Novel 6-(Trifluoromethyl)cytosines and 6-(Trifluoromethyl)uracils

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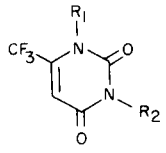
Ethyl 3-amino-4,4,4-trifluorocrotonate (**3**) has been converted by a one step reaction with alkyl and aryl isocyanates to novel 3-substituted-6-(trifluoromethyl)uracils. Also several 3-amino-4,4,4-trifluorocrotonitriles (**11a-c**) have been cyclized to novel 6-(trifluoromethyl)cytosines (**13a-c**) and then hydrolyzed to the corresponding uracils (**4**, **14b-c**). Alkylation studies with isopropyl bromide of three 6-(trifluoromethyl)uracils (**1**, **4**, **5**) are described.

Only one 6-(trifluoromethyl)uracil (**1**, R_1, R_2 = H) (1) has been reported in the literature; examples where R_1 and/or R_2 are substituents other than hydrogen are apparently unknown. We wish to report two different syntheses of novel examples of **1** where R_2 is other than hydrogen. Alkylation of **1** (R_1, R_2 = H) with isopropyl bromide is also discussed.



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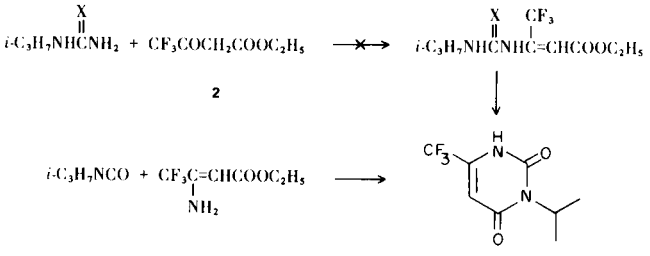
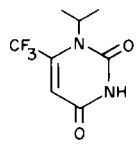
Principal means of synthesizing uracils are the condensations of a urea or thiourea with a β-keto ester (2) and an aminocrotonate with an isocyanate (3). In either case the resulting ureido intermediate is cyclized in the presence of base in a second step. Both methods are described in the patent literature (4) for the preparation of 6-methyl-3-substituted uracils from ethyl acetoacetate or its derived aminocrotonate. However, ethyl trifluoroacetoacetate (**2**) could not be induced to react with an alkylurea (X = O,S) with phosphoric acid, ethanolic hydrogen chloride, or sodium ethoxide as a catalyst. The aminocrotonate (**3**) also could not be made to react with isopropyl isocyanate in the presence of triethylamine. However, when **3** and an alkyl or aryl isocyanate were allowed to react in dimethylsulfoxide in the presence of an alkoxide, 3-substituted-6-(trifluoromethyl)uracils were formed in a single step (see Table I). Subsequent work with isopropyl isocyanate showed that other strong bases such as sodium hydride, potassium hydroxide and pentamethylguanidine and other solvents such as dimethylformamide, toluene, alcohols, ethyl acetate, and methyl isobutyl ketone would also yield 3-isopropyl-6-(trifluoromethyl)uracil (**4**) in one step.



2 **3** **4**

During one of the early preparations of **4** a solid isomeric by-product was detected. This compound could be isolated by fractional crystallization of the crude reaction product or, better, by fractional precipitation between *p*H 9.5-8.0 (**4** is precipitated between *p*H 8.0-3.0). Possible structures which were considered are positional isomers **5**, **6**, **7**, and ring isomer **8**. Since this by-product was stable to refluxing 20% hydrochloric acid for 11 hours, structures **6**, **7** (5), and **8** (6) were eliminated.



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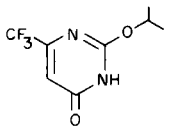

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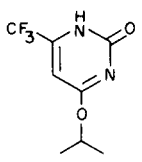

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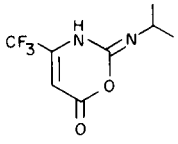

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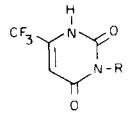
TABLE I

Experimental and Analytical Data for Compounds Prepared by General Method



	Recrystallization Solvent	% Yield Recrystallized	M.p., °C	Formula	Analytical Data									
					Calculated					Found				
					C	H	F	N	Cl	C	H	F	N	Cl
R = *n*-C_4H_9-	2:1 cyclohexane:benzene	60.5	174-176	$C_9H_{11}F_3N_2O_2$	45.8	4.7	24.1	11.9		45.7	4.7	24.1	11.7	
R = C_6H_{11}-	cyclohexane	63.8	195-197	$C_{11}H_{13}F_3N_2O_2$	50.4	5.0	21.7	10.7		50.6	5.0	21.6	10.5	
R = *n*-C_8H_{17}-	cyclohexane	50.6	130-133.5	$C_{13}H_{19}F_3N_2O_2$	53.4	6.6	19.5	9.6		53.6	6.8	19.2	9.5	
R = C_6H_5-	95% ethanol	52.9	233-236	$C_{11}H_7F_3N_2O_2$	51.6	2.8	22.3	10.9		51.8	2.8	22.2	10.8	
R = CH_3-	95% ethanol	76.0	236-238	$C_6H_5F_3N_2O_2$	37.1	2.6	29.4	14.4		37.3	2.6	29.2	14.4	
R = *n*-$C_{12}H_{25}$	95% ethanol	36.3	121-123	$C_{17}H_{27}F_3N_2O_2$	58.6	7.2	16.4	8.0		58.9	7.3	16.3	7.9	
R = C_2H_5-	95% ethanol	50.3	199-200.5	$C_7H_7F_3N_2O_2$	40.4	3.4	27.4	13.5		40.7	3.5	27.5	13.3	
R = *n*-C_3H_7-	95% ethanol	61.0	173-174	$C_8H_9F_3N_2O_2$	43.3	4.1	25.7	12.6		43.2	3.9	25.9	12.5	
R = 3,4-$Cl_2C_6H_3$-	95% ethanol	50.8	239-240	$C_{11}H_5Cl_2F_3N_2O_2$	40.6	1.6	17.5	8.6	21.8	40.9	1.4	17.8	8.6	22.0
R = $C_2H_5OCOCH_2$-	95% ethanol	48.2	149-151.5	$C_9H_9F_3N_2O_4$	40.6	3.4	21.4	10.5		41.0	3.4	21.4	10.6	
R = *sec*-C_4H_9-	cyclohexane	29.0	106.5-108	$C_9H_{11}F_3N_2O_2$	45.8	4.7	24.1	11.9		46.0	4.5	24.3	11.9	
R = C_3H_5-	95% ethanol	25.0	158-160	$C_8H_7F_3N_2O_2$	43.7	3.2	25.9	12.7		43.9	3.1	25.7	12.7	
R = *n*-C_6H_{13}-	95% ethanol	67.6 (crude with m.p. 140-143°)	143-144	$C_{11}H_{15}F_3N_2O_2$	50.0	5.7	21.8	10.6		50.1	6.2	21.6	10.7	
R = 4-ClC_6H_4-	$CHCl_3$:pet. ether	19.6	231-233	$C_{11}H_6ClF_3N_2O_2$	45.5	2.1	19.6	9.6	12.2	45.8	2.0	20.0	9.6	12.1

