was achieved, the reaction temperature gradually being increased to reflux. The flask was purged with nitrogen to remove excess phosgene, the solvent was evaporated, and the residue was distilled *in vacuo*. There was afforded 16.75 g (59.2%) of III: bp 100–103° (0.3 mm); mp 30–33°.

Anal. Calcd for $C_8H_4ClNO_2$: C, 52.93; H, 2.22; N, 7.71; Cl, 19.53. Found: C, 53.05; H, 2.42; N, 7.74; Cl, 19.49.

Di-*n*-butylamine titration: Calcd mol wt, 181.56. Found: mol wt, 181.3.

2-Diethylamino-4H-3,1-benzoxazin-4-one (IV, R = C_2H_5).—A solution of 2-isocyanatobenzoyl chloride (3.6 g, 0.02 mole) in benzene (10 ml) was added during 5 min at 24–70° to a solution of diethylamine (2.9 g, 0.04 mole) in benzene (20 ml). On cooling, diethylamine hydrochloride (2.0 g, 91.4%) precipitated and was removed by filtration. The solvent was evaporated and the remaining traces of amine hydrochloride were precipitated with ether and were removed. There was afforded 4.3 g of IV (R = C_2H_5) as a colorless oil: infrared spectra $\lambda_{max}^{CCl_4}$ C=O, 1761; C=N, 1667 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.73; H, 6.61; N, 13.00.

2-Di-*n*-butylamino-4H-3,1-benzoxazin-4-one (IV, R = *n*-C_4H_9).—A solution of 2-isocyanatobenzoyl chloride (5.4 g, 0.03 mole) in benzene (25 ml) was added during 5 min at 24–70° to a solution of di-*n*-butylamine (7.7 g, 0.06 mole) in benzene (50 ml). The reaction mixture was worked up in the manner stated above and there was afforded 7.9 g (96.3%) of IV (R = *n*-C_4H_9) as a greenish oil: infrared spectra $\lambda_{max}^{CCl_4}$ C=O, 1761; C=N, 1667 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69, 70; H, 8.14; N, 10.25.

Reaction of 2-Isocyanatobenzoyl Chloride with Isopropylamine.—2-Isocyanatobenzoyl chloride (1.8 g, 0.01 mole) was added slowly with stirring to a solution of isopropylamine (1.18 g, 0.02 mole) in benzene (15 ml). The precipitated solid products were collected and the isopropylamine hydrochloride was removed with water. Thus, 0.85 g (41.6%) of **3-isopropylquinazoline-2,4-dione** (VI, R = *i*-C_3H_7) was obtained: mp 193–194° (lit.[8] mp 188°); infrared spectra λ_{max}^{KBr} NH 3279; C=O 1704, 1639 cm^{-1}.

Evaporation of the mother liquor afforded 1.0 g (49%) of **2-isopropylamino-4H-3,1-benzoxazin-4-one** (V, R = *i*-C_3H_7): mp 138–140° (methanol); λ_{max}^{KBr} NH 3289; C=O 1736; C=N 1667 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}N_2O_2$: N, 13.72. Found: N, 13.81.

Registry No.—III, 5100-23-2; IV, R = C_2H_5, 14128-51-9; IV, R = *n*-C_4H_9, 14128-52-0; V, R = *i*-C_3H_7, 14128-53-1.

(8) R. P. Staiger and E. C. Wagner, *J. Org. Chem.*, **18**, 1427 (1953).

The Ring Opening and Defluorination of N-Cyclopropyl-α,α,α-trifluoro-*m*-toluamide with Lithium Aluminum Hydride[1]

