TABLE I

α-ALKYLACROLEINS, α-ALKYLACROLEIN OXIMES AND α-ALKYLACRYLONITRILES[a] $CH_2{=}\overset{R}{\overset{|}{C}}X$

X	R	Size run, moles	Yield, %	B. p., °C.	Mm.	$n^{20}D$	d^{20}_4	Analyses,[b] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
CHO	n-C_6H_{13}	2.0	70.3	69	41	1.4416	0.8407	77.10	77.15	11.49	11.47	...	...
	n-C_8H_{17}	0.85	70.7	69–70	2	1.4462	0.8412	78.50	78.28	11.99	11.84	...	...
CH=NOH	C_2H_5	1.5	81.7	78	30	1.4820[c]	....	60.58	60.60	9.15	9.18	14.13	14.16
	iso-C_3H_7	0.49	52.7	63	3.5	1.4744	....	63.67	63.48	9.80	9.79	12.38	12.75
	n-C_5H_{11}	.2	71.4	66	0.15	1.4770	....	68.04	68.17	10.71	10.55	9.92	10.11
	n-C_6H_{13}	.2	42.0	97	0.5	1.4750	....	69.63	69.60	11.03	11.05	9.03	9.05
	n-C_8H_{17}	.2	46.5	84	0.1	1.4754	....	72.07	72.12	11.55	11.68	7.64	7.67
CN	C_2H_5	1.4	30.2	111		1.4132	0.8075	74.03	74.20	8.70	8.71	17.27	17.24
	iso-C_3H_7	0.8	30.1	125–126		1.4128	.8038	75.74	75.13	9.53	9.76	14.73	15.06
	n-C_5H_{11}	.6	43.2	77–78	25	1.4310	.8213	78.00	78.28	10.63	10.46	11.37	11.31
	n-C_6H_{13}	.18	46.0	112	48	1.4350	.8242	78.77	78.73	11.02	10.92	10.21	10.19

[a] All constants reported were determined on analytical samples. [b] Analyses by Clark Microanalytical Laboratories. [c] $n^{21}D$ in this case.

A trace of hydroquinone was added and the mixture was distilled under reduced pressure. Best results for the higher members of the series were obtained by distilling from a 50-ml. standard taper flask attached directly to a cold-finger still-head, using carborundum chips for ebullition and a bath temperature of about 50° above the boiling point of the oxime.

α-Alkylacrylonitriles.—α-Ethylacrolein oxime was dehydrated by mixing with an equivalent amount of acetic anhydride, adding a crystal of *p-t*-butylcatechol and distilling the mixture through a 6-in. Vigreux column. The distillate was washed with 0.1 mole excess of sodium carbonate in water solution, the aqueous layer extracted with ether and the organic material dried and distilled, another crystal of inhibitor being added before distillation, through a small electrically-heated column packed with Berl saddles.

The other oximes were dehydrated by refluxing with acetic anhydride (fifteen minutes for the isopropyl homolog, thirty minutes for the others), treating the cooled reaction mixture with a solution containing 0.1 mole excess of sodium carbonate and steam-distilling this basic mixture. The nitrile was separated from the distillate, the aqueous layer extracted with ether and the organic material dried and distilled as above. In the case of the α-isopropylacrylonitrile some acetic acid and/or anhydride survived this treatment and it was necessary to wash the product with 10% sodium carbonate solution and redistil. As can be seen in Table I, the α-isopropylacrylonitrile was the least stable of the nitriles prepared, giving a poor analysis. This is in accord with the observations of Marvel, Myers and Saunders[2] on the parent acrolein. The oxime of α-*n*-octylacrolein could not be successfully dehydrated, the product apparently being a mixture from which the nitrile could not be separated by the fractionation procedures utilized.

Summary

Four new α-alkylacrylonitriles, which have as the alkyl substituents ethyl, isopropyl, *n*-amyl and *n*-hexyl groups, have been prepared by the dehydration of the oximes of the corresponding α-alkylacroleins and these nitriles have been characterized.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Amine and Enol Derivatives of 1,1,1-Trifluoropropane[1]

BY W. R. NES[2] AND ALFRED BURGER

The chemical literature lists only very few compounds containing the trifluoromethyl group which have been studied pharmacologically. Since this radical manifests interesting chemical properties, it was considered worthwhile to prepare trifluoromethyl analogs of known pharmacologically active compounds, and in particular to prepare potential pressor amines in order to determine the effect of the fluorine atoms on the activity of such compounds.