Stable tautomeric forms were rejected since solution (acetonitrile) infrared spectra of **4** and the isomer were not identical. Furthermore, reprecipitation of each compound from base did not give identical products as ascertained by tlc and infrared spectral comparisons.

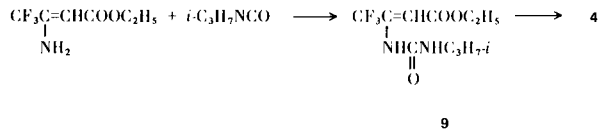
The surviving structure, **5**, has been assigned to the isomeric by-product on the basis of the following supportive analytical evidence. The proton nmr spectra (deuteriobenzene) of **4**, **5** and **1** (R_1 = H, R_2 = CH_3) were recorded with successive additions of Eu (fod)$_3$ (7). One might expect that this reagent would complex with the lone pair electrons on the carbonyl oxygen atoms, and therefore that aliphatic hydrogens in groups attached to the nitrogen flanked by two carbonyl groups would suffer the greatest shifts. The shifts of the olefinic proton, which might be expected to be similar in all three compounds, served as a convenient internal standard with which to compare the other shifts. The ratio of the shifts of the other protons to the olefinic proton shift is as follows (all shifts were downfield):

Compound	Olefinic CH	NH	*N*-Isopropyl CH	*N*-Isopropyl CH_3
1 (R_1 = H, R_2 = CH_3)	1	---	1.26 (CH_3)	---
4	1	0.97	1.45	0.66
5	1	1.31	0.29	0.30

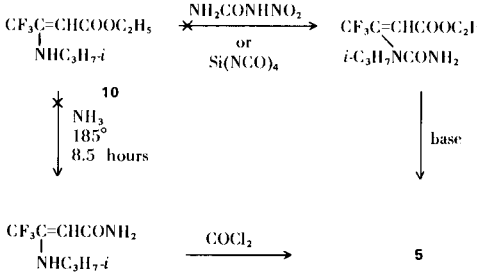
It is seen that with both **1** and **4** the shift of the N-CH protons is greater than the olefinic shift, but in **5** the opposite is the case. The isopropyl methyls in **4** are shifted more than those in **5** as expected. Also, the NH shift is greater in **5** than in **4**, but here shifts may be dependent upon hydrogen bonding as well as the effect of Eu (fod)$_3$.

Mass spectral analysis showed identical m/e = 222 for the molecular ions of each compound. Although a definitive structural assignment could not be made for **5**, the fact that it gave many more fragments than **4** suggested that the former was a less stable or less conjugated molecule than the latter. Compound **4** was found to undergo a bathochromic shift in the ultraviolet when the *p*H of a solution was raised from 7 to 13 while **5** did not. This behavior is in accord with other 1-N and 3-N monoalkylated uracils reported in the literature (8,9).

The formation of **5** has not been rationalized. A simple rearrangement of the isopropyl group from the 3-position to 1-position (or *vice-versa*) is not tenable since each compound could be quantitatively recovered from dimethylsulfoxide containing potassium *t*-butoxide at 80-85° after three hours. The ureido intermediate, **9**, has been prepared and when exposed to typical reaction conditions it gave only the 3-isopropyluracil (**4**). Therefore, **4** and **5** are clearly not formed from a common intermediate.



Several attempts were made to synthesize **5** by an unambiguous method, but none was successful. Compound **10** failed to react with precursors of cyanic acid either under aqueous or non-aqueous conditions. Sakai, *et al.* (10) reported a facile method for preparing 5-substituted-1-methyluracils in good yields, but adaptation to a synthesis for **5** was not successful since **1** (R_1, R_2 = H) could not be made to react with the hexamethyldisilazane-trimethylchlorosilane reagent.



An alternative route to the 6-(trifluoromethyl)uracil was also found starting with the appropriate aminotrifluorocrotononitrile (**11**) (11) and preceeding *via* novel cytosine intermediates (**13**). 5-Chloro-3-isopropyl-6-(trifluoromethyl)uracil (**14b**) was also prepared by treating **4** with sulfuryl chloride.

