

mmoles) was dissolved in 20 ml. of 33% aqueous ethylamine and 10.8 ml. (5.4 mmoles) of a 1*N* iodine in potassium iodide solution was added dropwise with stirring in an ice bath. After an hour at room temperature, the reaction mixture was acidified at 0° with 20% aqueous acetic acid. The supernatant solution was decanted and the residual oil was

crystallized from acetic acid. It melted at 184–186° after recrystallization from acetic acid, reported² m.p. 220°.

Anal. Calcd. for $C_{14}H_{10}O_4I_2$: C, 27.03; H, 1.46; I, 61.22. Found: C, 27.51; H, 1.46; I, 61.04.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF LEPETIT S.P.A.]

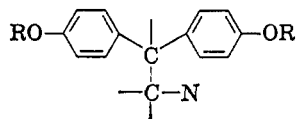
Bis(4-hydroxyphenyl)acetic Acid Derivatives

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Bis(4-hydroxyphenyl)acetic acid was obtained by a new synthesis from 4-hydroxy-4'-methoxydiphenylacetic acid. Some new derivatives of bis(4-acetoxyphenyl)- and bis(4-hydroxyphenyl)acetic acid are described.

A recent publication by M. H. Hubacher¹ on the synthesis of bis(4-hydroxyphenyl)acetic acid prompted us to publish the results of some work we carried out in this field and particularly the preparation of the above acid and of some derivatives of the same.² The purpose of our research was to obtain some amides of bis(4-hydroxyphenyl)acetic acid containing the structure



which, according to Schmidt and Seeger's observations³ is common to several substances having a particularly interesting laxative action.

Bis(4-hydroxyphenyl)acetic acid was obtained by Hubacher by direct condensation of glyoxylic acid with phenol and sulfuric acid and by demethylation with pyridinium chloride of bis(4-anisyl)acetic acid. In our new procedure, in which glyoxylic acid is not used, 4-hydroxy-4'-methoxydiphenylacetic acid⁴ is demethylated with 48% hydrobromic acid and glacial acetic acid by known methods⁵ to bis(4-hydroxyphenyl)acetic acid, the characteristics of which correspond to those described by Hubacher. 4-Hydroxy-4-methoxydiphenylacetic acid was prepared by condensing the cyanohydrin of anisaldehyde with phenol and sulfuric acid by a modification of a method described in the literature,⁶ and by subsequent alka-

line saponification of the 4-hydroxy-4'-methoxydiphenylacetonitrile obtained.

An attempt to condense the cyanohydrin of 4-hydroxybenzaldehyde with phenol, in order to avoid the subsequent demethylation, was unsuccessful as under the necessary reaction conditions sulfuric acid decomposes the cyanohydrin before it reacts with phenol. Bis(4-hydroxyphenyl)acetic acid was converted into the diacetyl ester and this latter into the acyl chloride from which, by reaction with different amines, the corresponding amides were prepared. The bis(4-acetoxyphenyl)acetamides were easily hydrolyzed to bis(4-hydroxyphenyl)acetamides. Bis(4-hydroxyphenyl)acetanilide and bis(4-hydroxyphenyl)acetomorpholide were converted also into bisphenylglyceryl ethers by reaction with glycerine α -chlorohydrin.

The substances listed in Table 1 were assayed for their laxative action, but found to be inactive.

EXPERIMENTAL

4-Hydroxy-4'-methoxydiphenylacetonitrile. The product, obtained according to Bistrzycki, *et al.*,⁶ after repeated experiments was always admixed with traces of colored impurities.⁷ We have found that by modifying as follows the reaction conditions, colorless 4-hydroxy-4'-methoxydiphenylacetonitrile is obtained in good yields.

In 720 g. of phenol heated to 50–60°, 450 g. of cyanohydrin of anisaldehyde⁴ was dissolved, the clear colorless solution was poured under strong stirring in 1860 ml. of 73% sulfuric acid at a temperature of 70–75°. The solution was then stirred for 10 min. at 100°. The reaction mixture, which during the addition became orange-red, after some minutes produced white-pink 4-hydroxy-4'-methoxydiphenylacetonitrile; it was cooled at about 40° and poured into 16 l. of water and ice. The white solid was collected on a Buchner, washed with water, and suspended in 5000 ml. of 2% sodium bicarbonate. After washing and filtering to neutral reaction with water the white product was crystallized from 75% acetic acid; yield 485 g. (73%) of 4-hydroxy-4'-methoxydiphenylacetonitrile, needles, m.p. 175–176°.

Bis(4-hydroxyphenyl)acetic acid. Four hundred and five grams of 4-hydroxy-4'-methoxydiphenylacetic acid obtained by alkaline hydrolysis of 4-hydroxy-4'-methoxy-

(1) M. H. Hubacher, *J. Org. Chem.*, **24**, 1949 (1959).

