Further Reactions of 3-Hydroxy-1(3*H*)-isobenzofuranone with Amines

Kenneth B. Sloan* and Suzanne A. M. Koch

College of Pharmacy, University of Florida,
Gainesville, Florida 32610

Received September 12, 1984

The reaction of 3-hydroxy-1(3*H*)-isobenzofuranone (III) with 2-phenylethylamines has been shown to give either monoalkylated VI or dialkylated VII products (prodrugs) depending on the number of equivalents of III used. The monoalkylated products disproprotionated to the dialkylated products unless they were stabilized as salts. In addition, the reaction of III with cytosine and adenine resulted in the formation of N^4- and N^6-alkylated products, respectively. The alkylated 2-phenylethylamines, and cytosine and adenine are representative of a new type of prodrug approach to modifying the physical chemical properties of these two important classes of drugs.

J. Heterocyclic Chem., **22**, 429 (1985).

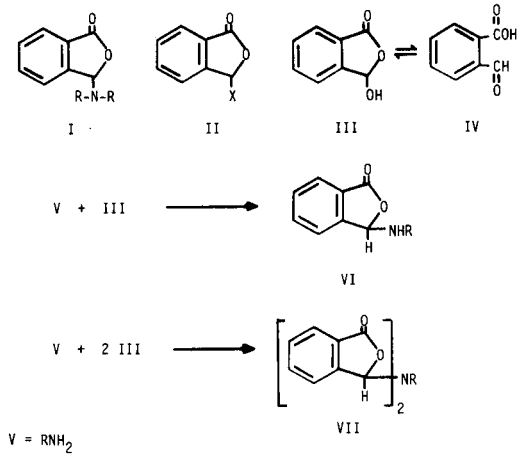
Introduction.

Recent interest in 3-amino-1(3*H*)-isobenzofuranones I has centered on two aspects of their chemistry. First, the reactions of 3-halo-1(3*H*)-isobenzofuranones II with amines to give I have provided useful insights into the effects of nucleophilicity and nucleofugicity on S_N2 reactions [1-3]. Second, the formation of I is reversible in water [4] so that there is a potential use for I as protected or latentiated (prodrug) forms of drugs that contain amino groups [5]. The most convenient synthesis of I, except for the 3-(1′-imidazolyl) derivatives which are prepared from the reactions of imidazoles with II [1], is from the reactions of 3-hydroxy-1(3*H*)-isobenzofuranones III with amines [6]. The reaction of III with secondary amines is straightforward since only a monoalkylated product can be obtained but with primary amines dialkylation as well as monoalkylation is possible [6]. Since monoalkylation introduces less lipophilicity into the product (prodrug) than dialkylation, and a balance between lipophilicity and hydrophilicity is necessary for efficient prodrug facilitated drug absorption [7-8], the conditions and structural parameters that could lead to optimization of monoalkylation of primary amines by III have been investigated. The results for models of two classes of drugs are reported here.

Results and Discussion.

The reaction of III with primary aliphatic amines has been reported to give only dialkylated products regardless of the equivalents of III used, except for the reactions of III with sterically hindered amines such as benzylamine or *t*-butylamine [6] which gave monoalkylated products, or for severely hindered amines such as dicyclohexylamine which gave the salt of IV [6]. Moreover, if refluxing methanol was used as the solvent, the dialkylated product was obtained even from the reaction of one equivalent of III with benzylamine [9]. Therefore, the reaction of III with primary amines exhibiting various degrees of steric hindrance to alkylation were examined under conditions that might influence the course of the reaction.

