THE REACTION OF ACETIC AND TRIFLUOROACETIC ANHYDRIDES WITH SOME SUBSTITUTED GUANIDINE HYDROCHLORIDES[1]

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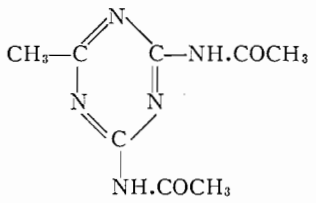
ABSTRACT

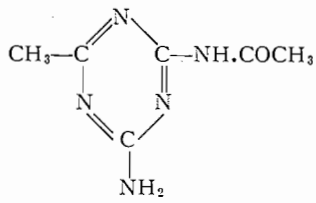
Acetylation of the hydrochlorides of guanidine, cyclohexylguanidine, and 1-guanylpiperidine has been found to yield substituted triazines. Trifluoroacetylation of 1-guanylpiperidine hydrochloride also gives a triazine, whereas guanidine hydrochloride and cyclohexylguanidine hydrochloride are converted to *bis*trifluoroacetyl derivatives. The same triazines can also be obtained by acylation of the appropriate biguanide.

During the course of a recent investigation, it became necessary to form derivatives of certain guanidine salts. To this end, a brief examination was made of the products obtained by subjecting various guanidine hydrochlorides to the action of acetic anhydride and trifluoroacetic anhydride. The results obtained form the subject of this paper.[2]

The acetylation of guanidine acetate with acetic anhydride was studied by Ryabinin (4), who found that the product obtained depended on the reaction conditions used and the method of working up. Relatively mild conditions (heating at 100°) yielded diacetylguanidine, while treatment with excess acetic anhydride at reflux temperatures gave 2,4-diacetamido-6-methyl-1,3,5-triazine (I). The latter was readily hydrolyzed by recrystallization from water to 2-acetamido-4-amino-6-methyl-1,3,5-triazine (II) which could be reacetylated to I. Repeated recrystallization of diacetylguanidine from 95% ethanol gave acetylguanidine acetate, which yielded I on treatment with boiling acetic anhydride.



I



II

The compounds used in the present investigation were the hydrochlorides of guanidine, cyclohexylguanidine, and 1-guanylpiperidine. The dried, powdered salts were stirred under reflux with a moderate excess of anhydride for several hours, the reaction mixture concentrated by vacuum evaporation, and the products purified by crystallization and sublimation. In two cases only, namely the reaction between trifluoroacetic anhydride and the hydrochlorides of guanidine and cyclohexylguanidine, were simple diacylguanidines obtained. The other reactions all yielded substituted triazines of the type described by Ryabinin (4). Thus, acetylation of guanidine hydrochloride, cyclohexylguanidine hydrochloride, and 1-guanylpiperidine hydrochloride gave 2,4-diacetamido-6-methyl-1,3,5-triazine (I), 4-acetamido-2-cyclohexylamino-6-methyl-1,3,5-triazine (III*a*), and 4-acetamido-6-methyl-2-piperidino-1,3,5-triazine (IV*a*) respectively, while trifluoro-

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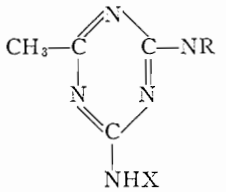
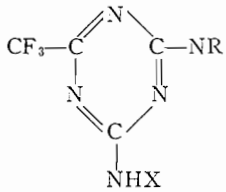
[2]*It should be noted that, in some cases, no attempt was made to establish maximum yields.*

acetylation of 1-guanylpiperidine hydrochloride gave 4-amino-2-piperidino-6-trifluoromethyl-1,3,5-triazine (VI*b*).