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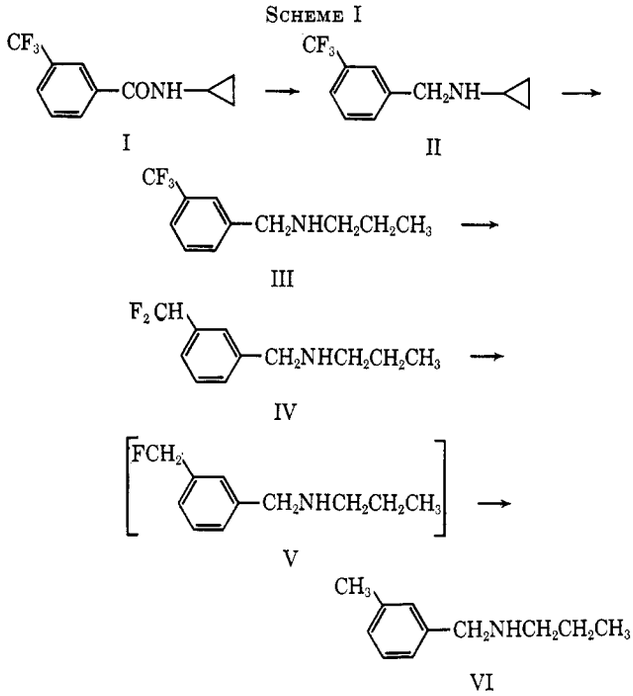
Kaiser and co-workers[2] have reported the opening of the cyclopropane ring in *trans*-N-(2-phenylcyclopropyl)formamide by lithium aluminum hydride and have described a mechanism for this reaction. We have observed that the lithium aluminum hydride reduction of N-cyclopropyl-α,α,α-trifluoro-*m*-toluamide (I) in tetrahydrofuran results not only in an analogous ring opening but also in a stepwise defluorination of intermediate products to give *m*-methyl-N-propylbenzylamine (VI) (Scheme I).

SCHEME I



The hydrogenolysis of the aryltrifluoromethyl group was completely unexpected. Moreover, this is not a general reaction, for when *m*-trifluoromethylacetanilide is reduced with a large excess of lithium aluminum hydride, the expected product, N-ethyl-(*m*-trifluoromethyl)aniline, is obtained in good yield. Under the same conditions 2-(trifluoromethyl)phenothiazine and 2-(trifluoromethyl)benzimidazole are recovered essentially unchanged.

Hydrogenolysis of C–F bonds by lithium aluminum hydride in aliphatic systems has been described previously by Papanastassiou and Bruni[3] and by Pettit and Smith.[4] We are unaware of any references to reduction of aryltrifluoromethyl groups with this reducing agent. However, methods for the conversion of aryltrifluoromethyl groups to methyl groups by use of Raney cobalt and nickel alloys[5] and also by electrochemical reduction[6] are known in the literature.

The products obtained by the reaction of I with lithium aluminum hydride were isolated by partition chromatography and identified by comparison of their physical constants with those of authentic materials. The nmr spectra are summarized in Table I. Expected patterns were obtained in each case. The chief distinguishing feature of *m*-(difluoromethyl)-N-propylbenzylamine (IV) was the triplet centered at 6.6 ppm (J = 57 cps) which is characteristic for a proton on a carbon atom also bonded to two fluorine atoms.

Product distributions of crude mixtures obtained under a variety of reaction conditions are represented in Table II. The approximate ratios were derived from the nmr spectra.

(1) Presented in part at the 154th National Meeting of The American Chemical Society, Chicago, Ill., Sept 1967.

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(3) Z. B. Papanastassiou and R. J. Bruni, *ibid.*, **29**, 2870 (1964).

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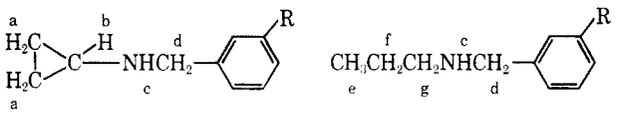
TABLE I
NMR SPECTRA OF N-CYCLOPROPYL-α,α,α-TRIFLUORO-*m*-TOLUAMIDE (I) AND REDUCTION PRODUCTS[a]