SCHEME I



V = RNH_2

Va, R = $-CH_2CH_2CH_3$

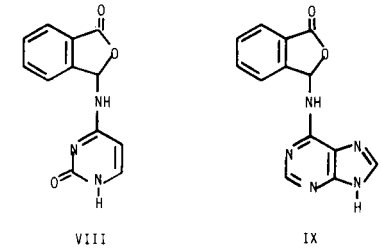
Vb, R = $-CH_2-C_6H_5$

Vc, R = $-CH_2CH_2-C_6H_5$

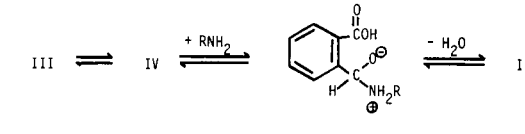
Vd, R = $-CH_2CH_2-C_6H_3-3,4-(OCH_3)_2$

Ve, R = $-CH_2CH_2-C_6H_4-4-OH$

Vf, R = $-CH_2CH_2CH_2CO_2H$



SCHEME II



In the case of propylamine, the dialkylated product was obtained as reported [9] regardless of whether the reaction with one equivalent of III was run at ice bath temperature or reflux, in a protic (methanol) or aprotic (dichloromethane) solvent, and regardless of the order of addition. In the case of the sterically hindered amine-benzylamine-only the number of equivalents of III used affected the course of the reaction; choice of solvent or order of addition had no effect. Further, the monoalkylated product was stable in solution or in the solid state towards disproportionation to the dialkylated product.

On the other hand, in the case of 2-phenylethylamine, which was less sterically hindered than benzylamine but more sterically hindered than propylamine, the monoalkylated product VIc could be obtained from the reaction of one equivalent of III with Vc in an aprotic solvent, but the product had to be quickly isolated (3 hours) and stabilized as its methanesulfonic acid salt otherwise it disproportionated to the dialkylated product VIIc overnight. Similarly, the reaction of one equivalent of III with Vd gave a monoalkylated product VId that had to be stabilized as its methanesulfonic acid salt to prevent it from disproportionating to VIId. In the cases of both Vc and Vd, their reactions with two equivalents of III gave good yields of dialkylated products VIIc and VIId, respectively, although the reaction usually took overnight to go to completion. Mixtures of mono- and dialkylated products and unreacted III were isolated if the reactions were processed as quickly as the monoalkylation reactions.

In the cases of primary aliphatic amines with additional polar groups attached to the molecule, it was not possible to isolate the monoalkylated products. For instance, in the case of Ve (which is a 2-phenylethylamine as are Vc and Vd), if a protic solvent such as methanol or an aprotic solvent such as dimethylformamide was used, mixtures of a di- and apparently a monoalkylated product were obtained regardless of how quickly the product was isolated. Compound Vc was soluble in those solvents so that the amine was always present in excess during the reaction, but, if a solvent such as dichloromethane was used in which Ve was not soluble, only the dialkylated product was obtained. Not unexpectedly, the reaction of III with 4-aminobutyric acid, which sould be similar to propylamine, gave only the dialkylated product VIIf regardless of the stoichiometry used. However it was surprising that the alkylated product was obtained from water - a solvent in which it is inherently unstable (see below).

Although the O-CH-N absorption in the nmr spectra of the dialkylated products VIIa, VIIb, VIIc and VIId appeared as single absorptions, the O-CH-N absorptions of VIIe and VIIf appeared as two sets of absorptions. In each case the upfield absorptions in the spectra of the crude products were much more intense than in the spectra of the recrystallized products. For example, in the case of VIIe the intensity of the upfield absorption decreased from 90% to 75% of the total O-CH-N absorption upon recrystallization. In fact, all of the dialkylated products can exist as a set of diastereomers (each of which would be composed of a set of enantiomers, *i.e., RS, SR* and *RR, SS*) because two asymmetric O-CH-N carbons are introduced nonspecifically into the products during the alkylation process. Consequently, all of the dialkylated products can exhibit two O-CH-N absorptions in their nmr spectra. Since the formation of any of these alkylated products involves the reversible reaction of the amine with the aldehyde group in the very small amount of ring opened tautomer of III (IV) in solutions of III [4] (see Scheme II) followed by reversible ring closure to I [4], the ratio of diastereomers is not always fixed by the initial reaction conditions, but changes with changes in solvent and temperature.