We have synthesized 1,1,1-trifluoro-2-amino-3-phenylpropane (I) and 1,1,1-trifluoro-2-amino-3-cyclohexylpropane (II), and these have been compared with the corresponding non-fluorinated analogs, amphetamine and its hexahydro derivative, respectively. An interesting difference has been found for the amine II, which produces central depression in rats in a dose range of 25–150 mg./kg. In contrast, 1-cyclohexyl-2-aminopropane causes central stimulation at a dose of 25 mg./kg. The amine II does not exhibit anticonvulsant activity in doses up to 150 mg./kg. The amphetamine analog I is devoid of central stimulating activity after doses up to 30 mg./kg. intraperitoneally; in cats anesthetized with pentobarbital sodium, doses of 5 or 10 mg./kg. intravenously produce slight depressor effects. No inhibition or potentiation of acetylcholine

(1) Presented before the Division of Organic Chemistry, American Chemical Society, Philadelphia, Pa., April 12, 1950.

(2) Smith, Kline & French Fellow, 1948–1949; du Pont Research Fellow, 1949; present address: Mayo Clinic, Rochester, Minnesota.

or epinephrine is produced by this compound. Doses of 75 or 100 mg./kg. intraperitoneally protect guinea pigs against aerosolized histamine.[3]

A synthesis of a compound designated as 1,1,1-trifluoro-2-amino-3-phenylpropane had been reported by Jones.[4] He prepared trifluoromethyl benzyl ketone from benzylmagnesium chloride and trifluoroacetonitrile, and from benzylzinc chloride and trifluoroacetyl chloride, but did not prove the structure of his non-crystalline ketone nor characterize it by a solid derivative. An oily oxime prepared from the ketone was hydrogenated in the presence of a palladium catalyst in anhydrous ether, and the resulting amine was converted to a hydrochloride of melting point 231–233°; no other derivatives were reported.

We prepared trifluoromethyl benzyl ketone (III) by hydrolyzing and decarboxylating α-phenyltrifluoroacetylacetonitrile (IV) which we obtained by condensation of phenylacetonitrile with ethyl trifluoroacetate under the influence of sodium ethoxide.

The hydrolysis of the nitrile stopped at the stage of α-phenyltrifluoroacetylacetamide (V) under conditions which ordinarily lead to the ketone[5] but trifluoromethyl benzyl ketone was obtained in a yield of 64% based on ethyl trifluoroacetate when the reaction conditions chosen were more drastic.

$$C_6H_5CH_2CN + CF_3CO_2C_2H_5 \xrightarrow{NaOC_2H_5}$$

$$C_6H_5CH(CN)COCF_3 \xrightarrow{H^+} C_6H_5CH(COCF_3)CONH_2 \xrightarrow{H^+}$$

(IV) V

$$C_6H_5CH_2COCF_3 \xrightarrow[Ni]{NH_3,\ H_2} C_6H_5CH_2CH(CF_3)NH_2$$

III I

The ketone (III) was characterized by its semicarbazone, oxime (VI), sodium bisulfite and hydantoin derivatives. Its structure was established unequivocally by alkaline degradation to phenylacetic acid.

We also observed that trifluoromethyl benzyl ketone gives a crystalline ammonia addition product, and could reductively alkylate ammonia in the presence of Raney nickel catalyst. 1,1,1-Trifluoro-2-amino-3-phenylpropane (I) was obtained in this reaction in a yield of 72%. The amine was characterized as the hydrochloride (m. p. 203–206°) and the acetyl derivative (m. p. 130–130.8°). The elementary analyses of these two derivatives were in excellent agreement with the calculated values.