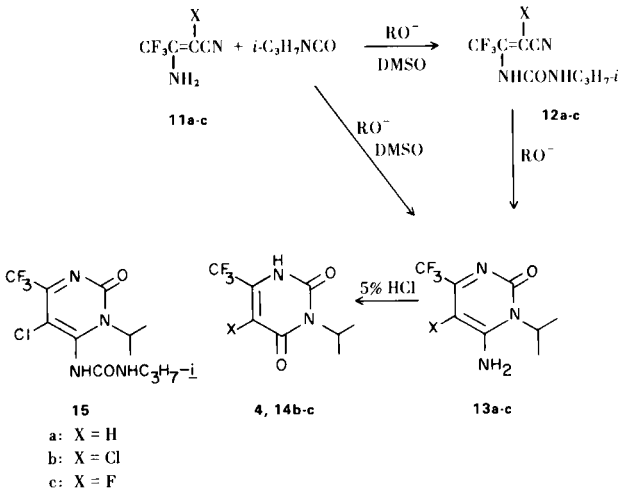


TABLE II

Spectral and Analytical Data

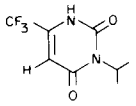
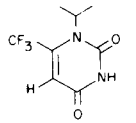
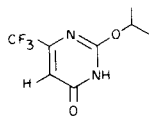
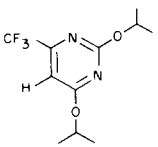
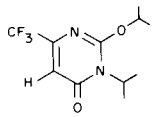
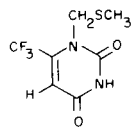
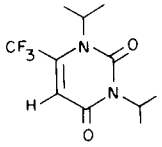
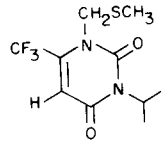
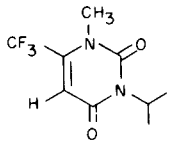
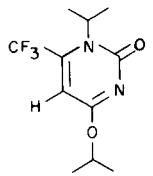
Compound	Structure	Nmr Data, Chemical Shifts (τ) CH_3 CH_3	Coupling Constants J, cps	H	Ring H	Other	Infrared Bands cm^{-1} C=O	Ultraviolet Maxima, (a) λ *p*H 7	*p*H 13	Mass Spectra Important Ions m/e	n_D^{25}	Elemental Analysis Required / Found C	H	F	N	S
												$C_8H_9F_3N_2O_2$				
4		8.60 (d)	7	4.98 (m)	3.91		1745, 1675	262.5	292	222		43.3 43.2	4.1 3.9	25.7 25.5	12.6 12.7	
												$C_8H_9F_3N_2O_2$				
5		8.43 (d)	6.5	5.76 (m)	3.80		1725, 1700	268	267	222 M.W. 224 (DMF)		43.3 43.2	4.1 4.2	25.7 25.5	12.6 12.4	
												$C_8H_9F_3N_2O_2$				
6		8.58 (d)	6.5	4.60 (m)	3.53		1700	275	273	222 203 $C_8H_9F_2N_2O_2$ 164 $C_5H_3F_3N_2O$		43.3 43.3	4.1 4.1	25.7 26.0	12.6 12.7	
		8.92 (d)	6.5	4.85								$C_{11}H_{15}F_3N_2O_2$				
16		8.95 (d)	6.5	4.95 (m)	3.68			267		264 206 $C_8H_9N_2O$ 191 $C_7H_6F_3N_2O$ 164 $C_5H_3F_3N_2O$	1.4328	50.0 50.0	5.7 5.9	21.6 21.5	10.6 10.9	
												$C_{11}H_{15}F_3N_2O_2$				
17		8.54 (d)	7	4.67 (m)	3.67		1700	282		264 164 $C_5H_3F_3N_2O$ 164 $C_6H_5F_3NO$	1.4450	50.0 50.2	5.7 5.7	21.6 21.7	10.6 10.9	
										240		$C_7H_7F_3N_2O_2S$				
18					3.68	5.00 (CH_2) 7.67 (CH_3S)	1740, 1700	270	267.5	193 $C_6H_4F_3N_2O_2$ 181 $C_5H_4F_3N_2O_2$ 178 $C_6H_3F_3NO_2$ 150 $C_5H_3F_3NO$		35.0 35.3	2.9 3.0	23.7 23.6	11.7 11.5	13.3 12.6

TABLE II (continued)

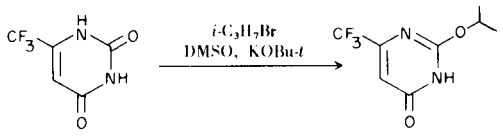
Compound	Structure	Nmr Data, Chemical Shifts (τ) CH_3 CH_3	Coupling Constants J, cps	H	Ring H	Other	Bands cm^{-1} C=O	Ultraviolet Maxima, (a) λ *p*H 7	*p*H 13	Mass Spectra Important Ions m/e	n_D^{25}	Elemental Analysis Required / Found C	H	F	N	S
19		8.41 (d) 8.56 (d)	6.5 7	5.75 4.90 (m)	3.95		1740, 1690	269.5		264 164 $C_6H_5F_3NO$	1.4563	$C_{11}H_{15}F_3N_2O_2$ 50.0 50.2	5.7 5.8	21.6 21.4	10.6 10.5	
20		8.74 (d)	7	5.08 (m)	3.95	5.08 (CH_2) 7.83 (CH_3S)	1725, 1680									
21		8.57 (d)	7	4.83 (m)	3.89	6.54 (CH_3)	1740, 1680					$C_9H_{11}F_3N_2O_2$ 45.8 46.1	4.7 4.2		11.9 11.7	
22		8.58 (d) 8.85 (d)	6.5 6.5	5.82 4.85 (m)	3.92		1700	281.5								

(a) The uv spectra were taken in ethanol (*p*H 7) and 10% ethanol in 0.1 *N* sodium hydroxide (*p*H 13).

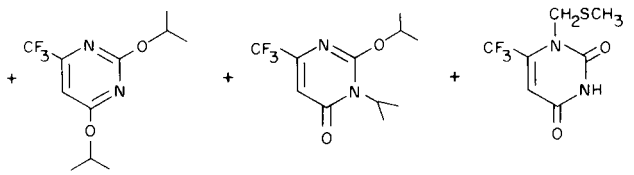
In the cyclization of **11** to **13**, depending upon incompletely defined variables, the intermediate ureido compound, **12**, and a carbamoyl derivative of **13b**, *i.e.* **15**, could be isolated. It appeared that the quantity of base used determined whether or not **12** could be isolated. One equivalent of base gave a substantial quantity of **12**, while two equivalents yielded the cytosine, **13**, in good yield without any detectable trace of **12**.