The alkylation of amino purines and pyrimidines with III was also studied because of the great number of drugs which contain those ring systems, and which need to be converted to more lipophilic derivatives to facilitate their absorption. Although adenine and cytosine formally contain primary amino groups, those exocyclic amino groups are essentially non-basic, exhibiting p*ka*'s in the region of -3 to -1 [10] based on the kinetics of their reactions with formaldehyde. Thus, the reaction of cytosine and adenine with III is entirely different from the reactions of V with III, and should be more similar to the reactions of III with amides. In fact, the reaction conditions that were finally found to give acceptable yields of alkylated adenine and cytosine (IX and VIII) were considerably more vigorous than any conditions used to affect alkylation of any other functional groups containing nitrogen [6,9]. The products (which are formally acyloxyalkyl derivatives) are more lipid soluble than their parent compounds [11]. Since the alkylated products can not be obtained from the reaction of (acyloxy)alkyl α-halides (*e.g.*, II) with adenine [12] or cytosine [11], the approach reported here offers a unique alternative for the syntheses of these types of derivatives of adenine or cytosine type molecules.

Since the reactions of formaldehyde with adenine and cytosine are generally considered to give alkylation on the exocyclic amino groups [13] and the reaction of III with amines is generally considered [4] to take place through the aldehyde tautomer IV, the alkylated cytosine and adenine compounds have been tentatively assigned N^4- and N^6-structures. In addition, ethoxymethylation [14], aminomethylation [15] and thiomethylation [16] of cytosine and adenine type molecules have been shown to take place on the exocyclic amino groups so that the assigned structures are consistent with the results of previous reactions of aldehydes with adenine and cytosine.

The spectroscopic evidence also suggests that alkylation has taken place on the exocyclic amino group. There are

two different types of N-H absorptions in the nmr spectra of VIII and IX. On the other hand, endocyclic alkylation would lead to products containing the intact exocyclic amino groups in the predominant tautomer, for instance in cytosine [17], which should appear as a single type of N-H absorption. The uv spectra of VII and IX exhibit bathochromic shifts in their absorption maxima in going from neutral to acid or basic solutions which are more consistent with exocyclic than endocyclic amine alkylation [18]. Thus, the preponderance of this data suggests that the assignment of VIII and IX is correct.

Although there was no question about whether the monoalkylation of amines was reversible [4], no one had previously examined the hydrolyses of the dialkylated derivatives VII. The results of some preliminary aqueous stability studies on representative VII showed that in a mixture of water and methanol the tryamine derivative VIIe and the 4-aminobutyric acid derivative VIIf hydrolyzed the quickest (complete dissolution and conversion to III and 3-methoxy-1(3*H*)-isobenzofuranone (X) took place in 22 and 24 hours, respectively), while the 2-(3',4'-dimethoxyphenyl)ethylamine derivative VIId took about 40 hours to dissolve and hydrolyze. The formation of variable amounts of X was the result of the reaction of III with methanol in the dichloromethane extracts during their concentration [6]. Examination of the water-methanol solutions by tlc and nmr spectroscopy during the first 0.2 hour of the hydrolyses showed only intact VII present in the solutions.

EXPERIMENTAL

The tlc were run on Brinkman Polygram Sil G/UV 254. The mp (corrected) were taken with a Thomas-Hoover capillary apparatus. The nmr spectra were recorded on a Varian T-60 or EM-390 spectrometer, ir spectra on a Beckman Accu Lab 1 spectrophotometer, and uv spectra on a Beckman model 25 spectrophotometer. The low *p*H spectra were obtained by adding one drop of 12*N* hydrochloric acid and the high *p*H spectra by adding one drop of 10% sodium hydroxide to the methanol solutions used to obtain the neutral uv spectra [19]. Microanalyses were obtained from Atlantic Microlab Inc., Atlanta, GA. Except for 3-hydroxy-1(3*H*)-isobenzofuranone, which was obtained from Aldrich, the chemical starting materials were obtained from Sigma. The bulk solvents were obtained from Fisher.

