J. Pharm. Pharmacol., 1964, **16**, 618–626 Received February 27, 1964

Synthesis of aliphatic amino-acid hydrazides as potential tuberculostatic agents

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Some dialkylamino-aliphatic acid hydrazides and bis(hydrazinocarbonyl) compounds have been prepared and tested for antituberculosis activity. None of these compounds was found to possess tuberculostatic activity of the same order as that of isoniazid.

THE success of isoniazid in the treatment of tuberculosis has led to the preparation and testing for antituberculosis activity of many other acid hydrazides and related compounds (Steenken & Wolinsky, 1952; Bernstein, Jambor, Lott, Pansy, Steinberg & Yale, 1953; Bavin, James, Kay, Lazare & Seymour, 1955). In the aliphatic series the most effective acid hydrazide tested was cyanacethydrazide (Hartyl, 1954), which was claimed to be comparable to isoniazid in the treatment of human pulmonary tuberculosis (Kirshner, 1957). *In vitro* experiments on other aliphatic acid hydrazides and related compounds showed that some of them possessed similar or greater activity than cyanacethydrazide (Mukherjee, Naha, Raymahasaya, Laskar & Gupta, 1955).

Long-chain fatty acids are known to have a marked inhibitory effect on *Mycobacterium tuberculosis*, and replacement of the carbonyl group by a dialkylaminoalkyl group has also produced active compounds. Furthermore, displacement of the carbonyl group toward the centre of the molecule has been shown to increase the activity of the fatty acid (Stanley, Coleman, Greer, Sacks & Adams, 1932).

In view of these observations, it was decided to synthesise a series of ω-dialkylamino-aliphatic acid hydrazides (I ; R = Me, Et, or Pr, and n = 1, 2, 3, or 4), by means of which the effect, on tuberculostatic activity, of a dialkylamino-group and also that of varying chain-length, could be studied. The effect of introducing a second hydrazide group with the amino-group in the centre of the molecule was later investigated. For this purpose, a smaller series of compounds (II ; R = H, Me, or Et)

$R_2N{\cdot}[CH_2]_n{\cdot}CO{\cdot}NH{\cdot}NH_2$ (I) $\qquad$ $RN(CH_2{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}NH_2)_2$ (II)

was prepared, in which the distances between the amino-group and each of the hydrazide groups corresponded with the chain-length of the most active of the monohydrazides.

All the hydrazides were prepared by the interaction of the corresponding ethyl or methyl ester with hydrazine hydrate in ethanolic solution. The routes by which these esters were prepared depended on the chain-lengths

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† This work forms part of the M.Sc. thesis of the Queen's University of Belfast by one of the authors (W. H. S.).

of the compounds. Ethyl diethylaminoacetate and the corresponding dimethylamino- and dipropylamino- compounds were obtained by the interaction of ethyl chloroacetate and the appropriate dialkylamine.

Ethyl β-diethylaminopropionate (III; R = Et) was prepared in good yield from ethyl acrylate and diethylamine by the method of Adamson (1949). Ethyl β-dimethylaminopropionate (III; R = Me) and ethyl

$$R_2N{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}O{\cdot}C_2H_5$$
(III)

β-dipropylaminopropionate (III; R = Pr) were prepared similarly. Ethyl γ-diethylaminobutyrate (IV; R = Et, $n = 1$) was prepared by chain extension according to the following scheme:

$$R_2N{\cdot}[CH_2]_n{\cdot}CO{\cdot}O{\cdot}Et \xrightarrow{LiAlH_4} R_2N{\cdot}[CH_2]_{n+1}{\cdot}OH \xrightarrow[(2)\ NaOH]{(1)\ SOCl_2}$$

$$R_2N{\cdot}[CH_2]_{n+1}{\cdot}Cl \xrightarrow[NaOC_2H_5]{CH_2(CO{\cdot}O{\cdot}Et)_2} R_2N{\cdot}[CH_2]_{n+1}{\cdot}CH(CO{\cdot}O{\cdot}Et)_2$$

$$\xrightarrow[reflux]{HCl} R_2N{\cdot}[CH_2]_{n+2}{\cdot}CO_2H{\cdot}HCl \xrightarrow[H_2SO_4]{EtOH} R_2N{\cdot}[CH_2]_{n+2}{\cdot}CO{\cdot}O{\cdot}Et$$
(IV)

Ethyl γ-dimethylaminobutyrate (IV; R = Me, $n = 1$), ethyl γ-dipropylaminobutyrate (IV; R = Pr, $n = 1$) and ethyl δ-diethylaminovalerate (IV; R = Et, $n = 2$) were similarly prepared.