III*a* NR = $C_6H_{11}NH$—, X = CH_3CO—
III*b* NR = $C_6H_{11}NH$—, X = H
IV*a* NR = $C_5H_{10}N$—, X = CH_3CO—
IV*b* NR = $C_5H_{10}N$—, X = H

V NR = $C_6H_{11}NH$—, X = H
VI*a* NR = $C_5H_{10}N$—, X = CF_3CO—
VI*b* NR = $C_5H_{10}N$—, X = H

On being heated with dilute aqueous methanolic alkali, the amides III*a* and IV*a* underwent ready hydrolysis to the corresponding amines III*b* and IV*b*. The latter were themselves quite stable to prolonged reflux in the same alkaline medium. The amine VI*b* was easily further trifluoroacetylated to VI*a*, which in turn could be hydrolyzed back to the amine under mild alkaline conditions. Trifluoroacetylation of V yielded an unstable product which could not be obtained sufficiently pure for characterization.

In order to confirm the triazine structure assigned to these products, they were synthesized by the method of Curd, Landquist, and Rose (2), from the appropriate biguanides, which were themselves prepared by the interaction of an amine with dicyandiamide in the presence of copper sulphate (3). Thus, acetylation of cyclohexylbiguanide and N,N-pentamethylenebiguanide gave III*a* and IV*a* respectively, while trifluoroacetylation of the same compounds yielded V and VI*a*. Identity with the compounds obtained by acylation of the guanidine salts was in all cases confirmed by melting point, mixed melting point, and infrared spectrum.

The fact that trifluoroacetylation of guanidine and cyclohexylguanidine hydrochlorides yielded *bis*trifluoroacetyl compounds rather than triazines could conceivably be due to the low reflux temperature of trifluoroacetic anhydride. Indeed, it is reported that acetylguanidine undergoes self-condensation to 2,4-diamino-6-methyl-1,3,5-triazine on being heated at 190–210° for 30 minutes (5). To check this possibility, *bis*trifluoroacetylcyclohexylguanidine was heated in a sealed tube (to prevent sublimation) at 140° for 1 hour. A quantitative recovery of starting material was obtained. Heating at 200° for 30 minutes caused some decomposition, but 52% of the starting material was recovered, and no evidence of triazine formation noted. Finally, cyclohexylguanidine hydrochloride was heated in a sealed tube at 140° for 2 hours, with trifluoroacetic anhydride. *Bis*trifluoroacetylcyclohexylguanidine was obtained in 86% yield, and again no triazine could be detected.

The ultraviolet spectra of all products, in the range 200–400 mμ, were measured, as an approximately 0.002% solution in cyclohexane or ethanol, using a 0.5 cm. quartz cell (see Table I).

For purposes of comparison, the trifluoroacetyl derivatives of *n*-butylamine, 3-diethylaminopropylamine, ethylenediamine, and piperidine were prepared, but found to give only end absorption.

EXPERIMENTAL

All melting points are corrected unless otherwise stated. Microanalyses are by Microtech Laboratories, Skokie, Ill., and by C. E. Reynolds of these laboratories. Infrared

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA OF ACETYLATION AND TRIFLUOROACETYLATION PRODUCTS

Compound	λ_{max}	ϵ_{max}
4-Amino-2-cyclohexylamino-6-methyl-1,3,5-triazine (III*b*)	207	27,400
	257	3,900
4-Acetamido-2-cyclohexylamino-6-methyl-1,3,5-triazine (III*a*)	221	32,200
	266	2,020
4-Amino-6-methyl-2-piperidino-1,3,5-triazine (IV*b*)*	213	21,300
	225	18,200
	263	4,160
4-Acetamido-6-methyl-2-piperidino-1,3,5-triazine (IV*a*)	228	32,300
	273	2,870
4-Amino-2-cyclohexylamino-6-trifluoromethyl-1,3,5-triazine (V)	207.5	24,500
	271	3,290
4-Amino-2-piperidino-6-trifluoromethyl-1,3,5-triazine (VI*b*)	206.5	18,800
	227	22,600
	277	3,310
4-Acetamido-2-piperidino-6-trifluoromethyl-1,3,5-triazine (VI*a*)	232	18,800
	246	18,500
	290	1,650
*Bis*trifluoroacetylguanidine	214	4,830
	258	11,500
*Bis*trifluoroacetylcyclohexylguanidine	229	8,540
	236	8,090
	267	11,900

**In ethanol. All others in cyclohexane.*

spectra were measured on a Baird Double Beam Recording Spectrophotometer, while the ultraviolet spectra were taken on a Cary Model 14 P.M. Recording Spectrophotometer.