The following products were obtained by allowing one or two equivalents of III to react with the appropriate amines at room temperature, usually in dichloromethane, for from one to twenty-four hours. The solutions were dried over sodium sulfate and filtered. The filtrates were concentrated at room temperature and the residue either crystallized or stabilized by converting the free base in dichloromethane solution to its methanesulfonic acid salt. In the case of 4-aminobutyric acid (Vf) the reaction was run in water and a suspension was obtained. When the reaction was completed, the whole reaction mixture was concentrated and that residue was crystallized.

N,N-Bis[1(3*H*)-isobenzofuranon-3-yl]propylamine (VIIa).

This compound was obtained from the reaction of one equivalent of III with Va, 44% yield, mp 178-179° from ethyl acetate (lit mp 175-176° [9]); nmr (deuteriochloroform): δ 6.27 (s, O-CH-N, 2H), 3.0-2.0 (m, N-CH_2, 2H).

N-[1(3*H*)-Isobenzofuranon-3-yl]benzylamine (VIb).

This compound was obtained from the reaction of one equivalent of III with Vb, 75% yield, mp 90-92° from ether-petroleum ether (lit mp 86-89° [6]); nmr (deuteriochloroform): δ 6.37 (s, O-CH-N, 1H), 4.07 (s, N-CH_2, 2H).

N,N-Bis[1(3*H*)-isobenzofuranon-3-yl]benzylamine (VIIb).

This compound was obtained from the reaction of two equivalents of III with Vb, 70% yield, mp: part at 141-143°, rest at 150-152° (lit mp 143-145° [6]); nmr (deuteriochloroform): δ 6.2 (s, O-CH-N, 2H), 4.3-3.5 (m, N-CH_2, 2H); tlc (silica gel, ether): two spots Rf 0.67, Rf 0.55.

N-[1'(3'*H*)-Isobenzofuranon-3'-yl]phenylethylamine (VIc).

This compound was obtained from the reaction of one equivalent of III with Vc as its methanesulfonic acid salt, 70% yield, foamed 108-110° from dichloromethane-tetrahydrofuran-ether; nmr (deuteriochloroform): δ 8.1-7.6 (m, aromatic and O-CH-N, 5H), 7.3 (s, aromatic, 5H), 4.1-3.7 (m, CH_2-N, 2H), 3.4-3.1 (m, CH_2-aromatic, 2H), 2.81 (s, CH_3SO_3, 3H); nmr (deuteriochloroform) of the free base: δ 6.37 (s, OCH-N, 1H), 3.3-3.05 (m, CH_2-N, 2H), 2.95-2.7 (m, aromatic CH_2, 2H).

Anal. Calcd. for $C_{17}H_{19}NO_5S \cdot 0.5H_2O$: C, 56.97; H, 5.62. Found: C, 57.06; H, 5.68.

N,N-Bis[1'(3'*H*)-isobenzofuranon-3'-yl]phenylethylamine (VIIc).

This compound was obtained from the reaction of two equivalents of III with Vc, 65% yield, mp 154-156° from ether; tlc (silica gel, ether) Rf 0.30; nmr (deuteriochloroform): δ 8.1-6.9 (m, aromatic, 11H), 6.26 (s, O-CH-N, 2H), 3.45-2.6 (m, N-CH_2-CH_2, 4H).

Anal. Calcd. for $C_{24}H_{19}NO_4$: C, 74.79; H, 4.97. Found: C, 74.82; H, 5.00.

N-[1''(3''*H*)-Isobenzofuranon-3''-yl]-2-(3',4'-dimethoxyphenyl)ethylamine (VId).

