Tetrahedron. Vol. 25, pp. 3267 to 3275. Pergamon Press 1969. Printed in Great Britain

THE ACTION OF BROMINE ON 5-UNSUBSTITUTED 3,4-DIPHENYL-4-IMIDAZOLIN-2-ONES

A NEW SYNTHETIC ROUTE TO 5-HYDROXYHYDANTOINS AND RELATED COMPOUNDS

A. MARSILI, V. NUTI and M. F. SAETTONE*

Istituto di Chimica Farmaceutica e Tossicologica dell'Università di Pisa, 56100 Pisa, Italy

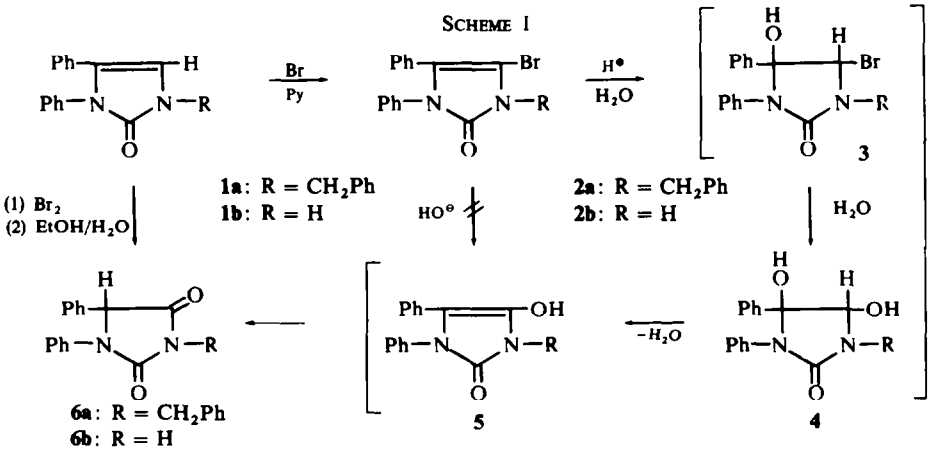
(*Received in the UK* 4 *March* 1969; *Accepted for publication* 17 *March* 1969)

Abstract—The behaviour of several 5-unsubstituted 3,4-diphenyl-4-imidazolin-2-ones towards bromination under different conditions was investigated. Treatment of 1-benzyl-3,4-diphenyl- (**1a**) and 3,4-diphenyl-4-imidazolin-2-one (**1b**) with one mole of bromine gave the corresponding 5-bromo derivatives **2a** and **2b**. These, on treatment with acids, could be converted respectively into 3-benzyl-1,5-diphenylhydantoin (**6a**) and 1,5-diphenylhydantoin (**6b**). Further bromination of the monobromo derivatives **2a** and **2b** afforded unstable adducts, containing three Br atoms per molecule. These, on treatment with alcohols, gave 5-alkoxyhydantoins of type **11** and **19**. The reaction of **1a**, other 1-alkyl-3,4-diphenyl-4-imidazolin-2-ones, and **1b** with two moles of bromine in acetic acid in the presence of sodium acetate, led directly to 5-acetoxyhydantoins of type **17**.

The presently reported reactions represent a new method for the preparation of 5-alkoxy-, 5-acetoxy- and 5-hydroxyhydantoins.

IT WAS reported in a previous paper[1] that 5-unsubstituted 4-imidazolin-2-ones (such as **1a**, Scheme I), when treated with bromine in chloroform solution and then with aqueous ethanol, undergo transformation into the corresponding 5-oxo derivatives, the hydantoins **6**, in fair to good (24–75%) yield. It was supposed that a labile intermediate of type **2**, formed by substitution of the 5-H atom of the imidazolinones by Br, might undergo nucleophilic attack by water to give the hydroxyimidazolinones **5**, whose tautomerization would lead to the end-products **6**.