Direct alkylation of **1** (R_1, R_2 = H) with an isopropyl halide seemed attractive as an alternative synthesis of **4** as well as a possible synthesis of **5** depending upon conditions employed. Baker and Jackson (12) had observed that 1-alkylation of a uracil in dimethylsulfoxide in the presence of potassium carbonate was preferred with "extremely reactive allylic halides" and 3-alkylation with "less reactive saturated alkyl halides." These findings contrasted with an earlier report (13) that alkylation of uracil itself gave 1-alkylation with either saturated or allylic halides. Subsequently, Baker *et al.* (14) observed a steric factor to be important, *viz.* a uracil with a 6-H gave exclusively 1-alkylation whereas a 6-substituted uracil such as 6-methyluracil yielded a 1:1 ratio of 1 to 3-alkylation products. In our case a 6-trifluoromethyl group would not be expected to differ very much sterically from a 6-methyl, but electronically a significant difference could be anticipated.

6-(Trifluoromethyl)uracil (**1**, R_1, R_2 = H) when allowed to react with isopropyl bromide and potassium *t*-butoxide in dimethylsulfoxide at 80-85° for three hours failed to give any **5** (N-1 alkylation) or any **4** (N-3 alkylation), but preferentially yielded *O*-alkylation products (**6**, **16**, and **17**). Compound **18** obviously was formed from solvent participation as an alkylating reagent probably through intermediate formation of CH_3S^+-CH_2Br^-.



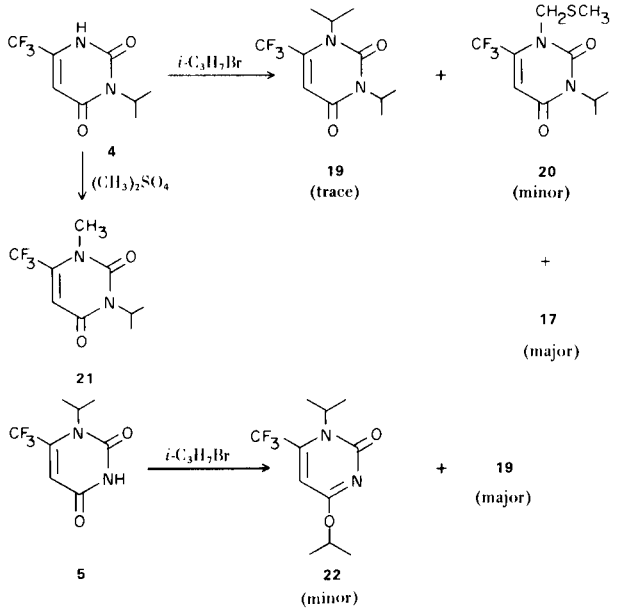
1 (R_1R_2 = H) 6



(major) (minor)

16 17 18

3-Isopropyl-6-(trifluoromethyl)uracil (**4**) and 1-isopropyl-6-(trifluoromethyl)uracil (**5**) when treated in the same manner with isopropyl bromide gave the following products. These experiments show that when the 3-position



4 19 (trace) 20 (minor)

21 17 (major)

5 22 (minor) 19 (major)

is blocked, alkylation on the 1-nitrogen is possible with a methyl group (**4** → **21**), but the bulkier isopropyl group is hindered and largely ends on an oxygen atom (**4** → **17**). If the 1-position is blocked, then alkylation with an isopropyl group on the 3-nitrogen atom preferentially occurs (**5** → **19**). Structural assignments were made on the basis of elemental analyses and infrared, ultraviolet, nuclear magnetic resonance, and mass spectral analyses (see Table II).

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus in capillary tubes and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Infracord spectrometer in mineral oil mulls. Nmr spectra were obtained in deuteriodimethylsulfoxide on a Varian A-60 Spectrometer with TMS as the internal reference. Glc analyses were performed on an F and M gas chromatograph, Model 500, using either a 3-foot column packed with 20% DEGS on Chromosorb W (column A) or a 3-foot column packed with 20% DEGS on Gas Chrom P (column B). Microanalyses were performed by Galbraith Laboratories, Inc.

Ethyl 3-amino-4,4,4-trifluorocrotonate (**3**).

An improved procedure for the reported (15) two-step preparation of this compound follows. Ethyl 4,4,4-trifluoroacetoacetate (50.0 g., 270 mmoles, PCR, Inc.) was warmed to 70° in a 3-neck flask fitted with a stirrer, thermometer, gas inlet tube and a dry ice condenser. Gaseous ammonia was allowed to enter the flask below the liquid level at a rate such that the internal temperature was maintained between 85° and 95°. When approximately 5.7 g. (330 mmoles) of ammonia had been led into the ester, the exotherm ceased and liquid ammonia began to form on the condenser surface. The reaction mixture temperature was then raised by means of a mantle to 100° ± 2° and held at this range for 2 hours. Some solid material was observed in the condenser. The liquid product was cooled, taken up in ether, dried with magnesium sulfate, and the ether removed *in vacuo* leaving a yellow liquid,

46.0 g. (93% yield) with n_D^{25} 1.4187. Glc analysis (column A at 95°) indicated the product was 80% (area) pure.

The purest sample, obtained after fractional distillation at 15 mm., had b.p. 83°, n_D^{25} 1.4213, and was a solid at room temperature (25°), but melted upon hand warming or under slight pressure.

3-Isopropyl-6-(trifluoromethyl)uracil (**4**).

The experimental details which follow favor the formation of **4** over **5** and are those resulting from a half-factorial study using as variables the temperature (0°-20°), base stoichiometry (1.25-1.45 equivalents) and isocyanate stoichiometry (1.15-1.25 equivalents).

