50° and was maintained at 40 to 50° by the occasional addition of portions of catalyst through the solid addition tube whenever the temperature dropped to 40°. In several experiments, the total amount of aluminum chloride used varied from 6 to 20 g. A shorter reaction time is possible with comparatively larger amounts of catalyst, but a corresponding drop in yield was noted. Reaction times were 6 to 8 hr. for the absorption of 332 g. (2.0 moles) of hexafluoroacetone. The reaction mixture was decomposed promptly (to avoid decomposition) by dropwise addition of 500 ml. of cold water over 30 min. Chloroform (200 ml.) was added; the organic layer was separated, water-washed, dried, and distilled. The yield was 344 g., 84% of theory.

This general procedure was employed to prepare other compounds as noted in Table III. In several cases, as noted, it was found preferable to operate stepwise, with intermediate isolation of the pure mono derivative. Carbon disulfide was found a suitable solvent for preparing the bis derivatives, when using either one step or two.

Perhalo Ketones. VI. Aromatic Amino Derivatives of the Perhaloacetones

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Twenty-two new carbinols were prepared by condensing tetrafluorodichloro-, pentafluoromonochloro-, and hexafluoroacetones with various aromatic amines. Addition of *p*-toluenesulfonic acid catalyst reduces the reaction time and temperature and improves product yield with hexafluoroacetone, makes possible the isolation of definite products with the fluorochloroacetones, and induces reaction with amines of low basicity. N.m.r. structural studies were made on eight of the compounds.

Knunyants and co-workers have reported facile electrophilic attack of aniline and of its N-methyl derivatives[1,2] by anhydrous or hydrated hexafluoroacetone to form the corresponding bis(trifluoromethyl)-carbinols. The present study, part of a general pro-

$$C_6H_5NH_2 + (F_3C)_2CO \longrightarrow (F_3C)_2C(OH)C_6H_4NH_2$$

gram on reaction and derivatives of the perhaloacetones,[3] involves extension of this type of reaction to other aromatic amines and to other perhaloacetones. A method employed by Knunyants, involving direct treatment of the amine with anhydrous hexafluoroacetone at 170–200°, was found to proceed fairly satisfactorily with other aromatic amines to form the products listed in Table I.

TABLE I

AROMATIC AMINO DERIVATIVES OF HEXAFLUOROACETONE

Amine used	Yield, %[a]	M.p., °C.[b]	Isomer[c]	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found
Aniline	60	151.5–152.5[d]	*p*[e,f]	41.7	41.2	2.7	2.5	...	...
2-Toluidine	47	136–137	*p*[e,f]	44.0	44.0	3.3	3.3	5.1	5.0
3-Toluidine	54	104–106	*o*[e–g]	44.0	43.8	3.3	3.1	5.1	5.4
4-Toluidine	55	109–110	*o*[e]	44.0	43.3	3.3	3.1	5.1	5.1
2,4-Dimethylaniline	45	113–114	*o*[f]	46.0	45.9	3.9	3.3	4.9	5.0
2,5-Dimethylaniline	61	162.5–163.5	*p*[f]	46.0	45.7	3.9	3.3	4.9	4.7
2,6-Dimethylaniline	66	174–175	*p*[e,f]	46.0	46.1	3.9	3.8	4.9	5.2
N-Methylaniline	55	89–90[h]	*p*[f]	44.0	43.8	3.3	2.9	5.1	5.1
N,N-Dimethylaniline[i]	58	79–80[j]	*p*	46.0	46.0	3.9	3.3	4.9	5.1
2-Methoxyaniline	29	129–130	*p*[e,f]	41.5	41.7	3.1	3.3	4.8	4.8
2-Chloroaniline[k]	30	122–123	*p*[l]	36.8	37.2	2.1	2.4	4.8	4.6
3-Chloroaniline[k,m]	27	84–86	*p*[l]	34.9	35.5	2.0	2.4	4.5	4.4
2-Hydroxyaniline	19	170–171	*p*[e]	39.3	38.9	2.6	2.7	5.1	4.9
2-Aminobiphenyl[k]	57	143–144	*p*[l]	53.7	54.2	3.3	3.7	4.2	4.4
4-Aminobiphenyl[k]	31	165–166	*o*[l]	53.7	53.7	3.3	2.5	4.2	4.1
1-Naphthylamine	60	164.5–165.5	*o*[e]	50.5	50.2	2.9	2.5	4.5	4.5
Acetanilide[i]	31	156–158	*p*[n]	43.9	43.8	3.0	3.6	4.7	5.0