In view of the different melting points of our hydrochloride and that described by Jones,[4] a direct comparison of the two amines became advisable. Through the courtesy of Dr. Reuben G. Jones we obtained a sample of his hydrochloride (m. p. 232–233°, cor.). A mixture melting point with our 1,1,1-trifluoro-2-amino-3-phenylpropane hydrochloride (m. p. 203–206°) was 178–183° (cor.). We then converted Dr. Jones' hydrochloride to an acetyl derivative which melted at 123–123.5° after undergoing a transition in crystal form at about 115°. A mixture of a sample with our 1,1,1-trifluoro-2-acetamido-3-phenylpropane melted at 93–107°. The analysis of the acetyl derivative prepared from Dr. Jones' hydrochloride supports the molecular composition $C_{11}H_{12}F_3NO$.

It appeared unlikely that either the reductive alkylation of ammonia with our ketone, or the hydrogenation of Jones' ketoxime could have given rise to isomeric amines. Isomerism of Jones' ketone, and our trifluoromethyl benzyl ketone might have arisen from the different synthetic procedures used in their preparation.[6] It is known that benzylmagnesium halides can react "abnormally" with the production of *o*-methylphenyl derivatives.[7] Upon our suggestion, Dr. Jones decomposed his ketone[4] with warm 10% potassium hydroxide solution and identified the resulting acid as *o*-toluic acid by melting point, and mixture melting point with an authentic sample. Therefore, the trifluoromethyl benzyl ketone, trifluoromethylbenzylcarbinol and 1,1,1-trifluoro-2-amino-3-phenylpropane reported in his paper[4] are in reality, *o*-trifluoroacetyltoluene, its oxime, trifluoromethyl-*o*-tolylcarbinol, and 1,1,1-trifluoro-2-amino-2-*o*-tolylethane, respectively.

Hydrogenation of pure crystalline trifluoromethyl benzyl ketoxime (VI) in 3.5% ethanolic hydrochloric acid in the presence of a platinum catalyst yielded, in several runs, always two products. One was an amine which was identified as 1,1,1-trifluoro-2-amino-3-cyclohexylpropane (II); the second product was a non-basic low-melting solid which proved to be 1,1,1-trifluoro-3-cyclohexylpropanone oxime (VII). This means that in the formation of this compound the aromatic ring had been reduced in preference to the oxime group.

The structures of the oxime VII and the amine II were proved by the following reactions. Acid hydrolysis of the oxime VII furnished 1,1,1-trifluoro-3-cyclohexylpropane (VIII); this ketone was characterized as the crystalline semicarbazone. Its structure was established by degradation to cyclohexaneacetic acid (IX) by the haloform reaction. The ketone was hydrogenated in ethanolic ammonia and yielded 60% of 1,1,1-trifluoro-2-amino-3-cyclohexylpropane (II) which was identical with that obtained from the hydrogenation of trifluoromethyl benzyl ketoxime.

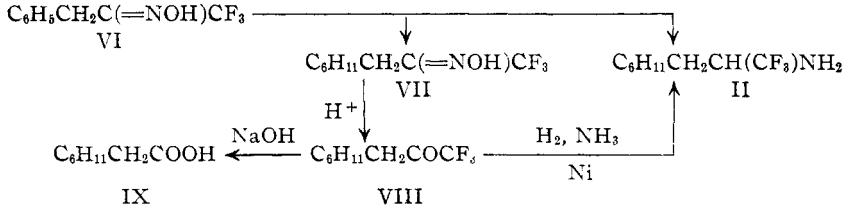
(3) We are grateful to Dr. E. J. Fellows of Smith, Kline & French Laboratories for communicating to us these observations.

(4) Jones, THIS JOURNAL, **70**, 143 (1948).

(5) Julian and Oliver, "Organic Syntheses," Col. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 391.

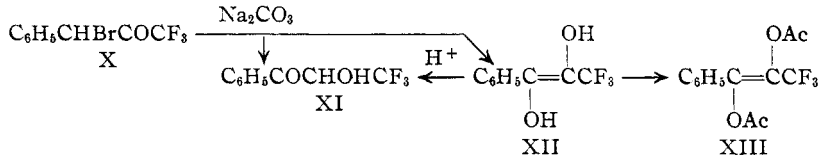
(6) We are obliged to Dr. Wilkins Reeve for this suggestion.

(7) Gilman and Kirby, THIS JOURNAL, **54**, 345 (1932); Austin and Johnson, *ibid.*, **54**, 647 (1932).



