for 15 minutes with 2.5 l. of the following solution (A)[27]: 1.7 l. of ether, 550 cc. of benzene and 170 cc. of 90% ethanol. Aqueous ammonium hydroxide (1:1, 425 cc.) was then added and shaking was continued for 48 hours. The extract was decanted from the ground root, the latter was washed three times with 100-cc. portions of solution A and the shaking process was repeated twice with 1 l. each of solution A. The combined extracts and washings were dried over sodium sulfate and evaporated to dryness *in vacuo*.[28] The residue, dissolved in 200 cc. of benzene, was chromatographed on 75 g. of neutral alumina (activity II). The ether eluates, after crystallization from acetone, yielded 85 mg. of *γ-sitosterol*,[29] m.p. 147–148°, $[\alpha]^{25}D$ −46°; acetate, m.p. 139–140°, $[\alpha]^{25}D$ −46°; benzoate, m.p. 147–149°, $[\alpha]^{25}D$ −19°.

Anal. Calcd. for $C_{36}H_{54}O_2$: C, 83.34; H, 10.49. Found: C, 83.60; H, 10.35.

The pooled ether–chloroform eluates after crystallization from methanol yielded 117 mg. of **reserpine** with m.p. 262–263°, undepressed upon admixture with an authentic sample isolated from *R. serpentina* and kindly supplied by Dr. M. W. Klohs, $[\alpha]^{22}D$ −115°, λ_{max}^{EtOH} 268 mμ (log ε 4.15) and shoulder at 288–297 mμ (log ε 3.95), infrared spectrum[20] identical with that of an authentic specimen.

Anal. Calcd. for $C_{27}H_{22}N_2O_3(OCH_3)_6$: C, 65.11; H, 6.62; N, 4.60; methoxyl, 30.59; mol. wt.. 608. Found: C, 65.25; H, 6.42; N, 4.54; methoxyl, 29.83; mol. wt. (Rast), 619.

Hot Extraction. Isolation of Serpentine, Ajmaline and Sucrose.—The ground root (250 g.) was extracted continuously for 60 hours in an atmosphere of nitrogen in a Soxhlet apparatus with 2.5 l. of absolute methanol. Upon concentration of the extract to a volume of 150 cc., colorless crystals appeared which were filtered and washed with chloroform furnishing 0.43 g. of **sucrose**, m.p. 186°, identified by mixture melting point and infrared comparison. The filtrate was diluted with 300 cc. of amyl alcohol and concentration (at 18 mm.) was continued until no more methanol remained. The resulting suspension was filtered, the resinous precipitate having been discarded, and then concentrated to a thick sirup. This residue was leached several times with 5% hydrochloric acid, the acid extracts were made basic at 0° with ammonium hydroxide[30] and extracted exhaustively with chloroform. After drying and evaporation of the solvent, the residue (2.4 g.) was subjected to a ten-stage countercurrent distribution between 100 cc. each of chloroform and citrate-phosphate buffer (*p*H 6.6) with the following results:

Fraction	Wt., g.	Fraction	Wt., g.
0	0.65	6	0.05
1	.22	7	.035
2	.17	8	.09
3	.13	9	.205
4	.09	10	.63
5	.08		

The amorphous material in fractions 0 and 1 was triturated with 50 cc. of 10% acetic acid, filtered, the filtrate was made basic with ammonium hydroxide and again filtered. The ammoniacal solution was made strongly alkaline at 0° with 20% sodium hydroxide, the resulting precipitate was collected, taken up in chloroform, dried and the solvent was evaporated. Crystallization of the residue from absolute ethanol furnished 0.13 g. of bright yellow crystals of **serpentine**[23,25] with m.p. 156–157°; identity was established by mixture melting point and infrared comparison with an authentic specimen furnished by Dr. M. W. Klohs.

Trituration of fractions 2–5 with methanol resulted in slow crystallization and recrystallization of the solid from methanol yielded 0.053 g. of colorless crystals of **ajmaline**, m.p. 158–160°, identical in all respects (mixture m.p. and infrared spectrum) with an authentic sample.

(27) This is a modification of the solvent system given in the British Pharmaceutical Codex, Pharmaceutical Press, London, 1949, pp. 762–763.

(28) After removal of the solvent, a colorless solid was observed to sublime from the residual material. This proved to be acetamide, presumably an artifact of the isolation procedure.