SCHEME I

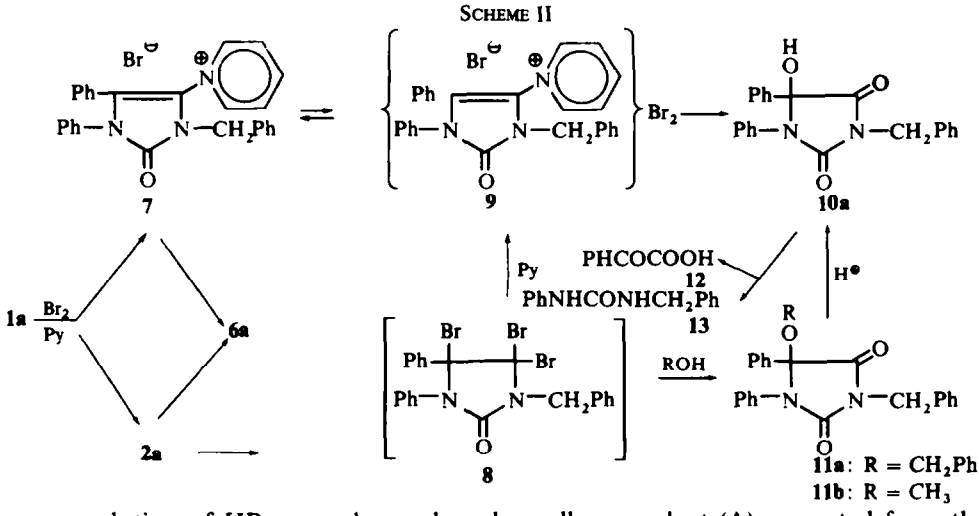


* Authors' names are in alphabetical order. This work was supported in part by a grant from Consiglio Nazionale delle Ricerche.

The present paper deals with the results of further work, which was directed at investigating the mechanism and scope of the reaction. It was our intention to explore new paths leading to hydantoin derivatives endowed with potential pharmacological activity. Indeed, although several compounds of this class have proved clinically useful as anticonvulsants, the search for safer and more active agents is still of interest.

A Bromination of 1-benzyl-3,4-diphenyl-4-imidazolin-2-one (**1a**) *in* $CHCl_3$. Compound **1a** was selected as a model for this study on account of its ease of preparation and characterization. Our first efforts were directed towards establishing the brominated intermediate **2a**, which had escaped isolation in previous experiments. When the bromination of **1a** was carried out in chloroform solution in the presence of pyridine,

SCHEME II



no evolution of HBr was observed, and a yellow product (A) separated from the solution. From the mother liquors of A, a monobrominated derivative (B) was isolated in 46% yield. For compound B, analytical and spectral data indicated the structure of 1-benzyl-5-bromo-3,4-diphenyl-4-imidazolin-2-one (**2a**). Although this product was recovered unchanged after a prolonged reflux in a 10% solution of KOH in ethanol, its treatment with dilute acids under mild conditions resulted in quantitative conversion into the hydantoin **6a**. This indicated that the previous failure to isolate compounds of type **2** was probably due to contamination of the crude bromination products by HBr, which would catalyse their conversion into hydantoins when crystallization from ethyl alcohol was attempted.

The facile acid-catalysed conversion of the 5-bromoimidazolinones **2** into hydantoins may be assumed to proceed through the intermediates **3**, formally originating from addition of water to the double bond. The Br atom of **3**, no longer of vinylic type, would readily undergo displacement by OH to give **4**. Water elimination from **4** would give **5**, and the tautomer **6**. The resistance of **2a** to nucleophilic attack can be put into relation with the analogous behaviour of other halogenated heterocycles,[2] while, in our opinion, the liability of the same compound to undergo Br substitution by OH under mild acidic conditions is rather interesting and might deserve further mechanistic investigation.

For the yellow, water-soluble compound A, analytical and spectral data indicated the structure **7** (Scheme II). It gave on treatment with bases unidentified tarry products,

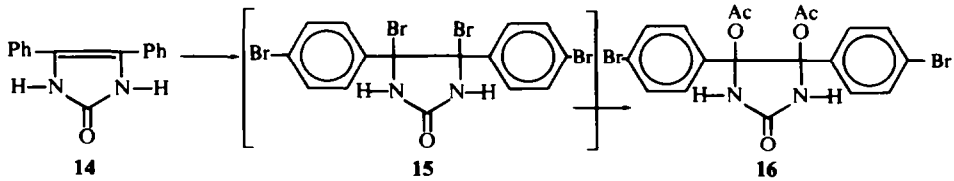
but was converted in 90% yield into the hydantoin **6a** when its acidified alcoholic solution was heated briefly under reflux. Treatment of **2a** with pyridine under conditions which would favour formation of a pyridinium salt, led to quantitative recovery of unchanged starting material. It was thus excluded that **7** might originate from **2a** and pyridine in the reaction medium. Evidence for an alternative mechanism leading to **7** was deduced as follows.