The method of preparing the last named compound gave poor yields in the final stages of hydrolysis, decarboxylation and re-esterification. An alternative scheme was therefore adopted for the syntheses of dimethylamino- and dipropylamino-valerates. The route shown below led to the formation of the methyl, instead of the ethyl, esters.

$$HO_2C{\cdot}[CH_2]_4{\cdot}CO{\cdot}O{\cdot}Me \xrightarrow{AgON_3} AgO_2C{\cdot}[CH_2]_4{\cdot}CO{\cdot}O{\cdot}Me \xrightarrow{Br_2}$$

$$Br{\cdot}[CH_2]_4{\cdot}CO{\cdot}O{\cdot}Me \xrightarrow{R_2NH} R_2N{\cdot}[CH_2]_4{\cdot}CO{\cdot}O{\cdot}Me$$

Di(2-ethoxycarbonylethyl)methylamine (V; R = Me) was prepared by the reaction of methylamine in ethanol with two equivalents of ethyl

$$RN(CH_2{\cdot}CH_2{\cdot}CO{\cdot}O{\cdot}Et)_2$$
(V)

acrylate. Di(2-ethoxycarbonylethyl)amine (V; R = H) was similarly prepared, using a solution of ammonia in ethanol in place of the solution of methylamine, and di(2-ethoxycarbonylethyl)ethylamine (V; R = Et) was prepared from it by reaction with ethyl iodide.

The dihydrochloride of δ-dipropylaminovalerohydrazide, monohydrochlorides of dimethylaminoacethydrazide and β-dimethylaminopropionhydrazide, and the salicylate of diethylaminoacethydrazide were obtained as colourless crystalline solids. No crystalline condensation products with either acetone or benzaldehyde were obtained from any of the hydrazides.

Infra-red spectra were obtained for all the hydrazides prepared, as an aid to characterisation of these compounds. As no information was available on the absorption due to the hydrazide grouping, formhydrazide, acethydrazide and butyrohydrazide were prepared and their spectra obtained. In the infra-red spectrum of formhydrazide, shown in Fig. 1,

FIG. 1. Infra-red spectrum of formhydrazide, KCl disc.

the only bands due to $\rightarrow$CH occur at 2895 cm^{-1} and 1380 cm^{-1}. The other bands are therefore due to vibrations occurring in the hydrazide grouping of this compound. The spectrum of δ-dipropylaminovalerohydrazide is shown in Fig. 2, and the other hydrazides prepared gave very similar spectra.

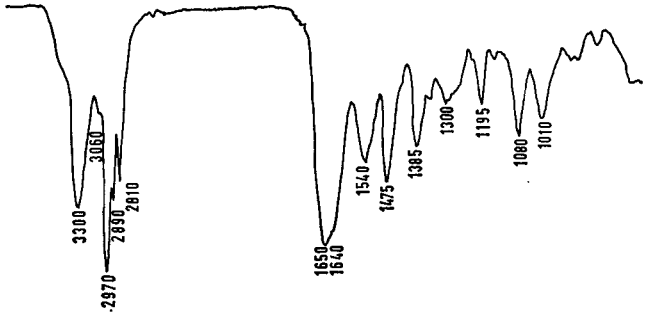

FIG. 2. Infra-red spectrum of δ-dipropylaminovalerohydrazide. Liquid film.

In the range 3,010–3,360 cm^{-1} two bands, one strong and one weak, usually occurred in the spectra of these compounds. There were also two strong bands in the range 1,635–1,685 cm^{-1}, and another between 1,505 and 1,550 cm^{-1}. All the dimethylaminohydrazides showed a band at 1,170–1,175 cm^{-1}, the diethylaminohydrazides at 1,200–1,205 cm^{-1}, and the dipropylamino-hydrazides at 1,190–1,195 cm^{-1}. With several compounds, strong and medium bands occurred below 1,000 cm^{-1}, but had no apparent correlation with the structures of the compounds.