1-Guanylpiperidine (Ref. 1)

An aqueous suspension of methylisothiourea sulphate was treated with two molecular equivalents of piperidine, and the mixture heated on the steam bath until evolution of mercaptan had ceased. 1-Guanylpiperidine sulphate commenced to crystallize out before the end of the reaction, and was purified by recrystallization from water. It was obtained in colorless prisms, m.p. 294.5° (uncorr.) with decomp., when the sample was inserted into the melting point apparatus at 285°. Yield, 43%. Found: C, 40.80, 40.91; H, 7.98, 8.17; N, 24.15, 24.15%. Calc. for $C_{12}H_{28}N_6O_4S$: C, 40.90; H, 8.01; N, 23.85%.

The sulphate was converted to the hydrochloride by passing an aqueous solution through a column of IRA-400 (Cl^-), and the product purified by recrystallization from a mixture of ethanol and acetone, being obtained as prismatic needles, m.p. 184–186°. Found: C, 44.52; H, 8.74; N, 25.18; Cl, 21.69%. Calc. for $C_6H_{14}N_3Cl$: C, 44.03; H, 8.62; N, 25.68; Cl, 21.67%.

A portion of the hydrochloride was converted to the free base by passage in ethanolic solution through a column of IRA-400 (OH^-) resin. The base, obtained by evaporation of the eluate to dryness *in vacuo*, was purified by sublimation at 80° and 0.001 mm. The sublimate consisted of colorless crystals, m.p. 145.5–147°, which dissolved in water to give a strongly alkaline solution. Found: C, 57.00, 57.03; H, 9.88, 10.08; N, 32.93, 33.12%. Calc. for $C_6H_{13}N_3$: C, 56.66; H, 10.30; N, 33.05%.

Cyclohexylguanidine

Cyclohexylguanidine sulphate was prepared from cyclohexylamine in a similar manner

as the above. Owing to its high solubility in water and ethanol, the sulphate could not be separated from the sparingly soluble cyclohexylamine sulphate. It was therefore passed in aqueous solution through a column of IRA-400 (OH^-) to convert it to the free base, and adsorbed on a column of IRC-50 (H^+). Elution with hydrochloric acid followed by evaporation of the acid solution *in vacuo* yielded the hydrochloride. The latter was purified by recrystallization from ethanol and yielded stubby needles, m.p. 224–226°. Found: C, 47.56; H, 8.85; N, 23.40; Cl, 19.80%. Calc. for $C_7H_{16}N_3Cl$: C, 47.32; H, 9.08; N, 23.65; Cl, 19.96%. The over-all yield was not accurately determined, but was approximately 20%, mainly because of losses on crystallization.

A portion of the hydrochloride was reconverted to the sulphate by passage in solution down a column of IRA-400 ($SO_4^=$), and the product purified by recrystallization from ethanol. The m.p. was 273° (uncorr.) with decomp. Found: C, 44.48, 44.39; H, 8.86, 8.57; N, 21.64, 21.83; S, 8.58, 8.56%. Calc. for $C_{14}H_{32}N_6O_4S$: C, 44.19; H, 8.48; N, 22.09; S, 8.43%.

N,N-Pentamethylenebiguanide

The general method of Curd and Rose (3) was followed, namely, the interaction of piperidine and dicyandiamide in the presence of copper sulphate. The product was obtained in 26% yield as the dihydrochloride, m.p. 213–217° with decomp. Found: C, 34.94, 34.84; H, 7.05, 7.17; N, 29.46, 29.18; Cl, 28.87, 28.90%. Calc. for $C_7H_{17}N_5Cl_2$: C, 34.72; H, 7.08; N, 28.93; Cl, 29.28%.

The free base was gummy and unsuitable for analysis.