The 5-bromoimidazolinone **2a**, on treatment with bromine in the presence of pyridine, gave an orange-coloured adduct containing three Br atoms and one mole of pyridine. This adduct, which could also be obtained on treatment of **7** with bromine, easily lost two Br atoms under various conditions (heating in EtOH, treatment with unsaturated compounds, etc) to give the pyridinium salt **7**. Its treatment with acids in EtOH at reflux temperature afforded 1-benzyl-3,4-diphenyl-5-hydroxyhydantoin (**10a**, structure proof, see below). The latter reaction indicates a structure with covalently bound bromine to carbon atoms 4 and 5. However, it was felt that even a π or a n adduct might be in equilibrium, in solution, with a covalent derivative which would afford **10a** on hydrolysis. Therefore, on account of the scarceness of data at hand, we prefer to formulate the compound as **9**, with no definite indication of the type of adduct.

When equimolar amounts of **9** and **1a** were mixed in the presence of pyridine at room temperature, they underwent quantitative transformation into a mixture of **7** and **2a**. Thus, the following pathway for formation of **7** as a by-product of the bromination of **1a** may be assumed. The initially formed **2a** might compete with **1a** in the reaction with bromine, and undergo further bromination to give the intermediate adduct **8**. This, in the presence of pyridine, would give the pyridinium salt **9**. The reaction of **9** with **1a** present in the reaction mixture would then lead to formation of **7** and **2a**.

Evidence for formation of a covalent adduct of type **8** on further bromination of **2a** was also obtained as follows. Bromination of **2a** in the absence of pyridine, followed by evaporation of the solvent ($CHCl_3$) gave an oily residue: this, on treatment with anhydrous benzyl alcohol afforded 3-benzyl-5-benzyloxy-1,5-diphenylhydantoin (**11a**), identical with a sample whose preparation by a different method has been described.[3] An analogous compound (**11b**) was obtained when methanol was used instead of benzyl alcohol. Either the 5-benzyloxyhydantoin **11a** or the methoxyhydantoin **11b** gave **10a** on a treatment with sulphuric acid.

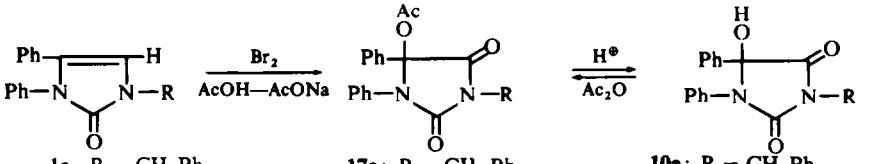
B *Bromination of* 1-*substituted* 3,4-*diphenyl*-4-*imidazolin*-2-*ones in acetic acid-sodium acetate.* A previous report[4] indicated that the bromination of 4,5-diphenyl-4-imidazolin-2-one (**14**), carried out in acetic acid in the presence of sodium acetate, gives, presumably through the intermediacy of a dibromo-adduct of type **15**, the 4,5-diacetoxyimidazolidinone **16**. It was felt of interest to investigate the reactivity of **1a** under similar conditions. It was observed that **1a** absorbed easily two molar equivalents of bromine to afford in good yield a compound, for which analytical and



14 **15** **16**

spectral data indicated the structure of 5-acetoxy-3-benzyl-1,5-diphenylhydantoin (**17a**, Scheme III). Structure proof was obtained by deacetylation of the compound to give the hydroxyhydantoin **10a**. Conversely, **10a** afforded **17a** on treatment with acetic anhydride.

SCHEME III



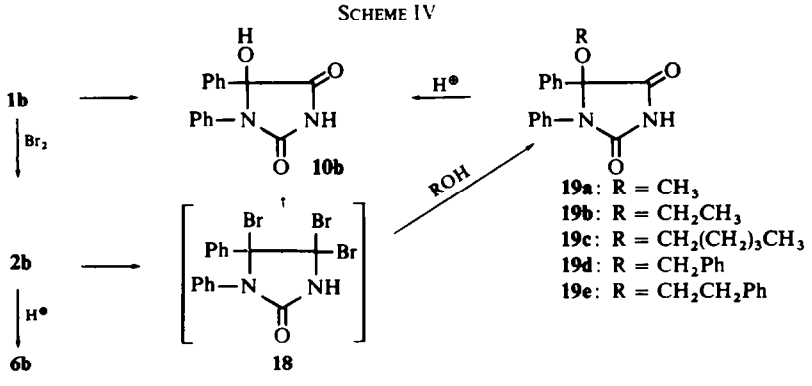
1a. R = CH_2Ph **17a**: R = CH_2Ph **10a**: R = CH_2Ph
1b: R = H **17b**: R = H **10b**: R = H
1c: R = CH_2CH_3 **17c**: R = CH_2CH_3 **10c**: R = CH_2CH_3
1d: R = $CH_2CH(CH_3)_2$ **17d**: R = $CH_2CH(CH_3)_2$ **10d**: R = $CH_2CH(CH_3)_2$
1e: R = Cyclohexyl **17e**: R = Cyclohexyl **10e**: R = Cyclohexyl