Trifluoromethyl benzyl ketone could be brominated readily to the bromo ketone X. This compound reacted strongly acidic and gave an α-methoxy ketone on treatment with sodium methoxide.

An interesting reaction was observed when the bromo ketone was treated with sodium carbonate solution. Instead of the expected trifluoroacetylphenylcarbinol, two products were obtained, *viz.*, trifluoromethylbenzoylcarbinol (XI) and the enediol, 1,1,1-trifluoro-3-phenylpropene-2,3-diol (XII). This enediol was isomerized to



the hydroxy ketone XI by refluxing with methanolic hydrochloric acid, and ultraviolet data suggested that this ketonization also took place in alkaline medium.

The hydroxy ketone XI was shown to contain the benzoyl radical rather than the trifluoroacetyl radical by strong conjugated carbonyl absorption bands in the infrared (1685 cm.$^{-1}$) and ultraviolet (2480 Å., E 1.34 × 10^4), spectra. The trifluoroacetyl radical does not exhibit conjugation, since trifluoromethyl benzyl ketone (I) shows a non-conjugated carbonyl absorption band in the infrared (1740 cm.$^{-1}$) and gives no conjugated maximum in the ultraviolet; 1,1,1-trifluoro-3-cyclohexylpropanone (VIII) also gives a non-conjugated carbonyl absorption band in the infrared (1750 cm.$^{-1}$). Trifluoromethylbenzoylcarbinol (XI) shows a band in the infrared spectrum at 3360 cm.$^{-1}$ which can be assigned to a hydrogen bonded hydroxyl group. In chloroform solution this band appears at 3464 cm.$^{-1}$.

1,1,1-Trifluoro-3-phenylpropene-2,3-diol (XII) exhibits *no* carbonyl band in its infrared spectrum. Moreover, the presence of hydroxyl is indicated by a strong band at 3410 cm.$^{-1}$ in the solid state, and perhaps also by a very weak broad band at about 3077 cm.$^{-1}$. In chloroform solution these bands are shifted to 3617 and 3363 cm.$^{-1}$ and may be interpreted as normal and hydrogen bonded hydroxyl, respectively. The enediol also forms a diacetate (XIII) under conditions which might be expected to yield a monoacetate from a hydroxy ketone.[8] It is interesting that this metastable enediol is not sterically hindered.

The hydrogen bonding which is indicated in the infrared spectra of these compounds probably results from a five-membered chelated ring involving the hydroxyl group and one fluorine atom. In addition, the shift of the hydroxyl bands to shorter wave lengths in solution suggests that intermolecular hydrogen bonding takes place in the solid state.

The infrared spectra of pure liquid trifluoromethyl benzyl ketone (III) and 1,1,1-trifluoro-3-cyclohexylpropanone (VIII) also exhibit weak bands at about 3250 and 3570 cm.$^{-1}$, respectively, which can be interpreted as hydroxyl stretching frequencies. These compounds apparently enolize to a certain extent in analogy with the findings of Swarts[9] that ethyl trifluoroacetoacetate is 66% enolized in ethanol solution.

Acknowledgments.—We are grateful to S. P. Sadtler and Sons, Inc., Philadelphia, Pennsylvania, and to Dr. H. S. Gutowsky and Miss E. M. Petersen of the University of Illinois for the infrared spectra reported in this paper. Doctor Gutowsky also has interpreted the spectra. We wish to thank Smith, Kline & French Laboratories for support of this work.

Experimental[10]

α-Phenyltrifluoroacetylacetonitrile (IV).—A mixture of 142 g. of ethyl trifluoroacetate and 110 g. of phenylacetonitrile was dropped into a hot solution of 23 g. of sodium in 250 cc. of ethanol over a period of one-half hour so that the mixture boiled gently. After the spontaneous boiling had ceased the mixture was refluxed for ten hours. The solution turned red. After standing overnight the clear solution was poured into 3 l. of cold water acidified with 100 cc. of concentrated hydrochloric acid. A small portion of the condensation product separated as a heavy oil and the mixture was extracted with two liters of ether. The ether extracts were dried over sodium sulfate. The ether was removed and the residual reddish oil was heated under reduced pressure. The oily residue was allowed to stand in the air overnight, and 190 g. (87%) of slightly yellow crystalline hydrate, m. p. 70–75°, was thus obtained. It was recrystallized from 150 cc. of benzene and appeared as colorless water-soluble needles, m. p. 82–84°.