Cyclohexylbiguanide

A similar reaction with cyclohexylamine yielded cyclohexylbiguanide dihydrochloride, m.p. 225° with decomp. Found: C, 37.45; H, 7.57; N, 27.63; Cl, 27.05%. Calc. for $C_8H_{19}N_5Cl_2$: C, 37.52; H, 7.47; N, 27.34; Cl, 27.68%. The dihydrochloride was converted to the free base by treatment in ethanolic solution with a twofold excess of silver oxide, removal of the silver salts by filtration, and evaporation of the filtrate to dryness. The base was a crystalline solid, m.p. 196–205° with decomp. Found: C, 43.87; H, 8.26; N, 31.78%. Calc. for $C_8H_{21}N_5O_2$: C, 43.81; H, 9.65; N, 31.94%. These figures indicate that the base was obtained as a dihydrate.

Trifluoroacetyl Derivatives of Amines

The amines were treated with trifluoroacetic anhydride in ether. Water was added to the reaction mixture, and the product solvent-extracted and distilled in the case of the liquid amides, or filtered off and recrystallized from aqueous ethanol in the case of the solid amide.

1-Trifluoroacetylaminobutane.—This colorless, mobile oil with an ester-like odor was purified by distillation in a Späth bulb at 9 mm. pressure, and an air-bath temperature of 100°, n_D^{25} 1.3803. Found: C, 43.23; H, 6.11; N, 8.37%. Calc. for $C_6H_{10}NF_3O$: C, 42.60; H, 5.96; N, 8.28%.

N-Trifluoroacetyl-N′,N′-diethyl-1,3-diaminopropane.—Colorless oil with an amine-like odor, distilled in a Späth bulb at 7 mm. pressure and an air-bath temperature of 130°, n_D^{25} 1.4183. Found: C, 47.67; H, 7.36; N, 12.70%. Calc. for $C_9H_{17}N_2F_3O$: C, 47.77; H, 7.57; N, 12.39%.

N,N′-Bistrifluoroacetyl-1,2-diaminoethane.—This amide was obtained as a white, non-wettable, crystalline solid, m.p. 200–201°. Found: C, 28.83; H, 2.41; N, 10.92%. Calc. for $C_6H_6N_2F_6O_2$: C, 28.59; H, 2.40; N, 11.11%.

Trifluoroacetylpiperidine.—Colorless oil with a penetrating odor of peppermint, b.p. 77° at 15 mm. pressure, n_D^{25} 1.4148. Found: C, 46.52, 46.42; H, 5.68, 5.80; N, 7.87, 7.82%. Calc. for $C_7H_{10}NF_3O$: C, 46.41; H, 5.56; N, 7.73%.

Reactions with Acetic Anhydride

Guanidine Hydrochloride

Guanidine hydrochloride (6.0 g.) and acetic anhydride (100 ml.) were heated under reflux with stirring for 2 hours. The undissolved guanidine hydrochloride (2.65 g.) was filtered off, and the red filtrate concentrated to 50 ml. On cooling to 15°, the solution deposited yellowish crystals, which were filtered off, washed with ether, and dried for several days *in vacuo* over potassium hydroxide. Weight, 2.07 g. Concentration of the mother liquor yielded a further 0.62 g. Both materials gave a negative test for chloride ion. They were combined and recrystallized from ethyl acetate, yielding 1.47 g. (40%) of colorless crystals, m.p. 209–213.5°. Rapid heating from 200° gave a melting point of 214–216° C. (uncorr.) with decomp. The m.p. of 2,4-diacetamido-6-methyl-1,3,5-triazine (I) is reported to be 217.5° (1). Found: C, 45.68, 45.71; H, 5.28, 5.24; N, 33.06, 32.93%. Calc. for $C_8H_{11}N_5O_2$: C, 45.94; H, 5.30; N, 33.48%.

