the monochloro compound was precipitated; m.p. 144–145°, yield 80%.

Anal. Calcd. for $C_5H_7N_2O_2Cl$: Cl, 21.79. Found: Cl, 21.45.

Likewise, acidification with carbon dioxide provided the corresponding brominated substance; m.p. 170–171° (from dichloromethane–hexane), yield 50%.

Anal. Calcd. for $C_5H_7N_2O_2Br$: Br, 38.60. Found: Br, 38.62.

(c) Using hypochlorous acid the N-monochloro-5,5-dimethylhydantoin was obtained in 75% yield; m.p. 144–147°.

Anal. Found: Cl, 21.80.

(d) To a suspension of 0.01 mole of 3-silver-5,5-dimethylhydantoin[9] in 75 ml. of anhydrous dichloromethane, externally cooled with ice and magnetically stirred, a solution in the same solvent of 0.01 mole of halogen (chlorine or bromine) was slowly added; after filtration of the silver halide the solvent was removed under diminished pressure. The N-monochloro-5,5-dimethylhydantoin was recrystallized from dioxane–hexane (without heating); yield 58%, m.p. 145–148°.

Anal. Found: Cl, 21.30.

The analogous brominated compound was purified from dichloromethane–hexane; yield 73%, m.p. 168–169° dec.

Anal. Found: Br, 38.09.

The chloro as well as the bromo-derivative resulting from the methods a–d were identical. This was proved by admixture melting point and coincidence of the infrared spectra; moreover the identity[20] of the samples (a and d) of the N-monobromo-5,5-dimethylhydantoin was also supported by comparison of their X-rays diffraction patterns. In each comparison samples purified from the same solvent system were employed.

Acetylation of N-Monobromo-5,5-dimethylhydantoin.—A 0.006-mole sample of this monobromo derivative dissolved in 3 ml. of acetic anhydride was heated for 4 hr. at 80°; by dilution with 9 ml. of carbon tetrachloride a product crystallized which was recrystallized from this solvent giving 0.685 g. (yield 46%) of the acetyl derivative, m.p. 119–125°. Further recrystallization from carbon tetrachloride did not furnish sharper melting material.

Anal. Calcd. for $C_7H_9N_2O_3Br$: Br, 32.13. Found: Br, 32.80.

This compound is different from the 1-acetyl-3-bromo-5,5-dimethylhydantoin described below.

A 0.001-mole sample of the acetyl compound was debrominated by refluxing its solution in 2.5 ml. of carbon tetrachloride with 0.001 mole of 2-ethoxynaphthalene until there was a negative test for positive bromine (about 1 hr.). After cooling in the refrigerator the crystals and the liquid phase were separated; from the latter upon solvent elimination and washing the residue

(15) The melting points (sealed capillaries) are not corrected. Infrared spectra were run in Nujol mull using a Perkin–Elmer 21 (sodium chloride prism) recording spectrophotometer and the pK_a values (uncorrected) measured using a Metrohm potenciograph E-336. The analyses of halogen refer to positive halogen, determined by iodometry.

(16) W. M. Dehn, *J. Am. Chem. Soc.*, **31**, 529 (1909).

(17) R. M. Chapin, *ibid.*, **56**, 2211 (1934).

(18) G. H. Cady, *Inorg. Syn.*, **5**, 156 (1957).

(19) O. O. Orazi, R. A. Corral, and J. D. Bonafede, *Anales asoc. quím. Arg.*, **45**, 139 (1957).

(20) Performed in the Research Division, Parke Davis & Company Detroit, Mich., through the kindness of Dr. H. M. Crooks.

with water, 0.274 g. (95%) of 1-bromo-2-ethoxynaphthalene, m.p. 67–68°, was obtained. On the other hand the crystals, 0.150 g. (88%), m.p. 114–118°, were identified (infrared spectra) as the compound presumed preferably to be the 2-enol-5,5-dimethylhydantoin acetate.[13] A sample of this substance was prepared by heating for 1 hr. at boiling temperature a solution of 5,5-dimethylhydantoin in excess acetic anhydride followed by evaporation to dryness and crystallization from ethyl acetate; m.p. 118–123°, yield 43%. Purification of this product by chromatography through neutral alumina did not succeed because deacetylation occurred leading to the parent hydantoin.

1-Acetyl-3-bromo-5,5-dimethylhydantoin.—In a solution of 0.01 mole of sodium hydroxide in 25 ml. of water, 0.01 mole of 1-acetyl-5,5-dimethylhydantoin[13] was dissolved and then successively 25 g. of ice and 0.01 mole of bromine were added. A white solid which began to separate very soon was filtered after several hours in the refrigerator; stirring it in an ice bath with 10 ml. of water containing 0.0005 mole of sodium hydroxide (removal of unchanged hydantoin), and subsequent recrystallization from water yielded 58% of the desired compound, m.p. 177–182° dec.