BACTERIOLOGICAL RESULTS

Preliminary assessment of the tuberculostatic activity of the hydrazides prepared was obtained against *Mycobacterium tuberculosis* var. *hominis*, (H37 Rv) in Peizer and Schechter medium. Some of the results are shown in Table 1.

TABLE 1. TUBERCULOSTATIC ACTIVITY OF HYDRAZIDES PREPARED

Compound	Inoculation (days	Minimum inhibitory concentration (μg/ml)	
		Test 1	Test 2
Dimethylaminoacethydrazide	14 21	— >100	— >100 (±100)
γ-Diethylaminobutyrohydrazide	14 21	— >100 (±100)	— >100 (±100)
δ-Diethylaminovalerohydrazide	14 21	— >100	— >100 (±100)
δ-Dipropylaminovalerohydrazide	14 21	— >100 (±100)	— >100
Di(2-hydrazinocarbonylethyl)amine	14 21	100 (±25) 100	100 (±50) 100
Di(2-hydrazinocarbonylethyl)methylamine ..	14 21	>100 (±100) >100	>100 (±100) >100 (±100)
Di(2-hydrazinocarbonylethyl)ethylamine ..	14 21	100 (>50) >100	100 >100
Isoniazid	14 21	— 0·02	— —

(±) signifies concentrations at which there was partial inhibition of growth.

None of the compounds examined was found to possess tuberculostatic activity of the same order as that of isoniazid. The dialkylamino-aliphatic acid hydrazides are less active than the bis(hydrazinocarbonyl) compounds. Alkylation of the amino-group appears to decrease the activity to some extent, the secondary amino-compound di(2-hydrazino-carbonylethyl)amine being the most active of the compounds examined.

Experimental

Ethyl dimethylaminoacetate was prepared by the method of Viscontini & Meier (1950).

Ethyl diethylaminoacetate. Ethyl chloroacetate (100 g), benzene (350 ml) and diethylamine (120 g) were mixed and allowed to stand for 18 hr. The reaction mixture was extracted with dilute hydrochloric acid, and the benzene layer containing neutral ethyl chloroacetate was discarded. The aqueous layer was treated with a slight excess of sodium hydroxide solution, extracted with ether, and the ethereal solution dried (Na_2SO_4). Ethyl diethylaminoacetate was obtained, after removal of solvent, as a colourless oil, b.p. 67–68°/13 mm, $n_D^{21\cdot5}$ 1·4230 (75·6 g).

Ethyl dipropylaminoacetate was prepared from ethyl chloroacetate (56 g) by the method used in the preparation of ethyl dimethylamino-acetate, and was obtained as a colourless oil, b.p. 96°/14 mm, $n_D^{20\cdot5}$

1·4271 (65·5 g). Found: equiv. 192·9; N, 7·2%. $C_{10}H_{21}NO_2$ requires equiv. 187·2; N, 7·5%.

Ethyl β-dipropylaminopropionate. Ethyl acrylate (100 g) and dipropylamine (100 g) were mixed and allowed to stand for 8 days. Fractional distillation yielded ethyl β-dipropylaminopropionate as a colourless oil, b.p. 100°/13 mm, n_D^{21} 1·4310 (170 g).

Di(2-ethoxycarbonylethyl)amine. An ethanolic solution of ammonia (170 ml 5%) was slowly added (1 hr) to ethyl acrylate (100 g), chilled in an ice-bath, and allowed to stand for 7 days. After evaporation of solvent, fractional distillation yielded the product as a colourless oil, b.p. 105–108°/0·3 mm, n_D^{16} 1·4429 (15·9 g). Found: N, 6·3%. $C_{10}H_{19}NO_4$ requires: N, 6·5%.

Di(2-ethoxycarbonylethyl)methylamine. A solution of methylamine in ethanol (55 ml 33%) was slowly added (45 min) to ethyl acrylate (100 g) cooled in an ice-bath, and allowed to stand for 4 days. Fractional distillation yielded the product as a colourless oil, b.p. 104–105°/0·5 mm, n_D^{19} 1·4407 (53·9 g). Found: N, 6·1%. $C_{11}H_{21}NO_4$ requires: N, 6·1%.

