

Perhaloketones XIX (1). Derivatives of Benzo-*N*-heterocycles

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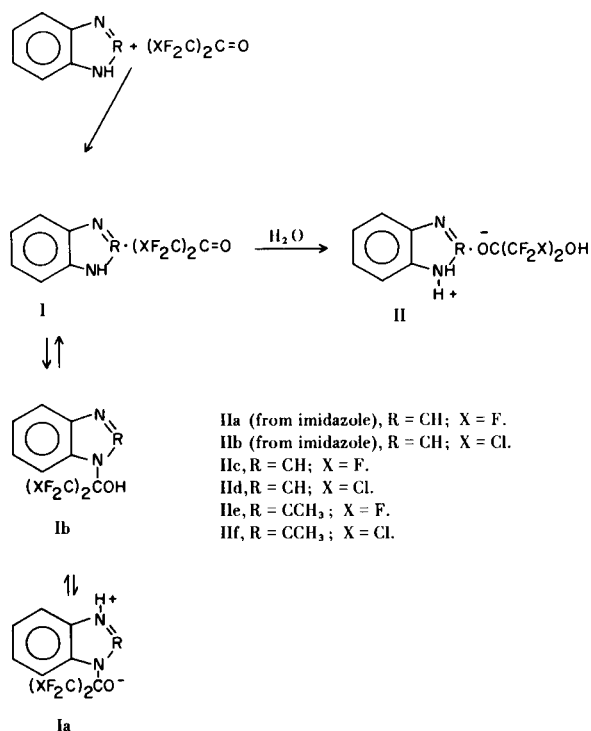
A study was made of the behavior of imidazole and six benzo-*N*-heterocyclic compounds upon direct treatment with anhydrous and hydrated hexafluoro- and *sym*-tetrafluorodichloroacetones. Two of the compounds did not react, and four gave addition compounds. Indole reacted with both ketones in the 3-position. Heterocyclic precursors were made by reacting *o*-phenylenediamine, *o*-aminophenol, and *o*-aminobenzenethiol with hexafluoroacetone hydrate, thus introducing the 2-hydroxyhexafluoro-2-propyl moiety into the ring *para* to the amino group. A similar product was made from *o*-phenylenediamine and tetrafluorodichloroacetone. These compounds were then converted to twenty-eight heterocyclic derivatives. Four of the latter underwent haloform cleavage of the hydroxyhexahalopropyl group, a novel, but not widely applicable, preparative approach to the corresponding heterocyclic carboxylic acids.

In the course of a program on the chemistry of perhaloketones, it was desired to prepare a series of nitrogen-containing benzoheterocycles substituted on the aromatic moiety by the 2-hydroxyhexahalopropyl groups (structures VIII, IX, X and XI), as derived from hexafluoro- and *sym*-tetrafluorodichloroacetones.

Our initial approach involved heating several unsubstituted heterocycles with the ketone hydrate, a procedure previously employed by us (2) and by others (3) for this type of ring substitution of aromatic amines. This technique in no case gave the desired type of product, even after prolonged heating. Carbazole and 2-benzoxazolinone were unchanged. Four compounds gave salt-like addition compounds, as indicated in Table I.

Three of the compounds gave moderately stable adducts comprising one mole each of heterocycle, ketone and water (IIa-f) (*cf.* Table I):

With benzimidazole and 2-methylbenzimidazole, the adducts could be prepared by starting with the anhydrous ketones, as well as from the ketone hydrates. With the anhydrous ketones, adducts with the bases were first formed; these upon exposure to atmospheric moisture gave the more stable monohydrated products. The imidazole adducts were prepared from the anhydrous ketones followed by exposure to air, or by adding a stoichiometric quantity of water. Only non-crystalline adducts with a higher degree of hydration resulted from the treatment of imidazole with hexafluoroacetone trihydrate.



Since the gem-diols of hexafluoro- and tetrafluoro-dichloroacetones are fairly strong acids (4), it is not surprising that their salts (IIa-f) should be quite stable. The corresponding adducts from the anhydrous ketones are considerably less stable, as evidenced by the low yield

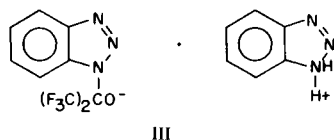
TABLE I  
Benzo-*N*-Heterocycle-Perhaloacetone Adducts

Heterocycle Used	Ketone Used (a)	Product (b)	M.P. °C	Analyses				Empirical Formula
				Calcd.		Found		
				C	H	C	H	
Imidazole	6A,6H (c)	IIa (d)	92-101	28.6	2.4	29.0	2.6	C <sub>6</sub> H <sub>6</sub> N <sub>2</sub> O <sub>2</sub>
Imidazole	4A	IIb	95-100 (dec.)	26.6 (e)	—	26.4 (e)	—	C <sub>6</sub> H <sub>6</sub> Cl <sub>2</sub> F <sub>4</sub> N <sub>2</sub> O <sub>2</sub>
Benzimidazole	6A,6H	IIc (f)	125-143 (dec.)	39.8	2.7	39.7	3.0	C <sub>10</sub> H <sub>8</sub> F <sub>6</sub> N <sub>2</sub> O <sub>2</sub>
Benzimidazole	4H	IId	135-142 (dec.)	35.8	2.4	36.0	2.4	C <sub>10</sub> H <sub>8</sub> Cl <sub>2</sub> F <sub>4</sub> N <sub>2</sub> O <sub>2</sub>
2-Methylbenzimidazole	6A (g), 6H	IIe (f)	165-171 (dec.)	41.8	3.2	41.8	3.2	C <sub>11</sub> H <sub>10</sub> F <sub>6</sub> N <sub>2</sub> O <sub>2</sub>
2-Methylbenzimidazole	4H	IIf	155-165 (dec.)	37.8	2.9	38.1	3.1	C <sub>11</sub> H <sub>16</sub> Cl <sub>2</sub> F <sub>4</sub> N <sub>2</sub> O <sub>2</sub>
Benzotriazole (h)	6A,6H	III (f)	86-90	44.6 (i)	2.5 (i)	44.9	2.61	C <sub>15</sub> H <sub>10</sub> F <sub>6</sub> N <sub>6</sub> O