Compd	a	b	c	d	e	f	g	R	Aromatic
I	0.7m	2.9m(4)	*b*					CF_3	7.27–8.25m
II	0.5m	2.2m(5)	1.85	3.9				CF_3	7.38–7.67m
III			1.35	3.83	0.95t(7)	1.5m(7)	2.62t(7)	CF_3	7.5–7.65m
IV			1.36	3.8	0.93t(7)	1.5m(7.5)	2.63t(7)	(CHF_2)6.6t(57)	7.42–7.58m
VI			1.22	3.71	0.92t(7)	1.5m(8)	2.62t(7)	(CH_3)2.32	6.9–7.2m

[a] Spectra were determined in $CDCl_3$ solution on a Varian A-60 spectrometer with tetramethylsilane as internal standard. Absorptions are given in parts per million. Signals are designated as follows: t, triplet; m, complex multiplet. All others are singlets. Figures in parentheses are coupling constants in cycles per second. [b] Signal for NH superimposed upon signal for aromatic protons.

TABLE II
RATIOS OF PRODUCTS IN THE REACTION OF N-CYCLOPROPYL-α,α,α-TRIFLUORO-*m*-TOLUAMIDE WITH LITHIUM ALUMINUM HYDRIDE

Molar ratio $LiAlH_4$:I	Reflux period, hr	Ratio of isolated products[a] II	III	IV	VI
1.5:1	1.5	75	25		
2:1	3	55	40	5	
2:1	24		20	50	30
4:1	48			30	60
4:1	72–81			27[b]	65

[a] Determined from nmr spectra by comparison of relative integrals of appropriate protons. [b] Ratio based on yields obtained by partition chromatography.

It is evident from these data that after initial reduction of the carbonyl group, ring opening of the cyclopropyl ring occurred even under mild conditions. Relatively little fluorine was removed after 3 hr at reflux temperature in a reaction with 2 mole equiv of lithium aluminum hydride. Under increasingly vigorous conditions, attack upon the trifluoromethyl group took place with the gradual removal of the fluorine atoms.

None of the nmr spectra of crude reaction mixtures gave any evidence for the presence of V, a monofluoro species. One might expect to observe a doublet at approximately 4.5–5 ppm (J = *ca.* 50 cps) attributable to the protons of the $-CH_2F$ group if this intermediate were present. Such was not the case and this region was always essentially clear of signals.

In contrast to the results of Table II, the reduction of I with diborane according to the procedure of Brown and Heim[7] gave a 93% yield of N-cyclopropyl-*m*-(trifluoromethyl)benzylamine (II), free of by-products as determined by thin layer chromatography.

Experimental Section

General procedures are given below for the preparation of the compounds described in this paper. Temperatures are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 137 Infracord. Thin layer chromatograms were developed on silica gel G plates usually with a 7:3 methanol–chloroform solvent system. Other solvents used were ethyl acetate and VIIa (the upper phase of a mixture of 1 part benzene, 2 parts water, and 2 parts of acetone). Spots were visualized by development of the plates in iodine. Partition chromatography was carried out with diatomaceous silica as adsorbent. Heptane–methanol and heptane–Methyl Cellosolve solvent systems were used. Per cent transmission was measured at 225 mμ.

(7) H. C. Brown and P. Heim, *J. Am. Chem. Soc.*, **86**, 3566 (1964).

N-Cyclopropyl-α,α,α-trifluoro-*m*-toluamide (I).—*m*-Trifluoromethylbenzoyl chloride (10 g, 0.05 mole) dissolved in 25 ml of dry benzene was slowly added with stirring and cooling to 6 g (0.1 mole) of cyclopropylamine in 50 ml of benzene. Precipitation began immediately. After 24 hr the precipitate was filtered off and washed with ether. The organic phases were combined, washed three times with water, dried ($MgSO_4$), and concentrated. The crude product, a white wax, was recrystallized from hexane. The yield of N-cyclopropyl-α,α,α-trifluoro-*m*-toluamide, mp 83–84°, was 9.7 g (85%).

Anal. Calcd for $C_{11}H_{10}F_3NO$: C, 57.6; H, 4.4; F, 24.9; N, 6.1. Found: C, 57.4; H, 4.7; F, 24.9; N, 6.0.