Di(2-ethoxycarbonylethyl)ethylamine. Di(2-ethoxycarbonylethyl)amine (20 g) and ethyl iodide (20 g) were mixed and heated under reflux for 30 min. Excess ethyl iodide was removed under reduced pressure, and the yellow viscous residue was dissolved in water, made alkaline with sodium hydroxide solution, and extracted with ether. After drying (Na_2SO_4), the solvent was evaporated to yield on distillation, the product as a colourless oil, b.p. 96–100°/0·35 mm, n_D^{20} 1·4410 (10·9 g). Found: N, 5·7%. $C_{12}H_{23}NO_4$ requires: N, 5·7%.

2-*Dipropylaminoethanol* was prepared by lithium aluminium hydride reduction of ethyl dipropylaminoacetate (134·5 g) and was obtained as a colourless oil, b.p. 81–82°/13 mm, $n_D^{20·5}$ 1·4378 (83·1 g).

3-*Dipropylaminopropanol* was prepared by lithium aluminium hydride reduction of ethyl β-diethylaminopropionate (150 g) and was obtained as a colourless oil, b.p. 76–77°/10 mm, n_D^{21} 1·4340 (96 g).

2-*Chloroethyldimethylamine.* Thionyl chloride (135 ml) in ether was added slowly (3 hr) to a stirred solution of 2-dimethylaminoethanol (150 g) in ether, and the solvent was carefully evaporated. The solid residue was dissolved in water, chilled in an ice-bath, and the solution made alkaline with sodium hydroxide solution. The oil which separated was extracted with ether, the ethereal solution dried (Na_2SO_4), and the solvent removed under reduced pressure to yield an amber-coloured oil, n_D^{16} 1·4287 (105 g). The product was not further purified.

2-*Chloroethyldiethylamine* was prepared from 2-diethylaminoethanol (31 g) by the above method and was obtained as a colourless oil, b.p. 50°/20 mm, n_D^{17} 1·4379 (22·3 g).

2-*Chloroethyldipropylamine* was prepared from 2-dipropylaminoethanol (83 g) by the above method and was obtained as a brown oil, n_D^{21} 1·4396 (85 g), which was not further purified.

3-*Chloropropyldiethylamine was prepared from* 3-diethylaminopropanol (96 g) by the above method and was obtained as an amber-coloured oil, n_D^{21} 1·4408 (70 g), which was not further purified.

3,3-*Diethoxycarbonyl)propyldimethylamine.* Diethyl malonate (160 g) was added slowly (30 min) to a solution of sodium (23 g) in dry ethanol (720 ml). To the cooled solution of sodium diethyl malonate, 2-chloroethyldimethylamine (105 g) was added slowly, and the mixture was heated under reflux for 3 hr. After evaporation of the solvent the residue was cooled, dissolved in water (200 ml), and extracted with ether. The ethereal solution was dried (Na_2SO_4), the solvent evaporated, and the residual liquid fractionally distilled to yield the product as a colourless oil, b.p. 131–133°/13 mm, n_D^{15} 1·4352 (98·8 g). Found: N, 6·0%. Calc. for $C_{11}H_{21}NO_4$: N, 6·1%. Selleri & Chiti (1957) report b.p. 106°/5 mm.

3,3-*Di(ethoxycarbonyl)propyldiethylamine* was prepared from 2-chloroethyldiethylamine (22 g) by the above method and was obtained as a colourless oil, b.p. 90–96°/0·45 mm, $n_D^{22·5}$ 1·4370 (19·3 g). Selleri & Chiti (1957) report b.p. 108–109°/4 mm. Magidson & Strukov (1933) report b.p. 136–142°/12 mm, n_D^{20} 1·4386.

3,3-*Di(ethoxycarbonyl)propyldipropylamine* was prepared from 2-chloroethyldipropylamine (85 g) by the above method and was obtained as a straw-coloured oil, b.p. 154°/12 mm, n_D^{22} 1·4420 (80 g). Found: C, 62·1; H, 10·2; N, 4·7%; $C_{15}H_{29}NO_4$ requires C, 62·7; H, 10·2; N, 4·9%.