(2) The pharmacological properties of diethylaminoethyl-ester of bis(4-hydroxyphenyl)acetic acid were described by S. S. Libermann, *Farmakol. i. Toksikol.*, **19**(6), 10 (1956); *Chem. Abstr.*, **51**, 7587c (1957), but no reference was made to the synthesis of the compound.

(3) L. Schmidt and E. Seeger, *Arzneimittel-Forsch.*, **6**, 22 (1956).

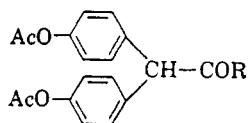
(4) O. E. Schultz and J. Schnekenburger, *Arch. Pharm.*, **291/63**, 362 (1958).

(5) R. Stoermer, *Ber. deut. chem. Ges.*, **41**, 323 (1908).

(6) A. Bistrzycki, J. Paulus, and R. Perrin, *Ber. deut. chem. Ges.*, **44**, 2596 (1911).

(7) R. Stoermer, *Ber. deut. chem. Ges.*, **44**, 1863 (1911).

TABLE I



| | R | M.P. | Yield, % | Formula | Calcd. | | | Found | | |
|-----|---|----------------------|-------------|--|--------|------|------|-------|------|------|
| | | | | | C | H | N | C | H | N |
| I | NH ₂ | 163-167 | 65 | C ₁₄ H ₁₇ O ₆ N | 66.05 | 5.24 | 4.28 | 66.35 | 5.35 | 4.11 |
| II | N $\begin{matrix} \diagup \text{CH}_3 \\ \diagdown \text{CH}_3 \end{matrix}$ | 129-133 | 70 | C ₂₀ H ₂₁ O ₆ N | 67.60 | 5.95 | 3.94 | 67.51 | 6.09 | 3.99 |
| III | NH-C ₆ H ₅ | 183-187 | 74 | C ₂₄ H ₂₁ O ₆ N | 71.45 | 5.25 | 3.45 | 71.63 | 5.55 | 3.20 |
| IV | -N $\begin{matrix} \diagup \text{CH}_2-\text{CH}_2 \\ \diagdown \text{CH}_2-\text{CH}_2 \end{matrix}$ CH ₂ | 166-169 | 81 | C ₂₃ H ₂₅ O ₆ N | 69.86 | 6.37 | 3.54 | 69.78 | 6.20 | 3.70 |
| V | -N $\begin{matrix} \diagup \text{CH}_2-\text{CH}_2 \\ \diagdown \text{CH}_2-\text{CH}_2 \end{matrix}$ O | 150-152 | 70 | C ₂₂ H ₂₃ O ₆ N | 66.50 | 5.83 | 3.52 | 66.82 | 6.15 | 3.54 |
| VI | NHC ₆ H ₄ OCH ₂ C ₆ H ₅ (p) | 204-209 ^a | 50 | C ₃₁ H ₂₇ O ₆ N | 73.07 | 5.33 | 2.67 | 72.82 | 5.77 | 2.76 |

^a From acetone

diphenylacetone nitrile⁴ was heated at reflux for 6 hr. with 4 l. of glacial acetic acid and 800 ml. of 48% hydrobromic acid. The solvent was removed *in vacuo* and the resinous residue, taken up with 2000 ml. of a saturated solution of sodium carbonate, yielded a white crystalline solid. The mixture was diluted with a small amount of water to obtain complete solution; it was washed with 1500 ml. of ether to extract the neutral fractions and the ether was discarded. The aqueous solution was acidified with 10% hydrochloric acid and the oil which separated was extracted three times with 1500 ml. of ether; the ether fractions were collected, washed until neutral, dried over sodium sulfate and evaporated to dryness. The semisolid residue was dissolved in 1000 ml. of water at 50-60°; on cooling 212 g. of crystalline bis(4-hydroxyphenyl)acetic acid monohydrate melting unsharply between 115° and 155° separated. By concentration of the mother liquors another crop of 100 g. with the same melting point was obtained. A sample was recrystallized from water.

Anal. Calcd. for C₁₄H₁₂O₄·H₂O: C, 64.13; H, 5.38. Found: C, 64.80; H, 5.54.

After drying for 2 hr. at 80° and 2 hr. at 110°/0.05 mm. the acid melted at 159-160°.

Anal. Calcd. for C₁₄H₁₂O₄: C, 68.85; H, 4.95. Found: C, 68.93; H, 5.30.

