20. *The Chemotherapy of Tuberculosis. Part VII.* Thiosemicarbazones of Substituted Phenyl- and Pyridyl-benzaldehydes.*

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The preparation of 4′-ethoxycarbonyl-, 4′-carboxy-, and 4′-methoxydiphenyl-4-aldehyde is described. The isosteric *p*-2-pyridylbenzaldehyde has been obtained by two synthetical routes, and the thiosemicarbazones of these aldehydes and of some related compounds have been tested against *Mycobacterium tuberculosis*.

The discovery of the tuberculostatic activity of *p*-substituted benzaldehyde thiosemicarbazones (Behnisch, Mietzsch, and Schmidt, *Angew. Chem.*, 1948, **60**, 113) prompted us to examine some derivatives of diphenyl-4-aldehydes. Diphenyl-4-aldehyde thiosemicarbazone proved highly active *in vitro*, and in view of its low solublity more soluble analogues were investigated. The only recorded example of the Gomberg and related reactions in which the product is an aldehyde is the action of *N*-nitrosoacetanilide on benzaldehyde (Grieve and Hey, *J.*, 1934, 1798) which afforded a mixture of isomers, including diphenyl-4-aldehyde. The unknown *p*-ethoxycarbonyl-*N*-nitrosoacetanilide could not be prepared by the action of nitrous fumes on the acetanilide which is thus similar to *p*-nitroacetanilide; the latter forms the nitroso-derivative with nitrosyl chloride (Haworth and Hey, *J.*, 1940, 361).

p-Ethoxycarbonylbenzenediazonium chloride coupled with benzaldehyde in the presence of sodium acetate to give, in low yield, 4′-ethoxycarbonyldiphenyl-4-aldehyde; acid hydrolysis of the ester group then gave 4′-carboxydiphenyl-4-aldehyde. A dicarboxylic acid, obtained as a by-product, had the properties expected for diphenyl-4 : 4′-dicarboxylic acid, and the same substance was obtained by acid hydrolysis of 4′-ethoxycarbonyldiphenyl-4-aldehyde thiosemicarbazone and oxidation of the product. Work directed towards a rigid proof of structure of 4′-carboxydiphenyl-4-aldehyde is in progress.

Condensation of *p*-methoxybenzenediazonium chloride and benzaldehyde gave only a minute yield of impure 4′-methoxydiphenyl-4-aldehyde, while the use of *p*-methoxy-*N*-nitrosoacetanilide afforded the crude aldehyde in 14·5% yield. The zinc cyanide modification (Adams and Montgomery, *J. Amer. Chem. Soc.*, 1924, **46**, 1518) of the Gattermann aldehyde synthesis failed with 4-hydroxydiphenyl. Attempted formylation of 4-methoxydiphenyl with *N*-methylformanilide and phosphorus oxychloride was unsuccessful, nor could a chloromethyl derivative be obtained from this compound by using chloromethyl ether and zinc chloride. An attempted reduction of 4′-methoxydiphenyl-4-carbonyl chloride with lithium hydride by Brandt's method (*Acta Chem. Scand.*, 1949, **3**, 1050) gave no aldehydic material.

4-Cyano-4′-hydroxydiphenyl was synthesised from 4′-amino-4-cyanodiphenyl with a view to using Stephen's aldehyde synthesis (*J.*, 1925, 1874); this route was not pursued, however, as the desired aldehyde was obtained by McFadyen and Stevens's method (*J.*, 1936, 584). Derivatives of the product were identical with those of the aldehyde previously obtained from *p*-methoxy-*N*-nitrosoacetanilide and benzaldehyde, thus confirming the 4 : 4′-orientation of the substituents.

The isosteric *p*-pyridylbenzaldehyde derivative was prepared in order to overcome the low water-solubility of the tuberculostatically active diphenyl-4-aldehyde. Diazotisation of *p*-2-pyridylaniline by the method of Butterworth, Heilbron, and Hey (*J.*, 1940, 355) followed by treatment with cuprous cyanide and hydrolysis gave a mixture of *p*-chloro-2-pyridylbenzene and *p*-2-pyridylbenzoic acid. Under the strongly acidic conditions used, partial conversion of some cuprous cyanide into the chloride may have occurred, the chloride then reacting by a normal Sandmeyer reaction.