(a) 6A = anhydrous hexafluoroacetone; 6H = hexafluoroacetone trihydrate; 4A = anhydrous *sym*-tetrafluorodichloroacetone; 4H = anhydrous *sym*-tetrafluorodichloroacetone used with added water. (b) Yields were 85-95 mole percent based on the heterocycle used, except as indicated. (c) Reaction with 6H gave a non-crystalline adduct of a higher degree of hydration. (d) The parent heterocycle was regenerated with sodium hydroxide. (e) Percent fluorine. (f) The parent heterocycle was regenerated with ammonium hydroxide. (g) Reaction with 6A gave a poor yield. (h) Benzotriazole did not form a stable adduct with 4A or 4H. (i) For a 2:1 molar ratio of heterocycle:ketone.

of IIc obtained with the anhydrous ketone, and the failure to obtain IId and IIe except when water was present.

Unlike the other compounds cited in Table I, benzotriazole did not form a stable adduct from tetrafluorodichloroacetone, and with hexafluoroacetone apparently formed a "hemiadduct" of possible structure III. This



behavior appears consistent with the fact that benzotriazole is the most weakly basic of the heterocycles used. The failure of tetrafluorodichloroacetone to form an adduct in comparison with the fully fluorinated ketone cannot be explained on the basis of different acidities of the two *gem*-diols, since those are about the same (4). Our work has shown, however, that the former ketone is generally less reactive (2), presumably because of the lower inductive effect and higher steric requirement of the chlorodifluoromethyl group as compared with the trifluoromethyl group. A further evidence of this difference in ketone reactivity is the greater ease of adduct formation of the anhydrous fully fluorinated ketone with benzimidazole and 2-methylbenzimidazole, as noted above.

The chemical behavior of the compounds appears consistent with the assigned adduct structures (II and III). As noted in Table I, they melt over a range and several of them decompose at their melting points with gas evolution.

They regenerate the parent heterocycles upon treatment with ammonium hydroxide at room temperature. Imidazole, being more basic than the other compounds, not unexpectedly gave a hexafluoroacetone adduct (IIa) which did not decompose at its melting point or upon treatment with ammonium hydroxide. Facile cleavage was noted with sodium hydroxide, however.

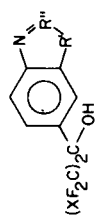
The infrared spectra of the adducts showed the presence of the expected NH, OH and trihalomethyl groups. The NMR spectra indicated the lack of substitution on the ring carbon atoms. The salt-like character of IIa was also shown by comparing its NMR spectrum with those of imidazole, its benzoate and its hydrochloride. Relative chemical shifts for the acidic protons were proportional to the respective *pK*<sub>a</sub> values of the acids used, taking that for (HO)<sub>2</sub>C(CF<sub>3</sub>)<sub>2</sub> as 6.58 (4).

Although we favor structure II, a monohydrate corresponding to Ia cannot be entirely excluded, and we have proposed a structure of this type for III. This type of compound has precedent, since earlier work at this laboratory (5) has shown that amides similarly yield unstable adducts with hexafluoroacetone by reaction on the weakly basic nitrogen atom.

Indole reacted easily with anhydrous hexafluoroacetone, but the product was stable in contrast to the adducts described above. It was identified as IVa by spectral data and by haloform cleavage (6) to V.

Tetrafluorodichloroacetone gave a similar compound (IVb), but it was a viscous oil which could not be crystallized or distilled without decomposition. These results are consistent with the high reactivity of the 3-position in indole. Prolonged refluxing of indole with hexafluoro-