Methyl ester. Three and five-tenth grams of the acid was refluxed in 35 ml. of methanol in the presence of hydrogen chloride as a catalyst. After removal of the solvent the residue was recrystallized from a 50% water-methanol mixture; m.p. 151-153°.¹

The *ethyl ester* was similarly obtained; m.p. 166-167°¹ (ethanol).

The *hydrazide* was obtained as follows: 2.6 g. of the above methyl ester dissolved in 25 ml. of absolute methanol was boiled 2 hr. with 3.2 g. of 80% hydrazine hydrate. After concentration to a small volume and dilution with water the product (2 g.), crystallized from water and from ethanol, melted at 249-250°.

Anal. Calcd. for C₁₄H₁₄N₂O₄: C, 65.13; H, 5.45; N, 10.85. Found: C, 65.50; H, 5.65; N, 10.60.

Bis(3,5-dibromo-4-hydroxyphenyl)acetic acid. To a solution of 200 mg. of bis(4-hydroxyphenyl)acetic acid in 2 ml. of water an alcohol solution of bromine (2 ml. of bromine in 10 ml. of absolute ethanol) was added dropwise until no decoloration was observed. The separated white solid (300 mg.), crystallized from ethyl alcohol, melted at 239-244° dec.

Anal. Calcd. for C₁₄H₈Br₂O₄ (559.88): Br, 57.3. Found: Br, 56.85.

Bis(4-acetoxyphenyl)acetyl chloride. Twenty-five grams of bis(4-hydroxyphenyl)acetic acid were refluxed for 3 hr. with 250 ml. of acetic anhydride. The anhydride was completely removed by distillation *in vacuo* and the residue (26 g.), which did not crystallize from the usual solvents, was dissolved in 30 ml. of benzene and boiled for 2.5 hr. with 20 g. of thionyl chloride. The excess thionyl chloride was distilled *in vacuo* and the residue was washed several times with benzene; yield 26 g. of white crystals melting at 90-97°. On recrystallization from benzene, the melting point rose to 96-97°.

Anal. Calcd. for C₁₈H₁₅O₄Cl: C, 62.34; H, 4.36; Cl, 10.22. Found: C, 62.60; H, 4.51; Cl, 10.55.

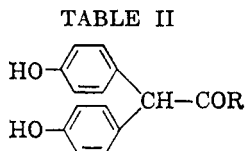
Bis(4-acetoxyphenyl)acetamides. General procedure. To 0.02 mole of bis(4-acetoxyphenyl)acetyl chloride dissolved in 180 ml. of ether a solution of 0.044 mole of amine in 20 ml. of ether was added dropwise at 0° taking care to avoid moisture.

The mixture was stirred for 5-10 min. and the crystalline precipitate was collected, washed with water, and crystallized from ethanol.

4-Hydroxyanilide of bis(4-acetoxyphenyl)acetic acid. Four and seven-tenth grams of benzyloxylanilide of bis(4-acetoxyphenyl)acetic acid (VI, Table I) dissolved in 100 ml. of absolute ethanol was hydrogenated with 0.5 g. of 5% palladium on charcoal under atmospheric pressure. After filtering off the catalyst, the solution was concentrated to a small volume to give 3.2 g. of a product melting at 163-166° (83%).

Anal. Calcd. for C₂₄H₂₁NO₆ (419.4): C, 68.73; H, 5.08; N, 3.30. Found: C, 68.51; H, 5.18; N, 3.48.

N-[Bis(4,4'-diacetoxyphenyl)-acetyl]-N-methylpiperazine hydrochloride. To 5.8 g. of N-methylpiperazine in 200 ml. of anhydrous ether a solution of 10 g. of bis(4-acetoxyphenyl)acetyl chloride in 500 ml. of ether was added in 15 min. The crystalline precipitate of piperazine hydrochloride was removed by filtration and in the ether solution concentrated to 400 ml. dry gaseous hydrochloric acid was bubbled. The hygroscopic hydrochloride was dried *in vacuo*, first at room temperature and then at 60-70°. A product (12 g.) melting at 105° was obtained. By recrystallization from acetone and immediately washing the crystalline precipitate with ether, 6 g. (47%) of a product are obtained. This, dried 12 hr. at 90° over phosphorus pentoxide, showed a melting point of 135° dec.