Sodium methoxide (2.97 g., 55 mmoles) was placed in a 3-neck flask fitted with a stirrer, thermometer, addition funnel and drying tube. Ethyl 3-amino-4,4,4-trifluorocrotonate (**3**) (10.0 g., 55 mmoles) was dissolved in dimethylsulfoxide (19 ml., dried over molecular sieves) and added over a 15 minute period with cooling to maintain the temperature at 20°. A solution of isopropyl isocyanate (4.67 g., 55 mmoles) in dimethylsulfoxide (2.5 ml.) was added dropwise over a 15 minute period with cooling so that the temperature remained as close as possible to 20°. After a 15 minute hold period another quantity of sodium methoxide (1.34 g.) was added and the reaction mixture stirred for 15 minutes at 20°. Additional isopropyl isocyanate (1.17 g.) was then added (exotherm) and the mixture stirred 15 minutes at 20°. A light suspension remained at this point, which when diluted with water (50 ml.) resulted in a clear solution. The aqueous solution was then extracted with 3 x 50 ml. of ether and the extracts discarded.

The aqueous phase upon acidification with concentrated hydrochloric acid (8 ml.) deposited a white semi-solid, which was extracted into ether (3 x 50 ml.). The ether phase after washing with 2 x 50 ml. portions of water was dried over calcium sulfate and then stripped *in vacuo*. The residue was a powdery solid which weighed 9.95 g. (82% yield). Glc analysis showed this crude product to contain a trace of **5**. The crude product after reshaking with water and vacuum drying (50°) overnight weighed 8.53 g. (70% yield) and was essentially pure by glc analysis (column A at 210°, R_t **4** = 4.8′, **5** = 5.7′). The analytical sample had m.p. 139-142° (see Table II for analytical and spectral data).

General Method for the Syntheses of 3-Alkyl/aryl-6-(trifluoromethyl)uracils (Table I).

A typical procedure is given. No attempt was made to isolate the other 1-substituted uracils which may have been formed along with the 3-substituted uracils.

3-Isopropyl-6-(trifluoromethyl)uracil (**4**).

1-Isopropyl-6-(trifluoromethyl)uracil (**5**).

Ethyl 3-amino-4,4,4-trifluoroacetate (**3**) (98.7 g., 540 mmoles) was added to a stirred suspension of potassium *t*-butoxide (60.6 g., 540 mmoles) in 200 ml. of dimethylsulfoxide while maintaining the temperature at 25-30°. To this solution isopropyl isocyanate (50.2 g., 590 mmoles) was slowly added over the same temperature range. The reaction mixture after stirring for 3 hours at room temperature was poured into 200 ml. of water and extracted with ether. The aqueous phase was slowly acidified with concentrated hydrochloric acid from a starting *p*H of 9.5 to a final *p*H of 3.0. The compound which separated out between *p*H 8.0-3.0, inclusive, proved to be **4**. The product which was precipitated between *p*H 9.5-8.0 was **5** with some **4** as contaminant. This latter fraction was taken up in benzene and repeatedly extracted with saturated potassium bicarbonate solution to remove **4**. When the aqueous extracts failed to precipitate any more **4** upon acidification, the benzene solution was concentrated to dryness *in vacuo*. The residual brown oil readily crystallized and upon recrystallization from 120 ml. 1/1.4 ethanol/water gave 31.5 g. (26%) of a solid with m.p. 115-118°. See Table II for spectral and analytical data.

Ethyl 3-(3-Isopropylureido)-4,4,4-trifluorocrotonate (**9**) (16).

A solution of potassium *t*-butoxide (6.16 g., 55 mmoles) in 25 ml. of dimethylformamide was cooled to -10° by means of a dry ice-acetone bath. With the temperature maintained between -10° and 0° the aminocrotonate (**3**) (10.0 g., 55 mmoles) was added portionwise. Isopropyl isocyanate (5.2 g., 60 mmoles) was added all at once and after 10 seconds (temperature rising to +15°) the reaction was poured on ice. The solid (**9**) which precipitated was removed by filtration and after drying in a vacuum oven at 25° weighed 3.3 g. (23%) with m.p. 95-98°. After recrystallization from cyclohexane the m.p. was 105-106°; nmr τ 8.88 (doublet, J = 6.5 Hz, 6, isopropyl methyls), 6.32 (multiplet, 1, methine H), 4.24 (singlet, 1, vinyl H), 2.94 (br, 1, 3-NH), 0.99 (br, 1, 1-NH).

Anal. Calcd. for $C_{10}H_{15}F_3N_2O_3$: C, 44.8; H, 5.6; F, 21.3; N, 10.4. Found: C, 45.0; H, 5.5; F, 21.5; N, 10.6.

The aqueous filtrate from above was extracted with ether (discarded) and then acidified with concentrated hydrochloric acid and reextracted with ether. These latter ether extracts were washed, dried and the ether removed *in vacuo* leaving 7.0 g. (57%) of **4**.

Ethyl 4,4,4-Trifluoro-3-isopropylaminocrotonate (**10**).

Ethyl 4,4,4-trifluoroacetoacetate (20.0 g., 109 mmoles) was mixed with isopropylamine (7.0 g., 118 mmoles) in a glass pressure vessel. An exotherm occurred with the immediate formation of a solid. After the exotherm subsided, the vessel was sealed and heated in an oil bath at 150° for 3 hours (25 psi). The clear liquid was distilled at 20 mm. giving as the best fraction the portion having boiling point 99-116° (8.68 g., 35%). Additional product was present in fractions on either side of this portion. The fraction with b.p. 106-113°/20 mm., n_D^{25} 1.4253 was homogeneous by glc (column A programmed between 85-225° at 11°/min.).

Anal. Calcd. for $C_9H_{14}F_3NO_2$: C, 48.0; H, 6.3; F, 25.3; N, 6.2. Found: C, 47.9; H, 6.3; F, 25.0; N, 6.5.

1-[2-Cyano-1-(trifluoromethyl)vinyl]-3-isopropylurea (**12a**).

3-Isopropyl-6-(trifluoromethyl)cytosine (**13a**).