TABLE II  
Preparation of Type VIII Heterocycles



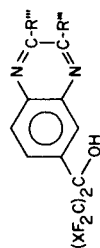
Substrate	Reagent	Reference to Procedure	Designation	X	R'	R''	Name (a)	Yield %	M.P. °C	Analyses						
										Calcd.			Found			Empirical Formula
										C	H	N	C	H	N	
VIIa	HONO	7	VIIIa	F	NH	N	6-(X)-benzotriazole	98	211	37.9	1.7	14.8	38.3	1.7	14.9	C <sub>9</sub> H <sub>5</sub> F <sub>6</sub> N <sub>3</sub> O
VIIa	HCOOH	8	VIIIb	F	NH	CH	6-(X)-benzimidazole	98	248	42.3	2.1	9.9	42.0	2.1	10.1	C <sub>10</sub> H <sub>6</sub> F <sub>6</sub> N <sub>2</sub> O
VIIa	CH <sub>3</sub> COOH	9	VIIIc	F	NH	CCH <sub>3</sub>	2-Methyl-6-(X)-benzimidazole	100	297	44.3	2.7	9.4	44.4	2.7	9.4	C <sub>11</sub> H <sub>8</sub> F <sub>6</sub> N <sub>2</sub> O
VIIa	COCl <sub>2</sub>	10	VIII d	F	NH	COH	2-Hydroxy-6-(X)-benzimidazole (b)	91	270	40.0	2.0	9.3	39.8	2.1	9.5	C <sub>10</sub> H <sub>6</sub> F <sub>6</sub> N <sub>2</sub> O <sub>2</sub>
VIIa	SOCl <sub>2</sub>	11	VIII e	F	N	S	6-(X)-2,1,3-benzothiadiazole (c)	100	170	-	-	9.3	-	-	9.2	C <sub>9</sub> H <sub>4</sub> F <sub>6</sub> N <sub>2</sub> OS
VIIb	HONO	7	VIII f	F	S	N	6-(X)-1,2,3-benzothiadiazole	93	181	35.8	1.3	9.3	35.6	1.3	9.2	C <sub>9</sub> H <sub>4</sub> F <sub>6</sub> N <sub>2</sub> OS
VIIb	HCOOH	8	VIII g	F	S	CH	6-(X)-benzothiazole	77	240	40.0	1.7	4.7	40.3	1.7	4.8	C <sub>10</sub> H <sub>5</sub> F <sub>6</sub> NOS
VIIb	CH <sub>3</sub> COOH	12	VIII h	F	S	CCH <sub>3</sub>	2-Methyl-6-(X)-benzothiazole	63	310	-	-	4.5	-	-	4.6	C <sub>11</sub> H <sub>7</sub> F <sub>6</sub> NOS
VIIb	C <sub>6</sub> H <sub>5</sub> COCl	13	VIII i	F	S	CC <sub>6</sub> H <sub>5</sub>	2-Phenyl-6-(X)-benzothiazole	95	234	51.0	2.4	3.7	51.2	2.5	3.7	C <sub>16</sub> H <sub>9</sub> F <sub>6</sub> NOS
VIIb	CH <sub>3</sub> NCS	14	VIII j	F	S	CNHCH <sub>3</sub>	2-Methylamino-6-(X)-benzothiazole	55	277	40.0	2.4	8.5	39.8	2.4	8.5	C <sub>11</sub> H <sub>8</sub> F <sub>6</sub> N <sub>2</sub> OS
VIIb	n-C <sub>7</sub> H <sub>15</sub> NCS	14	VIII k	F	S	CNHC <sub>7</sub> H <sub>15</sub>	2-(n-Heptylamino)-6-(X)-benzothiazole	60	156	-	-	6.8	-	-	6.7	C <sub>17</sub> H <sub>20</sub> F <sub>6</sub> N <sub>2</sub> OS
VIIb	C <sub>6</sub> H <sub>5</sub> NCS	14	VIII l	F	S	CHNC <sub>6</sub> H <sub>5</sub>	2-Phenylamino-6-(X)-benzothiazole	67	185	-	-	7.2	-	-	7.2	C <sub>16</sub> H <sub>10</sub> F <sub>6</sub> N <sub>2</sub> OS
VIIb	COCl <sub>2</sub>	10	VIII m	F	S	COH	2-Hydroxy-6-(X)-benzothiazole (b)	82	221	37.8	1.6	4.4	37.7	1.6	4.2	C <sub>10</sub> H <sub>5</sub> F <sub>6</sub> NO <sub>2</sub> S
VIIb	(COOC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	15	VIII n	F	S	CCOOC <sub>2</sub> H <sub>5</sub>	2-(Ethoxycarbonyl)-6-(X)-benzothiazole	48	205	-	-	3.8	-	-	3.9	C <sub>13</sub> H <sub>9</sub> F <sub>6</sub> NO <sub>3</sub> S
VIIc	COCl <sub>2</sub>	10	VIII o	F	O	COH	2-Hydroxy-6-(X)-benzoxazole (b)	95	162	40.0	1.7	4.7	39.8	1.7	5.0	C <sub>10</sub> H <sub>5</sub> F <sub>6</sub> NO <sub>3</sub>
VIIc	CH <sub>3</sub> COOH	16	VIII p	F	O	CCH <sub>3</sub>	2-Methyl-6-(X)-benzoxazole	75	262	-	-	4.7	-	-	4.6	C <sub>11</sub> H <sub>7</sub> F <sub>6</sub> NO <sub>2</sub>
VIIc	C <sub>6</sub> H <sub>5</sub> COOH	16	VIII q	F	O	CC <sub>6</sub> H <sub>5</sub>	2-Phenyl-6-(X)-benzoxazole	75	267	-	-	3.9	-	-	4.2	C <sub>16</sub> H <sub>6</sub> F <sub>6</sub> NO <sub>2</sub>
VII d	HONO	7	VIII r	Cl	NH	N	6-(Y)-benzotriazole	88	208	34.0	1.6	13.2	34.3	1.4	13.3	C <sub>9</sub> H <sub>5</sub> Cl <sub>2</sub> F <sub>4</sub> N <sub>3</sub> O
VII d	HCOOH	8	VIII s	Cl	NH	CH	6-(Y)-benzimidazole	95	227	37.8	1.9	-	37.8	2.1	-	C <sub>10</sub> H <sub>6</sub> Cl <sub>2</sub> F <sub>4</sub> N <sub>2</sub> O
VII d	COCl <sub>2</sub>	10	VIII t	Cl	NH	COH	2-Hydroxy-6-(Y)-benzimidazole (b)	94	234	36.0	1.8	8.4	36.3	1.7	8.4	C <sub>10</sub> H <sub>6</sub> Cl <sub>2</sub> F <sub>4</sub> N <sub>2</sub> O <sub>2</sub>



(a) X = 2-hydroxyhexafluoro-2-propyl; Y = 2-hydroxytetrafluorodichloro-2-propyl. (b) Infrared spectral data favors the isomeric structure: -NHCO-. (c) Ring structure:

TABLE III

## 2,3-Di-substituted-6-(2-Hydroxyhexahalo-2-propyl)-quinoxalines (IX)



Substrate	Reagent	Reference to Procedure	Designation	X	R''	R'''	Yield %	M.P. °C	Analyses						
									Calcd.			Found			Empirical Formula
								C	H	N	C	H	N		
VIIa	(CHO) <sub>2</sub>	17	IXa	F	H	H	95	200	44.6	2.0	9.4	44.9	2.0	9.1	C <sub>11</sub> H <sub>6</sub> F <sub>6</sub> N <sub>2</sub> O
VIIa	(CH <sub>3</sub> CO) <sub>2</sub>	17	IXb	F	CH <sub>3</sub>	CH <sub>3</sub>	95	207	48.1	3.1	8.6	48.4	3.3	8.7	C <sub>13</sub> H <sub>10</sub> F <sub>6</sub> N <sub>2</sub> O
VIIa	(C <sub>6</sub> H <sub>5</sub> CO) <sub>2</sub>	17	IXc	F	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	91	198	61.6	3.1	6.3	61.5	3.1	6.5	C <sub>23</sub> H <sub>14</sub> F <sub>6</sub> N <sub>2</sub> O
VIIa	(COOH) <sub>2</sub>	18	IXd	F	OH	OH	95	338	—	—	—	—	—	—	C <sub>11</sub> H <sub>6</sub> F <sub>6</sub> N <sub>2</sub> O <sub>3</sub>
VIIa	(C <sub>3</sub> H <sub>4</sub> NCO) <sub>2</sub> (a)	17	IXe	F	2-Pyridyl	2-Pyridyl	95	245	56.0	2.7	12.5	56.2	2.7	12.5	C <sub>21</sub> H <sub>12</sub> F <sub>6</sub> N <sub>4</sub> O
VIIId	(COOH) <sub>2</sub>	18	IXf	F	OH	OH	78	330	36.6	1.7	7.8	36.4	1.6	7.8	C <sub>11</sub> H <sub>6</sub> Cl <sub>2</sub> F <sub>4</sub> N <sub>2</sub> O <sub>3</sub>

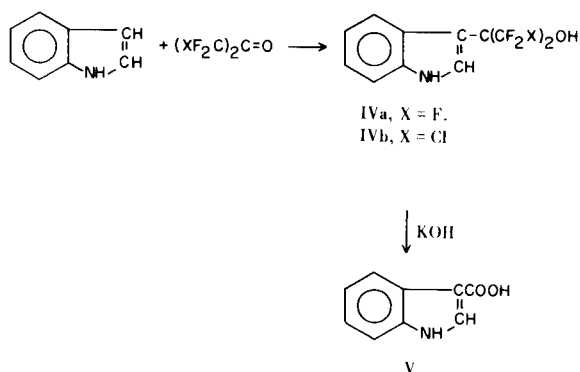
(a) Di-(2-pyridyl)glyoxal.

TABLE IV

## Acids from VIII and IX by Haloform Cleavage

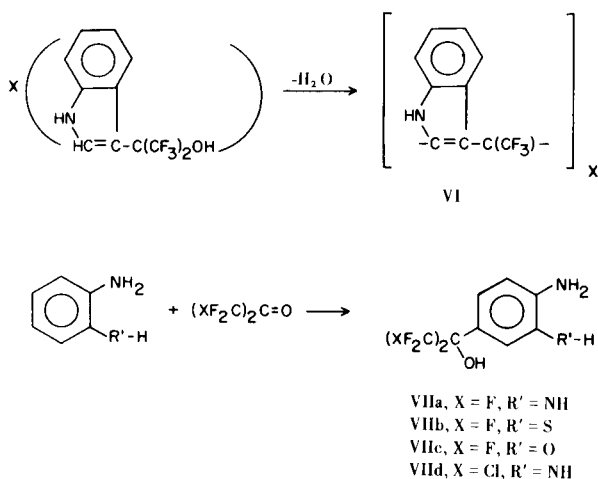
Substrate	Designation	R'	R''	Name	Yield %	M.P., °C	Empirical Formula
VIIIa	XIIa	NH	N	Benzo-triazole-6-carboxylic acid	95	310 (dec.) (a)	C <sub>7</sub> H <sub>2</sub> N <sub>3</sub> O <sub>2</sub>
VIIIb	XIIb	NH	CH	Benzimidazole-6-carboxylic acid	100	333 (dec.) (b)	C <sub>9</sub> H <sub>8</sub> N <sub>2</sub> O <sub>4</sub>
VIIIc	XIIc	NH	COH	2-Hydroxybenzimidazole-6-carboxylic acid	84	396 (dec.) (c)	C <sub>8</sub> H <sub>6</sub> N <sub>2</sub> O <sub>3</sub>
IXd	XIII	OH (d)	OH (d)	2,3-Dihydroxyquinoxaline-6-carboxylic acid	66	>400 (e)	C <sub>9</sub> H <sub>6</sub> N <sub>2</sub> O <sub>4</sub>

(a) Ref. 19 gives "above 270°". (b) As the formic acid salt; ref. 20 gives "300 to 325" (dec.). (c) Ref. 20 gives "above 360°". (d) R'''. (e) Ref. 18 gives no m.p.



acetone trihydrate gave in good yield a white solid melting from about  $50^\circ$  to over  $300^\circ$ , from which no single product could be extracted. Analytical and infrared spectral data (absence of OH, presence of NH) suggest a mixture of polymers of the possible general structure VI, formed through the reactive 2-position.