| | R | M.P. | Yield, % | Formulas | Calcd. | | | Found | | |
|------|---|---------|-------------|---|--------|------|------|-------|------|------|
| | | | | | C | H | N | C | H | N |
| VII | $\text{—N} \begin{cases} \text{CH}_3 \\ \text{CH}_3 \end{cases}$ | 238–241 | 86 | $\text{C}_{16}\text{H}_{17}\text{NO}_3$ | 70.83 | 6.38 | 5.16 | 70.61 | 6.42 | 4.99 |
| VIII | $\text{—NH—C}_6\text{H}_5$ | 210 | 95 | $\text{C}_{20}\text{H}_{17}\text{NO}_3$ | 75.25 | 5.37 | 4.37 | 75.60 | 5.63 | 4.45 |
| IX | $\text{—N} \begin{cases} \text{CH}_2\text{—CH}_2 \\ \text{CH}_2\text{—CH}_2 \end{cases} \text{O}$ | 218–220 | 95 | $\text{C}_{18}\text{H}_{19}\text{NO}_4$ | 69.00 | 6.25 | 4.41 | 69.17 | 6.37 | 4.30 |

Anal. Calcd. for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_5\text{Cl}$ (446): N, 6.27; Cl, 7.94; COCH_3 , 19.22; tert. N, 3.13. Found: N, 6.07; Cl, 7.96; COCH_3 , 18.9; tert. N, 3.33.

Bis(4-hydroxyphenyl)acetamides by hydrolysis of the corresponding bis(4-acetoxyphenyl)acetamides. General procedure. To 0.03 mole of the bis(4-acetoxyphenyl)acetamide dissolved in 250–300 ml. of methanol 72 ml. (0.18 mole) of 10% sodium hydroxide was added. After 1 hr. at room temperature with occasional stirring the solution was neutralized with 10% hydrochloric acid, diluted with 350 ml. of water and the methanol was removed *in vacuo*.

The crystalline product was collected and recrystallized from ethanol or ethanol-water mixture.

Bisglyceryl ether of bis(4-hydroxyphenyl)acetanilide. To a gently boiling solution of sodium ethoxide (from 7 ml. of absolute ethanol and 0.46 g. of metallic sodium) 3.19 g. of bis(4-hydroxyphenyl)acetanilide (VIII) dissolved in 9 ml. of absolute ethanol was added. After 10 min., 2.21 g. of glycerol- α -chlorohydrin were dropped in, the solution was refluxed for 1 hr., cooled, the sodium chloride formed was

filtered off and alcohol was removed by distillation. The resinous residue was taken up with ethyl ether giving a white amorphous solid (5.5 g., 95%) melting at about 100° dec.

Anal. Calcd. for $\text{C}_{28}\text{H}_{29}\text{NO}_7$: N, 2.99; OH, 14.54. Found: N, 2.97; OH, 14.32.

The bisglyceryl ether of bis(4-hydroxyphenyl)acetomorpholide (IX), similarly obtained, is a hygroscopic, very light violet solid melting at about 100° dec.

Anal. Calcd. for $\text{C}_{24}\text{H}_{31}\text{O}_8\text{N}$: N, 3.04; OH, 15.25. Found: N, 2.85; OH, 14.7.

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MILAN, ITALY

[CONTRIBUTION FROM THE PIONEERING RESEARCH DIVISION, TEXTILE FIBERS DEPARTMENT AND THE CENTRAL RESEARCH DEPARTMENT, E. I. DU PONT DE NEMOURS & CO., INC.]

Preparation of Some 9,10-Difunctional Derivatives of 9,10-Dihydro-9,10-ethanoanthracene^{1a}

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Two routes to 9,10-diamino-9,10-dihydro-9,10-ethanoanthracene (I. X = NH_2) have been developed, in which ethylene is added to simple difunctional anthracene derivatives. For example, ethylene was added to 9,10-dinitroanthracene and the resulting product (I. X = NO_2) was hydrogenated. The diamine was converted to the diol (I. X = OH) and other difunctional derivatives. These intermediates have been converted into condensation polymers. Certain of the derivatives of the diamines including polymers have been shown to liberate ethylene upon heating and to revert to anthracene derivatives.

The synthesis of condensation polymers with unusual properties has been facilitated by the development of low temperature techniques² which permit the use of a wide range of reactive intermediates.

(1) (a) Presented at 138th ACS National Meeting, Sept. 12, 1960, New York. (b) Present address: Department of Chemistry, Harvard University.

(2) E. L. Wittbecker and P. W. Morgan, *J. Polymer Sci.*, **40**, 289–297 (1959) and following papers.

As ethylene is known to add to the 9,10-positions of substituted anthracenes^{3–8} to give bridgehead

(3) C. L. Thomas, U. S. Patent **2,406,645**, August 27, 1946.

(4) J. S. Meek, V. C. Godefroi, and W. B. Evans, 123rd National Meeting of the American Chemical Society, Los Angeles, Calif., April 1953.

(5) S. J. Cristol and N. L. Hause, *J. Am. Chem. Soc.*, **74**, 2193 (1952).

(6) M. Wilhelm and D. Y. Curtin, *Helv. Chim. Acta*, **40**, 2129 (1957).