In view of the poor yield obtained in this synthesis, an alternative route was devised making use of the known addition of organolithium compounds exclusively to the carbon

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atom of the azomethine linkage in aromatic heterocyclic compounds (*e.g.*, Gilman and Blume, *J. Amer. Chem. Soc.*, 1943, **65**, 2476). Reaction of *p*-tolyl-lithium with pyridine by an adaptation of Evans and Allen's method (*Org. Synth.*, Coll. Vol. II, 1944, 517) afforded *p*-2-pyridyltoluene. While potassium permanganate failed to oxidise this compound in acetone, reaction occurred readily in hydrochloric acid, affording *p*-2-pyridylbenzoic acid. Its methyl ester, identical with that obtained from *p*-2-pyridylaniline, was readily converted, *via* the hydrazide, into the benzenesulphonylhydrazine. Decomposition of this with alkali in presence of thiosemicarbazide by Fox's method (*J. Org. Chem.*, 1952, **17**, 555) gave the derivative directly in 25% yield.

An improved preparation of this aldehyde was the direct oxidation of *p*-2-pyridyltoluene with chromic acid in presence of acetic anhydride, which afforded *p*-2-pyridylbenzaldehyde and its diacetate, both readily giving derivatives identical with one another and with those prepared from the same aldehyde obtained by McFadyen and Stevens's method.

The thiosemicarbazones were kindly examined for antituberculous activity by Professor S. D. Rubbo; they inhibited completely the growth of *Mycobacterium tuberculosis* H37Rv *in vitro* after 14 days at 37° in Youmans's medium at dilutions of M/128,000 to M/512,000 in presence of 10% of serum. 4'-Carboxydiphenyl-4-aldehyde thiosemicarbazone was an exception in that it had greatly reduced activity (M/32,000). A full account of the bacteriological aspects will be given elsewhere.

Experimental

Diphenyl-4-aldehyde Thiosemicarbazone.—(With J. N. Baxter.) The *thiosemicarbazone*, obtained in quantitative yield, crystallised from methanol as yellowish plates, m. p. 202—202·5° (Found : C, 66·0; H, 5·2; N, 16·6; S, 12·45. $C_{14}H_{13}N_3S$ requires C, 65·85; H, 5·15; N, 16·45; S, 12·55%).

A suspension of the thiosemicarbazone (1·28 g.) in ethanol (100 c.c.) was refluxed with methyl iodide (0·6 c.c.) for 3½ hr., the resulting solution evaporated to dryness *in vacuo*, and the residue triturated with dry ether giving *diphenyl-4-aldehyde S-methylthiosemicarbazone hydriodide* (1·87 g., 92%), needles (from *iso*propanol–ether), m. p. 175—176°, after softening at 167° (Found : N, 10·75. $C_{15}H_{16}N_3SI$ requires N, 10·6%).

4'-Ethoxycarbonyldiphenyl-4-aldehyde.—A suspension of ethyl *p*-aminobenzoate (100 g.) in hydrochloric acid (330 c.c.; 10N) and water (180 c.c.) was diazotised at 0—5°, and the solution stirred vigorously with benzaldehyde (500 c.c.) at 5—10° under nitrogen while a saturated solution of sodium acetate trihydrate (330 g.) was added dropwise. After 3 days, benzaldehyde was removed by steam distillation, and was shown to be free from higher-boiling material. The residual oil was purified by dissolution in ether and the aldehyde obtained from it by formation of the bisulphite compound (18·4 g., 8%). The *thiosemicarbazone* crystallised from aqueous acetone as needles, m. p. 235° (decomp.) (Found : C, 62·4; H, 5·3; N, 13·0. $C_{17}H_{17}O_2N_3S$ requires C, 62·4; H, 5·25; N, 12·85%), and the 2 : 4-*dinitrophenylhydrazone* formed red needles, m. p. 263°, from ethyl acetate–xylene (Found : C, 61·1; H, 4·5; N, 13·1. $C_{22}H_{18}O_6N_4$ requires C, 60·85; H, 4·2; N, 12·9%). Acid hydrolysis of the thiosemicarbazone followed by treatment of the neutralised solution with a few drops of hydrogen peroxide (10%) gave on acidification an acid (decomp. above 345°) showing the properties of diphenyl-4 : 4'-dicarboxylic acid.

