ethanol in tufts of colorless needles; m.p. 152–155°, $[\alpha]_D^{25°}$ −61.9°.

Anal. Calcd. for $C_{24}H_{28}O_8Br_2$: C, 47.70; H, 4.67; Br, 26.45; CH_3O, 30.81. Found: C, 47.64 (A), 47.65 (B); H, 4.64 (A), 4.60 (B); Br, 26.42 (A), 26.02 (B); CH_3O, 30.76 (A), 30.46 (B).

(C) *Oxidation with nitric acid.* Dibromodimethyl lirioresinol-*B*, 140 mg., was added in small portions to 1.4 ml. of nitric acid (d. 1.42) at room temperature. The solution became dark violet in color and turned to an orange red after one hour. The mixture was then heated for an hour on a steam bath. Upon cooling, crystalline material separated, 2 vol. of water were added, and the mixture was filtered; yield of crude material, 53.3 mg. (34%) of 4-bromo-5,6-dinitropyrogallol trimethyl ether, m.p. 126–129°. After crystallization from 95% ethanol, the very light yellow needles melted at 133–134°.

The aqueous filtrate was combined with a corresponding filtrate obtained from lirioresinol-*A*, was neutralized with sodium bicarbonate, the solution was evaporated to dryness and extracted with ether to recover the bis(hydroxymethyl)-succinic acid dilactone. A very small yield was obtained, m.p. 158–160°, $[\alpha]_D^{26}$ +253° (water). The rotation was observed on 0.0029 g. of material in 3.0 ml. of solution and must be regarded as an approximation.

Preparation of syringaresinol. (A) *Crude almond emulsin.* Using the general procedure of Bourquelot,[21] 10.6 g. of crude emulsin was prepared from 340 g. of sweet almonds.

(B) *Enzymic synthesis of syringaresinol from syringin.* Using the general procedure of Freudenberg and Dietrich[10] 2.5 g. of syringin[22] was dissolved in 125 ml. of water, 0.1 g. of thymol and 0.25 g. of crude enzyme were added, and the mixture was incubated at 37°. An additional amount of 0.25 g. of the enzyme was added daily until a total of 2.0 g. had been added. Colorless crystals, m.p. 172–174°, began to form after five days, and the reaction was stopped after eleven days. The mixture was treated with 2–3 g. of "Fibra-Flo-C"[23] and filtered, the filter cake was washed with water, air dried, and extracted with chloroform at room temperature. Upon evaporation of the chloroform, crude syringaresinol was obtained; yield, 0.85 g. (60.2%). After two crystallizations from 95% ethanol, 0.57 g. of purified material was obtained, the main portion melted at 170–172° with a small amount melting at 176–178°. The product was optically inactive. In a second experiment the yield of crude syringaresinol after 17 days was 0.958 g. (68%). Freudenberg and Dietrich[10] obtained syringaresinol, m.p. 174–175° in a 66% yield after seven weeks.

The aqueous filtrate from the reaction mixture was extracted three times with chloroform; yield of oily material believed to be crude sinapyl alcohol, 0.46 g. (32.6%). The combined yield of syringaresinol and sinapyl alcohol was 92.8%.

Syringaresinol diacetate. The acetate was prepared from the lignan, acetic anhydride, and pyridine; colorless crystals m.p. 179–181°, from 95% ethanol. Freudenberg and Dietrich[10] reported the m.p. 181–183° for this derivative.

Hydrolysis of liriodendrin with crude almond emulsin. Using the above procedure, 0.5 g. of liriodendrin was dissolved in 125 ml. of water, 0.1 g. of thymol and 0.25 g. of the crude enzyme were added, and the mixture was incubated at 37°. More enzyme, 0.25 g., was added on the second, third, sixth, and fifteenth days; the reaction was stopped after twenty-three days. Filter aid was added, the filter cake was air dried and extracted with chloroform; yield of crude lirioresinol-*C*, 0.1565 g. (55%). After two crystallizations from 95% ethanol the lirioresinol-*C* melted 185–186°, $[\alpha]_D^{28}$ +48.9° (in chloroform). The infrared spectrum was nearly identical with that of syringaresinol (Fig. 1).

APPLETON, WIS.

(21) E. Bourquelot, *Archiv. Pharm.*, **245**, 172–180 (1907).

(22) Syringin was isolated from the bark of the common lilac by the general procedure of K. Freudenberg, R. Kraft, and W. Heimberger, *Chem. Ber.*, **84**, 472–476 (1951).

