identical to the product obtained by means of lithium aluminum hydride.

When II was boiled under reflux for 1 hr., 57 per cent was recovered as a fraction boiling at 182–189°/750 mm., n_D^{20} 1.4761. The remainder was an orange-amber viscous sirup which could not be distilled.

Treatment of II with 2,4-dinitrophenylhydrazine hydrochloride in 95% ethanol gave 5,6-dihydroxyhexanal 2,4-dinitrophenylhydrazone, m.p. 119–121°, a compound described more completely in a succeeding section.

2-Acetoxymethyl-2,3-dihydro-4H-pyran (V). A solution of 20 g. (0.175 mole) of II in 40 ml. of pyridine was allowed to stand overnight with 54 g. (0.53 mole) of acetic anhydride before the pyridine was distilled and the residue was hydrolyzed in ice and water. Ether extraction and distillation of the extract gave 14 g. (54 per cent) of racemic 6-*O*-acetyl-3,4-dideoxyglucal (V), b.p. 101–104°/14 mm., n_D^{20} 1.4578.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.30; H, 7.85.

Attempted preparation of 6-hydroxymethyltetrahydropyran-2-ol (IV). When 20 g. (0.175 mole) of II was dissolved in 80 ml. of 0.2*N* hydrochloric acid, heat was immediately evolved. A portion of the hydrolysis mixture was neutralized to the phenolphthalein end point and an attempt was made to fractionate at 1-mm. pressure. However, except for water no distillate was obtained at less than 250°. A second portion of the hydrolysis mixture was made basic and extracted with ten portions of ether. These were combined, dried, and evaporated under vacuum at room temperature to give a 25% recovery of a mixture of unidentified solid and liquid. The water was distilled from a third portion to leave a viscous orange liquid which was treated with acetic anhydride and pyridine in an exothermic reaction. However, distillation at 1 mm. pressure of the washed, ether extract of the ice water hydrolysate from that mixture resulted in decomposition.

Addition of one drop of 6*N* hydrochloric acid to a turbid mixture of 3.4 g. of the hydroxymethyl compound II and 5 ml. of water almost immediately resulted in a clear solution. This was made slightly basic and vacuum-dried at room temperature and finally vacuum dried over phosphorus pentoxide. The clear viscous residue was obtained in quantitative conversion. It was examined by infrared.

5,6-Dihydroxyhexanal 2,4-dinitrophenylhydrazone. A portion of the above sirupy mixture of 5,6-dihydroxyhexanal (IVa) and 6-hydroxymethyltetrahydropyran-2-ol (IV) was dissolved in alcohol and treated with alcoholic 2,4-dinitrophenylhydrazine in the usual way[12] to give long, orange needles of 5,6-dihydroxyhexanal 2,4-dinitrophenylhydrazone, m.p. 122–123°.

The same compound with an identical melting point was obtained by addition of 2,4-dinitrophenylhydrazine to a solution of II in alcohol-water containing a few drops of hydrochloric acid.

Anal. Calcd. for $C_{12}H_{16}O_6N_4$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.13; H, 5.13; N, 17.80.

2-Ethoxy-6-hydroxymethyltetrahydropyran (VI). A solution of 20 g. (0.175 mole) of 2-hydroxymethyl-2,3-dihydro-4*H*-pyran (II) in 100 ml. of absolute alcohol containing a drop of dilute hydrochloric acid was allowed to stand over night. Distillation from several pellets of solid sodium hydroxide gave 68% of the mixture of ethyl 2,3,4-trideoxyaldohexopyranosides (VI), b.p. 90–94°/7 mm., 151–154°/98 mm., n_D^{20} 1.4510.

Anal. Calcd. for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 60.11; H, 10.12.

CHICAGO 14, ILL.

(12) R. L. Shriner and R. C. Fuson, *Systematic Identification of Organic Compounds*, Third Edition, John Wiley and Sons, Inc., New York, 1948, p. 171.

[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

Tuberculostatic *N*-Arylglycines and Derivatives

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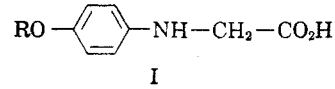
A large number of *N*-arylglycines, especially *para*-substituted *N*-phenylglycines, have been synthesized, along with their esters, hydrazides, and other derivatives, for biological evaluation as potential tuberculostatic agents.

Primary arylamines with substitutions in *para* position have repeatedly been found to show notable inhibitory activity against tubercle bacilli in *in vitro* tests;[1] their high toxicity, however, has limited both *in vivo* studies and practical application, and several attempts have therefore been made to prepare less toxic derivatives (anils, glucosides, etc.)[2] Recently, Bersch and Döpp[3] found that conversion of certain *p*-alkyloxyanilines to the corresponding *N*-arylglycines leads to compounds possessing very high *in vivo* tuberculostatic activity, such as *N*-(4-ethoxyphenyl)- (I; R = C_2H_5) and *N*-(4-butoxyphenyl)glycine (I; R = *n*-C_4H_9), but no *in vivo* studies were made with these substances.