Anal. Calcd. for $C_{10}H_6F_3NO\cdot H_2O$: C, 51.95; H, 3.46; N, 6.06. Found: C, 51.53; H, 3.31; N, 6.52.

α-Phenyltrifluoroacetylacetamide (V).—A mixture of 20 g. of IV and 10 g. of water was stirred slowly into 20 cc. of concentrated sulfuric acid at 5° and the mixture was heated at 95° for 3.5 hours with occasional shaking. The resulting two-phase reddish mixture was cooled to 10° and added slowly to 100 cc. of cold water, whereby the amide hydrate precipitated as colorless crystals in a yield of 9 g. After recrystallization from benzene the material melted at 92–93°, resolidified at about 98° and showed a final melting point of 120–121°.

(8) Fuson, Scott, Horning and McKeever, THIS JOURNAL, **62**, 2091 (1940).

(9) Swarts, *Bull. classe sci. Acad. roy. Belg.*, [5] **12**, 671–720 (1926).

(10) All melting points have been corrected. Most of the microanalyses have been performed by Clark Microanalytical Laboratory Urbana, Illinois.

Anal. Calcd. for $C_{10}H_8F_3NO_2 \cdot H_2O$: C, 48.19; H, 4.04. Found: C, 48.69; H, 4.07.

When the amide was heated with 10% sodium hydroxide for one to two minutes until solution occurred, and the mixture was cooled immediately, phenylacetamide precipitated as colorless flakes, m. p. 155–156°, which were identified by a mixture melting point with an authentic sample.

Trifluoromethyl Benzyl Ketone (III).—α-Phenyltrifluoroacetylacetonitrile hydrate (245 g.) was added to a mixture of 425 g. of 98% sulfuric acid and 250 cc. of water in a flask equipped with a dropping funnel and a 30-cm. unpacked insulated column. The mixture was heated to 160° and steam distillation from the top of the column began at 95–98°. Water was added slowly from the dropping funnel at such a rate that the volume remained constant. The temperature rose slowly and was maintained at 100–110° by adjusting the rate of addition of water. After six hours the mixture darkened and the distillate no longer gave a precipitate with 28% ammonium hydroxide. The distillate was extracted with ether and the extract dried over sodium sulfate and fractionated. The colorless liquid ketone boiled at 51–52° (2 mm.) and showed $n^{25}D$ 1.4432. It weighed 146 g. (73%).

Anal. Calcd. for $C_9H_7F_3O$: C, 57.43; H, 3.75. Found: C, 57.50; H, 3.60.

The ketone reduced Tollens reagent and formed a crystalline **sodium bisulfite addition product** which was soluble in an excess of the reagent. When treated with ammonium hydroxide, a colorless crystalline **ammonia addition** product precipitated. It crystallized from benzene as colorless needles, m. p. 80–84°, which were too unstable to be analyzed.

The oxime (VI) was prepared by boiling the reagents in pyridine for three hours, decomposing the cooled reaction mixture with cold 3 *N* hydrochloric acid and extracting into ether. It distilled as a colorless oil at 91–92° (3 mm.) and solidified in the receiver, m. p. 40–42°. The yield was 87%.

Anal. Calcd. for $C_9H_8F_3NO$: N, 6.89. Found: N, 7.35.

The semicarbazone crystallized from 50% methanol as colorless needles, m. p. 129–130°.

Anal. Calcd. for $C_{10}H_{10}F_3N_3O$: N, 17.14. Found: N, 17.04.

Trifluoromethyl benzyl ketone underwent the haloform reaction when heated with 10% sodium hydroxide solution. Fluoroform was evolved, the mixture was acidified after twenty minutes, and the precipitated solid recrystallized from ether–petroleum ether. The lustrous flakes were identified as phenylacetic acid by melting point (74–76°) and mixture melting point.

5-Trifluoromethyl-5-benzylhydantoin.—Ten grams of trifluoromethyl benzyl ketone was added to a mixture of 4.4 g. of potassium cyanide and 18.4 g. of ammonium carbonate in 75 cc. of 50% ethanol and heated at 70° for six hours. The solution was concentrated, acidified, and the precipitated oil was separated and allowed to crystallize from ethanol. The yield was 1.2 g. of pale tan flakes, m. p. 174–175°.

