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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(3) S. Kakimoto, J. Seydel, and E. Wempe, *ibid.*, **12**, 127 (1962).

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(5) H. Plieninger and C. E. Castro, *Ber.*, **87**, 1760 (1954).

ml. of water. The resulting precipitate was collected by filtration. The product was recrystallized from ethanol to afford 1.1 g. of 4-methylaminobenzonitrile, m.p. 86°. In the case of ethyl-, propyl-, and butylaminobenzonitrile, method B was better than method A.

4-Methylaminobenzothioamide (Table III).—4-Methylaminobenzonitrile (2 g.) was dissolved in a mixture of 10 ml. of pyridine and 5 ml. of triethylamine, and the solution was treated with H_2S for 4 hr. The reaction mixture was evaporated under reduced pressure and the residual product was triturated with water. The precipitated product was collected by filtration and purified by recrystallization from ethanol to yield 2 g. of pure product, m.p. 170°. Other alkylaminobenzothioamides were prepared by the same method.

TABLE III

4-ALKYLAMINOBENZOTHIOAMIDES: p-RNHC$_6$H$_4$CSNH$_2$

R	M.p., °C.	% calcd. C	% calcd. H	% found C	% found H
CH_3	170	57.80	6.06	58.14	6.06
C_2H_5	165	59.96	6.71	60.46	6.69
n-C_3H_7	164	61.81	7.26	61.84	7.43
i-C_3H_7	172	61.81	7.26	61.68	7.32
n-C_4H_9	131	63.42	7.74	63.42	7.96
i-C_4H_9·H_2O	183	58.37	8.02	58.45	7.96
n-C_5H_{11}	142	64.82	8.16	64.06	8.07
i-C_5H_{11}	154	64.82	8.16	64.61	8.31
$C_6H_5CH_2$	178	69.38	5.82	69.06	6.05
C_6H_5	174	68.39	5.30	68.77	5.71

4-Phenylaminobenzothioamide.—A solution of 10 g. of NaCN in 25 ml. of water was added to a solution of 8 g. of $CuSO_4$ in 50 ml. of water. A diazo solution was prepared from 9.5 g. of p-aminodiphenylamine, 45 ml. of 6% HCl, and 4 g. of $NaNO_2$. The diazo solution was added to the warm well-stirred CuCN solution in 10 min. After 15 min., the reaction mixture was extracted with ether. The ether was distilled, the resulting syrup (1.4 g.) was treated with H_2S as usual to afford 1.1 g. of the crude 4-phenylaminobenzothioamide. Recrystallization from ethanol gave 0.6 g. of pure substance, m.p. 174°.

Extinction Coefficient, E_{max}, in Infrared Absorption Spectra.—The CN stretching band (2215–2230 cm.$^{-1}$) was measured in KBr disks (10 μmoles in 1 g.).

In Vitro **Antituberculous Activity.**—The *in vitro* test against human-type tubercule bacilli, strain H37Rv, using Kirchner's medium was conducted according to the method described in a previous paper.[6] The minimum inhibitory concentrations (MIC) are shown in Table I.

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Antituberculous Compounds. XXIII.[1] Alkyl- and Acylisonicotinic Acid Hydrazides

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Among acyl derivatives of isonicotinic acid hydrazide (INH) Rieche, *et al.*,[2] reported that in the series having unbranched carbon chains from C_6 to C_{18}, the undecanoyl derivative was the most active and showed approximately the same activity as INH against tubercule bacilli.

Acetyl, propionoyl, and butyryl derivatives of INH have almost no activity. In the literature,[3] these substances are all described as anhydrous compounds, but we have found that they crystallize with water of crystallization from water or aqueous solvent. As alkyl derivatives of INH, N-isopropyl-N′-isonicotinoylhydrazine has been reported as a good antituberculous compound, but only a few other alkyl derivatives have been described with chemical data and biological activities. Fox and Gibas[4] reported the synthesis of monoalkyl derivatives of INH, and McMillan, *et al.*,[5] prepared some higher homologs.

We have prepared the ethyl, propyl, and butyl derivatives and have shown that these compounds are more active than the acyl derivative containing the same number of carbon atoms, as shown in Table I.

TABLE I

MINIMUM INHIBITORY CONCENTRATION OF ALKYL DERIVATIVES OF INH AGAINST H37Rv IN KIRCHNER'S MEDIUM (28 DAYS, 38°)

C$_5$H$_4$NCONHNHR

R	MIC, μmole/l.
H (INH)	1
$COCH_3$	400
C_2H_5	40
COC_2H_5	400
C_3H_7	40
COC_3H_9	400
C_5H_{11}	5

Experimental Section

N-Acyl-N′-isonicotinoylhydrazine.—The crude crystalline material obtained by the literature[3] methods was recrystallized from water or aqueous ethanol and acetone. The pure crystalline material contained solvate water as shown in Table II. Anhydrous substances were obtained by recrystallization from absolute ethanol or acetone and by drying under reduced pressure.

In Vitro **Antituberculous Activity.**—The *in vitro* test against human tubercule bacilli, strain H37Rv, using Kirchner's medium was conducted according to the method described in a previous paper.[6] The minimum inhibitory concentration (MIC) is shown in Table I.

TABLE II

C$_5$H$_4$NCONHNHCOR

R	Water of crystn., moles	M.p., °C.	Anhydrous m.p., °C.	% calcd. C	% calcd. H	% calcd. H_2O	% found C	% found H	% found H_2O
CH_3	2	76	158	44.64	6.09	16.75	44.48	6.38	16.61
C_2H_5	2	95	131.5	47.15	6.60	15.72	47.13	6.41	15.82
C_3H_7	1	84	139	53.32	6.71	8.00	53.32	6.81	7.76

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The Use of Substituent Constants in the Correlation of Demethylation Rates

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In continuing our study[1-4] of substituent effects on the biological activity of congeneric drugs we have in

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