(23) Filter aid manufactured by Johns-Manville.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DE PAUL UNIVERSITY]

Racemic 2-Hydroxymethyl-2,3-dihydro-4*H*-pyran, a Model Carbohydrate[1]

ROBERT ZELINSKI,[2] ANTHONY VERBISCAR, AND HERMAN J. EICHEL

Received June 25, 1957

2-Hydroxymethyl-2,3-dihydro-1*4H*-pyran, a racemic dideoxyglucal, has been converted to 2,3,4-trideoxyaldohexose and its derivatives.

It has been demonstrated that 2,3-dihydro-4*H*-pyran can readily be converted to polydeoxyaldopentoses by hydration[3] and hydroxylation.[4] In similar manner, these glycal-like properties have now been extended to the formation of polydeoxyaldohexoses from 2-hydroxymethyl-2,3-dihydro-4*H*-pyran (II) with the ultimate, but as yet unrealized object, of synthesizing these in optically active forms of the D- or L-series.

The preparation of the precursor II, a racemic 3,4-dideoxyglucal, by reduction of 2,3-dihydro-4*H*-pyran-2-carboxaldehyde (I)[5] with aluminum alk-

(1) Abstracted from the senior thesis of Anthony Verbiscar (1951) and the master's thesis of Herman J. Eichel (1956). Part of this material has been reported at the Student Affiliate Symposium of the American Chemical Society, Chicago Section, in May 1951.

(2) Present address: 1653 S. Elm Avenue, Bartlesville, Okla.

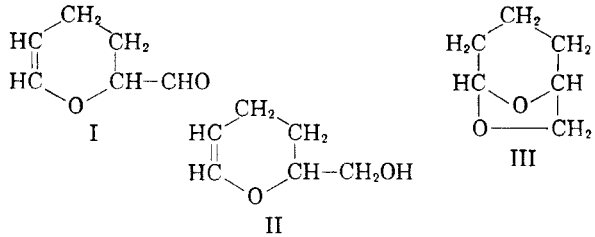
(3) L. E. Schniepp and H. H. Geller, *J. Am. Chem. Soc.*, **68**, 1646 (1946).

(4) C. D. Hurd and C. D. Kelso, *J. Am. Chem. Soc.*, **70**, 1484 (1948); C. D. Hurd and O. E. Edwards, *J. Org. Chem.*, **14**, 680 (1949); and C. D. Hurd, J. Moffat, and L. Rosnati, *J. Am. Chem. Soc.*, **77**, 2793 (1955).

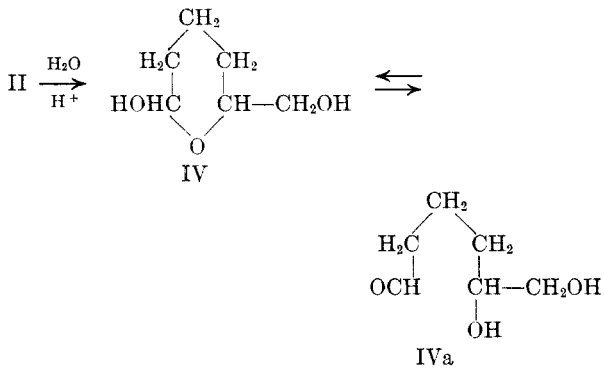
(5) K. Alder and E. Rüden, *Ber.*, **74**, 320 (1941); K. Alder, H. Offermans and E. Rüden, *Ber.*, **74**, 905 (1941). A sample of this compound, acrolein dimer, was generously supplied by the Shell Development Co., Emoryville, Calif.

oxide has been reported,[6] but a better laboratory procedure was desired. Accordingly, satisfactory procedures for the reduction of the carboxaldehyde (I) in 61–63% yield were devised with lithium aluminum hydride or, more conveniently and safely, with sodium borohydride as the reducing agent.

The 2-hydroxymethyldihydropyran (II) was stable in the absence of acid[7] but upon heating under reflux for an hour, half of it polymerized to undistillable material. The expected product was 6,8-dioxabicyclo[3.2.1]octane (III).[8]

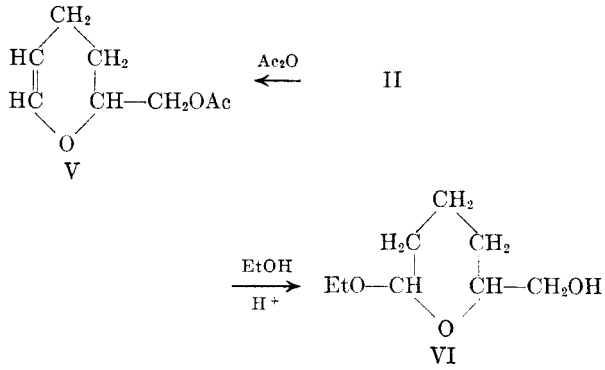


Compound II was stable in neutral or alkaline water solutions which failed to give a positive Benedict test. However, its sensitivity to acid was demonstrated by its ready reaction with 2,4-dinitrophenylhydrazine hydrochloride in 95% alcohol to form 5,6-dihydroxyhexanal 2,4-dinitrophenylhydrazone, probably *via* intermediate hydrolysis to a tautomeric mixture of racemic 5,6-dihydroxyhexanal and 2-hydroxymethyltetrahydropyran-2-ol (IV).