Anal. Calcd. for $C_{11}H_9F_3N_2O_2 \cdot H_2O$: N, 10.15. Found: N, 10.26.

1,1,1-Trifluoro-2-amino-3-phenylpropane (I).—A solution of 19 g. of trifluoromethyl benzyl ketone (III) in 150 cc. of 10% absolute ethanolic ammonia was hydrogenated in the presence of 4 g. of Raney nickel at 150 atm. pressure and 140–150° for five hours. The colorless amine boiled at 65–66° (2 mm.) and weighed 14 g. (72%).

The colorless **hydrochloride** was prepared in ether–petroleum ether and was purified for analysis by sublimation at 125° (2 mm.), m. p. 203–206° (sealed tube).

Anal. Calcd. for $C_9H_{10}F_3N \cdot HCl$: C, 47.95; H, 4.92; N, 6.21. Found: C, 48.19; H, 5.09; N, 6.89.

The N-acetyl derivative obtained by the Schotten–Baumann method using acetic anhydride crystallized from dilute ethanol as needles, m. p. 130–130.8°.

Anal. Calcd. for $C_{11}H_{12}F_3NO$: C, 57.14; H, 5.23; N, 6.06. Found: C, 57.20; H, 5.35; N, 6.06.

A sample of an amine hydrochloride obtained from Dr. R. G. Jones of Indianapolis was converted to an acetyl derivative by the same reaction. It crystallized from ethanol, m. p. 123–123.5°, after undergoing a transition to a different crystalline state at about 115°.

Anal. Calcd. for $C_{11}H_{12}F_3NO$: C, 57.14; H, 5.23; N, 6.06. Found: C, 57.48; H, 5.10; N, 5.63.

A mixture melting point of this compound with the acetyl derivative of m. p. 130–130.8° described above was 93–107°.

1,1,1-Trifluoro-2-amino-3-cyclohexylpropane (II).—A solution of 45 g. of trifluoromethyl benzyl ketoxime (V) in 100 cc. of absolute ethanol containing 10 cc. of concentrated hydrochloric acid was hydrogenated with 1.0 g. of Adams platinum catalyst under 100–120 atm. pressure at 140° for two and one-half hours. The reaction mixture was poured into dilute hydrochloric acid. A heavy oil consisting of 1,1,1-trifluoro-3-cyclohexylpropanone oxime precipitated and was extracted into ether. It will be described below. The aqueous layer was made alkaline with dilute sodium carbonate solution, and the precipitated oil was extracted into ether, dried over sodium sulfate, and fractionated. The colorless liquid amine (6 g., 14%) boiled at 56–58° (2 mm.).

The hydrochloride was prepared in ether–petroleum ether and was purified for analysis by sublimation at 125° (2 mm.), m. p. 249–252° (sealed tube). The salt began to sublime at about 150° at atmospheric pressure.

Anal. Calcd. for $C_9H_{17}ClF_3N$: C, 46.65; H, 7.40; N, 6.04. Found: C, 46.91; H, 7.53; N, 6.19.

The N-acetyl derivative crystallized from dilute ethanol as needles, m. p. 86–87°.

Anal. Calcd. for $C_{11}H_{18}F_3NO$: N, 5.90. Found: N, 5.81.

1,1,1-Trifluoro-3-cyclohexylpropanone Oxime (VII).—The ethereal extract of the acid reduction mixture described above was dried over sodium sulfate and fractionated to yield 12 g. (26%) of colorless liquid oxime, b. p. 91–92° (1 mm.), which solidified and showed melting point 32–35°. A mixture melting point with a sample of the starting material (VI) gave a deep depression.

Anal. Calcd. for $C_9H_{14}F_3NO$: N, 6.70. Found: N, 6.95.

1,1,1-Trifluoro-3-cyclohexylpropanone (VIII).—Eight grams of the oxime VII was hydrolyzed by refluxing with 30 cc. of concentrated hydrochloric acid for six hours. The mixture was cooled, diluted with water and extracted with ether. The extract was dried and fractionated yielding 5 g. of colorless liquid ketone, b. p. 49–50° (1 mm.).