4,4-*Di(ethoxycarbonyl)butyldiethylamine* was prepared from 3-chloropropyldiethylamine (77·5 g) by the above method and was obtained as a colourless oil, b.p. 160–162°/13 mm, $n_D^{21·5}$ 1·4407 (45 g). Magidson & Strukov (1933) report b.p. 149–151°/4 mm, n_D^{20} 1·4416. Marvel, Zartman & Bluthard (1927) report b.p. 163–170°/23 mm, n_D^{25} 1·4380.

Ethyl γ-dimethylaminobutyrate. 3,3-Di(ethoxycarbonyl)propyldimethylamine (98·5 g) was heated under reflux for 3·5 hr with hydrochloric acid (600 ml), and the mixture evaporated to dryness under reduced pressure. The semi-solid residue was heated under reflux with ethanol (720 ml) and sulphuric acid (72 ml) for 5 hr, and the excess of ethanol was evaporated. Water (70 ml) was added to the residue, which was then made alkaline with sodium hydroxide solution and extracted with ether and benzene. After drying (Na_2SO_4) and removal of solvent, ethyl γ-dimethylaminobutyrate was obtained by distillation of the mixed extracts as a colourless oil, b.p. 79–80°/16 mm, n_D^{16} 1·4232 (6 g). Prelog (1931) reports b.p. 78–90°/18 mm.

Ethyl γ-diethylaminobutyrate was prepared from 3,3-di(ethoxycarbonyl)propyldiethylamine (19·3 g) by the above method and was obtained as a colourless oil, b.p. 98–99°/13 mm, n_D^{20} 1·4337 (7·2 g). Found: equiv., 186·2. Calc. for $C_{10}H_{21}NO_2$: equiv. 187·2. Magidson & Strukov (1933) report b.p. 103–105°/16–17 mm, n_D^{20} 1·4342. Reppe & Mitarbeiter (1955) report b.p. 98–103°/14 mm.

Ethyl γ-dipropylaminobutyrate was prepared from 3,3-di(ethoxycarbonyl)propyldipropylamine (80 g) by the above method and was obtained as a colourless oil, b.p. 120–122°/14 mm, n_D^{22} 1·4328 (14·7 g). This compound without further characterisation was used in the preparation of γ-dipropylaminobutyrohydrazide.

Ethyl δ-diethylaminovalerate was prepared from 4,4-di(ethoxycarbonyl)-butyldiethylamine (10·5 g) by the above method and was obtained as a

colourless oil, b.p. 118–120°/12 mm, $n_D^{19.5}$ 1·4349 (3·3 g). Magidson & Strukov (1933) report b.p. 130–131°/25 mm, n_D^{20} 1·4354.

Methyl δ-bromovalerate was prepared from methyl hydrogen adipate as described in Organic Synthesis (1946), b.p. 57–58°/0·7 mm, n_D^{19} 1·4663.

Methyl δ-dimethylaminovalerate. Methyl δ-bromovalerate (45·5 g), dimethylamine (35 g) and benzene (100 ml) were heated under reflux for 5 hr. The reaction mixture was extracted as described in the preparation of ethyl diethylaminoacetate and methyl δ-dimethylaminovalerate was obtained as an amber-coloured oil, n_D^{20} 1·4310 (5·4 g). Solov'ev, Arendaruk & Skoldinov (1961) report n_D^{20} 1·4322.

Methyl δ-dipropylaminovalerate was prepared from methyl δ-bromovalerate (35 g) and dipropylamine as described above, and was obtained as a straw-coloured oil, b.p. 125–126°/12 mm, $n_D^{15.5}$ 1·4400 (18·8 g). Found: equiv., 211·1. $C_{12}H_{25}NO_2$ requires equiv. 215·3.

Dimethylaminoacethydrazide. Ethyl dimethylaminoacetate (11·5 g) in ethanol (21 ml) was heated under reflux with hydrazine hydrate (5 ml) for 3 hr and allowed to stand for 18 hr. After evaporation under reduced pressure the residual oil was distilled and *dimethylaminoacethydrazide* was obtained as a colourless, viscous oil, b.p. 86–88°/0·6 mm, n_D^{17} 1·4886 (7·8 g). Found: equiv., 122·9; C, 40·7; H, 9·2; N, 35·1%. $C_4H_{11}N_3O$ requires equiv., 117·1; C, 41·0; H, 9·5; N, 35·9%. The *monohydrochloride* was precipitated with dry hydrogen chloride from a dry ethereal solution of the hydrazide and recrystallised (ethanol-ether), m.p. 180–182°. Viscontini & Meier (1950) reported m.p. 181–183°.

