L-Valinyl bromide hydrobromide (IIIb) was prepared as above (yield 78%, m.p. 195–202° dec.). An analytical sample was crystallized from methyl alcohol; m.p. 203.5–204° dec.

Anal. Calcd. for $C_5H_{13}Br_2N$: Br, 64.71; N, 5.67. Found: Br, 64.50; N, 5.71.

D-Valinylthiosulfuric Acid (IVb).—A mixture of 29.6 g. (0.12 mole) of D-valinyl bromide hydrobromide, 90 g. (0.12 mole) of thallous thiosulfate,[9] and 240 ml. of water was agitated by means of a magnetic stirrer for 6 hr. The aqueous phase was removed by filtration, and the filter cake was washed twice with water at 50° and with 2 vol. of boiling methyl alcohol. The combined filtrates were evaporated in a flash evaporator below 50°, and the residue was slurried in acetone. The yield of product was 9.4 g., m.p. 178–182° dec. An additional 3.4 g. (m.p. 175–177° dec.) of product was recovered from the wash liquids. An analytical sample was crystallized from methyl alcohol; m.p. 188° dec.

Benzoyl-DL-tyrosine Methyl Ester (VIf).—To a solution of 184 g. (0.66 mole) of benzoyl-DL-tyrosine[17] in 1500 ml. of dry methyl alcohol was added with agitation a stream of dry HCl to saturation at room temperature. Agitation was continued overnight, after which the excess solvent was flash evaporated. The residue was dissolved twice in methyl alcohol and evaporated to remove the excess HCl. The syrupy product was then dissolved in water, made slightly ammoniacal, and refrigerated overnight. The ester was removed by filtration, ground, washed free of chloride with water, and dried under vacuum (H_2SO_4) at 50° overnight. The yield of product was 156 g. (79%), m.p. 155–159°. An analytical sample was prepared by recrystallization from a mixture of methyl alcohol and isopropyl alcohol; m.p. 159.5–160.5°.

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.54; H, 5.73; N, 4.78.

Dibenzoyl-DL-ornithine methyl ester (VIg) was prepared from benzoyl-DL-ornithine[18] by the method described for the preparation of VIf. The yield of product was 80%, m.p. 144–147°. An analytical sample was crystallized from isopropyl alcohol; m.p. 145–146°.

Anal. Calcd. for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.86; H, 6.70; N, 7.34.

Benzoyl-DL-tyrosinol (VIIf).—To a solution of 75 g. (0.25 mole) of VIf in 750 ml. of THF was added 7.1 g. (0.275 mole, 84.6% assay) of $LiBH_4$. The mixture was agitated and kept under reflux for 6 hr. After evaporation of the THF, the boron was removed by boiling a methyl alcoholic solution of the residue in the presence of 10 ml. of concentrated HCl to a reduced volume. This procedure was repeated twice with the addition of methyl alcohol. The crude product, dissolved in a small volume of methyl alcohol, was precipitated by addition of water. It was washed free of lithium salts with water and dried at 70° overnight. The yield of VIIf was 90%, m.p. 160–164°. An analytical sample was obtained by recrystallization from water, m.p. 164–165°.

Anal. Calcd. for $C_{16}H_{18}NO_3$: C, 70.57; H, 6.66; N, 5.14. Found: C, 70.83; H, 6.50; N, 5.22.

Dibenzoyl-DL-ornithinol (VIIg) was prepared as above for VIIf. The yield of product was 36%, and an analytical sample was crystallized from a mixture of isopropyl alcohol and isopropyl ether; m.p. 153–154°.

Anal. Calcd. for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.46; H, 6.67; N, 8.93.

DL-Tyrosinol Hydrobromide (VIIIf).—Sixty grams (0.21 mole) of VIIf was heated under reflux with 720 ml. of 24% HBr overnight. After cooling to 5°, benzoic acid was removed by filtration, and the filtrate was extracted several times with ether. The filtrate was evaporated to near dryness under reduced pressure, and the residue was further dried under vacuum over H_2SO_4 for several days. The yield of product was 53.5 g. (97%), m.p. 167–172°. An analytical sample could not be prepared.

Benzyl-DL-histidinol Dihydrobromide (XIh).—To 1500 ml. of THF was added 76.6 g. (0.28 mole) of benzoyl-DL-histidine methyl ester (VIh),[11] and the solution was cooled to 10°. Lithium aluminum hydride (25.2 g., 0.67 mole) was added in small portions with agitation and continued cooling. Upon completion of addition of the hydride, the mixture was allowed to come to room temperature and was then heated under reflux for 2 hr. It was allowed to cool to room temperature with stirring overnight. The excess hydride was decomposed with water at 40° and the aqueous THF was removed by filtration. The filter cake was extracted twice with THF, and the combined filtrates were treated with charcoal and flash evaporated to yield a syrupy product. To 51 g. of this product was added 450 ml. of 20% HBr, and the mixture was warmed with intermittent shaking until a clear solution was obtained. It was treated several times with decolorizing carbon and evaporated to dryness under reduced pressure. The solid residue was slurried in acetone, filtered, and dried at 70° overnight. The product was obtained in 90% yield (78 g.), and an analytical sample was prepared by crystallization from isopropyl alcohol; m.p. 187–188°.