This compound was obtained from the reaction of one equivalent of III with Vd as its methanesulfonic acid salt, 76% yield, foamed 112-116° from dichloromethane-ether; nmr (deuteriochloroform): δ 8.9-7.3 (m, NH_2, O-CH-N and aromatic, 7H), 6.67 (s, aromatic, 3H), 3.83 (s, OCH_3, 6H), 3.4-2.9 (m, N-CH_2CH_2, 4H), 2.76 (s, CH_3SO_3, 3H); nmr (deuteriochloroform) of the free base: δ 6.30 (s, O-CH-N, 1H).

Anal. Calcd. for $C_{19}H_{23}NO_7S \cdot 0.5H_2O$: C, 54.51; H, 5.78; N, 3.35. Found: C, 54.32; H, 5.84; N, 3.41.

N,N-Bis[1''(3''*H*)-isobenzofuranon-3''-yl]-2-(3',4'-dimethoxyphenyl)ethylamine (VIId).

This compound was obtained from the reaction of two equivalents of III with Vd, 66% yield, mp 160-162° from methanol; nmr (deuteriochloroform): δ 8.0-6.25 (m, aromatic, 11H), 6.23 (s, O-CH-N, 2H), 3.83, 3.80 and 3.71 (three s, OCH_3, 6H), 3.35-2.4 (m, N-CH_2CH_2, 4H); tlc (silica gel, ether-methanol, 10:1) Rf 0.25.

Anal. Calcd. for $C_{26}H_{23}NO_6$: C, 70.10; H, 5.20; N, 3.15. Found: C, 69.96; H, 5.20; N, 3.13.

N,N-Bis[1''(3''*H*)-isobenzofuranon-3-yl]-2-(4'-hydroxyphenyl)ethylamine (VIIe).

This compound was obtained from the reaction of two equivalents of III with Ve, 60% yield, mp 193-194° from chloroform-ether-hexane; nmr (deuteriodimethylsulfoxide:deuteriochloroform): δ 8.70 (s, OH, 1H), 7.95-7.20 (m, aromatic, 8H), 6.75 (s, aromatic, 3H), 6.53 (s, aromatic, 1H), 6.40 (s, O-CH-N, 0.5H), 6.20 (s, O-CH-N, 1.5H); tlc (silica gel, ether) Rf 0.23.

Anal. Calcd. for $C_{24}H_{19}NO_5$: C, 71.81; H, 4.77; N, 3.49. Found: C, 71.57; H, 4.83; N, 3.42.

N,N-Bis[1'(3'*H*)-isobenzofuranon-3'-yl]-4-aminobutyric acid (VIIf).

This compound was obtained from the reaction of two equivalents of III with Vf, 66% yield, mp 178-180° from ether-chloroform; nmr (deuteriodimethylsulfoxide): δ 7.85-7.35 (m, aromatic, 8H), 6.8 (s, O-CH-N, 0.75H), 6.37 (s, O-CH-N, 1.25H), 3.3-0.9 (m, N-$CH_2CH_2CH_2$, 6H); tlc (silica

gel, ether) Rf 0.04, Rf 0.17.

Anal. Calcd. for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.67; N, 3.81. Found: C, 65.32; H, 4.67; N, 3.79.

N^4-[1′(3′*H*)-Isobenzofuranon-3′-yl]cytosine (VIII).