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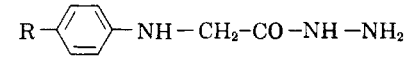


II

In the framework of a general investigation on the relationship between chemical structure and tuberculostatic activity,[4] a large number of new *N*-arylglycines, especially those bearing an alkyl, alkyloxy, or halogen substituent in the *para*

(1) M. Kuroya, *Japan J. Exp. Med.*, **7**, 255 (1929); J. P. Jouin and N. P. Buu-Hoï, *Ann. Inst. Pasteur*, **72**, 580 (1946); B. L. Freedlander *et al.*, *Am. Rev. Tuber.*, **56**, 360 (1947); *Stanford Med. Bull.*, **12**, 33 (1954).

(2) H. Erlenmeyer, *et al.*, *Helv. Chim. Acta*, **28**, 1406 (1945); **30**, 2058 (1947); **32**, 605 (1949).

(3) H. W. Bersch and W. Döpp, *Arzneimittel-Forsch.*, **5**, 183, 335 (1955).

(4) N. P. Buu-Hoï, N. D. Xuong, *et al.*, *Experientia*, **10**, 169 (1954); **11**, 97 (1955); **12**, 102, 474 (1956); *Compt. rend.*, **236**, 635 (1953); **237**, 498 (1953); **238**, 295 (1954).

TABLE I

NEW *N*-ARYLGLYCINES

Aryl Radical	Formula	M.P., °C.	Analyses Calcd. C	Calcd. H	Found C	Found H
4-Fluorophenyl	$C_8H_8FNO_2$	140	56.8	4.7	57.0	4.9
3-Chloro-2-methylphenyl	$C_9H_{10}ClNO_2$	169	54.2	5.0	54.5	5.4
5-Chloro-2-methoxyphenyl	$C_9H_{10}ClNO_3$	182	50.1	4.6	50.4	4.6
2,3-Dimethylphenyl	$C_{10}H_{13}NO_2$	176	67.0	7.3	66.7	7.2
2,6-Dimethylphenyl	$C_{10}H_{13}NO_2$	154	67.0	7.3	67.4	7.5
3,4-Dimethylphenyl	$C_{10}H_{13}NO_2$	149	67.0	7.3	66.9	7.1
4-Ethylphenyl	$C_{10}H_{13}NO_2$	142	67.0	7.3	66.7	7.0
4-Propylphenyl	$C_{11}H_{15}NO_2$	136	68.4	7.8	68.2	7.8
4-Butylphenyl	$C_{12}H_{17}NO_2$	139	69.6	8.2	69.8	8.4
4-Cyclohexylphenyl	$C_{14}H_{19}NO_2$	178	72.1	8.2	72.0	8.2
4-Propoxyphenyl	$C_{11}H_{15}NO_3$	135	63.2	7.2	63.2	6.9
4-Isopropoxyphenyl	$C_{11}H_{15}NO_3$	141	63.2	7.2	62.9	7.4
4-Isoamyloxyphenyl	$C_{13}H_{19}NO_3$	119	65.8	8.0	65.8	8.2
4-Heptyloxyphenyl	$C_{15}H_{23}NO_3$	122	67.9	8.7	67.6	8.7

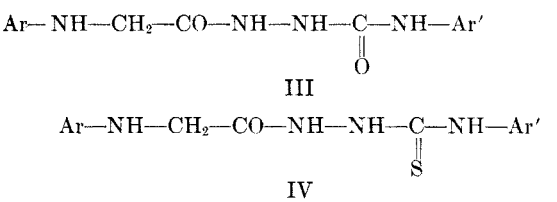
TABLE II

ETHYL ESTERS $ArNHCOOC_2H_5$ OF *N*-ARYLGLYCINES

Aryl Radical	Formula	B.P., °C./Mm.	M.P., °C.	Analyses Calcd. C	Calcd. H	Found C	Found H
4-Fluorophenyl	$C_{10}H_{12}FNO_2$		72	60.9	6.1	60.6	6.1
3-Chloro-2-methylphenyl	$C_{11}H_{14}ClNO_2$	185/30		58.0	6.2	57.7	6.5
4-Ethylphenyl	$C_{12}H_{17}NO_2$	165/17		69.6	8.2	69.3	8.3
4-Propylphenyl[a]	$C_{13}H_{19}NO_2$	175/20		70.6	8.6	70.5	8.4
4-Butylphenyl[b]	$C_{14}H_{21}NO_2$	180/17		71.5	8.9	71.2	8.6
4-Heptylphenyl[c]	$C_{17}H_{27}NO_2$	180/13		73.7	9.8	73.6	9.9
4-Propoxyphenyl	$C_{13}H_{19}NO_3$	175/14		65.8	8.0	65.7	8.0
4-Isopropoxyphenyl	$C_{13}H_{19}NO_3$	180/17		65.8	8.0	65.6	8.1
4-Butoxyphenyl	$C_{14}H_{21}NO_3$	195/18		66.9	8.4	66.8	8.5
4-Isoamyloxyphenyl[d]	$C_{15}H_{23}NO_3$	190/16		67.9	8.7	67.7	8.5
4-*p*-Diphenylyl	$C_{16}H_{17}NO_2$		96–97	75.3	6.7	75.2	6.8
4-Cyclohexylphenyl	$C_{16}H_{23}NO_2$		65	73.6	8.8	73.4	8.9