Cyclohexylguanidine Hydrochloride

The guanidine salt (311 mg.) was refluxed with acetic anhydride (15 ml.) with stirring for 10 hours. The excess anhydride was distilled off under vacuum, and the brown residue recrystallized from acetone, using decolorizing charcoal. Yield of 4-acetamido-2-cyclohexylamino-6-methyl-1,3,5-triazine (III*a*), 64 mg. (35%), m.p. 188–189°. Found: C, 57.74; H, 7.69; N, 28.11%. Calc. for $C_{12}H_{19}N_5O$: C, 57.81; H, 7.68; N, 28.09%.

This amide (90 mg.) was dissolved in 4 ml. of hot methanol, 0.5 ml. of 2.5 *N* sodium hydroxide solution was added, and the solution refluxed for 1 hour. The hot solution was filtered from a small amount of flocculent material, and concentrated to 1 ml. *in vacuo*. A crystalline solid suddenly precipitated, and was filtered off and washed with water. Yield of III*b*, 75 mg., m.p. 185–186°. A strong depression in melting point was obtained on admixture with the starting material. Found: C, 57.85; H, 8.26; N, 33.78%. Calc. for $C_{10}H_{17}N_5$: C, 57.94; H, 8.27; N, 33.79%.

1-Guanylpiperidine Hydrochloride

This reaction was similar to the previous one. The product was purified by recrystallization from acetone – petroleum ether, followed by sublimation at 110° and 0.02 mm. pressure, and was obtained as colorless crystals, m.p. 145–147°. Yield of 4-acetamido-6-methyl-2-piperidino-1,3,5-triazine (IV*a*), 20%. Found: C, 56.68, 56.54; H, 7.12, 7.31; N, 30.10, 29.86%. Calc. for $C_{11}H_{17}N_5O$: C, 56.15; H, 7.28; N, 29.77%.

Cyclohexylbiguanide

Cyclohexylbiguanide dihydrate was refluxed in acetic anhydride for $2\frac{1}{2}$ hours, and the reaction solution diluted with twice its own volume of water. The product was filtered off and recrystallized from acetone. Yield of 4-acetamido-2-cyclohexylamino-6-methyl-1,3,5-triazine (III*a*) 27%, m.p. 189–190.5°. A mixture with the product, m.p. 188–189°, of the acetylation of cyclohexylguanidine hydrochloride melted at 189–190°. Identity was confirmed by a comparison of the infrared spectra.

N,N-Pentamethylenebiguanide

Pentamethylenebiguanide dihydrochloride (1.21 g.) was converted to the free base by shaking with 3 g. of silver oxide in 75 ml. of ethanol. The slightly gummy solid obtained by evaporation of the ethanol solution was refluxed overnight with 40 ml. of acetic

anhydride, yielding a brown solution. This was treated with decolorizing charcoal, filtered, and the filtrate evaporated to dryness *in vacuo*. The residue (1.1 g.) was recrystallized twice from acetone (10 ml., then 5 ml.) using decolorizing charcoal, to give 0.52 g. (44%) of colorless crystals of 4-acetamido-6-methyl-2-piperidino-1,3,5-triazine (IV*a*), m.p. 146–146.5°. No depression in melting point was obtained on admixture with the product, m.p. 146–147°, of acetylation of 1-guanylpiperidine hydrochloride, and both compounds yielded identical infrared spectra.

This acetamidotriazine (106 mg.) was dissolved in 2 ml. of methanol containing 1 ml. of water by gentle warming. Five drops of 2.5 *N* sodium hydroxide was added and the solution boiled for 5 minutes, the methanol being allowed to distill off. The product crystallized spontaneously, and was filtered off and washed with water. Yield of IV*b*, 83 mg. (95%), m.p. 185–187°. Found: C, 55.99, 55.75; H, 7.65, 7.68; N, 35.76, 35.47%. Calc. for $C_9H_{15}N_5$: C, 55.93; H, 7.82; N, 36.24%.