Anal. Calcd. for $C_{13}H_{19}Br_2N_3O$: C, 39.72; H, 4.87; N, 10.69. Found: C, 39.32; H, 4.80; N, 10.38.

Dibenzyl-DL-ornithinol dihydrobromide (XIg) was prepared in the same manner as XIh. The yield of product was 31%, m.p. 235.5–236.5° (analytical sample).

Anal. Calcd. for $C_{19}H_{29}Br_2N_2O$: C, 49.46; H, 6.35; N, 6.07. Found: C, 49.43; H, 6.22; N, 5.96.

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2-Trifluoromethyladenosine

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A number of 2-substituted adenosines, in particular 2-chloroadenosine, has been shown to inhibit the adenosine diphosphate induced aggregation of platelets[1] and to possess vasodilator properties.[2] 2-Trifluoromethyladenosine has been synthesized for evaluation of its vasodilator and antiagglutination effects.

Fusion[3] of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose[4] with 2-trifluoromethyl-6-chloropurine[5] in the presence of *p*-toluenesulfonic acid followed by simultaneous removal of the blocking groups and amination with methanolic ammonia gave a gel-like crude product from which pure 2-trifluoromethyladenosine was isolated by crystallization first from 1-propanol and then from water.

Preliminary pharmacological evaluation of 2-trifluoromethyladenosine in this department[6] has shown

TABLE I
RELATIVE POTENCY

Compd.	Inhibition of ADP[a]-induced aggregation	Vasodilator effect
Adenosine	1	1
2-Chloroadenosine	4	4
2-Trifluoromethyladenosine	0.025	0.05

[a] ADP = adenosine diphosphate.

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(3) For the acid-catalyzed fusion reaction of purines with tetra-*O*-acetyl-D-ribofuranose to give β-nucleosides see (a) T. Sato, T. Simadate, and Y. Ishido, *Nippon Kagaku Zasshi*, **81**, 1440 (1960); (b) T. Simadate, Y. Ishido, and T. Sato, *ibid.*, **82**, 938 (1961); (c) T. Simadate, *ibid.*, **82**, 1261 (1961); (d) W. W. Lee, A. P. Martinez, G. T. Tong, and L. Goodman, *Chem. Ind.* (London), 2007 (1963).

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(6) By courtesy of Miss D. Radford and Mr. F. Michal of this Department.

that it is much less active than 2-chloroadenosine in the inhibition of the adenosine diphosphate induced agglutination of platelets, and that it possesses only weak vasodilator properties[6] in the isolated cat hind limb (Table I).

Experimental Section[7]

A mixture of 2-trifluoromethyl-6-chloropurine (5.86 g., 0.0263 mole) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (12.8 g., 0.0254 mole) was heated *in vacuo* in a rotating flask at 130–135° until a clear orange melt was obtained. The reaction flask was cooled to room temperature, anhydrous *p*-toluenesulfonic acid (20 mg.) was added, and the flask was again heated *in vacuo* with rotation at 135° for 35 min. A vigorous gas evolution occurred, and a light brown clear melt was obtained. The flask was cooled to room temperature, and the clear glass obtained was dissolved in chloroform (100 ml.). The $CHCl_3$ solution was washed with saturated aqueous $NaHCO_3$ (50 ml.) and with two 50-ml. portions of water, then filtered and dried (Na_2SO_4). Evaporation of $CHCl_3$ left an orange glass, which was triturated with hexane to give a cream powder (16.2 g.) $[\alpha]^{22}D$ $-54.9 \pm 0.9°$ (*c* 1.02, $CHCl_3$). This was dissolved in absolute methanol and the solution was cooled to 0° and saturated with NH_3. The ammoniacal solution was kept in an autoclave at room temperature for 5 days. Evaporation *in vacuo* left an oil which triturated repeatedly with chloroform until an amorphous brownish solid (7.1 g., 86%) remained. Recrystallization of 6 g. of this from 1-propanol gave a white amorphous powder (3.65 g.) which recrystallized from water as white microcrystals (2.5 g.), m.p. 193–195°. Two more crystallizations from water gave pure **2-trifluoromethyladenosine**, m.p. 194–195°, $[\alpha]^{22}D$ $-51.8 \pm 0.4°$ (*c* 0.922, MeOH), $\lambda_{max}^{pH\ 1}$ 256 mμ (ε 10,400), $\lambda_{max}^{pH\ 13}$ 255 mμ (ε 12,600).