3-Amino-4,4,4-trifluorocrotononitrile (**11a**) (11) (3.0 g., 22 mmoles) was added to a suspension of sodium methoxide (1.2 g., 22 mmoles) in 30 ml. of dimethylformamide using an ice bath to maintain a temperature of 20°. Isopropyl isocyanate (1.87 g., 22 mmoles) was added slowly at 20°. The reaction solution was stirred at room temperature for 1 hour and then poured into 60 ml. of water. After extraction with ether to remove neutral products, the aqueous phase was acidified with concentrated hydrochloric acid and then reextracted with ether. Removal of the solvent yielded a cream-colored solid, which after recrystallization from ethanol-water, gave fine white needles weighing 0.55 g. (11%). The analytical sample, m.p. 159-160°, was obtained by a further recrystallization from chloroform.

Anal. Calcd. for $C_8H_{10}F_3N_3O$: C, 43.4; H, 4.6; F, 25.8; N, 19.0. Found: C, 43.4; H, 4.6; F, 25.8; N, 18.9.

After removal of **12a** by extraction of the acidified aqueous phase, the *p*H of the filtrate was adjusted to 6-7 with 28% ammonium hydroxide. The solution was evaporated *in vacuo* to leave 2-3 ml. of a yellow oil containing suspended ammonium chloride. After filtration to remove solids, the addition of 5 ml. of water to the oil caused a white solid to form which was

recrystallized from ethanol-water to give **13a** weighing 0.69 g. (14%), with m.p. 233-235°.

Anal. Calcd. for $C_8H_{10}F_3N_3O$: C, 43.4; H, 4.6; F, 25.8; N, 19.0. Found: C, 43.6; H, 4.4; F, 25.9; N, 18.9.

1-[2-Chloro-2-cyano-1-(trifluoromethyl)vinyl]-3-isopropylurea (**12b**).

3-Amino-2-chloro-4,4,4-trifluoromethylcrotononitrile (**11b**) (11) (2.5 g., 14.5 mmoles) was added with stirring to a solution of potassium *t*-butoxide (1.64 g., 14.5 mmoles) in 10 ml. of dimethylformamide at -10°. After cooling to -25°, isopropyl isocyanate (1.3 g., 15.3 mmoles) was added all at once allowing the reaction to run 10 seconds (exotherm from -25° to -15°) before pouring it over ice water with vigorous stirring. The aqueous solution, after extraction with ether (discarded), was acidified to *p*H 2 with concentrated hydrochloric acid and reextracted with ether. This ether layer was dried over calcium sulfate and evaporated *in vacuo* to give 2.3 g. (62%) of an orange oil which slowly formed a semi-solid. Crystallization from 1:1 ethanol-water gave 0.9 g. (24%) of product with m.p. 166-168°, (homogeneous by tlc on a 2″ x 8″ silica gel glass plate with 10% methanol-benzene); nmr τ 8.90 (doublet, J = 6.5 Hz, 6, methyls), 6.30 (multiplet, 1, methine H), 3.30 (doublet, 1, 3-NH), 0.99 (singlet, 1, 1-NH).

Anal. Calcd. for $C_8H_9ClF_3N_3O$: C, 37.6; H, 3.5; Cl, 13.9; F, 22.3; N, 16.4. Found: C, 37.6; H, 3.5; Cl, 13.8; F, 22.5; N, 16.5.

A second crop of 0.4 g. (11%) with m.p. 147-152° was also obtained.

1-[2-Cyano-2-fluoro-1-(trifluoromethyl)vinyl]-3-isopropylurea (**12c**).

3-Amino-2,4,4,4-tetrafluorocrotononitrile (**11c**) (11) (1.0 g., 6.5 mmoles) was added with stirring to a suspension of sodium methoxide (0.35 g., 6.5 mmoles) in dimethylformamide at 20°. When the reaction mixture became clear, isopropyl isocyanate (0.55 g., 6.5 mmoles) was added with stirring at 20°. The reaction was heated to 45° for 30 minutes and then cooled to room temperature. After 1.5 hours the reaction solution was poured into water, extracted with ether, and the aqueous phase acidified to *p*H 2 with concentrated hydrochloric acid to produce a brown oil. This oil slowly crystallized to a beige solid, 0.40 g. (26%) with m.p. 142-145°; nmr τ 8.86 (doublet, J = 6.5 Hz, 6, methyls), 6.22 (multiplet, 1, methine H), 3.43 (br, 1, 3-NH), 1.30 (br, 1, 1-NH).

Anal. Calcd. for $C_8H_9F_4N_3O$: C, 40.2; H, 3.8; F, 31.8; N, 17.6. Found: C, 40.2; H, 3.8; F, 31.6; N, 17.6.

5-Chloro-3-isopropyl-6-(trifluoromethyl)cytosine (**13b**).

5-Chloro-3-isopropyl-4-isopropylcarbamoyl-6-(trifluoromethyl)-cytosine (**15**).

From **11b**.

3-Amino-2-chloro-4,4,4-trifluorocrotononitrile (7.0 g., 41 mmoles) was added in a dropwise manner with stirring to a solution of potassium *t*-butoxide (4.6 g., 41 mmoles) in 25 ml. of dimethylsulfoxide at 20°. Isopropyl isocyanate (4.0 g., 47 mmoles) was then slowly added to the yellow solution while keeping the temperature at 20°. After stirring the reaction for an additional 30 minutes, more potassium *t*-butoxide (4.6 g., 41 mmoles) was added and stirred for another 30 minutes. The reaction solution was poured into 50 ml. of water, and this solution extracted with ether (discarded) before acidifying it to *p*H 2 with concentrated hydrochloric acid. The solid which precipitated was removed and recrystallized once from chloroform to give in several crops 6.85 g. (65%) of product with m.p. 213-216°. Another recrystallization from 1/8 95% ethanol:chloroform gave material melting at 218-220°; nmr τ 8.50 (doublet, J = 6.5 Hz, 6, methyls), 5.27 (multiplet, 1, methine H), 1.63 (br, 2, NH_2).