[a] Of once-recrystallized product, based on either reagent. [b] Uncorrected. [c] Indicates position of the 2-hydroxyperhalo-2-propyl moiety with respect to the amino group. [d] Ref. 2 gives 151–152°. [e] Proved by hydrolysis to the carboxylic acid. [f] As indicated by n.m.r. [g] 1-(2-Hydroxyhexafluoro-2-propyl)-2-amino-4-methylbenzene. [h] Ref. 1a gives 87–89°. [i] $AlCl_3$ used as catalyst. [j] Ref. 1a gives 75–176°. [k] *p*-Toluenesulfonic acid catalyst added; otherwise no catalyst was used. [l] Orientation not proven. [m] Pentafluorochloroacetone used. [n] Proved by hydrolysis to 1-(2-hydroxyhexafluoro-2-propyl)-4-aminobenzene.

When efforts to extend the reaction to tetrafluorodichloroacetone yielded only intractable tars, it was found that the use of a small quantity of *p*-toluenesulfonic acid as catalyst greatly facilitated reaction and made possible the isolation of the desired products (Table II), although in generally lower yields than noted with hexafluoroacetone. Lower yields have also been noted[3] in the aluminum chloride catalyzed condensation of aromatic hydrocarbons with the fluorochloroacetones as contrasted with hexafluoroacetone. Both of these effects are explainable by lowered electrophilic character and consequent reduced reactivity of the carbonyl carbon as fluorine is replaced by chlorine, and

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(1) 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).

(2) (a) I. L. Knunyants, C. Ching-Yun, and N. P. Gambaryan, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **No. 4**, 686 (1960); *Chem. Abstr.*, **54**, 20962 (1960). (b) I. L. Knunyants, C. Ching-Yun, N. P. Gambaryan, and E. M. Rokhlin, *Zh. Vses. Khim. Obshchestva im. P. I. Mendeleeva*, **5**, No. 1, 114 (1960); *Chem. Abstr.*, **54**, 20962 (1960).

(3) Perhalo Ketones. V: B. S. Farah, E. E. Gilbert, and J. P. Sibilia, *J. Org. Chem.*, **30**, 998 (1965).

TABLE II

AROMATIC AMINO DERIVATIVES OF *sym*-TETRAFLUORODICHLOROACETONE[a]

Amine used	Yield, %[b]	M.p., °C.[c]	Isomer[d]	% C		% H		% N		% Cl	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
Aniline	51	149–150	*p*	37.0	37.5	2.4	2.6	4.8	4.7	24.3	23.9
2-Toluidine	41	108–109	*p*	39.2	39.7	3.0	3.5	4.6	5.0	23.2	23.5
3-Toluidine	58	85–86	*p*	39.2	39.7	3.0	3.3	4.6	4.5	23.2	23.6
2,4-Dimethylaniline	31	130–138	*o*	41.3	41.2	3.5	3.4	4.4	4.4	22.1	21.9
2,5-Dimethylaniline	41	121–122	*p*	41.3	41.0	3.5	3.0	4.4	4.4	22.1	22.1
2,6-Dimethylaniline	66	169–170	*p*	41.3	41.7	3.5	3.8	4.4	4.4	22.1	22.3
2-Methoxyaniline	25	139–141	*p*	37.3	37.5	2.8	3.2	4.4	4.4	22.0	22.3
2-Chloroaniline	20	101–102	*p*	33.1	33.5	1.9	2.2	4.3	4.3	..	..