Diethylaminoacethydrazide was prepared from ethyl diethylaminoacetate (20 g) by the above method and was obtained as a colourless, viscous oil, b.p. 84–87°/0·45 mm, $n_D^{27.5}$ 1·4763 (16·3 g). Found: equiv., 149·4; C, 49·5; H, 10·2; N, 29·2%. Calc. for $C_6H_{15}N_3O$: equiv., 145·1; C, 49·6; H, 10·4; N, 29·0%. Momose & Tanaka (1953) report b.p. 105°/2 mm. The *salicylate* was prepared by mixing ethanolic solutions of the hydrazide and salicylic acid, and evaporation of solvent. The product was obtained (from acetone-ether) as colourless crystals, m.p. 126–128°. Found: N, 14·3%. $C_{13}H_{21}N_3O_4$ requires N, 14·8%.

Dipropylaminoacethydrazide was prepared from ethyl dipropylaminoacetate (30 g) by the above method, and was obtained as a colourless, viscous oil, b.p. 116–117°/0·55 mm, $n_D^{21.5}$ 1·4696 (21 g). Found: equiv., 178·4; C, 56·1; H, 10·9; N, 24·4%. $C_8H_{19}N_3O$ requires equiv., 173·3; C, 55·4; H, 11·0; N, 24·3%.

β-Dimethylaminopropionhydrazide was prepared from ethyl β-dimethylaminopropionate (Adamson, 1949) (42 g) by the above method, and was obtained as a colourless, viscous oil, b.p. 112–113°/0·5 mm, n_D^{17} 1·4928 (25·3 g). Found: equiv., 138·8; C, 45·3; H, 9·6; N, 32·3%. $C_5H_{13}N_3O$ requires equiv., 131·1; C, 45·8; H, 10·0; N, 32·1%. The *monohydrochloride* (from ethanol-ether), m.p. 124–125°. Found: Cl, 21·5%. $C_5H_{14}ClN_3O$ requires Cl, 21·2%.

β-Diethylaminopropionhydrazide was prepared from ethyl β-diethylaminopropionate (Adamson, 1949) (30·3 g) by the above method, and was

obtained as a colourless, viscous oil, b.p. 121–123°/1·4 mm, n_D^{21} 1·4879 (18·4 g). Found: equiv., 172·3; C, 52·2; H, 10·7; N, 26·6%. $C_7H_{17}N_3O$ requires equiv., 159·2; C, 52·8; H, 10·8; N, 26·4%.

β-Dipropylaminopropionhydrazide was prepared from ethyl β-dipropylaminopropionate (30 g) by the above method and was obtained as a colourless, viscous oil, b.p. 142–144°/1·2 mm, n_D^{18} 1·4819 (17·4 g). Found: equiv., 193·2; C, 56·8; H, 11·1; N, 21·8%. $C_9H_{21}N_3O$ requires equiv., 187·2; C, 57·7; H, 11·3; N, 22·5%.

Di(2-hydrazinocarbonylethyl)amine was prepared from di(2-ethoxycarbonylethyl)amine (11·7 g) by the above method and was obtained as a white solid. Recrystallisation from ethanol yielded *di(2)-hydrazinocarbonylethyl)amine* as colourless crystals, m.p. 124° (6·7 g). Found: equiv., 191·7; C, 37·9; H, 7·3; N, 37·1%. $C_6H_{15}N_5O_2$ requires equiv., 189·2; C, 38·1; H, 7·9; N, 37·0%.

Di(2-hydrazinocarbonyl)ethylmethylamine was prepared from di(2-ethoxycarbonylethyl)methylamine (22·7 g) by the above method, and was obtained as a very viscous, amber-coloured oil, n_D^{20} 1·5300, which solidified on refrigeration. *Di(2-hydrazinocarbonylethyl)methylamine* was recrystallised from ethanol as yellowish-white crystals, m.p. 114° (9·3 g). Found: equiv., 213·0; C, 41·4; H, 8·5; N, 33·6%. $C_1H_{17}N_5O_2$ requires equiv., 203·2; C, 41·4; H, 8·4 N, 34·5%.