The bromination in acetic acid–sodium acetate was similarly performed on other 1-substituted 3,4-diphenyl-4-imidazolin-2-ones (**1c, d** and **e**) with analogous results. The 5-acetoxyhydantoins (**17c, d** and **e**) could be easily deacetylated to give the corresponding hydroxy derivatives **10c, d** and **e**; while a treatment of the latter compounds with acetic anhydride resulted in acetylation. Structure proof for **10a**, one of the 5-hydroxyhydantoins, was obtained by hydrolysis of the compound to a mixture of phenylglyoxylic acid (**12**) and N-benzyl-N′-phenylurea (**13**): analogous cleavages of 5-hydroxyhydantoins have been reported.[5]

C *Bromination of* 3,4-*diphenyl*-4-*imidazolin*-2-*one* (**1b**). A study on the bromination of the above compound was carried out in order to determine the effect on reactivity of unsubstitution at the 1-position. Treatment of **1b** with bromine in chloroform solution afforded, after evaporation of the solvent and crystallization from ethanol, the 4-bromo derivative **2b** in good yield, even in the absence of pyridine. The formation of a yellow pyridinium salt, analogous to **7**, was not observed when the bromination was carried out in the presence of pyridine.

It was found that, in analogy with **2a**, **2b** was unaffected by prolonged treatment with boiling 10% ethanolic KOH, but was easily converted by dilute acids into the known[6] 1,5-diphenylhydantoin (**6b**). However, **2b** is to be considered more stable than the corresponding 1-substituted bromoimidazolinones (as e.g. **2a**) in the presence of acids, since the latter compounds cannot be isolated in the absence of added pyridine.

SCHEME IV

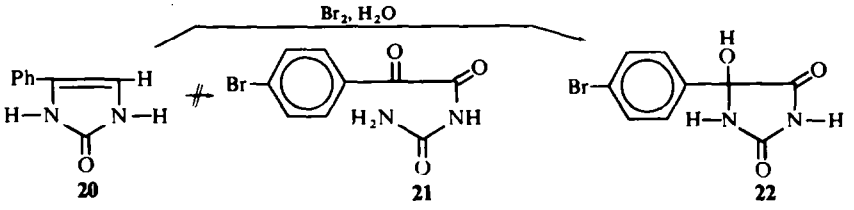


19a: R = CH_3
19b: R = CH_2CH_3
19c: R = $CH_2(CH_2)_3CH_3$
19d: R = CH_2Ph
19e: R = CH_2CH_2Ph

When **2b** was submitted to further bromination, and the crude product was treated with alcohols, conversion into 1,5-diphenyl-5-alkoxyhydantoins of type **19** (Scheme IV) resulted in good yield. Formation of these compounds can also be assumed to occur by a mechanism involving an intermediate of type **18**. All 5-alkoxyhydantoins could be hydrolyzed by treatment with sulphuric acid to give the known[7] 1,5-diphenyl-5-hydroxyhydantoin (**10b**), thus providing a proof of their structure. The same compound could also be obtained on further bromination of **2b** followed by treatment with NaOH and acidification, on oxidation of **2b** with CrO_3, or on oxidation of **1b** with HNO_3.

The bromination of **1b** in acetic acid-sodium acetate gives, in analogy with the similar treatment of **1a**, 5-acetoxy-1,5-diphenylhydantoin (**17b**, Scheme III), which can be deacetylated to **10b**. These reactions have been briefly described.[3]

D *Bromination of* 4-*phenyl*-4-*imidazolin*-2-*one* (**20**). The above compound appeared as the only 5-unsubstituted 4-imidazolinone whose bromination had been studied. Its reaction with bromine vapours followed by crystallization of the crude product from water has been reported[8] to yield *p*-bromophenylglyoxylylurea (**21**). Our attempts to brominate **20** in a variety of solvents afforded no definite product, while a treatment



20 **21** **22**

of the compound with bromine vapours gave the described product, m.p. 186–187°. However, its IR spectrum shows a typical hydantoin carbonyl absorption. This finding, and the analogy with other brominations of imidazolones reported in the present paper, led us to formulate the compound as 5-*p*-bromophenyl-5-hydroxyhydantoin (**22**), cyclic tautomer of **21**.