[a] Toluenesulfonic acid catalyst used throughout. [b] Of once-recrystallized product, based on either reagent. [c] Uncorrected. [d] Indicates probable position of the 2-hydroxytetrafluorodichloro-2-propyl moiety with respect to the amino group; orientations not proven.

also by the greater lability of the carbon–chlorine bond as opposed to carbon–fluorine.

Although a catalyst is not generally necessary for the amines to react with hexafluoroacetone, its use made possible reductions in reaction times and temperatures with accompanying increases in yields. Still further improvement was obtained with a solvent such as xylene. The chloroanilines were found to be too weakly basic to react directly with hexafluoroacetone, but addition of the catalyst made reaction possible. The observed catalytic effect presumably results from enhancement of the electrophilic character of the carbonyl carbon by protonation of the oxygen atom. Generally, similar catalysis has been noted in reacting the perhaloacetones with aromatic hydrocarbons,[3] and with phenols.[4]

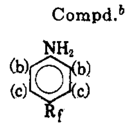
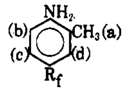
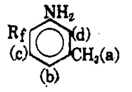
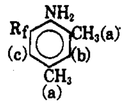
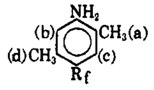
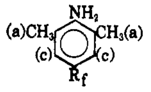
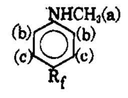
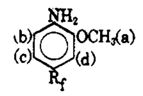
In agreement with Knunyants, it was noted in the present study that unstable salt-like addition compounds were formed immediately from the amines and ketones. These slowly gave the carbinols by rearrangement at the reaction temperature.

The entering 2-hydroxyperhalo-2-propyl group occupies a position largely *para* to the amino group, although some *ortho* isomer is also formed in some cases. The product is entirely *ortho* if the *para* position is blocked. Product structures were proved in some cases, as indicated in Table I, by hydrolysis to the corresponding amino acid by excess KOH in refluxing diethylene glycol. This technique, which proceeds in generally good yields, has proved widely applicable and is discussed in more detail in a separate paper.[5] Several of the compounds were also examined by n.m.r. and were concluded to have the structures assigned.

N.m.r. spectra were obtained on eight of the compounds cited in Table I; the results are given in Table III. Alcoholic and amino protons could not be detected because of solvent interference. All of the compounds which had only two adjacent nonequivalent aromatic protons were characterized by their typical AB patterns. Coupling constants were between 7 and 9 c.p.s. Protons *ortho* to the electron-withdrawing fluorinated propyl group were deshielded more than the other aromatic protons and therefore occurred at lower fields. A methyl group *ortho* to the fluorinated group was also shifted to lower fields. Both of these factors were important in structural assignment.

TABLE III

N.M.R. DATA FOR AROMATIC AMINO DERIVATIVES OF HEXAFLUOROACETONE[a]

Compd.[b]	Proton chemical shifts, p.p.m.[c]			
	a	b	c	d
	..	6.21 6.36	7.00 7.15	..
	2.00	6.27 6.42	6.85 *ca.* 6.98	*ca.* 6.98
	2.05	6.16 6.29	6.75 6.88	6.29
	2.04	6.67	6.71	..
	2.02	6.49	7.15	2.42
	2.00	..	6.83	..
	2.57	6.19 6.32	6.99 7.12	..
	3.55	6.30 6.43	6.64 6.77	6.77

[a] Tested as 20% by weight in methanol. [b] *R*f denotes the 2-hydroxyhexafluoro-2-propyl moiety. [c] Downfield from tetramethylsilane used as internal standard.