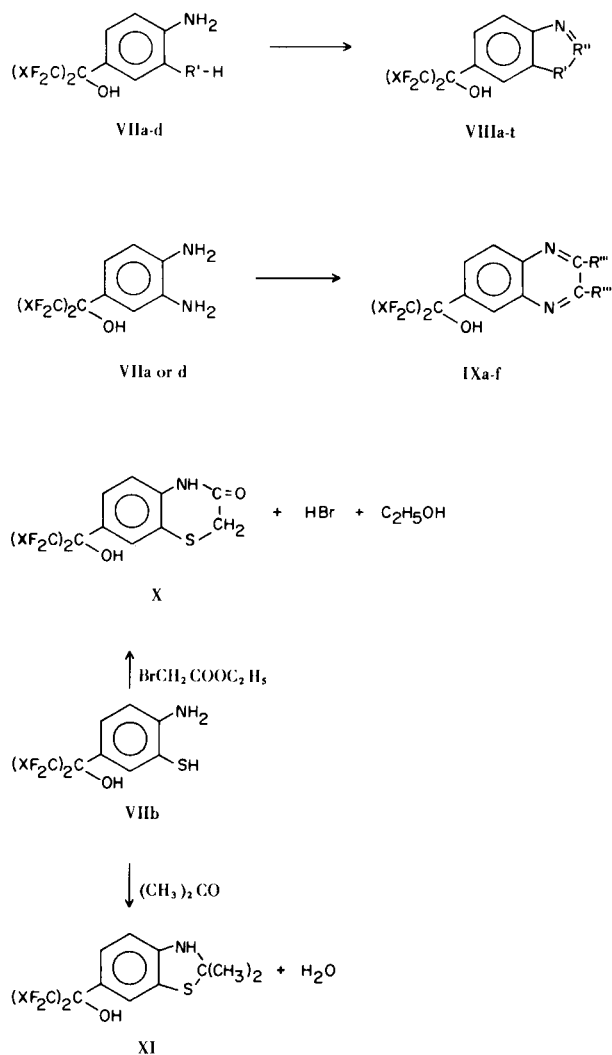
Attention was then turned to a second synthetic approach for preparing the desired heterocycles. This involved as the first step the preparation of compounds of structure VII.



These compounds, all new except VIIc, were easily prepared by refluxing the amine with excess ketone hydrate, a procedure employed by Knunyants and co-workers (3) with other amines. Compound VIIc, previously prepared by us in poor yield using anhydrous hexafluoroacetone (2), was obtained in greatly improved yield in the present study by employing the ketone hydrate. In reaction with *o*-phenylenediamine, tetrafluorodichloroacetone gave lower yields of a less pure product (VIIId) than hexafluoroacetone, and 1,1,3-trifluorotrchloroacetone formed only decomposition products. Although *o*-aminobenzenethiol formed VIIb satisfactorily with hexafluoroacetone trihydrate, attempts to prepare the analogue

of VIIb from tetrafluorodichloroacetone were unsuccessful. These observations appear consistent with the lower chemical stability of the fluorochloroacetones compared with hexafluoroacetone as noted by us previously (2). As indicated in an earlier report from this laboratory on the proton NMR spectra of aromatic diamines ring-substituted by the 2-hydroxyhexahalo-2-propyl group (2), the protons *ortho* to that group in compounds VIIa-d are shifted downfield from the normal position. Solid state infrared spectra of these compounds indicate zwitterion formation between the acidic hydroxyl proton and the amino group.

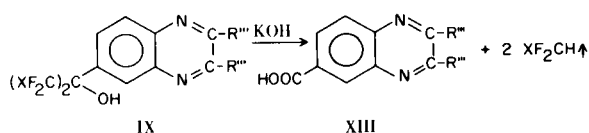
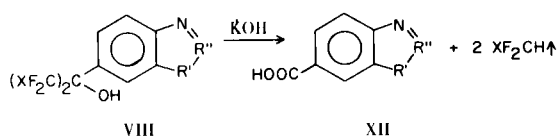
The conversion of compounds VIIa-d to the corresponding heterocyclic derivatives of types VIII, IX, X and XI was effected without difficulty by following published procedures (Tables II, III).



It is noteworthy that the hydroxyl group did not interfere with heterocyclic ring formation, even though it can undergo normal esterification, carbamate formation, etc. Apparently reaction occurs primarily with the more nucleophilic amino group, followed by ring formation.

Infrared and NMR spectra support the assigned structures. The two benzotriazoles (VIIIa and VIIIr) have broad NH band ranges from 3200 to 2300  $\text{cm}^{-1}$ , which reflect the presence of the tautomerism,  $-\text{NHN}=\text{N}- \rightleftharpoons -\text{N}=\text{NNH}-$ . Benzimidazoles VIIIb, c, and d have similar band ranges indicating  $-\text{NHCR}=\text{N}- \rightleftharpoons -\text{N}=\text{CRNH}-$ . Compounds VIII d, m, o, and t show a strong absorption band at 1650  $\text{cm}^{-1}$ , indicating the  $-\text{NHCO}-$  linkage rather than  $-\text{N}=\text{COH}-$ . Benzothiazoles VIIIg and i and benzothiadiazole VIII f gave solid state infrared spectra with a broad, intense band at 3000-3100  $\text{cm}^{-1}$ , corresponding to very strong hydrogen bonding. Such bonding is characteristic of highly fluorinated alcohols of this general type (4).

Haloform cleavage of aromatic compounds substituted by one or two 2-hydroxyhexafluoro-2-propyl groups constitutes a general procedure developed at this laboratory for the preparation of aromatic mono- and dicarboxylic acids (6). It therefore seemed of interest to consider an analogous approach for the preparation of heterocyclic carboxylic acids of types XII and XIII from VIII and IX, respectively.



As indicated in Table IV, four compounds could be thus converted to the corresponding acids. Several (VIIIc, e, and s; IXb, c, and f) gave only decomposition products, while others (IXa and e) were recovered unchanged. VIIIg was hydrolyzed to the parent compound VIIb. This method is therefore concluded to be less generally applicable to the preparation of heterocyclic than of aromatic acids.