Dihydropyran is known to hydrolyze readily in dilute acid to a tautomeric mixture of tetrahydropyran-2-ol and 5-hydroxypentanal which either neat or in solution contains these substances in a ratio of about 95:5.[3,9] In like manner, 2-hydroxymethyltetrahydropyran almost immediately dissolved in very dilute acid to form a tautomeric mixture of 2-hydroxymethyltetrahydropyran-2-ol (IV) and 5,6-dihydroxyhexanal (IVa). As expected, infrared scanning of the hydrolysis product after neutralization and removal of water showed the presence of only a small carbonyl concentration. Although the tautomeric mixture could not be distilled, neturalization of the hydrolyzate and reduction with sodium borohydride gave 1,2,6-hexanetriol.[10] Both the hydrolysis mixture and the residue left by vacuum drying gave immediate Benedict and Schiff tests. With 2,4-dinitrophenylhydrazine both formed the compound we choose to call 5,6-dihydroxyhexanal 2,4-dinitrophenylhydrazone.

The racemic 3,4-dideoxyglucal (II) was readily acetylated in pyridine to the acetate V, racemic 6-*O*-acetyl-3,4-dideoxyglucal. Treatment with absolute ethanol and a trace of acid rapidly formed a mixture of 2-ethoxy-6-hydroxymethyltetrahydropyrans (VI) which may be described as racemic forms of ethyl 2,3,4-trideoxyaldohexopyranosides.



EXPERIMENTAL[11]

2-Hydroxymethyl-2,3-dihydro-4H-pyran (II). A mixture of 4.0 g. (0.11 mole) of lithium aluminum hydride and 90 ml. of anhydrous ethyl ether was stirred under nitrogen for 1 hr. A solution of 33.6 g. (0.30 mole) of 2,3-dihydro-4*H*-pyran-2-carboxaldehyde[5] in 25 ml. of ether was added dropwise with stirring in 2 hr. Fifteen minutes after addition was completed, 7.6 ml. (0.42 mole) of water was added, the first 0.5 ml. being introduced cautiously. The resultant gelatinous mixture was diluted somewhat with benzene, mixed with Super Cel or Celite and filtered. The filtrate was dried over sodium sulfate and distilled to give 20.7 g. (61 per cent) of II, b.p. 92–93°/25 mm., n_D^{25} 1.4757, n_D^{21} 1.4775 (lit.[4] b.p. 81–82°/13 mm., n_D^{20} 1.4848).

Anal. Calcd. for $C_6H_{10}O_2$: C, 63.13; H, 8.83. Found: C, 63.03; H, 8.52.

A safer and more convenient route to II involved the addition of a solution of 5.0 g. (0.18 mole) of sodium borohydride in 100 ml. of methanol to a chilled solution of 11.2 g. (0.10 mole) of the carboxaldehyde I in 150 ml. of methanol. Reaction temperature was allowed to rise to 30° during the 15-min. addition and was maintained there during 1 hr. of stirring. Most of the methanol was removed on the steam bath and 10 ml. of water was added to the residue which was then extracted with two 100-ml. portions of ether and one of benzene. The combined extract was dried and distilled to give 6.9 g. (62 per cent) of II, b.p. 100–103°/47 mm., n_D^{25} 1.4764. The infrared spectrum was

(6) H. Schulz and H. Wagner, *Angew. Chem.*, **62**, 105 (1950).

(7) A sample stored three years remained unchanged and had the same infrared spectrum as a freshly prepared sample.

(8) R. R. Whetstone, U. S. Patent **2,511,891** (June 20, 1950).

(9) C. D. Hurd and W. H. Saunders, *J. Am. Chem. Soc.*, **74**, 5324 (1952).

(10) R. Zelinski and H. J. Eichel, to be published.

(11) Analyses by Micro Tech Laboratories, Skokie, Ill.

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]

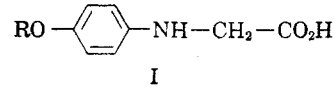
Tuberculostatic *N*-Arylglycines and Derivatives

N. B. TIEN, N. P. BUU-HOÏ, AND N. D. XUONG

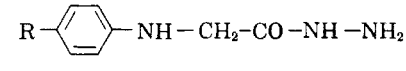
Received June 25, 1957

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.



I



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).