Experimental

Reaction of Aniline with Hexafluoroacetone. A. Without Catalyst.—In a 500-ml. three-necked flask equipped with stirrer, thermometer, Dry Ice condenser, and gas inlet tube, was placed 93.1 g. (1 mole) of aniline, which was heated to 170°. Hexafluoroacetone (b.p. −28°) was bubbled in while maintaining a temperature of 170–180°, and a total of 175 g. (1.05 mole) was introduced over 2 hr. During the reaction there was some sublimation of a low-melting solid up into the condenser, but this could be mostly removed by flaming. After the addition was completed, the gas inlet tube was removed, the vessel was stoppered, and

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(4) Perhalo Ketones. VII: B. S. Farah, E. E. Gilbert, M. Litt, J. A. Otto, and J. P. Sibilia, *J. Org. Chem.*, **30**, 1003 (1965).

(5) Perhalo Ketones. VIII: B. S. Farah, E. E. Gilbert, E. S. Jones, and J. A. Otto, *ibid.*, **30**, 1006 (1965).

heating and stirring were continued at 170–180° for 0.5 hr. The liquid product was then poured into a 1-l. beaker and allowed to cool. The crude solid was dissolved in ether, petroleum ether was added, and the mixture was concentrated and then cooled. There was obtained 131 g. of product, m.p. 148–150°, and from the mother liquor 45 g. of crude product, m.p. 80–100°, lit.[2] m.p. 151–152°.

B. With Catalyst.—The above procedure was repeated with 186 g. (2 moles) of aniline containing 5 g. of *p*-toluenesulfonic acid. Ketone (365 g., 2.2 moles) was added at 170–180° over 1.75 hr. There was little difficulty with sublimation during the reaction. Recrystallization of the crude product gave 291 g. of solid, m.p. 149–151°, and from the mother liquor 130 g. of crude product.

C. With Catalyst and Solvent.—Into a solution of 46.6 g. (0.5 mole) of aniline and 1 g. of *p*-toluenesulfonic acid dissolved in 100 ml. of xylene heated to 100° was bubbled 88 g. (0.53 mole) of hexafluoroacetone over 0.5 hr. The temperature rose to 133° and was maintained at 130–135° by heating during the addition and for 1 hr. afterward. The mixture was cooled and filtered to give 103 g. crude product, m.p. 110–140°, and from the mother liquor 16 g. of the low-melting isomer, m.p. 85–90°, was isolated. Recrystallization of the main fraction gave 78 g. of product, m.p. 150–151°.

Preparation and Rearrangement of the Aniline–Hexafluoroacetone Adduct.—Into 18.6 g. (0.2 mole) of aniline at room temperature was bubbled 35 g. (0.2 mole) of hexafluoroacetone with stirring and cooling at 25–50°. The solid which separated was filtered and recrystallized from ether–petroleum ether to give 17.9 g. of adduct, m.p. 65–68°. The adduct (13.0 g.) was heated at 130–150° for 1.5 hr., cooled, and filtered. Recrystallization from ether–petroleum ether gave 5.5 g. of 1-(2-hydroxyhexafluoro-2-propyl)-4-aminobenzene, m.p. 150–152°.

Reaction of Aniline with Tetrafluorodichloroacetone.—Aniline (23.3 g., 0.25 mole) and *p*-toluenesulfonic acid (1.9 g.) were mixed, and 55 g. (0.27 mole) of *sym*-tetrafluorodichloroacetone was added dropwise. The temperature rose spontaneously to 83° and was maintained at 80–100° by heating during the addition, which took 0.75 hr. The mixture was refluxed for an additional hour after the addition was complete, at which time the pot temperature was 135°. After cooling, hexane was added, the mixture was chilled, and the solid was filtered. Recrystallization from ether–hexane gave 37.1 g. of product, m.p. 149–150°. Omission of the catalyst in this experiment gave an intractable tar.

Perhalo Ketones. VII. Phenolic Derivatives of the Perhaloacetones

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Thirty new carbinols have been prepared by condensation of tetrafluorodichloro-, pentafluoromonochloro-, and hexafluoroacetones with various mono- and dihydric phenols and with phenolic ethers. Several acidic catalysts were employed, the choice of which determines whether orientation of the entering 2-hydroxyperhalo-2-propyl group is *ortho* or *para* to the phenolic group. An n.m.r. study of nine of the compounds indicated that electron-donating hydroxyl and alkyl groups largely neutralize the electron-withdrawing effect of the entering highly fluorinated alkyl group.