In conclusion, it can be said that these reactions may represent a useful new route for the preparation of 5-alkyloxy-, acetoxy- or hydroxyhydantoins. Compounds of this type have been occasionally prepared by one of the following methods: (a) treatment of alloxan with bases;[9] (b) bromination of some hydantoins, followed by treatment of the unstable 5-bromo derivatives with water or compounds possessing active hydrogens;[7,10] (c) treatment of some hydantoins with oxidating agents;[5,7] (d) condensation of pyruvic acid with urea under particular conditions.[11]

Pharmacological data for the compounds described herein, and for analogous ones, will be reported elsewhere.

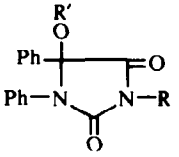
EXPERIMENTAL

M.ps (Kofler block) are uncorrected. IR spectra were recorded on nujol mulls using a Perkin–Elmer Infracord Mod. 137 spectrophotometer. UV and VIS absorption spectra were measured using a Beckman Mod. DU spectrophotometer. "Pet ether" refers to the fraction of boiling range 60–80°.

Bromination of **1a** *in* $CHCl_3$-*pyridine*

To a soln of **1a**[12] (4 g) in $CHCl_3$ (10 ml) and pyridine (2 ml), a 16·7% w/v soln of Br_2 in $CHCl_3$ (10 ml) was slowly added, while stirring and cooling externally with ice. A yellow ppt (A) separated and was collected

TABLE 1. 5-HYDROXYHYDANTOINS AND RELATED COMPOUNDS



Compd No.	R	R′	Yield %	Recrystallization Solvent[c]	m.p. °C	Molecular Formula	Analysis					
							C%		H%		N%	
							Calcd.	Found	Calcd.	Found	Calcd.	Found
10a	$-CH_2-Ph$	H	89	B	167–169	$C_{22}H_{18}N_2O_3$	73·73	73·71	5·06	5·03	7·82	8·01
10b[b]	H	H	96	B	185–187	$C_{15}H_{12}N_2O_3$	—	—	—	—	—	—
10c	$-CH_2-CH_3$	H	76	E	169–171	$C_{17}H_{16}N_2O_3$	68·90	68·66	5·44	5·66	9·45	9·28
10d	$-CH_2-CH(CH_3)_2$	H	97	E	157–160	$C_{19}H_{20}N_2O_3$	70·35	70·18	6·22	6·37	8·64	8·65
10e	Cyclohexyl	H	90	B/Ep	148–150	$C_{21}H_{22}N_2O_3$	71·98	72·14	6·33	6·24	8·00	8·19
11a[a]	$-CH_2-Ph$	$-CH_2-Ph$	90	B/Ep	121–123	$C_{29}H_{24}N_2O_3$	—	—	—	—	—	—
11b	$-CH_2-Ph$	$-CH_3$	78	E	128–130	$C_{23}H_{20}N_2O_3$	74·17	74·42	5·41	5·42	7·52	7·31
17a	$-CH_2-Ph$	$-CO-CH_3$	68	E	125–127	$C_{24}H_{20}N_2O_4$	71·98	71·80	5·03	5·03	7·00	7·02
17b[a]	H	$-CO-CH_3$	45	E/B	196–198	$C_{17}H_{14}N_2O_4$	—	—	—	—	—	—
17c	$-CH_2-CH_3$	$-CO-CH_3$	18	E	120–123	$C_{19}H_{18}N_2O_4$	67·44	67·30	5·36	5·55	8·28	8·27
17d	$-CH_2-CH(CH_3)_2$	$-CO-CH_3$	18	E	103–106	$C_{21}H_{22}N_2O_4$	68·83	68·88	6·05	6·15	7·65	7·60
17e	Cyclohexyl	$-CO-CH_3$	67	E	155–157	$C_{23}H_{24}N_2O_4$	70·39	70·12	6·16	5·87	7·14	7·35
19a	H	$-CH_3$	40	B/Ep	178–181	$C_{16}H_{14}N_2O_3$	68·07	68·26	5·00	4·84	9·92	9·92
19b	H	$-CH_2-CH_3$	72	E	166–168	$C_{17}H_{16}N_2O_3$	68·90	68·86	5·44	5·30	9·45	9·37
19c	H	$-CH_2-(CH_2)_3-CH_3$	56	B/Ep	131–133	$C_{20}H_{22}N_2O_3$	70·98	71·17	6·55	6·38	8·28	8·40
19d	H	$-CH_2-Ph$	72	E	176–178	$C_{22}H_{18}N_2O_3$	—	—	—	—	—	—
19e	H	$-CH_2-CH_2-Ph$	50	B/Ep	167–169	$C_{23}H_{20}N_2O_3$	74·17	74·20	5·41	5·25	7·52	7·47