#### EXPERIMENTAL

##### Methods.

Melting points were taken in capillary tubes on a Mel-Temp

apparatus and are uncorrected. Yields are expressed as mole percent of good quality crude product, based on fluorine-containing compound used, except as indicated. The perhaloketones were obtained from Specialty Chemicals Division, Allied Chemical Corporation, Morristown, New Jersey. The proton NMR spectra were obtained on a Varian Associates Model A-60 Spectrometer in 20% dioxane solution with tetramethylsilane as internal reference. Infrared spectra were taken on a Perkin-Elmer Model 521 Spectrophotometer.

##### Imidazole-hexafluoroacetone (IIa).

Hexafluoroacetone (19 g., 0.115 mole) was bubbled at room temperature over 1 hour into a well-stirred slurry of 7 g. (0.1 mole) imidazole in 250 ml. anhydrous benzene or ethyl ether. A clear solution was soon formed, followed by precipitation of the anhydrous crystalline complex I. The filtered complex soon became gelatinous on exposure to the air, but was hard, friable and non-hygroscopic after a few hours. It was recrystallized from 1,2-dichloroethane. The other adducts could be prepared similarly, except II d and II f. Adducts II c, II e and III were also prepared from hexafluoroacetone trihydrate, the following procedure being typical.

##### Benzotriazole-hexafluoroacetone (III).

Benzotriazole (6 g., 0.05 mole) and 11 g. (0.05 mole) of hexafluoroacetone trihydrate were refluxed (ca. 105°) for 24 hours. The clear solution was evaporated to dryness; air drying to constant weight at 50° gave crude III as a free-flowing, white solid with no residual odor of hexafluoroacetone. It was recrystallized from 1,2-dichloroethane.

##### Benzimidazole-tetrafluorodichloroacetone (II d).

Benzimidazole (6 g., 0.051 mole), 10 g. (0.05 mole) of tetrafluorodichloroacetone, and 25 ml. anhydrous benzene were mixed and heated to reflux for 10 minutes. To the resulting clear solution was added 0.9 ml. (0.05 mole) of water. The solution was immediately converted to a gelatinous paste with heat evolution. The entire mass was dried to crude II d by heating at 50° for 6 hours in a gentle stream of air. It was recrystallized from 1,2-dichloroethane.

The adducts were reconverted to the parent heterocycles by dissolving 2 g. in 25 ml. methanol, adding 5 ml. concentrated ammonium hydroxide, and allowing the clear solution to stand at room temperature for 3 hours. The mixture was evaporated to one-third volume, water was added to turbidity, and crystallization was induced by cooling and stirring. The identities of the compounds were established by comparison with authentic samples.

Chemical shifts noted in the NMR spectra for the protons in the 4 and 5 position of imidazole, adduct II a, imidazole benzoate and imidazole hydrochloride were 7.15, 7.20, 7.35, 7.75 ppm. Shifts for the proton in the 2-position were 7.70, 8.20, ~8.15 ± 1.0, and 9.00 ppm. The relative shifts are in direct correlation with the respective pK<sub>a</sub> values of the acids involved.

##### 3-(2-Hydroxyhexafluoro-2-propyl)indole (IV a) (21).

This compound was prepared by bubbling excess hexafluoroacetone into a stirred solution of 5 g. (0.043 mole) of indole in 100 ml. of anhydrous ethyl ether at room temperature over 1 hour. Evaporation of the solvent gave a yellow oil in 92% yield; it solidified slowly at 0° to white crystals. Recrystallization from hexane gave m.p. 77°. The infrared spectrum showed the presence of OH, NH<sub>2</sub> and CF<sub>3</sub> groups.

Anal. Calcd. for C<sub>11</sub>H<sub>7</sub>F<sub>6</sub>NO: C, 46.6; H, 2.5. Found: C, 46.3; H, 2.7.

Compound IVa underwent haloform cleavage with potassium hydroxide to 3-indolecarboxylic acid using the procedure detailed below, except that a lower temperature (100°) was employed in this case. The acid had m.p. 219° dec. (lit. (22) 220-224° dec.)

Refluxing 12 g. (0.1 mole) of indole with 132 g. (0.6 mole) of hexafluoroacetone trihydrate for 112 hours yielded a clear, light-pink solution. Dilution with water gave 18 g. of white solid (VI), which melted over a wide range (50° to >300°), and could not be resolved into pure compounds. The infrared spectrum showed the absence of OH groups, and the presence of NH. The nitrogen content suggests a close to 2:1 molar ratio of indole:hexafluoroacetone.

*Anal.* Calcd. for  $C_{19}H_{12}F_6N_2$ : N, 7.3. Found: N, 7.0.

#### 3-(2-Hydroxytetrafluorodichloro-2-propyl)indole (IVb).

Indole (12 g., 0.1 mole) and 20 g. (0.1 mole) of tetrafluorodichloroacetone were dissolved in a mixture of 50 ml. each of hexane and ethyl ether. The yellow solution gradually became lighter on standing at room temperature. After 72 hours the solvent was removed *in vacuo*, yielding 32 g. (100%) of a viscous oil which could not be crystallized or distilled without decomposition. The infrared spectrum is similar to that of IVa and strongly supports the assigned structure.

#### 1-(2-Hydroxyhexafluoro-2-propyl)-3,4-diaminobenzene (VIIa).

*o*-Phenylenediamine (54 g., 0.5 mole) was refluxed with 220 g. (1.0 mole) of hexafluoroacetone trihydrate for 24 hours. The solution was then added with stirring to 1 liter of cold water to precipitate the solid product, which was filtered, washed with cold water, and air dried to constant weight. The yield was 127 g., 93% of theory. Reducing the reaction time to 8 hours gave a 75% yield. Recrystallization from toluene gave m.p. 142-144°. The aromatic region of the proton NMR spectrum of VIIa showed one doublet at 6.6 ppm ( $J = 9$  cps), a second doublet at 6.9 ppm ( $J = 9$  cps.), and a singlet at 7 ppm, each having a relative area of 1. This pattern is consistent with the assigned 1,2,4-orientation. The infrared spectrum of VIIa showed deformation frequencies at about 450 and 800  $cm^{-1}$ , and an absence of overtone above 1900  $cm^{-1}$ , both of which support 1,2,4-orientation. In dilute carbon tetrachloride solution, the hydroxyl group frequency was noted at 3595  $cm^{-1}$ , and that for the amino group at 3450 and 3365  $cm^{-1}$ . A solid state curve showed no free hydroxyl group, and a broad band system from 3200 to 2500  $cm^{-1}$ , indicative of the  $NH_3^+$  group. This corresponds to the structure  $^{-}OC(CF_3)_2-C_6H_3-(NH_2)(NH_3^+)$ .