The Lithium Aluminum Hydride Reduction of N-Cyclopropyl-α,α,α-trifluoro-*m*-toluamide. Procedure A.—A solution of 1 part of N-cyclopropyl-α,α,α-trifluoro-*m*-toluamide (I) in 50 parts of tetrahydrofuran (THF) was slowly added with stirring and ice bath cooling to a solution of 1–4 mole equiv of lithium aluminum hydride in 40–160 parts of THF under a nitrogen atmosphere. The reaction mixture was heated at reflux temperature from 1 to 81 hr. Decomposition of the lithium aluminum complex was achieved with stirring and cooling by the careful dropwise addition of 1–4 parts of water, followed by a threefold amount each of 15% aqueous NaOH and water. The reaction mixture was filtered and the precipitate was washed with ether. The organic filtrates were dried ($MgSO_4$) and concentrated to a yellow oil. In some experiments the product mixtures were separated by partition chromatography. The products were identified by comparison of the nmr and infrared spectra with authentic samples and by melting points and microanalyses of hydrochloride salts. In reactions where selected aliquots were taken at various time intervals, quenching was done using 6% NaOH. The course of the reaction was followed by thin layer chromatography of quenched aliquots. The spots produced by product mixtures were compared to authentic standards.

***m*-(Difluoromethyl)-N-propylbenzylamine hydrochloride** (IV) was obtained in 14% yield by procedure A using a 4 mole equiv excess of lithium aluminum hydride and a 72–81-hr reflux period. The product was separated from the reaction mixture by partition chromatography. The base in ether solution was converted into the hydrochloride by the addition of ethanolic hydrogen chloride and the salt was recrystallized from ethanol, mp 184–186°.

Anal. Calcd for $C_{11}H_{16}ClF_2N$: C, 56.1; H, 6.8; Cl, 15.0; F, 16.1; N, 6.0. Found: C, 56.1; H, 7.2; Cl, 15.2; F, 16.2; N, 5.7.

N-Cyclopropyl-*m*-(trifluoromethyl)benzylamine Hydrochloride (II). Procedure B. Reaction of Amines with Benzyl Halides.—*m*-(Trifluoromethyl)benzyl chloride (15.5 g, 0.08 mole) was slowly added with stirring and cooling to 22 ml of cyclopropylamine. After standing at room temperature for 5 days, the reaction mixture was concentrated under vacuum on the water bath at 50° to remove the excess cyclopropylamine. The residue was acidified with 20 ml of 5 *N* HCl and extracted twice with 100-ml portions of ether. The acid was made alkaline with 30 ml of 5 *N* NaOH and extracted twice with 150-ml portions of ether. The ether extracts were dried ($MgSO_4$) and concentrated, and the product was distilled. The yield of N-cyclopropyl-*m*-(trifluoromethyl)benzylamine, bp 106–108° (10–12 mm), was 13.6 g (80%). The hydrochloride

was prepared by the addition of 28 ml of 2.5 *N* ethanolic HCl to the base dissolved in ether. The salt was recrystallized from ethanol, mp 184–186°.

Anal. Calcd for $C_{11}H_{13}ClF_3N$: C, 52.5; H, 5.2; Cl, 14.1; F, 22.7; N, 5.6. Found: C, 52.6; H, 5.3; Cl, 14.6; F, 22.3; N, 5.6.

***m*-Methyl-N-propylbenzylamine (VI)** was prepared by procedure B from α-bromo-*m*-xylene and *n*-propylamine in 68% yield, bp 120–122° (10–12 mm). The hydrochloride was recrystallized from acetone, mp 176–178°.

Anal. Calcd for $C_{11}H_{18}ClN$: C, 66.2; H, 9.1; Cl, 17.8; N, 7.0. Found: C, 66.0; H, 9.3; Cl, 17.7; N, 6.9.

N-Propyl-*m*-(trifluoromethyl)benzylamine (III) was prepared by the above procedure from *m*-(trifluoromethyl)benzyl chloride and *n*-propylamine in 86% yield, bp 110–112° (20 mm). The hydrochloride was recrystallized from ethanol, mp 211–212°.