Reactions with Trifluoroacetic Anhydride

Guanidine Hydrochloride

Guanidine hydrochloride (2 g.) was stirred under reflux with 10 ml. of trifluoroacetic anhydride for 17 hours. The resulting clear yellow solution was evaporated at 60° and 12 mm. pressure to an oil (5.1 g.). Addition of 15 ml. of anhydrous ether caused part of the oil to dissolve, leaving a crystalline residue, which was filtered off and washed with ether, yielding 1.3 g. of white crystals, m.p. 155–158°. This was proved by mixed melting point and infrared spectrum to be guanidine trifluoroacetate (36% recovered).

The filtrate was evaporated to an oil *in vacuo*, and heated in a wide tube at 70° and 0.01 mm. pressure. There was obtained a colorless oil in the cooler part of the tube and, partially mixed with it, a white crystalline solid in the lower part of the tube. The tube was inverted to allow the oil to drain off, and the crystalline sublimate gently warmed to drive off the last traces of oil. The solid weighed 1.29 g., m.p. 78–81°. This material tended to become mushy on being left in a stoppered vial overnight. Two more sublimations in a horizontal tube raised the m.p. to 82–83.5°, the material being then quite stable. Found: C, 23.72, 24.09; H, 1.37, 1.41%. Calc. for $C_5H_3N_3F_6O_2$: C, 23.92; H, 1.20%.

Pure *bis*trifluoroacetylguanidine is not hygroscopic; in fact it forms a non-wettable film on the surface of water, which nevertheless rapidly acquires an acid reaction due to hydrolysis. The yield was 40%, based on recovered material.

The colorless oil obtained from the first distillation described above was redistilled in a Späth bulb at 12 mm. pressure and an air-bath temperature of 120°. Found: C, 24.72; H, 1.34. This is close to the figures for *bis*trifluoroacetylguanidine, and the oil could conceivably be an isomeric form. However, it was not conclusively identified.

Cyclohexylguanidine Hydrochloride

The reaction mixture obtained by refluxing cyclohexylguanidine hydrochloride in excess trifluoroacetic anhydride for 27 hours was concentrated *in vacuo* to a yellow oil. This was dissolved in a few milliliters of anhydrous ether, and the solution filtered from a fine crystalline precipitate, which proved to be cyclohexylguanidine trifluoroacetate, m.p. 204–206.5° (9% recovery). The ether solution was again concentrated, leaving an oily residue, which crystallized on being left overnight, m.p. 55–59°. Sublimation at 50° and 0.02 mm. pressure gave a white crystalline solid, m.p. 61–62°. Yield of *bis*trifluoroacetylcyclohexylguanidine, 89%. Found: C, 39.71, 39.53; H, 3.85, 3.93%. Calc. for $C_{11}H_{13}N_3F_6O_2$: C, 39.65; H, 3.93%.

This compound could be readily hydrolyzed in aqueous methanolic alkali to cyclohexylguanidine trifluoroacetate. However, it was quantitatively recovered unchanged after being heated in a sealed tube at 140° for 1 hour. Heating for 30 minutes at 200° caused some decomposition to an oil, only 52% of the *bis*trifluoroacetylcyclohexylguanidine being recovered. It is unlikely that this oil is a triazine, as the compound which might be expected as a result of cyclization, 4-amino-2-cyclohexylamino-6-trifluoromethyl-1,3,5-triazine (V), is a solid, m.p. 165–168° (see below).

The reaction was also carried out by heating 0.5 g. of cyclohexylguanidine hydrochloride with 10 ml. of trifluoroacetic anhydride in a sealed tube at 140° for 2 hours. *Bis*trifluoroacetylcyclohexylguanidine was obtained in 86% yield and, again, no evidence of triazine formation was obtained.

1-Guanylpiperidine Hydrochloride

One gram of this salt was refluxed with 15 ml. of anhydride for 18 hours, and the excess anhydride removed by distillation *in vacuo*. The oily residue was dissolved in 15 ml. anhydrous ether, and the solution filtered from a white crystalline solid, 0.27 g., m.p. 234° with decomp. This was proved by analysis, and a mixed melting point with an authentic sample, to be 1-guanylpiperidinetrifluoroacetate, yield 22%.