Anal. Calcd. for $C_8H_9ClF_3N_3O$: C, 37.6; H, 3.5; Cl, 13.9; F, 22.3; N, 16.4. Found: C, 37.7; H, 3.6; Cl, 13.8; F, 22.2; N, 16.2.

The chloroform filtrate from the first recrystallization of **13b** was concentrated to a brown gum (1.79 g.) and was essentially homogeneous by tlc. Crystallization from ethanol-water gave the analytical sample with m.p. 139-141°; nmr τ 8.82 (doublet, J = 6.5 Hz, 6, carbamoyl isopropyl methyls), 8.48 (doublet, J = 6.5 Hz, 6, ring isopropyl methyls), 6.28 (multiplet, 2, methine H's), 5.83 (br, 1, 3-NH), 0.83 (br, 1, 1-NH).

Anal. Calcd. for $C_{12}H_{16}ClF_3N_4O_2$: C, 42.3; H, 4.7; Cl, 10.4; F, 16.7; N, 16.4. Found: C, 42.3; H, 4.7; Cl, 10.3; F, 16.6; N, 16.4.

From **12b**.

A small sample of 1-[2-chloro-2-cyano-1-(trifluoromethyl)vinyl]-3-isopropylurea (**12b**) was dissolved in methanol containing an excess of sodium methoxide and brought to reflux for 30 minutes. After evaporation of the methanol *in vacuo*, the resulting solid was dissolved in water and the solution acidified with concentrated hydrochloric acid which precipitated **13b**, identical by ir spectrum and tlc to the above preparation.

5-Fluoro-3-isopropyl-6-(trifluoromethyl)cytosine (**13c**).

The procedure followed was that described for **12c** allowing 3-amino-2,4,4,4-tetrafluorocrotononitrile (**11c**) (7.0 g., 45 mmoles) to react with sodium methoxide (2.45 g., 45 mmoles) and isopropyl isocyanate (3.83 g., 45 mmoles) to give 2.65 g. (24%) of a crude brown solid. Recrystallization of the product from acetonitrile gave 1.50 g. (14%) of solid with m.p. 207-209°; nmr τ 8.49 (doublet, J = 6.5 Hz, 6, methyls), 5.28 (multiplet, 1, methine H), 1.51 (singlet, 2, NH_2).

Anal. Calcd. for $C_8H_9F_4N_3O$: C, 40.2; H, 3.8; N, 17.6; F, 31.8. Found: C, 40.0; H, 3.8; N, 17.5; F, 31.8.

5-Chloro-3-isopropyl-6-(trifluoromethyl)uracil (**14b**).

From **4**.

3-Isopropyl-6-(trifluoromethyl)uracil (80 g., 360 mmoles) was dissolved in one liter of acetic anhydride in acetic acid (10% v/v). Sulfuryl chloride (97 g., 720 mmoles) was added, and the solution heated to 50-60°. When no starting compound could be detected by glc (after 3 hours), the solution was poured into 2 liters of water. The resulting white solid, after collection by filtration and air drying, weighed 61.5 g. with m.p. 143-144°; nmr τ 8.53 (doublet, 6, methyls), 4.88 (multiplet, 1, methine H), 2.56 (singlet, 1, NH).

Anal. Calcd. for $C_8H_8ClF_3N_2O_2$: C, 37.5; H, 3.2; Cl, 13.8; F, 22.2; N, 10.9. Found: C, 37.5; H, 3.3; Cl, 13.9; F, 22.3; N, 10.9.

Another 16.7 g. with m.p. 142-145° was obtained from the filtrate by ether extraction which raised the yield to 85%.

From **13b**.

5-Chloro-3-isopropyl-6-(trifluoromethyl)cytosine (1.0 g., 4 mmoles) was suspended in 10 ml. of 5% hydrochloric acid and heated under reflux for 45 minutes. The precipitated product which was collected by filtration and dried weighed 0.70 g. (70%) with m.p. 145-147°. Its ir spectrum was identical to that of **14b** prepared from **4**.

5-Fluoro-3-isopropyl-6-(trifluoromethyl)uracil (**14c**).

From **13c**.

5-Fluoro-3-isopropyl-6-(trifluoromethyl)cytosine (0.40 g., 1.67 mmoles) was dissolved in 10 ml. of 10% hydrochloric acid and brought to reflux for 1 hour. A white solid which precipitated was collected and dried to give 0.30 g. (75%) of product with m.p. 150-153°. The product was shown to be homogeneous by tlc (10% methanol-benzene on silica gel F_{254}) and by glc (column B at 90°).

Anal. Calcd. for $C_8H_8F_4N_2O_2$: C, 40.0; H, 3.4; N, 11.7; F, 31.6. Found: C, 39.7; H, 3.6; N, 11.5; F, 31.6.

From **12c**.

1-[2-Cyano-2-fluoro-1-(trifluoromethyl)vinyl]-3-isopropylurea (100 mg.) was dissolved in methanol containing an excess of sodium methoxide and brought to reflux for 45 minutes. After evaporation of the methanol *in vacuo*, the residual solid was dissolved in water and the solution acidified with concentrated hydrochloric acid. Concentration of this solution, followed by chilling, yielded a solid with m.p. 147-149° and an ir spectrum identical to that of **14c** prepared from **13c**. Tlc R_f values were the same for **14c** prepared by either route.

3-Isopropyl-6-trifluoromethyluracil (**4**) from **11a**.

3-Amino-4,4,4-trifluorocrotononitrile (**11a**) (11) (1.0 g., 7.4 mmoles) was allowed to react with sodium methoxide (0.40 g., 7.4 mmoles) and isopropyl isocyanate (0.63 g., 7.4 mmoles) in dimethylformamide as described above. At the step where the reaction solution was poured into water, extracted with ether and then acidified, the 3-isopropyl-6-(trifluoromethyl)cytosine (**13a**) remained in solution, probably as the hydrochloride salt. After removal of any ureido compound (**12a**) by ether extraction, the aqueous phase was heated at reflux for 1 hour, then cooled and extracted again with ether. Evaporation of the ether *in vacuo* gave **4** as shown by glc (column B at 225°) and tlc (2″ x 8″ silica gel glass plate, 10% methanol-benzene) comparison with an authentic sample.