4'-Carboxydiphenyl-4-aldehyde.—The bisulphite compound of 4'-ethoxycarbonyldiphenyl-4-aldehyde was refluxed under nitrogen with aqueous alcohol (25% v/v) containing sulphuric acid (20% v/v). The mixture was made alkaline with sodium carbonate solution and extracted with benzene. A small amount of insoluble sodium salt was obtained and afforded an acid with properties in agreement with those recorded for diphenyl-4 : 4'-dicarboxylic acid (Doebner, *Ber.*, 1876, **9**, 272). Acidification of the alkaline solution gave the crude carboxyaldehyde, whose *thiosemicarbazone* formed pale brown microcrystals (from aqueous acetone), m. p. 240° upwards (decomp.) (Found : C, 59·95; H, 4·7; N, 13·8. $C_{15}H_{13}O_2N_3S$ requires C, 60·15; H, 4·4; N, 14·0%), and 2 : 4-*dinitrophenylhydrazone*, red needles (benzene–pyridine), m. p. 312° (decomp.) (Found : C, 59·6; H, 3·7; N, 13·65. $C_{20}H_{14}O_6N_4$ requires C, 59·15; H, 3·5; N, 13·8%).

4-Cyano-4'-hydroxydiphenyl.—4-Amino-4'-cyanodiphenyl, obtained by Angeletti and Gatti's

method (*Gazzetta*, 1928, **58**, 630), crystallised from toluene as buff microcrystals, m. p. 161—162°, softening at 155°. Angeletti and Gatti (*loc. cit.*) give m. p. 157°.

The amine (6·58 g.) was diazotised at 0°, and the solution diluted with an equal volume of water and filtered. The filtrate was added dropwise to a boiling solution of copper sulphate (80 g.) in water (80 c.c.) and the product obtained on filtering the cooled mixture was dissolved in potassium hydroxide solution and reprecipitated with hydrochloric acid to give *4-cyano-4'-hydroxydiphenyl* (4 g., 60%), prisms, m. p. 193—194° (after sublimation at 205°/0·3 mm.) (Found : C, 79·8; H, 4·8; N, 7·2. $C_{13}H_9ON$ requires C, 79·95; H, 4·65; N, 7·2%).

4-Acetyl-4'-methoxydiphenyl.—The 2 : 4-*dinitrophenylhydrazone* formed red needles (from toluene), m. p. 217° (Found : C, 62·25; H, 4·5; N, 13·75. $C_{21}H_{18}O_5N_4$ requires C, 62·05; H, 4·45; N, 13·8%). The *thiosemicarbazone* crystallised from benzene as yellow microcrystals, m. p. 210°, resolidifying and remelting at 290° (decomp.), which contained solvent of crystallisation not removed at 100° (Found : C, 67·2, 67·3; H, 5·8, 5·7. $C_{16}H_{17}ON_3S,\frac{1}{2}C_6H_6$ requires C, 67·4; H, 5·9%). Crystallisation from acetone–light petroleum (b. p. 60—90°) gave white microcrystals, m. p. 290° (decomp.) (Found : C, 64·0; H, 5·85. $C_{16}H_{17}ON_3S$ requires C, 64·2; H, 5·7%).

4-Acetyl-4'-hydroxydiphenyl.—4-Acetyl-4'-methoxydiphenyl (1·5 g.) (Johnson, Gutsche, and Offenhauer, *J. Amer. Chem. Soc.*, 1946, **68**, 1648), acetic acid (20 c.c.), and hydrobromic acid (5·2 c.c.; 48%) were refluxed for 6·5 hr. The mixture was poured into water and gave a quantitative yield of the ketone, m. p. 202°. Fieser and Bradsher (*J. Amer. Chem. Soc.*, 1936, **58**, 1738) give m. p. 205—206° for the compound prepared by the Fries reaction. The 2 : 4-*dinitrophenylhydrazone* crystallised as red needles (from aqueous acetic acid), m. p. 250° (decomp.) (Found : C, 60·1; H, 4·25. $C_{20}H_{16}O_5N_4,\frac{1}{2}H_2O$ requires C, 60·1; H, 4·25%). The *thiosemicarbazone* formed yellow microcrystals (from acetic acid), m. p. 280° (decomp.) (Found : C, 63·6; H, 5·4. $C_{15}H_{15}ON_3S$ requires C, 63·15; H, 5·3%).

4-Methoxydiphenyl-4'-carboxyl Chloride.—Treatment of 4-methoxydiphenyl-4'-carboxylic acid (Johnson, Gutsche, and Offenhauer, *loc. cit.*) with thionyl chloride gave the acid chloride, which formed yellow crystals, m. p. 97—98°, from light petroleum (b. p. 90—100°). The methyl ester had m. p. 171—172° (Fieser and Bradsher, *loc. cit.*, give m. p. 172—173°).