Anal. Calcd. for $C_7H_9N_2O_3Br$: Br, 32.13. Found: Br, 31.48.

Methylation of N-Monohalo-5,5-dimethylhydantoin.—To a solution of 0.003 mole of the chloro compound in 1 ml. of anhydrous dimethylformamide kept in an ice bath, was added 0.003 mole of sodium hydride as oil dispersion; when hydrogen evolution was ended, and after addition of 0.0033 mole of dimethyl sulfate (freshly purified and stored over potassium carbonate), the mixture was left for 12 hr. at room temperature. Upon evaporation to dryness *in vacuo*, the residue was extracted several times with boiling hexane. Concentration of the combined extract to a small volume led to a crystalline product which was stirred with 4 ml. of water (ice bath) furnishing 0.330 g. (yield 62%), m.p. 88–89.5°; on recrystallization from hexane, it melted at 89–90°.

Anal. Calcd. for $C_6H_9N_2O_2Cl$: Cl, 20.07. Found: Cl, 19.89.

It was shown to be the 1-chloro-3,5,5-trimethylhydantoin by comparison (mixture melting point and infrared spectra) with the above described specimen.

The monobromo derivative was methylated in a similar fashion but the reaction mixture was kept 12 hr. in the refrigerator. The product which crystallized during this period was separated by centrifugation from the mother liquor, washed with small portions of carbon tetrachloride and finally recrystallized from the same solvent; there was obtained 0.216 g. (yield 33%), m.p. 159–160° dec., identified as 1-bromo-3,5,5-trimethylhydantoin[19] by admixture melting point and comparison of the infrared spectra.

Anal. Calcd. for $C_6H_9N_2O_2Br$: Br, 36.19. Found: Br, 35.72.

Control experiments were made to exclude transfer of the halogen from N_3 to N_1 in the methylation conditions. For this purpose 0.001 mole of the 3,5,5-trimethylhydantoin and 0.001 mole of 3-chloro- or 3-bromo-1,5,5-trimethylhydantoin, were subjected to the corresponding conditions (without addition of dimethyl sulfate), resulting in a 5% yield of 1-chloro-3,5,5-trimethylhydantoin (identified by melting point and mixture melting point) and none of the analogous bromo derivative.

Isolation of Intermediates in the Preparation of N-Monohalohydantoin.—A 0.0055-mole sample of 5.5-dimethylhydantoin was dissolved in 20 ml. of water plus 0.005 mole of sodium hydroxide and, in an ice bath under vigorous stirring, a solution of 0.005 mole of chlorine in 8.5 ml. of carbon tetrachloride was added at once; by scratching crystallization was made faster and after 2 min., 0.168 g. of 1,3-dichloro-5,5-dimethylhydantoin, nearly pure, was filtered.

Anal. Calcd. for $C_5H_6N_2O_2Cl_2$: Cl, 36.0. Found: Cl, 35.0.

An experiment made likewise but with bromine added without solvent, gave a product (0.329 g.) being essentially, according to its positive bromine content, 1,3-dibromo-5.5-dimethylhydantoin, together with a small proportion of the N-monobromo compound.

Anal. Calcd. for $C_5H_6N_2O_2Br_2$: Br, 55.9. Found: Br, 54.3.

Other reactions in which the time before filtration was successively extended led to products whose halogen content were correlatively decreasing, being finally (about 4 hr.) the pure N-monobromo-5,5-dimethylhydantoin.

Anal. Found: Br, 38.1.

3-Silver-5,5-dimethylhydantoin (0.0055 mole) and a solution of chlorine (0.005 mole) in carbon tetrachloride (12 ml.) were vigorously stirred and heated during 2 min.; upon filtration and elimination of solvent there resulted 0.143 g. of a solid containing 1,3-dichloro-5,5-dimethylhydantoin as indicated by halogen analysis.

Anal. Found: Cl, 26.4.

From halogenation employing hypochlorous acid was evident the formation of the 1,3-dichloro compound, when a product with 28.2 % of positive chlorine was obtained.

Positive Halogen Transfer (Table II).—(a) 1,3-Dihalo-5,5-dimethylhydantoins with 5,5-dimethylhydantoin: the reaction with the bromo derivative in an aqueous suspension was done essentially as indicated in the literature[7] for the corresponding dichloro compound. This, as well as other experiments using as a solvent the required amount of acetone to get a homogeneous medium, are summarized in Table II. Identification of the resulting 1-halo-5,5-dimethylhydantoin, was performed by halogen analysis and direct comparison with the samples obtained (see above) by halogenation.

(b) 3-Halo-1,5,5-trimethylhydantoins with 3,5,5-trimethylhydantoin: when run in organic medium, the necessary amount of solvent to have a solution was employed; in water the proportion was that one used in the competitive reactions. Fractionation of the products and pertinent identifications were made as described in the latter reactions.