Anal. Calcd. for $C_{11}H_{12}F_3N_5O_4$: C, 39.42; H, 3.58; N, 20.89. Found: C, 39.54; H, 3.74; N, 21.05.

(7) Melting points were determined on a Kofler Reichert and are corrected. Ultraviolet spectra were obtained on a Perkin-Elmer Model 350 spectrophotometer, and optical rotations were measured on a Hilger polarimeter. Microanalyses were done by the Australian Microanalytical Service, Division of Organic Chemistry, C.S.I.R.O., and University of Melbourne

Antituberculous Compounds. XXII.[1] Monoalkylaminobenzothioamides

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In earlier communications[2,3] the relation of chemical constitution to antituberculous activity was discussed, especially in derivatives of benzothioamide, and it was concluded that a substituent *para* to the thiocarbamoyl group was important to activity. One of the authors in a previous paper suggested[4] that the extinction coefficient, E_{max} of the C≡N stretching vibration in the infrared absorption spectrum of the parent nitrile ultimately parallels the activity of the benzothioamide.

In order to test this hypothesis, several new monoalkyl, phenyl, and benzyl derivativeso f 4-aminobenzothioamide and their precursor nitriles were prepared in a pure state. 4-Monoalkylaminobenzonitriles were prepared by the direct alkylation of 4-aminobenzonitrile (method A) and alkylation of 4-acetylaminobenzonitrile followed by mild hydrolysis (method B). Phenylaminobenzonitrile was prepared through the diazo compound of 4-aminodiphenylamine. Thioamides were derived by passing H_2S into a solution of the nitrile in pyridine and trimethylamine (see Table I).

TABLE I
p-$RC_6H_4CSNH_2$

R	MIC, μ*M*	E_{max}, ln (I_0/I)
NH_2	425	0.387
CH_3CONH	500	0.124
CH_3NH	425	0 499
$(CH_3)_2N$	350	0.465
C_2H_5NH	425	0.459
n-C_3H_7NH	425	0.577
i-C_3H_7NH	500	...
n-C_4H_9NH	350	0.342
i-C_4H_9NH	425	...
n-$C_5H_{11}NH$	150	0.602
i-$C_5H_{11}NH$	150	0.453
$C_6H_5CH_2NH$	175	...
C_6H_5NH	150	...

Experimental Section

4-Methylaminobenzonitrile (Table II). A.—4-Aminobenzonitrile (2 g.) was added to 3 ml. of methyl iodide and 1 ml. of piperidine and refluxed for 3 hr. The reaction mixture was evaporated to dryness under reduced pressure to yield a syrup, which was triturated with water. The crude product was collected by filtration. Recrystallization from ethanol did not give the compound in a pure state. The product was converted to the salt with HCl and was recrystallized from ethanol; m.p. 175°. 4-Methylaminobenzonitrile was obtained from the salt by liberation with NH_4OH. Recrystallization from ethanol gave 0.2 g. of a colorless product, m.p. 86°. A mixture with *p*-aminobenzonitrile (m.p. 86°) melted at 60°. In the case of butyl-, amyl-, and benzylaminobenzonitrile, the crude nitrile could be purified in good yield by vacuum distillation.

TABLE II
4-ALKYLAMINOBENZONITRILES: p-$RNHC_6H_4CN$

R	M.p., °C.	N, % Calcd.	N, % Found
CH_3	86	21.20	21.42
C_2H_5	74	19.16	19.12
n-C_3H_7	52	17.49	17.25
n-C_4H_9	41	16.08	16.16
n-C_5H_{11}	60	14.88	14.92
i-C_5H_{11}	44	14.88	15.00

B.—It was reported[5] that N-methyl-*p*-anisidine was obtained in good yield from N-acetyl-*p*-anisidine by methylation followed by hydrolysis; the following is an adaptation of this method.

To a well-stirred solution of 3 g. of acetylaminobenzonitrile in 30 ml. of toluene was added 1.5 g. of $NaNH_2$, and the mixture was refluxed for 2 hr. After cooling, 3 ml. of methyl iodide was added to the reaction mixture, and it was refluxed for 2 hr. The resulting mixture was allowed to cool and the crystalline solid was collected by filtration. The filtrate was evaporated under reduced pressure to obtain a yellow syrup. The solid and the syrupy product were triturated with ice–water, and the resulting precipitate was recrystallized from ethanol to obtain colorless needles, m.p. 142°. The N-methylacetylaminobenzonitrile was hydrolyzed by refluxing with 20 ml. of 0.5 *N* methanolic KOH solution for 2 hr. The solution was poured into 50

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