The semicarbazone crystallized from 50% methanol as colorless needles, m. p. 122–124° (sintering at 113°). A mixture melting point with trifluoromethyl benzyl ketone semicarbazone was 93–110°.

Anal. Calcd. for $C_{10}H_{16}F_3N_3O$: N, 16.73. Found: N, 16.88.

Haloform degradation of the ketone with 20% sodium hydroxide solution for about 15 minutes followed by acidification yielded a solid, m. p. 28.5–30°. A mixture melting point with an authentic sample of cyclohexaneacetic acid (m. p. 28–30°) was 28–30°. The amide of our acid (m. p. 166.5–168.5°) showed no melting point depression when mixed with cyclohexaneacetamide.

Reductive Amination of VIII.—A solution of 5 g. of 1,1,1-trifluoro-3-cyclohexylpropanone in 30 cc. of 10% absolute ethanolic ammonia was hydrogenated using 3 g. of Raney nickel catalyst under a pressure of 170 atm. at 135–140° for six hours. The amine (II) was obtained in a yield of 60% as a colorless liquid, b. p. 61–65° (3–4 mm.). **The hydrochloride** was prepared in petroleum ether, m. p. 247–252° (sealed tube) (softening at 238°) and gave no melting point depression with the hydrochloride of the amine (II) described above. **The N-acetyl derivative** crystallized from dilute ethanol, m. p. 84–86°.

A mixture melting point with the acetyl derivative described above gave no depression.

1,1,1-Trifluoro-3-bromo-3-phenylpropanone (X).—To a solution of 95 g. of trifluoromethyl benzyl ketone (III) in 75 cc. of carbon tetrachloride irradiated with two 150 watt flood light bulbs, was added a solution of 161.4 g. of bromine in 100 cc. of carbon tetrachloride over a period of two and one-half hours. The solution boiled gently and was refluxed for another forty-five minutes after completion of the addition. The solvent was removed in a vacuum and the residue fractionated. The bromo ketone boiled as a greenish-yellow oil at 56–57° (0.7 mm.), $n^{25}D$ 1.4901; yield 118 g. (89%).

Anal. Calcd. for $C_9H_6BrF_3O$: C, 40.48; H, 2.27. Found: C, 40.63; H, 2.50.

When the bromo ketone was allowed to stand in air for thirty minutes, it solidified as a hydrate, m. p. 42–45°. This compound was too unstable to be analyzed. The bromo ketone was less soluble in water at temperatures above 40° than below this temperature. The aqueous solution reacted strongly acidic. It also dissolved in ethanol exothermically to form an acid solution but since the bromo ketone was recovered unchanged, no hydrogen bromide could have been split off and the acidity must have been due to enolization.

1,1,1-Trifluoro-3-methoxy-3-phenylpropanone.—The bromo ketone X reacted exothermically with sodium methoxide in methanol solution with an immediate precipitation of sodium bromide. The reaction mixture was poured into cold 10% hydrochloric acid and the precipitated oily ether was extracted into ether. Fractionation yielded a slightly greenish-yellow oil, b. p. 65–66° (2 mm.).

Anal. Calcd. for $C_{10}H_9F_3O_2$: C, 55.04; H, 4.16. Found: C, 54.86; H, 4.29.

Alkaline Hydrolysis of 1,1,1-Trifluoro-3-bromo-3-phenylpropanone (X).—A suspension of 10 g. of the bromo ketone X in 150 g. of 33% potassium carbonate solution was shaken for twenty minutes. The colorless semi-solid which formed was extracted into ether and dried. The ether was removed, petroleum ether added to the residue, and the resulting oil was allowed to crystallize at −20°. The crystals (3 g.) were washed with ether–petroleum ether and crystallized from dilute ethanol and finally from ether–petroleum ether. The colorless needles melted at 148–150° after softening at 143°. This compound was identified as 1,1,1-trifluoro-3-phenylpropene-2,3-diol (XII).

Anal. Calcd. for $C_9H_7F_3O_2$: C, 52.93; H, 3.45. Found: C, 53.17; H, 3.47.