[a] Cf. Ref. 3. [b] Cf. Ref. 7. [c] B = benzene; Ep = pet ether, boiling range 60–80°; E = ethanol.

by filtration. The filtrate from (A), after addition of Et_2O (50 ml), was thoroughly washed with H_2O, dried ($MgSO_4$) and partially evaporated. Addition of pet ether caused crystallization of **2a** (2·3 g) as colourless needles, m.p. 126–128°; λ_{CO} 5·87 μ. (Found: C, 65·00; H, 3·95; N, 7·25; Br, 19·74. $C_{22}H_{17}N_2OBr$ requires: C, 65·19; H, 4·22; N, 6·91; Br, 19·71%).

The above compound was recovered unchanged after a 6 hr heating under reflux in a 30% alcoholic soln of KOH. A 5 min reflux in a 3% ethanolic soln of H_2SO_4 caused conversion of **2a** in practically quantitative yield into **6a**,[12] m.p. 186–188°.

The ppt (A), 600 mg, consisted of pure **7**. It gave yellow prisms from EtOH, m.p. 268–269°; λ_{CO} 5·98 μ; λ_{max} (ε) in 95% EtOH, 257 (1·40 × 10^4) and 398 (1·16 × 10^3) mμ. (Found: C, 67·04; H, 4·41; N, 8·75; Br, 16·16. $C_{27}H_{22}N_3OBr$ requires: C, 66·94; H, 4·57; N, 8·67; Br, 16·49%).

A brief treatment with a dil alcoholic soln of H_2SO_4 under reflux, as described for **2a**, caused conversion of **7** into the hydantoin **6a** in 90% yield.

Compound **9**

(a) *From* **2a**. To a soln of **2a** (0·25 g) in $CHCl_3$ (3 ml) and pyridine (0·2 ml), a 16·7% w/v soln of Br_2 in $CHCl_3$ (0·6 ml) was slowly added, while stirring at room temp. The pink solid which separated was collected, washed with $CHCl_3$ and dried (0·2 g). The product was not purified; m.p. 184–187°; λ_{CO} 5·90 μ. (Found: Br, 37·45. $C_{27}H_{22}N_3OBr_3$ requires: Br, 37·26%).

(b) *From* **7**. To a stirred suspension of **7** (70 mg) in $CHCl_3$ (2 ml) and pyridine (0·1 ml), 0·3 ml of a 16·7% w/v soln of Br_2 in $CHCl_3$ was added. Stirring was continued 30 min, then the solid was collected, washed with $CHCl_3$ and dried to give **9** (50 mg).

Reactions of **9**

(a) *Conversion to* **7**. Crystallization of **9** from EtOH–H_2O resulted in practically quantitative conversion to **7**.

(b) *Treatment with acid*. A suspension of **9** (250 mg) in 10% H_2SO_4 aq was refluxed until the yellow colour had disappeared, then the solid was collected (0·3 g) and crystallized from EtOH–H_2O to afford **10a** (110 mg); λ_{CO} 5·61 (w), 5·85 (s) μ; other data, cf Table 1.

(c) *Reaction with* **1a**. A finely powdered mixture of **9** (0·45 g) and **1a** (0·23 g), suspended in $CHCl_3$ (15 ml) and pyridine (0·2 ml) was stirred overnight at room temp. The yellow solid was then collected (0·3 g) and identified as **7**. Evaporation of the solvent and crystallization of the residue from benzene–pet ether gave pure **2a** (0·2 g).

3-Benzyl-5-benzyloxy-1,5-diphenylhydantoin (**11a**) *and 3-benzyl-5-methoxy-1,5-diphenylhydantoin H*(**11b**)

To a suspension of finely ground **2a** in $CHCl_3$ (4 ml) and pyridine (0·2 ml), a 16·7% w/v soln of Br_2 in $CHCl_3$ (0·5 ml) was added at room temp. Benzyl alcohol (0·5 ml) was then added to the resulting homogeneous soln, and the mixture was evaporated under reduced press. Crystallization of the residue from EtOH–H_2O afforded **11a** (0·3 g; phys. constants, Table 1), identical with an authentic sample.