4-Methoxydiphenyl-4'-carboxyhydrazide.—Methyl 4-methoxydiphenyl-4'-carboxylate (13·3 g.), hydrazine hydrate (13 c.c.; 100%), and 2-ethoxyethanol (30 c.c.) were refluxed for 3·25 hr., and on cooling gave plates of the *hydrazide* (10·44 g., 79%), m. p. 203—204° (Found : C, 69·2; H, 5·75; N, 11·5. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 5·85; N, 11·55%).

N-(*4'-Methoxydiphenyl-4-carbonyl*)-N'-*benzenesulphonylhydrazine.*—The hydrazide (9·85 g.), suspended in pyridine (160 c.c.), was treated with benzenesulphonyl chloride (5·5 c.c.) at 0°. The solution was set aside overnight at room temperature and then poured into ice and dilute hydrochloric acid, the mixture filtered, and the residue washed (water) giving the *benzenesulphonylhydrazine* (15·3 g., 99%), needles (from aqueous acetone), m. p. 208—209° (decomp.) (Found : C, 62·95; H, 4·6. $C_{20}H_{18}O_4N_2S$ requires C, 62·8; H, 4·75%).

4-Methoxydiphenyl-4'-aldehyde.—(i) A solution of the benzenesulphonylhydrazine (6 g.) in ethylene glycol (60 c.c.) was treated at 160° with anhydrous sodium carbonate (4·5 g.), added all at once. The mixture was kept at 170° for 80 sec. and then poured into hot water (200 c.c.). The *aldehyde* crystallised from light petroleum (b. p. 90—100°) as needles (1·96 g., 59%), m. p. 101·5—102° (Found : C, 79·1; H, 5·85. $C_{14}H_{12}O_2$ requires C, 79·2; H, 5·7%). The 2 : 4-*dinitrophenylhydrazone* formed red needles (from aqueous acetone), m. p. 240—241° (Found : C, 59·85; H, 4·65. $C_{20}H_{16}O_5N_4,\frac{1}{2}H_2O$ requires C, 59·85; H, 4·3%). The *thiosemicarbazone* crystallised from aqueous alcohol as yellow microcrystals, m. p. 212—213° (decomp.) (Found : C, 62·75; H, 5·6. $C_{15}H_{15}ON_3S$ requires C, 63·1; H, 5·3%).

(ii) A solution of *p*-methoxy-*N*-nitrosoacetanilide (17·4 g.; Haworth and Hey, *J.*, 1940, 361) in benzaldehyde (200 c.c.) was dried (Na_2SO_4) and set aside at room temperature in an atmosphere of nitrogen for 24 hr., then warmed to 50° for 1 hr., and finally distilled with steam. The residue was purified *via* the bisulphite compound (4·2 g., 14·5%). It afforded a 2 : 4-dinitrophenylhydrazone, m. p. 241—242°, and a thiosemicarbazone, m. p. 213°, undepressed with the derivatives prepared in (i).

Sandmeyer Reaction with p-2-*Pyridylaniline Dihydrochloride.*—Diazotisation of *p*-2-pyridylaniline (m. p. 310—313°; Forsyth and Pyman, *J.*, 1926, 2912, record m. p. >310°) and treatment of the salt with cuprous cyanide was carried out by Butterworth, Heilbron, and Hey's method (*J.*, 1940, 355). The product (42%) was a mixture and was hydrolysed directly with sodium hydroxide solution (20%). The non-acidic portion crystallised from light petroleum (b. p. 40—60°) as flat needles, m. p. 52—53° (picrate, m. p. 169°, from methanol) and was thus

p-chloro-2-pyridylbenzene (lit., m. p. 52—53°; picrate, m. p. 169—170°). The crude acid was esterified with methanol and concentrated sulphuric acid giving methyl *p*-2-pyridylbenzoate as prisms, m. p. 97° alone and mixed with a sample from the alternative synthesis (below). Butterworth, Heilbron, and Hey (*loc. cit.*) give m. p. 90°.

p-2-*Pyridyltoluene*.—*p*-Tolyl-lithium, prepared from *p*-bromotoluene (39 g.) by Gilman, Zoellner, and Selby's method (*J. Amer. Chem. Soc.*, 1932, **54**, 1957), was treated with anhydrous pyridine by Evans and Allen's method (*Org. Synth.*, Coll. Vol. II, 1944, p. 517) except that the toluene solution was refluxed for 7 hr. Distillation gave p-2-*pyridyltoluene* as a pale yellow oil (23·6 g., 61%), b. p. 140—142°/2 mm., 91—92°/0·001 mm., n_D^{15} 1·6160 (Found : N, 8·1. $C_{12}H_{11}N$ requires N, 8·25%), which slowly darkened. The *picrate* crystallised from ethanol as yellow prisms, m. p. 180—180·5° (Found : N, 14·4. $C_{12}H_{11}N,C_6H_3O_7N_3$ requires N, 14·1%).