The ether was distilled off *in vacuo*, into a dry ice trap. The contents of the trap were combined with the trap residue obtained during the distillation of excess anhydride, described above, and the mixture fractionated by means of a small Vigreux column. The oil left after removal of the more volatile anhydride and ether was distilled at 75° and 12 mm. pressure. Weight 364 mg., n_D^{25} 1.3963. Found: C, 40.56; H, 4.49; N, 5.97%. This material had the same peppermint odor as trifluoroacetylpiperidine, and gave an infrared spectrum which was virtually identical, except for a sharp peak at 1800 cm.$^{-1}$, which could indicate persistent contamination with trifluoroacetic anhydride. This would also account for the low analysis figures. Yield, as trifluoroacetylpiperidine, 33%.

The residue from the ether solution was crystallized from ether – petroleum ether, giving 264 mg. of colorless prisms, m.p. 160°. This material could be readily vacuum-sublimed unchanged. Found: C, 44.11; H, 4.95; N, 27.91%. Calc. for $C_9H_{12}N_5F_3$: C, 43.72; H, 4.89; N, 28.33%. This substance, 4-amino-2-piperidino-6-trifluoromethyl-1,3,5-triazine (VI*b*), could be further trifluoroacetylated by refluxing with excess anhydride for 90 minutes. The crystalline residue, m.p. 94–96°, obtained by evaporation of the excess anhydride, was purified by vacuum sublimation at 80° and 0.05 mm. pressure. Yield 95%, m.p. 107.5–108.5°. Found: C, 38.70; H, 3.63; N, 20.77%. Calc. for $C_{11}H_{11}N_5F_6O$: C, 38.49; H, 3.23; N, 20.41%. This amide (VI*a*) was very readily hydrolyzed by cold aqueous methanolic alkali back to the aminotriazine (VI*b*), m.p. 160°.

The mother liquors from the crystallization of VI*b* were evaporated to dryness, and the residue sublimed at 120° and 0.005 mm. pressure. This yielded in the hotter part of the tube a further 148 mg. of VI*b* (total yield 55%) and in the cooler part 46 mg. of crystals, m.p. 90–91°. Found: C, 40.58, 40.12; H, 3.49, 3.42; N, 18.11%. No reasonable structure has been found to fit this analysis.

The same products were obtained when free guanylpiperidine base was used as starting material.

Cyclohexylbiguanide

The reaction was carried out as above. Removal of the volatile constituents *in vacuo* left an oily residue, which was distilled in a Späth bulb at 0.01 mm. and an air-bath temperature of 150°. This yielded a yellow glass, which was crystallized from ligroin

(50–60°) in chunks. Recrystallization from ether/ligroin gave colorless crystals, m.p. 165–168°. Yield, 50%. Found: C, 46.04; H, 5.44; N, 26.35%. Calc. for $C_{10}H_{14}N_5F_3$: C, 45.97; H, 5.40; N, 26.81%. The analysis figures correspond to 4-amino-2-cyclohexylamino-6-trifluoromethyl-1,3,5-triazine (V). This amine, on further treatment with trifluoroacetic anhydride, yielded an oily product which could be distilled in a Späth bulb at 100° and 0.01 mm. pressure, the distillate setting to a glass. This material appeared to decompose, however, a strong smell of trifluoroacetic acid rapidly becoming evident. No method of purification was devised.

N,N-Pentamethylenebiguanide

The product of trifluoroacetylation was sublimed at 90° and 0.05 mm. pressure, giving a white crystalline solid, m.p. 105–106°. Found: C, 38.73; 38.69; H, 3.12; 3.23; N, 19.67%. Calc. for $C_{11}H_{11}N_5F_6O$: C, 38.49; H, 3.23; N, 20.41%. Hydrolysis with aqueous methanolic alkali gave a crystalline product, m.p. 159–160°. This substance was proved by mixed melting point and infrared spectrum to be identical to VI*b*, m.p. 160°, obtained by trifluoroacetylation of 1-guanylpiperidine hydrochloride.

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