When MeOH instead of benzyl alcohol was added to the mixture, compound **11b** (Table 1) was obtained.

The same compounds **11a** and **11b** were obtained in analogous yields when **1a** (instead of **2a**) was used as starting material, and the amount of added Br_2 was doubled.

Hydrolysis of **11a** *and* **11b**

The above compounds (0·1 g) were dissolved in cold conc H_2SO_4 (3 ml). The solns, which showed a deep cherry-red colour (λ_{max} 350–355 mμ) were then poured onto cracked ice. The resulting ppts were collected and crystallized from EtOH–H_2O to afford pure **10a** (75–80% yield).

Bromination of **1a** *and other 1-substituted 4-imidazolinones in acetic acid-sodium acetate*

5-Acetoxyhydantoins **17a, c, d, e**. The preparation of the starting materials, **1c, d** and **e** has been described.[1] The general bromination procedure is as follows: Freshly fused AcONa (0·3 g) was dissolved in a warm soln of the imidazolone (0·01 mole) in glacial AcOH (3 ml). To the cooled soln, a 3% w/v solution of Br_2 in glacial AcOH (9·5 ml) was added; the mixture was then poured into H_2O (100 ml). The white ppt was collected, washed with H_2O and crystallized from EtOH to afford the 5-acetoxyhydantoin (Table 1). All compounds showed a typical hydantoin carbonyl absorption, λ_{CO} 5·60(w) and 5·80(s) μ.

5-Hydroxyhydantoins **10a, c, d, e**. The above 5-acetoxyhydantoins **17** (0·5 g) were added portionwise, while stirring, to cold conc H_2SO_4 (15 ml). The resulting deep-red solns (λ_{max} 350–355 mμ) were then poured

onto cracked ice; the white ppts were collected and crystallized from the appropriate solvent to afford the hydroxy derivatives **10** in the yields reported in Table 1. All compounds showed OH absorption in the 2·9–3·0 μ region and CO absorption in the 5·60–5·65(w) and 5·85–5·90(s) μ regions.

All 5-hydroxyhydantoins, on treatment with Ac_2O at 120° for 3 hr gave, after the usual workup, the corresponding 5-acetoxy hydantoins in excellent yields.

Structure proof of **10a**. Compound **10a** (0·5 g) was dissolved, with gentle warming, in 10% NaOH aq (10 ml): precipitation of a white solid ensued almost immediately. This was collected, washed with H_2O, dried (250 mg) and identified as **13**, m.p. 168–170° (lit.[13] m.p. 170°), identical with an authentic sample. The filtrate from **13** was acidified with 10% HCl aq and extracted with Et_2O. Evaporation of the dried ($MgSO_4$) ethereal extract afforded **12** (160 mg), m.p. 64–65° (lit.[14] m.p. 65–66°), identical with an authentic sample.

Bromination of **1b**

5-Bromo-4,5-diphenyl-4-imidazolin-2-one (**2b**). To a suspension of **1b** (1 g) in $CHCl_3$ (15 ml) was slowly added, while stirring and cooling externally with ice, a 16·7% w/v soln of Br_2 in $CHCl_3$ (4 ml). The resulting soln was evaporated under reduced press, and the oily residue was treated with a little EtOH. This produced copious evolution of HBr and separation of a solid, which was collected and crystallized from EtOH to afford **2b** (0·85 g), m.p. 225–227°; λ_{CO} 5·71 μ. (Found: C, 57·02; H, 3·45; N, 8·80; Br, 25·70. $C_{15}H_{11}N_2OBr$ requires: C, 57·17; H, 3·53; N, 8·80; Br, 25·40%).

Concentration of the ethanolic mother liquors from **2b** afforded a small amount of **19b**.

1,5-*Diphenylhydantoin* (**6b**). A soln of **2b** (0·1 g) in 3% ethanolic H_2SO_4 (6 ml) was heated 1 hr under reflux. Dilution with H_2O caused crystallization of pure **6b** (60 mg), m.p. 204–206°, identical with an authentic sample.[6]

1,5-*Diphenyl-5-alkoxyhydantoins* (**19a–e**)

General procedure. To a suspension of **2b** (0·5 g) in $CHCl_3$ (10 ml), a 16·7% w/v solution of Br_2 in $CHCl_3$ (1·5 ml) was added slowly, with stirring. The solvent was then evaporated, and the oily residue was treated with twice the theoretical amount of the appropriate alcohol. The resulting mixture was heated 10–15 min on a steam bath. Evaporation of the excess alcohol under reduced press followed by crystallization of the residue from EtOH–H_2O afforded the 5-alkoxyhydantoin (yields and physical constants are reported in Table 1).