*Anal.* Calcd. for  $C_9H_8F_6N_2O$ : C, 39.4; H, 2.9; N, 10.2. Found: C, 39.2; H, 3.0; N, 10.4.

#### 1-(2-Hydroxyhexafluoro-2-propyl)-3-thiol-4-aminobenzene (VIIb).

*o*-Aminobenzenethiol (25 g., 0.2 mole) and 88 g. (0.4 mole) of hexafluoroacetone trihydrate were mixed and refluxed for 70 hours. The reaction mixture was added with stirring to 1 liter of cold water to precipitate the solid product, which was filtered and air dried to constant weight. The yield was 50 g. (93%). Reducing the proportion of hexafluoroacetone to 0.3 mole yielded a gummy product which was difficult to purify. After two recrystallizations from carbon tetrachloride, VIIb gave m.p. 115-125°. The proton NMR spectrum of VIIb showed one doublet at 6.75 ppm ( $J = 9$  cps), a second doublet at 7.45 ppm ( $J = 9$  cps), and a broad singlet (or a possible doublet) at 7.75 ppm ( $J = 2-3$  cps). This pattern is consistent with the assigned structure. The broadening of the singlet may result from the presence of the thiol group. The infrared spectrum showed the hydroxyl group at 3590 and the

amino group at 3490 and 3385  $cm^{-1}$ . In the solid state, the same broad band system from 2500 to 3200  $cm^{-1}$  was observed as with VIIa, indicating zwitterion formation.

*Anal.* Calcd. for  $C_9H_7F_6NOS$ : C, 37.2; H, 2.4; N, 4.8. Found: C, 37.2; H, 2.5; N, 4.8.

#### 1-(2-Hydroxyhexafluoro-2-propyl)-3-hydroxy-4-aminobenzene (VIIc).

The following modified procedure is preferred to that previously reported (2). Recrystallized *o*-aminophenol (33 g., 0.31 mole) was refluxed for 24 hours with 152 g. (0.69 mole) of hexafluoroacetone trihydrate. The warm reaction mixture was diluted to 450 ml. with water, and cooled for crystallization of the product, which was filtered, washed with cold water and air dried. The yield was 56 g. (64%). Recrystallization from benzene or 1,2-dichloroethane gave an off-white product, m.p. 163-168° (lit. (2) 170-171°). Evaporation of the aqueous filtrate to dryness gave an additional 30 g. of solid; two recrystallizations were required to purify this material. The proton NMR spectrum of VIIc exhibited a doublet at 6.65 ppm ( $J = 9$  cps), a second doublet at 7.1 ppm ( $J = 9$  cps), and a singlet at 7.0 ppm. This pattern is consistent with 1,2,4-orientation.

#### 1-(2-Hydroxytetrafluorodichloro-2-propyl)-3,4-diaminobenzene (VIIId).

*o*-Phenylenediamine (20 g., 0.185 mole), 60 g. (0.3 mole) of tetrafluorodichloroacetone and 10 g. (0.56 mole) of water were mixed and refluxed for 20 hours. The reaction mixture was added with stirring to 50 ml. of cold water and the precipitated solid was filtered, washed with cold water and air dried. The yield was 29 g. (48%). Recrystallization from 300 ml. of benzene gave some insoluble material and 14 g. of VIIId, m.p. 158-160°. This reaction was found to be quite sensitive to reaction conditions. None of the desired product was formed in anhydrous medium with various solvents, or when employing a lower proportion of water. Scaleup also resulted in lower yields. The proton NMR spectrum showed a doublet at 6.6 ppm ( $J = 9$  cps), a second doublet at 7.0 ppm ( $J = 9$  cps), and a singlet at 7.05 ppm. This pattern is consistent with the assigned structure. The infrared spectrum resembled that of VIIa relative to evidence for 1,2,4-orientation and zwitterion formation in the solid state. In dilute carbon tetrachloride solution, OH group absorption was noted at 3580  $cm^{-1}$ , and  $NH_2$  group absorption at 3440 and 3358  $cm^{-1}$ .

*Anal.* Calcd. for  $C_9H_8Cl_2F_4N_2O$ : C, 35.2; H, 2.6; N, 9.1. Found: C, 35.3; H, 2.4; N, 8.8.

Procedures reported in the literature for preparing the analogous unsubstituted heterocycles were found suitable for making the type VIII and IX derivatives listed in Tables II and III in all cases except as indicated. The compounds are soluble in warm aqueous sodium hydroxide, which reflects the acidity of the hydroxyl group. The infrared spectra were consistent with the structures assigned.

#### 7-(2-Hydroxyhexafluoro-2-propyl)-3-keto-3,4-dihydro-2H-1,4-benzothiazine (X).

The procedure of Unger (23) was modified as follows. Compound VIIb (6 g., 0.02 mole), 3.5 g. (0.02 mole) of ethyl bromoacetate, 1.6 g. (0.02 mole) pyridine and 35 ml. ethylene glycol were heated with stirring for 8 hours in an open beaker at 105-116°. The clear solution was cooled and poured with stirring into 200 ml. cold water to precipitate the solid product. The yield of crude X was 6.6 g. (100%). Recrystallization from a large volume of xylene gave m.p. 233°.