Alkylation of 6-(trifluoromethyl)uracil **1** (R_1, R_2 = H) to give 2,4-Diisopropoxy-6-(trifluoromethyl)pyrimidine (**16**); 2-Isopropoxy-6-(trifluoromethyl)-4(3*H*)pyrimidinone (**6**); 2-Isopropoxy-3-isopropyl-6-(trifluoromethyl)-4(3*H*)pyrimidinone (**17**); 1-[(Methylthio)methyl]-6-(trifluoromethyl)uracil (**18**).

To a solution of 6-(trifluoromethyl)uracil (**1**) (1) (5.0 g., 27.8 mmoles in 15 ml. of dimethylsulfoxide (dried over molecular sieves) containing isopropyl bromide (3.42 g., 27.8 mmoles) was added potassium *t*-butoxide (3.12 g., 27.8 mmoles) at room temperature. The resulting suspension was placed in a pressure tube and heated in an oil bath at 80-85° for 3 hours. The reaction mixture was then poured into 100 ml. of water, the *p*H adjusted to 14 and the insoluble, neutral fraction (A) separated by ether extraction. Acidification of the aqueous phase to *p*H 1 followed by ether extraction gave the acidic fraction (B). This acidic fraction (B) was then separated further into strong acid (C) and weak acid (D) fractions by extracting it with saturated aqueous potassium bicarbonate solution. The aqueous phase upon reacidification followed by ether extraction gave acid (C) as 0.35 g. of a solid residue which by tlc (silica gel plate, 1/5 acetic acid/benzene) and ir spectrum proved to be starting material (**1**).

The ether solution containing acid fraction (D) was dried and concentrated to a residue of 0.80 g. solid containing two compounds (tlc). Preparative tlc (one pass with 1/12 acetic acid/benzene, two passes with benzene) separated D into its two fractions. The faster moving fraction after one recrystallization from cyclohexane gave **6** as white needles with m.p. 131-131.5°. The slower moving fraction after one recrystallization from cyclohexane gave a white powder (**18**) with m.p. 120-121°.

Examination of acid fractions C and D by glc failed to show the presence of either **4** or **5**. Neutral fraction A, 0.68 g., was separated by glc (column A programmed between 100-225° at 11°/min.) into liquid components **16** (3.9′) and **17** (5.1′). See Table II for analytical data.

Alkylation of 3-Isopropyl-6-(trifluoromethyl)uracil (**4**) to give 2-Isopropoxy-3-isopropyl-6-(trifluoromethyl)-4(3*H*)pyrimidinone (**17**); 1,3-Diisopropyl-6-(trifluoromethyl)uracil (**19**); 3-Isopropyl-1-[(methylthio)methyl]-6-(trifluoromethyl)uracil (**20**).

To a solution of 3-isopropyl-6-(trifluoromethyl)uracil (**4**) (5.0 g., 22.5 mmoles) in 15 ml. of dimethylsulfoxide (dried over molecular sieves) contained in a pressure tube was added potassium *t*-butoxide (2.52 g., 22.5 mmoles). An exotherm occurred and the solution became dark brown. The mixture was cooled to room temperature, isopropyl bromide (2.80 g., 22.5 mmoles) was added and the sealed vessel heated in an oil bath for three hours at 80-85°. The reaction mixture was then poured into 100 ml. water, the *p*H adjusted to 14 and the insoluble neutral fraction separated by ether extraction. The ether solution was dried and concentrated *in vacuo*, giving 2.40 g. of a mobile liquid which was separated by glc (same conditions as given for **16** and **17**) to give **19** (4.8′), **17** (5.1′) and **20** (7.5′). See Table II for analytical data. The small sample size of **20** did not allow elemental analyses to be obtained, and therefore its structure assignment rests on its nmr and ir spectra.

Alkylation of 1-Isopropyl-6-(trifluoromethyl)uracil (**5**) to give 4-Isopropoxy-1-isopropyl-6-(trifluoromethyl)-2(1*H*)pyrimidone (**22**); 1,3-Diisopropyl-6-(trifluoromethyl)uracil (**19**).

1-Isopropyl-6-(trifluoromethyl)uracil (**5**) was alkylated as described for **4**. After the prescribed reaction time, the mixture was poured into 100 ml. of water, the *p*H adjusted to 14 and the insoluble neutral fraction separated by ether extraction. The basic aqueous phase was acidified to *p*H 1 with hydrochloric acid and reextracted with ether. The ether solution was dried and removed by evaporation leaving a residue of 1.56 g. of thick oil which upon short standing crystallized. Tlc examination using 1/5 acetic acid/benzene on silica gel showed this solid to be starting material **5**. The dried ether extracts containing the neutral fraction were concentrated to 3.95 g. of a thick yellow oil which was separated by glc (same conditions as given for **16** and **17**) to give **19** (4.7′) and **22** (6.2′). See Table II for analytical data. The sample size of **22** did not allow elemental analyses to be obtained, and therefore its structure assignment rests on its nmr, ir, and uv spectra.

3-Isopropyl-1-methyl-6-(trifluoromethyl)uracil (**21**).

A solution of 3-isopropyl-6-(trifluoromethyl)uracil (**4**) (0.50 g., 2.25 mmoles) and dimethyl sulfate (0.28 g., 2.25 mmoles) in 10 ml. of 0.5 *N* sodium hydroxide was allowed to stir at room temperature for one hour. Another 0.28 g. of dimethyl sulfate was then added and the mixture stirred overnight. The reaction mixture was extracted with ether, the ether layers washed with water, dried and then stripped *in vacuo* to leave a thick oily residue. Glc examination (same conditions as for **16** and **17**) showed the presence of two major fractions which were collected as liquid **21** (5.5′) and unreacted starting material **4**. See Table II for analytical data.

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