[a] n_D^{22} 1.5365. [b] n_D^{22} 1.5359. [c] n_D^{22} 1.5253. [d] n_D^{22} 1.5223.

position, have been prepared by condensation of various primary arylamines with chloroacetic acid in the presence of sodium acetate.[5] The *N*-arylglycines thus obtained in good yields, except in the case of sterically hindered arylamines, are listed in Table I. In view of the known tuberculostatic activity of numerous hydrazides,[6] a large number of hydrazides (general formula II) derived from *N*-arylglycines, have been synthesized by hydrazinolysis of the corresponding ethyl esters, which were prepared by condensation of primary arylamines with ethyl chloroacetate in the presence of sodium acetate; these new esters are listed in Table II, and the new hydrazides in Table III. The reaction of hydrazides II with various aryl isocyanates and isothiocyanates[7] readily afforded the corresponding 1-acyl-4-arylsemicarbazides (III) and 1-acyl-4-arylthiosemicarbazides (IV).



III

IV

Biological studies on these compounds showed that several *N*-arylglycines bearing a bulky *p*-substituent (especially a higher alkyloxy group) are tuberculostatic *in vitro* at a concentration of 10γ per ml. Dubos culture medium (*Mycobacterium tuberculosis* var. *hominis*, strain $H_{37}RvD$), while the corresponding hydrazides are inactive. Unfortunately, all the *N*-arylglycines tested showed such a high degree of toxicity that no *in vivo* activity could be detected.[8]

(5) A. Hausdörfer, *Ber.*, **22**, 1799 (1889).

(6) H. A. Offe, W. Siefken, and G. Domagk, *Naturwissenschaften*, **39**, 118 (1952); see literature in E. Krüger-Thiemer, *Jahresber. Tuberkulose-Forschungsinstituts Borstel*, **3**, 192 (1956).

(7) N. P. Buu-Hoï, N. D. Xuong, and N. H. Nam, *J. Chem. Soc.*, 2160 (1956).

(8) N. P. Buu-Hoï, N. D. Xuong, N. B. Tien, J. M. Gazave, J. Pillot, and G. Dufraisse, *Experientia*, **13**, 235 (1957).

TABLE III

HYDRAZIDES DERIVED FROM *N*-ARYLGLYCINES

Aryl Radical	Formula	M.P., °C.	Analyses, N % Calcd.	Found
4-Fluorophenyl	$C_8H_{10}FN_3O$	115	22.9	22.5
4-Chlorophenyl	$C_8H_{10}ClN_3O$	140	21.1	21.3
4-Bromophenyl	$C_8H_{10}BrN_3O$	161	17.2	17.4
4-Tolyl	$C_9H_{13}N_3O$	152	23.5	23.1
4-Ethylphenyl	$C_{10}H_{15}N_3O$	148	21.8	22.2
4-Propylphenyl	$C_{11}H_{17}N_3O$	140	20.3	20.6
4-Butylphenyl	$C_{12}H_{19}N_3O$	145	19.0	18.7
4-Heptylphenyl	$C_{15}H_{25}N_3O$	146	16.0	15.6
4-Diphenylyl	$C_{14}H_{15}N_3O$	167	17.4	17.1
4-Cyclohexylphenyl	$C_{14}H_{21}N_3O$	160	17.0	16.9
3-Chloro-2-methylphenyl	$C_9H_{13}ClN_3O$	159	19.7	19.4
4-Ethoxyphenyl	$C_{10}H_{15}N_3O_2$	132	20.1	20.4
4-Propoxyphenyl	$C_{11}H_{17}N_3O_2$	135	18.8	18.8
4-Isopropoxyphenyl	$C_{11}H_{17}N_3O_2$	114	18.8	18.6
4-Butoxyphenyl	$C_{12}H_{19}N_3O_2$	135	17.7	17.5
β-Naphthyl	$C_{12}H_{13}N_3O$	152	19.5	19.0

EXPERIMENTAL

Preparation of intermediates. *p*-Alkylanilines and *p*-cyclohexylaniline were prepared by Beckmann rearrangement of the oximes of the corresponding *p*-substituted acetophenones. *p*-Alkyloxyanilines were prepared by alkylation of *p*-benzalaminophenol with alkyl halogenides and sodium hydroxide in aqueous ethanol, and subsequent hydrolysis of the aldimines with hydrochloric acid.