*Anal.* Calcd. for  $C_{11}H_7F_6NO_2S$ : C, 39.8; H, 2.1; N, 4.2. Found: C, 40.0; H, 2.2; N, 4.4.

2,2-Dimethyl-6-(2-hydroxyhexafluoro-2-propyl)benzothiazoline (XI).

Compound VIIIb was dissolved in acetone and the solution was slowly evaporated to dryness at room temperature in an air stream (24). The solid residue was recrystallized from carbon tetrachloride, m.p. 92°. The proton NMR spectrum showed a strong singlet for the methyl groups at 1.7 ppm, and a broad peak at 4.0 for the NH and OH protons. The aromatic protons appeared as a pair of doublets at 6.6 and 7.2 ppm ( $J = 9$  cps), and a singlet at 7.4 ppm.

*Anal.* Calcd. for  $C_{12}H_{11}F_6NOS$ : N, 4.2. Found: N, 4.4. Hydrolysis to Acids XII and XIII.

The procedure used (6) was that previously employed by us for preparing aromatic acids, except that a lower temperature and a shorter time were used in the present study. Compound VIIIa (5 g., 0.018 mole), 11 g. (0.20 mole) of potassium hydroxide pellets, and 20 ml. 2,2'-oxydiethanol were mixed in an open Erlenmeyer flask and heated rapidly with magnetic stirring. A clear solution formed at about 100°, and at about 140° gas evolution took place over a 5-minute period. Heating and stirring were continued for an additional 15 minutes, after which time the solution was cooled, diluted with 50 ml. cold water, and acidified with 13 ml. concentrated hydrochloric acid. The precipitated acid (XIIa) was washed with cold water and air dried to constant weight. The yield was 2.7 g. (95%). The acid was purified by boiling in a 3% aqueous sodium hydroxide solution with decolorizing carbon, filtering, and acidifying, m.p. 310° dec. The same acid prepared from 3,4-diaminobenzoic acid by treatment with nitrous acid using a known procedure (19) melted at 313° dec., and had an identical infrared spectrum. Acids XIIc and XIII (Table IV) were prepared similarly. Acid XIIb was recrystallized from dilute formic acid (20) using decolorizing carbon. These three acids were likewise found to have infrared spectra and decomposition temperatures identical with those made by known methods from 3,4-diaminobenzoic acid.

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#### REFERENCES

(1) Paper XVIII: R. E. A. Dear and E. E. Gilbert, *J. Agr.*

*Food Chem.*, in press.

(2) E. E. Gilbert, E. S. Jones, and J. P. Sibia, *J. Org. Chem.*, **30**, 1001 (1965).

(3a) I. L. Knunyants, N. P. Gambaryan, C. Ching-Yun, and E. M. Rokhlin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, No. 4, 684 (1962); *Chem. Abstr.*, **57**, 12305 (1963); (b) I. L. Knunyants, C. Ching-Yun, N. P. Gambaryan and E. M. Rokhlin, *Zh. Vses. Khim. Obshchestva im. D. I. Mendeleeva*, **5**, No. 1, 114 (1960); *Chem. Abstr.*, **54**, 20926 (1960).

(4) W. J. Middleton and R. V. Lindsey, Jr., *J. Am. Chem. Soc.*, **86**, 4948 (1964).

(5) P. E. Newallis and E. J. Rumanowski, *J. Org. Chem.*, **29**, 3114 (1964).

(6) B. S. Farah, E. E. Gilbert, E. S. Jones, and J. A. Otto, *ibid.*, **30**, 1006 (1965).

(7) R. E. Damschroder and W. D. Peterson, *Org. Syn.*, Coll. Vol. **3**, 106 (1955).

(8) E. C. Wagner and W. H. Millett, *ibid.*, Coll. Vol. **2**, 65 (1943).

(9) W. O. Pool, H. J. Harwood, and A. W. Ralston, *J. Am. Chem. Soc.*, **59**, 178 (1937).

(10) A. Hartmann, *Ber.*, **23**, 1046 (1890).

(11) P. Pope and L. A. Wiles, *J. Chem. Soc. (C)*, 1283 (1966).

(12) A. W. Hofmann, *Ber.*, **13**, 8 (1880).

(13) The procedure of H. P. Lankelma and A. E. Knauf (*J. Am. Chem. Soc.*, **53**, 309 (1931)) was modified by the use of pyridine instead of dimethylaniline.

(14) A. W. Hofmann, *Ber.*, **20**, 1788 (1887).

(15) E. Campaigne and J. E. Van Verth, *J. Org. Chem.*, **23**, 1344 (1958).

(16) D. W. Hein, R. J. Alheim, and J. J. Leavitt, *J. Am. Chem. Soc.*, **79**, 427 (1957).

(17) O. Hinsberg, *Ann.*, **237**, 327 (1887).

(18) K. G. Kleb, E. Siegel, and K. Sasse, *Angew Chem.*, Intern. Engl. Ed., **3**, (6), 413 (1964).

(19) T. Zincke, *Ann.*, **291**, 336 (1896).

(20) A. Zehra, *Ber.*, **23**, 3625 (1890).

(21) This experiment was run by Mr. E. J. Rumanowski.

(22) F. P. Doyle, W. Ferrier, D. O. Holland, M. D. Mehta, and J. H. C. Naylor, *J. Chem. Soc.*, 2853 (1956).

(23) O. Unger, *Ber.*, **30**, 607 (1897).

(24) R. C. Elderfield and E. C. McClenachan, *J. Am. Chem. Soc.*, **82**, 1982 (1960).

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