A mixture of cytosine (0.55 g, 0.005 mole) and III (0.75 g, 0.005 mole) was heated on a hot plate at 200° for 2 minutes. The melt that was obtained was dissolved in 150 ml of boiling ethanol which was concentrated to 50 ml and cooled to give 0.37 g (mp >250°, 30% yield) of VIII; uv (methanol): λ max 283 (shoulder, $\epsilon = 7.9 \times 10^3$ l/mole), 275 nm ($\epsilon = 8.7 \times 10^3$ l/mole); uv (methanol, H^+): λ max 289 nm (shoulder, $\epsilon = 1.19 \times 10^4$ l/mole), 283 nm ($\epsilon = 1.2 \times 10^4$ l/mole); uv (methanol, OH^-): λ max 286 nm ($\epsilon = 9.79 \times 10^3$ l/mole); nmr (deuteriodimethylsulfoxide): δ 11.0-10.33 (m, N-H, 1H), 8.33-8.30 (m, N-H, 1H), 7.54 (d, J = 7 Hz, CH=C, 1H), 5.74 (d, J = 7 Hz, CH=C, 1H), 8.0-7.3 (m, aromatic and O-CH-N, 5H); tlc (silica gel, ether-methanol, 10:2) Rf 0.33.

Anal. Calcd. for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.73; N, 17.27. Found: C, 59.03; H, 3.70; N, 17.21.

N^6-[1′(3′*H*)-Isobenzofuranon-3′-yl]adenine (IX).

A mixture of 0.68 g (0.005 mole) of adenine and 0.75 g (0.005 mole) of III was heated on a hot plate at 200° for 2 minutes. The reaction mixture was crystallized twice from boiling ethanol to give 0.73 g (mp >250°, 55% yield) of IX; tlc (silica gel, ether-methanol, 10:2) Rf 0.40; uv (methanol): λ max 275 nm (shoulder, $\epsilon = 1.4 \times 10^4$ l/mole), 266 nm ($\epsilon = 1.78 \times 10^4$ l/mole); uv (methanol, H^+): λ 278 nm ($\epsilon = 2.2 \times 10^4$ l/mole); uv (methanol, OH^-): λ max 278 nm ($\epsilon = 1.42 \times 10^4$ l/mole); nmr (deuteriodimethylsulfoxide): δ 13.5-13.2 (m, N-H, 1H), 9.35-9.25 (m, N-H, 1H), 8.30 (s, N=CH-N, 1H), 8.20 (s, N=CH-N, 1H), 8.0-7.5 (m, aromatic and O-CH-N, 5H).

Anal. Calcd. for $C_{13}H_9N_5O_2$: C, 58.43; H, 3.39; N, 26.21. Found: C, 58.31; H, 3.44; N, 26.23.

Hydrolyses of 1(3*H*)-Isobenzofuranon-3-yl Derivatives. The procedure was a modification of the method of Bender, *et al.*, [4]. Suspensions of 0.20 g each of the derivatives VIId, VIIe and VIIf in 120 ml of water-methanol (1:1) were stirred at room temperature for up to 72 hours. Samples of the suspended materials were analyzed periodically to determine what the suspended materials were by nmr spectroscopy, tlc and mp. If the suspensions were completely dissolved, as soon as dissolution was complete the solution that resulted were treated with 1 ml of concentrated hydrochloric acid and were extracted with 150 ml of dichloromethane. The dichlormethane layers were dried over sodium sulfate and concentrated. The residues were analyzed by nmr spectroscopy, tlc and mp. In each case the residue was a mixture of III and 3-methoxy-1(3*H*)-isobenzofuranone (X); III, mp 96-98° (lit mp 97-98° [4]); tlc (silica gel, ether) Rf 0.5; and nmr (deuteriochloroform): δ 8.0-7.4 (m, aromatic, 4H), 6.9 (s, O-CH-OH, 1H) and 4.3-4.0 (m, OH, 1H); X, mp 42°, (lit mp 42-44° [4]); tlc (silica gel, ether) Rf 0.56; nmr (deuteriochloroform): δ 8.0-7.35 (m, aromatic, 4H), 6.3 (s, O-C*H*-OCH_3, 1H) and 3.63 (s, O-CH-OCH_3, 3H). The material balance for compounds containing the furanone moiety was 73% for VIId, 72% for VIIe and 60% for VIIf.

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