Preparation of N-arylglycines. A mixture of 1.5 moles of the primary arylamine, 1 mole of chloroacetic acid, and 2 moles of sodium acetate (dissolved in a minimum of water) was heated at 50–60° on a water bath for one hour; the solid obtained on cooling was washed with water, treated with a 10% aqueous solution of ammonium carbonate, and the filtrate acidified with hydrochloric acid. The precipitate formed was washed with ether to remove the imino derivative $ArN(CH_2CO_2H)_2$, and the residue recrystallized from benzene or a mixture of ethanol and benzene, giving colorless prisms in every instance. The yields varied from 65% for the *p*-substituted anilines, to 25% for the sterically hindered 2,6-dimethylaniline and 15% for the even more hindered 2,6-diethylaniline.

The same procedure was applied, with similar results, to α-bromobutyric acid; for example, α-(*p*-tolylamino)butyric acid, thus obtained in 60% yield, crystallized from benzene in shiny colorless needles, m.p. 158°; Bischoff and Mintz[9] gave m.p. 153–156° for a sample prepared by alkaline hydrolysis of the corresponding ethyl ether. α-(2-Naphthylamino)butyric acid, prepared from β-naphthylamine (7 g.), α-bromobutyric acid (5 g.) and sodium acetate (12 g.), crystallized from benzene in shiny colorless prisms (3.5 g.), m.p. 157°; Bischoff and Mintz[9] gave m.p. 158°. This compound is similar to the tuberculostatic β-(2-naphthylamino)-dihydrohydnocarpic acid.[10]

Preparation of ethyl esters of N-arylglycines. A mixture of 1 mole of the primary arylamine, 1 mole of redistilled ethyl chloroacetate, and 2 moles of sodium acetate (dissolved in a minimum of water) was heated on a water bath for one hour; after cooling, water was added, and the precipitate formed was taken up in benzene. The benzene solution was then dried over sodium sulfate, the solvent removed, and the residue vacuum-fractionated and if solid, crystallized from petroleum ether. The yields varied from 50 to 70%.

Preparation of hydrazides derived from N-arylglycines. A solution of 1 mole of the ethyl ester of the corresponding *N*-arylglycine and 2 moles of 95% hydrazine hydrate in ethanol was refluxed for 5 to 6 hr. on a water bath, the solvent distilled off *in vacuo*, and the solid residue recrystallized several times from ethanol, to give shiny colorless needles, in 85–90% yield.

Preparation of 1-acyl-4-arylsemicarbazides (III). To a solution of 1 mole of the hydrazide of the appropriate *N*-arylglycine in dry benzene, 1 mole of the aryl isocyanate was added, and the mixture warmed for a few minutes at 50–60°; after cooling, the precipitate obtained was recrystallized from benzene. Yield: 80–90%. For example, *1-(β-naphthylaminoacetyl)-4-p-chlorophenylsemicarbazide* was thus obtained as shiny colorless prisms, m.p. 213°.

Anal. Calcd. for $C_{19}H_{17}ClN_4O_2$: N, 15.2. Found: N, 14.9.

1-(p-Phenetylamino)acetyl-4-p-bromophenylsemicarbazide was shiny colorless needles, m.p. 219°.

Anal. Calcd. for $C_{17}H_{19}BrN_4O_3$: N, 13.8. Found: N, 13.5.

Preparation of 1-acyl-4-arylthiosemicarbazides (IV). These compounds were prepared as above, with aryl isothiocyanates.

1-(p-Phenetylamino)acetyl-4-phenylthiosemicarbazide crystallized from ethanol in shiny colorless prisms, m.p. 172°.

Anal. Calcd. for $C_{17}H_{20}N_4O_2S$: N, 16.3. Found: N, 16.4.

1-(p-Phenetylamino)acetyl-4-p-chlorophenylthiosemicarbazide crystallized from ethanol in colorless prisms, m.p. 189°.

Anal. Calcd. for $C_{17}H_{19}ClN_4O_2S$: N, 14.8. Found: N, 14.7.

1-p-(Cyclohexylphenyl)aminoacetyl-4-phenylthiosemicarbazide crystallized from ethanol in colorless leaflets, m.p. 196°.

Anal. Calcd. for $C_{21}H_{26}N_4OS$: N, 14.7. Found: N, 14.6.

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(9) C. A. Bischoff and N. Mintz, *Ber.*, **25**, 2319, 2324 (1892).

(10) N. P. Buu-Hoï and P. Cagniant, *Ber.*, **76**, 1269 (1943).