1,5-*Diphenyl-5-hydroxyhydantoin* (**10b**)

(a) *From alkoxyhydantoins* (**19**). The compounds **19**, on treatment with conc H_2SO_4 as described for the hydrolysis of **11a** and **11b**, gave **10b** in average 90% yield. The product was identical with an authentic sample.[7]

(b) *By bromination of* **2b**. Compound **2b** was brominated as described for the preparation of 5-alkoxyhydantoins **19**. After evaporation of the solvent, the oily residue was dissolved in 10% NaOH. Acidification of the soln caused precipitation of **10b** in 88% yield.

(c) *By chromic acid oxidation of* **2b**. A soln of **2b** (0·4 g) in glacial AcOH (20 ml) was treated with a 8N soln of CrO_3 in AcOH (0·32 ml). The mixture was heated 5 min at 70°, then was diluted with H_2O and extracted with Et_2O. Evaporation of the dried ($MgSO_4$) ethereal extract afforded **10b** in 65% yield.

(d) *By nitric acid oxidation of* **1b**. To a well cooled soln of **1b** (0·5 g) in glacial AcOH (5 ml) HNO_3 (*d*. 1·50, 1·5 ml) was slowly added. The solid which separated was collected and crystallized from EtOH to give **10b** in 60% yield.

Bromination of **20**: 5-p-*bromophenyl-5-hydroxyhydantoin* (**22**)

Finely powdered **20**[15] (2 g) was exposed to Br vapours at room temp for 12 hr. The resulting oily material was worked up as indicated by Rupe[8] to afford a crystalline product, m.p. 185–186° (1·5 g); IR spectrum, λ_{max} 2·98, 3·03, 5·67 (w), 5·81 (s), 7·08, 8·05, 9·12, 9·85, 10·45, 11·94, 12·85, 13·0 μ. (Found: C, 40·01; H, 2·44; N, 10·47; Br, 29·75. $C_9H_7N_2O_3Br$ requires: C, 39·85; H, 2·58; N, 10·33; Br, 29·52%).

REFERENCES

[1] M. F. Saettone and V. Nuti, *J. Pharm. Sci.* **57**, 1798 (1968).
[2] Cf e.g. R. Gompper and H. Rühle, *Liebigs Ann.* **626**, 83 (1959).
[3] A. Marsili, M. F. Saettone and E. Bucci, *J. Org. Chem.* **33**, 2884 (1968).

[4] H. Greenberg, T. van Es and O. G. Backeberg, *Ibid.* **31**, 3951 (1966).
[5] H. Aspelund, *Acta Acad. Aboensis, Math. Phys.* **46**, 3 (1962).
[6] [a] G. A. Holmberg, *Finska Kemistsamhandets Medd.* **59**, 25 (1950);
[b] E. Testa and R. Ettorre, *Arch. Pharm.* **290**, 532 (1957).
[7] G. A. Holmberg, *Acta Chem. Scand.* **4**, 821 (1950); cf also Ref. 5.
[8] H. Rupe, *Ber. Dtsch. Chem. Ges.* **28**, 251 (1894).
[9] See e.g. F. R. Fisher and A. R. Day, *J. Am. Chem. Soc.* **77**, 4894 (1955), and Refs therein.
[10] [a] S. Gabriel, *Liebigs Ann.* **350**, 118 (1906);
[b] J. Klosa, *Arch. Pharm.* **285**, 274 (1952);
[c] K. Bodendorf and N. Schölzel, *Ibid.* **292**, 558 (1959).
[11] S. Murahashi, H. Yuki, K. Kosai and F. Doura, *Bull. Chem. Soc. Japan* **39**, 1559 (1966).
[12] M. F. Saettone, *J. Org. Chem.* **31**, 1959 (1966).
[13] H. Ley and P. Krafft, *Ber. Dtsch. Chem. Ges.* **40**, 697 (1907).
[14] L. Claisen, *Ibid.* **10**, 429 (1877).
[15] H. Rupe, *Ibid.* **27**, 582 (1894).