The enediol reduced Tollens reagent at 40°, but did not reduce cupric acetate. It was soluble in 10% sodium hydroxide solution to give a colorless solution. The enediol was not altered by standing in air.

By fractional crystallization of the mother liquors from ether–petroleum ether and from dilute ethanol at −20°, 3 g. of colorless crystals, m. p. 80.5–82.5°, was obtained. The compound was found to be **trifluoromethylbenzoylcarbinol** (XI); it was soluble in the common organic solvents except cold hexane.

Anal. Calcd. for $C_9H_7F_3O_2$: C, 52.93; H, 3.45. Found: C, 52.77; H, 3.65.

The hydroxy ketone reduced Tollens reagent at 0° and cupric acetate on warming. It was soluble with yellow color in 10% sodium hydroxide solution and could not be recovered on acidification.

A number of similar experiments were conducted but the conditions of fractional crystallization were varied and the time of reaction was varied up to one and one-quarter hours. The best yield of the enediol was 32% in one run and that of the hydroxy ketone 20% from another batch.

1,1,1-Trifluoro-2,3-diacetoxy-3-phenylpropene-2 (XIII).—A solution of 0.5 g. of the enediol XII in 10 cc. of acetic anhydride was refluxed for three hours, decomposed with water, and worked up by extracting the diacetate into ether. From the washed and dried ether solution, 0.25 g. of colorless crystals, m. p. 161–163°, was obtained.

Anal. Calcd. for $C_{13}H_{11}F_3O_4$: C, 54.17; H, 3.85. Found: C, 54.09; H, 4.11.

Isomerization of 1,1,1-Trifluoro-3-phenylpropene-2,3-diol.—A solution of 0.1 g. of the enediol XII in 6 cc. of a 1:1 mixture of concentrated hydrochloric acid and methanol was refluxed for three hours; the clear solution was cooled and a few drops of water were added. The hydroxy ketone XI crystallized on standing at −20° for two hours and was recrystallized from dilute ethanol to melting point 79–81°. A mixture melting point with a sample of trifluoromethylbenzoylcarbinol obtained by hydrolysis of the bromo ketone X showed no depression.

The colorless crystalline material of m. p. 60–70° obtained by allowing the enediol XII to stand in a saturated 1:1 aqueous methanolic solution of sodium carbonate for 2.5 hours showed a broad maximum at 2460–2570 Å. (E *ca.* 1×10^3) in ethanol solution. A 1:2 mixture of the hydroxy ketone XI and the enediol XII exhibited a broad maximum at 2460–2510 Å. (E *ca.* 4×10^3) in the same solvent.

Summary

1. Trifluoromethyl benzyl ketone was prepared from ethyl trifluoroacetate and phenylacetonitrile by way of α-phenyltrifluoroacetylacetonitrile. The structure of the ketone was proved by degradation to phenylacetic acid.

2. Reductive alkylation of ammonia with trifluoromethyl benzyl ketone yielded 1,1,1-trifluoro-2-amino-3-phenylpropane, while hydrogenation of trifluoromethyl benzyl ketoxime furnished a mixture of 1,1,1-trifluoro-2-amino-3-cyclohexylpropane and 1,1,1-trifluoro-3-cyclohexylpropanone oxime. The latter was hydrolyzed to the ketone, which could then be hydrogenated to 1,1,1-trifluoro-2-amino-3-cyclohexylpropane in the presence of ammonia. The structure of the cyclohexyl ketone was confirmed by degradation to cyclohexaneacetic acid.

3. Mild alkaline hydrolysis of 1,1,1-trifluoro-3-bromo-3-phenylpropanone gave two products, namely, trifluoromethylbenzoylcarbinol, and an enediol, 1,1,1-trifluoro-3-phenylpropene-2,3-diol. The structures of these isomers are based on chemical and spectroscopic evidence.

4. The trifluoromethyl benzyl ketone, trifluoromethyl benzyl ketoxime, trifluoromethylbenzylcarbinol and 1,1,1-trifluoro-2-amino-3-phenylpropane reported in the literature[4] are, in reality, *o*-trifluoroacetyltoluene, its oxime, trifluoromethyl-*o*-tolylcarbinol, and 1,1,1-trifluoro-2-amino-2-*o*-tolylethane, respectively.

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