(29) Reported (Elsevier's "Encyclopedia of Organic Chemistry," **14**, 91 (1940)): γ-sitosterol, m.p. 147–148°, $[\alpha]D$ −43°; acetate, m.p. 143–144°, $[\alpha]D$ −45.3°; benzoate, m.p. 152°, $[\alpha]D$ −19.6°.

(30) This treatment is not sufficient to liberate all of the serpentine.

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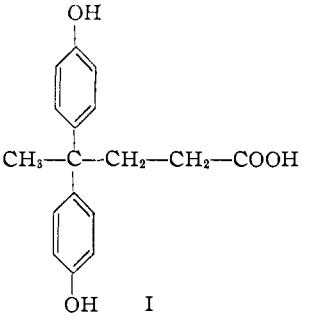
NOTES

γ,γ-Bis-(*p*-hydroxyphenyl)-valeric Acid

BY ALFRED R. BADER AND ANTHONY D. KONTOWICZ

RECEIVED APRIL 21, 1954

A study of the reaction of phenol with levulinic acid has shown that the condensation to yield the bisphenol I proceeds easily in the presence of acids such as sulfuric, hydrochloric and phosphoric; with polyphosphoric acid a mixture of condensation products and phenyl levulinate[1] results.



I

The bisphenol I is dimorphic; an amorphous modification forms crystalline solvates with aromatic hydrocarbons, and a crystalline, solvent-free modification melts at 171–172°.

Experimental

γ,γ-Bis-(*p*-hydroxyphenyl)-valeric Acid (I).—A cooled mixture of 94 g. (1 mole) of phenol, 58 g. (0.5 mole) of levulinic acid, 45 g. of water and 180 g. of concd. sulfuric acid was stirred at 25° for 20 hours. The reaction is slightly exothermic. The mixture was diluted with water and extracted with ethyl acetate. The organic solution was in turn extracted exhaustively with aqueous sodium bicarbonate, stripped and distilled to yield 20 g. of unreacted phenol. The almost colorless bicarbonate extract was acidified, extracted with ether and the washed ether extract stripped *in vacuo* to yield 87 g. (0.30 mole, 77% yield based on unrecovered phenol) of I, an almost colorless glass, m.p. *ca.* 90°, acid value found 192, calcd. 195.

(1) A. R. Bader and A. D. Kontowicz, THIS JOURNAL, **75**, 5416 (1953).

A similar yield of I is obtainable with a catalyst mixture of 75 cc. of concd. hydrochloric acid and 37 cc. of water, and a reaction temperature of 90–95°. With 85% phosphoric acid at 90–95° the yield is smaller and the product darker.

The amorphous product forms crystalline solvates with aromatic hydrocarbons. From benzene it crystallizes in flat, white needles, m.p. 120–122°; from toluene in stout needles, m.p. 108–109°; from *m*-xylene in flat needles, m.p. 96–98°. Removal of the solvent of crystallization *in vacuo* at 90° leaves the glass, m.p. *ca.* 90°. Crystallization of the benzene solvate from *m*-xylene yielded the *m*-xylene solvate.

Anal.[2] Benzene solvate: Calcd. for $C_{17}H_{18}O_4 \cdot {}^1/_2C_6H_6$: C, 73.82; H, 6.51. Found: C, 73.48; H, 6.62. Toluene solvate: Calcd. for $C_{17}H_{18}O_4 \cdot {}^1/_2C_7H_8$: C, 74.07; H, 6.67. Found: C, 74.44; H, 7.02.

After many unsuccessful attempts to obtain I crystalline and solvent-free, a large batch crystallized solvent-free from a mixture of toluene and acetone, m.p. 168–170°. It formed hard, white rosettes from water containing a trace of acetic acid, m.p. 171–172°, and could also be crystallized well from mixtures of heptane and ethyl acetate, or benzene and acetone. Hot solutions of the amorphous modification in aromatic hydrocarbons when seeded with solvent-free crystals, yielded the crystals, m.p. 171–172°, on cooling.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 70.99, 70.94; H, 6.62, 6.46.