Ethyldi (2-hydrazinocarbonylethyl)amine was prepared from di(2-ethoxycarbonylethyl)ethylamine (10·8g) by the above method, and was obtained as a colourless, viscous oil, b.p. 134–135°/0·45 mm, $n_D^{19·5}$ 1·5036 (3·6 g). Found: equiv., 193·0; C,44·7; H, 9·2; N, 31·5%. $C_8H_{19}N_5O_2$ requires equiv., 217·3; C, 44·2; H, 8·8; N, 32·3%.

γ-Dimethylaminobutyrohydrazide was prepared from ethyl γ-dimethylaminobutyrate (6 g) by the above method, and was obtained as a colourless, viscous oil, b.p. 119°/0·4 mm, $n_D^{20·5}$ 1·4852 (4·8 g). Found: equiv., 147·1; C, 49·6; H, 10·2; N, 27·8%. $C_6H_{15}N_3O$ requires equiv., 145·1; C, 49·6; H, 10·4; N, 29·0%.

γ-Diethylaminobutyrohydrazide was prepared from ethyl γ-diethylaminobutyrate (7·2 g) by the above method, and was obtained as a colourless, viscous oil, b.p. 120–121°/0·55 mm, n_D^{16} 1·4837 (5·7 g). Found: equiv., 182·3; C, 55·6; H, 11·3; N, 23·6%. $C_8H_{19}N_3O$ requires equiv., 173·2; C, 55·4; H, 11·1; N, 24·3%.

γ-Dipropylaminobutyrohydrazide was prepared from ethyl γ-dipropylaminobutyrate (14·5 g) by the above method, and was obtained as a colourless, viscous oil, b.p. 150–152°/0·35 mm, $n_D^{20·5}$ 1·4735 (4·6 g). Found: equiv., 205·2; C, 59·3; H, 11·5; N, 20·2%. $C_{10}H_{23}N_3O$ requires equiv., 201·2; C, 59·7; H, 11·5;N, 20·9%.

δ-Diethylaminovalerohydrazide was prepared from ethyl δ-diethylaminovalerate (3·3 g) by the above method, and was obtained as a colourless, viscous oil, b.p. 155–156°/0·9 mm, n_D^{18} 1·4846 (2 g). Found: equiv., 188·5; C, 57·4; H, 11·3; N, 22·4%. $C_9H_{21}N_3O$ requires equiv., 187·2; C, 57·7; H, 11·3; N, 22·5%.

δ-Dimethylaminovalerohydrazide was prepared from methyl δ-dimethylaminovalerate (5·4 g) by the above method and was obtained as a colourless,

viscous oil, b.p. 148–150°/0·45 mm, $n_D^{20·5}$ 1·4826 (3·5 g). Found: equiv., 169·1; C, 48·6; H, 10·9; N, 26·6%. $C_7H_{17}N_3O$ requires equiv., 159·2; C, 52·8; H, 10·8; N, 26·4%.

δ-*Dipropylaminovalerohydrazide* was prepared from methyl δ-dipropylaminovalerate (18 g), by the above method and was obtained as a colourless, viscous oil, b.p. 154–156°/1·3 mm, n_D^{18} 1·4780 (11·8 g). Found: equiv., 220·0; C, 61·1; H, 11·8; N, 19·4%. $C_{11}H_{25}N_3O$ requires equiv., 215·2; C, 61·4; H, 11·7; N, 19·5%. The *dihydrochloride* was prepared by passing dry hydrogen chloride into a dilute solution of the hydrazide in dry ether. It was obtained (from ethanol) as colourless crystals, m.p. 194°. Found: equiv., 148·0; C, 46·0; H, 9·6; Cl, 24·4; N, 14·4%. $C_{11}H_{27}Cl_2N_3O$ requires equiv., 144·1; C, 45·8; H, 9·4; Cl, 24·7; N, 14·6%.

Acknowledgement. We would like to thank Dr. S. R. M. Bushby of the Wellcome Research Laboratories for carrying out the bacteriological tests.

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