p-2-*Pyridylbenzoic Acid*.—A solution of *p*-2-pyridyltoluene (8·55 g.) in hydrochloric acid (8·55 c.c.; 10N) and water (150 c.c.) was treated at 100° with powdered potassium permanganate (22·6 g.) during 0·5 hr. with vigorous stirring. Heating and stirring were continued for a further 0·5 hr., and the precipitate was then extracted repeatedly with boiling sodium carbonate solution. The combined extracts were extracted with ether (the non-acidic material gave a picrate, m. p. 180·5°, corresponding to 12% of *p*-2-pyridyltoluene), and concentrated *in vacuo*. Cautious acidification gave the acid (5·67 g., 60%), m. p. 232—232·5° (Butterworth, Heilbron, and Hey, *loc. cit.*, give m. p. 232°); the methyl ester (61%) had m. p. 97° [from light petroleum (b. p. 60—90°)].

p-2-*Pyridylbenzhydrazide*.—Methyl *p*-2-pyridylbenzoate (3 g.) and hydrazine hydrate (1 c.c.; 100%) were refluxed in ethanol (10 c.c.) for 6 hr. and then cooled. p-2-*Pyridylbenzhydrazide* (1·78 g., 59%) crystallised as glistening plates, m. p. 161·5° (Found : N, 19·8. $C_{12}H_{11}ON_3$ requires N, 19·7%). Some ester (0·74 g., 25%), m. p. 89—94°, was recovered.

N-*Benzenesulphonyl*-N'-p-2'-*pyridylbenzoylhydrazine*.—A mixture of the hydrazide (2·73 g.), dry pyridine (5 c.c.), and benzenesulphonyl chloride (1·77 c.c.) was set aside for 2 days, pyridine removed *in vacuo*, and the residue triturated with dilute ammonia giving the *hydrazine* (4·49 g., 96%) as prisms (from ethanol), m. p. 210° (decomp.) (Found : N, 12·0. $C_{18}H_{15}O_3N_3S$ requires N, 11·9%).

p-2-*Pyridylbenzaldehyde*.—(i) A mixture of the benzenesulphonylhydrazine (1·7 g.), anhydrous sodium carbonate (0·85 g.), and thiosemicarbazide (0·58 g.) in ethylene glycol (5 c.c.) was heated at 160° for 15 min. Dilution with water gave the *thiosemicarbazone* (0·31 g., 25%) as pale yellow microcrystals (from ethanol), m. p. 214—215° (decomp.) (Found : C, 60·65; H, 4·7; N, 21·4. $C_{13}H_{12}N_4S$ requires C, 60·9; H, 4·7; N, 21·85%).

(ii) Sulphuric acid (34 c.c.) was added dropwise with vigorous stirring to a solution of *p*-2-pyridyltoluene (22·4 g.) in acetic acid (230 c.c.) and acetic anhydride (230 c.c.), the temperature being kept below 10°. Chromic acid (40 g.) was added gradually at 5°, and the mixture was then stirred for a further hour below 10° and finally allowed to warm to 30° during 15 min. The viscous green mixture was treated with ice–water (1 l.), neutralised (ammonia solution), and filtered. Extraction of the filtrate gave more solid, the combined solids crystallising from aqueous ethanol as plates, m. p. 103—104°, of p-2-*pyridylbenzaldehyde diacetate* (7·07 g., 19%) (Found : C, 67·05; H, 5·15. $C_{16}H_{15}O_4N$ requires C, 67·35; H, 5·3%). Dilution of the combined mother liquors gave an oil which was purified *via* the bisulphite complex, from which p-2-*pyridylbenzaldehyde* (5·3 g., 20%) was obtained as glistening plates, m. p. 55° (from aqueous alcohol) (Found : C, 78·55; H, 4·95. $C_{12}H_9ON$ requires C, 78·65; H, 4·95%). The 2 : 4-*dinitrophenylhydrazone* formed red needles (from chlorobenzene), m. p. 254—255° (decomp.) (Found : C, 59·35; H, 3·7. $C_{18}H_{13}O_4N_5$ requires C, 59·5; H, 3·6%), and the thiosemicarbazone crystallised from ethanol as cream needles, m. p. 219° (decomp.), undepressed on admixture with the product obtained in (i).

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