The present study was undertaken as part of a general program on reactions and derivatives of hexafluoroacetone and the analogous perhalogenated fluorochloro ketones.[2] Brief reports on the reaction of three phenolic compounds with two of these ketones have already appeared.[3,4] Knunyants and co-workers[3] showed that phenol reacts with hexafluoroacetone at 2:1 molar ratio at 100° for 10 hr. in the presence of a large quantity of anhydrous HF to form a "bisphenol" derivative as follows. Only the 2:1 product was isolated, although the 1:1 compound, $HOC_6H_4C(CF_3)_2OH$, was postulated as the intermediate. England, in a patent[4] published after completion of the present study, showed that *ortho* 1:1 and 1:2 products, respectively, resulted by heating phenol or hydroquinone with hexafluoroacetone at 150–200° in a bomb for 8 hr. without a catalyst. With $AlCl_3$ as catalyst, the 2-hydroxyhexafluoro-2-propyl moiety was introduced *para* in diphenyl ether; with the same catalyst, tetrafluorodichloroacetone likewise substituted *para* to the hydroxyl group in 2-ethylphenol.

$$2C_6H_5OH + (F_3C)_2CO \xrightarrow{HF} (HOC_6H_4)_2C(CF_3)_2 + H_2O$$

The present study has generally confirmed the above observations and, at the same time, has substantially broadened the scope of the reaction as applied to hexafluoroacetone (Table I) and tetrafluorodichloroacetone (Table II); both reacted at 1:1 molar ratio with a series of phenols and phenolic ethers. Although these ketones will effect *ortho* substitution of phenol when heated with it under pressure without solvent or catalyst, we have found that operation at atmospheric pressure with xylene as reaction solvent and toluenesulfonic acid as catalyst is more convenient and rapid and yields a purer product. This catalyst preferentially forms the *ortho* derivatives, except when available *ortho* positions are blocked or when formation of the *ortho* compound is sterically somewhat unfavorable, as in 2-*t*-butylphenol. Boron trifluoride, on the other hand, forms only the *para* isomer, which upon prolonged standing with excess phenol yields the same 2:1 "bisphenol" product earlier noted with anhydrous HF.[3] Aluminum chloride was found to give *para,para'* substitution of diphenyl ether, as observed by England. However, this catalyst induced *ortho* substitution of phenol by hexafluoroacetone in the present study, although England noted *para* substitution of 2-ethylphenol using $AlCl_3$ with tetrafluorodichloroacetone. The reason for this difference in orientation is not clear, since the reaction conditions were similar, and, as indicated in Table II, the chlorinated ketone is sterically capable of substitution in a position *ortho* to the phenolic group. Aluminum chloride catalysis in the usual sense is probably not involved here, since phenols react easily with $AlCl_3$, forming phenoxides.[5]

Although phenols undergo uncatalyzed condensation with anhydrous hexafluoroacetone, no reaction occurs

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[1] To whom inquiries should be addressed.

[2] Perhalo Ketones. VI: E. E. Gilbert, E. S. Jones, and J. P. Sibilia, *J. Org. Chem.*, **30**, 1001 (1965).

[3] I. L. Knunyants, C. Ching-Yun, N. P. Gambaryan, and E. M. Rokhlin, *Zh. Vses. Khim. Obshchestva im. D. I. Mendeleeva*, **5**, 114 (1960); *Chem. Abstr.*, **54**, 20962 (1960).

[4] D. C. England, French Patent 1,325,204 (1963); *Chem. Abstr.*, **59**, 11339 (1963).

[5] G. A. Olah, "Friedel-Crafts and Related Reactions," Vol. 1, G. A. Olah, Ed., Interscience Publishers, Inc., New York, N. Y., 1963.