Anal. Calcd for $C_{11}H_{15}ClF_3N$: C, 52.1; H, 6.0; Cl, 22.5; F, 14.0; N, 5.5. Found: C, 52.5; H, 6.1; Cl, 22.0; F, 14.1; N, 5.3.

Procedure C. Reduction of N-Cyclopropyl-α,α,α-trifluoro-*m*-toluamide with Diborane.—A solution of 2.3 g (0.01 mole) of N-cyclopropyl-α,α,α-trifluoro-*m*-toluamide in 10 ml of THF was added dropwise under nitrogen to a cooled solution of 1 *M* borane in THF (20 ml, 0.02 mole). The reaction mixture was heated at reflux temperature for 2 hr. The mixture was cooled to room temperature, 5 ml (0.025 mole) of 5 *N* HCl was added, and the reaction mixture was heated on the steam bath to distil off the THF. The mixture was diluted with 10 ml of water, cooled, made alkaline with 3 g of NaOH pellets, and extracted with ether. Concentration of the ether solution yielded an oil which produced only one spot on thin layer chromatography. The yield of N-cyclopropyl-*m*-(trifluoromethyl)benzylamine was 2 g (93%). The hydrochloride was prepared by the addition of ethanolic HCl to the amine dissolved in ether, mp 185–186°.

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Phenazines, Phenoxazinones, and Dioxopiperazines from *Streptomyces thioluteus*[1]

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Streptomyces thioluteus is known to produce thiolutin, aureothricin,[2] aureothin,[3] 1,6-phenazinediol (**1**),[4] 1,6-phenazinediol 5-oxide, and 1,6-phenazinediol 5,10-dioxide (iodinin).[5] In our study of this organism we have encountered all of these metabolites as well as several new ones described here.

Using previously described methods[6] the chloroform extracts of washed cells and filtered beer from *S. thioluteus* fermentations were fractionated to give pure compounds which were then compared with authentic samples. Thus identified was 1-phenazinol (**2**),[7] 2-amino-3H-phenoxazin-3-one (**6**),[8] 6-methoxy-1-phenazinol (**3**), and 1,6-dimethoxyphenazine (**4**).[9] Although **4** is a known compound and **3** has been made recently by the reduction of myxin,[10] neither had been found before in nature.

Two other phenazines, not identical with any known naturally occurring phenazines, were isolated in amounts too small for complete identification. Their intense yellow-orange color with sodium hydrosulfite solution showed that both had a carbonyl containing substituent in conjugation with the ring system.[11] The ester resembled, but was not identical with, the methyl ester of phenazine-1-carboxylic acid (**5**).[12] The phenol had an ultraviolet and visible absorption spectrum identical with that of griseolutic acid (1-hydroxymethyl-4-methoxyphenazine-6-carboxylic acid).[13] The isolation of such a variety of substituted phenazines from one organism is unusual and suggests that all types of naturally occurring phenazines are biosynthesized from a common intermediate.[14]

S. thioluteus also produced a phenoxazinone which resembled **6** in color tests and spectra but was more polar. The mass spectrum molecular weight of 256 and important fragmentation products of $M - H_2O$ and $M - CH_2OH$ suggested the previously unknown structure, **7**, 2-ethanolamino-3H-phenoxazin-3-one. This was synthesized in two steps[15] from 2-hydroxy-3H-phenoxazin-3-one[16] and found to be identical with the natural product.

When the cell-extract residue was treated with hexane, then ethanol, the insoluble portion contained 3,6-dibenzylidene-2,5-dioxopiperazines. The major one, compound **8**, recognized by its absorption at 338 mμ and basic hydrolysis to benzaldehyde, was identical with an authentic sample.[17] The minor one had an nmr band at δ 3.61 suggesting a methoxyl group. Therefore glycine anhydride, benzaldehyde, and anisaldehyde were condensed[18] to give a mixture of **8**, **9**, and the dianisylidenedioxopiperazine. After separation, the previously unknown **9**, 3-anisylidene-6-benzylidene-2,5-dioxopiperazine, was identical with the natural product.

Phenazines **3** and **4** showed some weak antibacterial

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