$\lambda_{max}^{EtOH-0.1\% HOAc}$, mμ 225.0 (log *E* 4.20); 227.5 (infl., log *E* 4.18)
279.0 (log *E* 3.57); 282.5 (infl., log *E* 3.53)
λ_{min} 250.0 (log *E* 2.71)

The ultraviolet spectra of the solvates are very similar. The infrared spectrum of I in a nujol mull shows a strong band at 12.0 μ (indicative of *para* substitution), and no band at 13.2–13.4 μ.

Solvent-free, crystalline I forms a methyl ester which crystallizes from aqueous methanol with water of crystallization and melts at 87–89°.

Anal. Calcd. for $C_{18}H_{20}O_4 \cdot 3H_2O$: C, 61.00; H, 7.40. Found: C, 61.43; H, 7.60.

(2) Analyses by the Micro-Tech Laboratories, Skokie, Ill.

THE RESEARCH LABORATORIES
THE PAINT DIVISION
THE PITTSBURGH PLATE GLASS COMPANY
MILWAUKEE, WISCONSIN

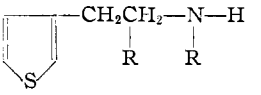
3-Substituted Thiophenes. VIII.[1] 3-Thienylalkylamines[2]

BY E. CAMPAIGNE AND WALTER C. MCCARTHY[3]

RECEIVED MAY 3, 1954

β-2-Thienylethylamine was shown to have vasopressor action by Tainter.[4] More recently, N-methyl-β-2-thienylethylamine and β-2-thienylisopropylamine and its N-methyl derivative were reported by Blicke and Burckhalter[5] to be semi-quantitatively similar to their phenyl analogs. Related compounds were the subject of a patent by Van Zoeren,[6] and pharmacological data have been reported by Warren, *et al.*,[7] and Alles and Feigen.[8]

We have prepared four β-3-thienylethylamines, I, in order to compare the physiological activity of these with the corresponding 2-thienyl and phenyl analogs. β-3-Thienylethylamine (Ia) was prepared in three different ways: Curtius degradation



I

a. R = R′ = H; b, R = H, R′ = CH_3; c, R = CH_3, R′ = H; d, R = R′ = CH_3

of β-3-thienylpropionic acid, reduction of ω-nitro-3-vinylthiophene with lithium aluminum hydride,[9] and reduction of 3-thienylacetonitrile with lithium aluminum hydride.[10] The second method proved best, affording a 74% yield of amine, in contrast to 53 and 50% yields by the other methods, respectively. N-Methyl-β-3-thienylethylamine (Ib) was obtained by lithium aluminum hydride reduction of N-methyl-3-thienylacetamide. The attempted methylation of N-benzal-β-3-thienylethylamine, according to the method of Decker and Becker,[11] gave only a trace of this secondary amine. Since reductive amination of 3-thienylacetone by the Leuckart reaction gave only an 11% yield of 1-(3-thienyl)-2-aminopropane (Ic), a second method, reduction of 1-(3-thienyl)-2-nitropropene with lithium aluminum hydride, was tried and an 85% yield of amine was obtained. The Leuckart reaction proved adequate for the preparation of 1-(3-thienyl)-2-methylaminopropane (Id).

In preliminary experiments by Dr. A. M. Lands, of the Sterling–Winthrop Research Institute, Ia was shown to have about $^1/_3$ the pressor potency of its phenyl analog by direct comparison, and an average potency of $^1/_{132}$ the assay dose of epinephrine. From this, it appears that the 3-thiophene isomer is about 3 to 4 times as active as the 2-isomer, which Tainter[4] reported to be about $^1/_{531}$ as active as epinephrine.

Experimental[12]

Diethyl 3-Thenylmalonate.—A procedure was used similar to that reported by Marvel[13] for the benzyl analog. From 1 l. of absolute ethanol, 47.5 g. (2.07 gram atoms) of sodium, 340 g. (2.12 moles) of diethyl malonate and 354 g. (2.0 moles) of 3-thenyl bromide,[14] a yield of 251 g. (48%) of a product boiling from 135° to 164° (4 mm.) was obtained. For analysis a sample was redistilled through a column. The major fraction distilled at 146° (3 mm.), $n^{20}D$ 1.4960, d^{20}_4 1.142.

Anal. Calcd. for $C_{12}H_{16}O_4S$: S, 12.51. Found: S, 12.51.

3-Thenylmalonic Acid.—Diethyl 3-thenylmalonate (48.7 g., 0.19 mole) was saponified by refluxing with a 20% aqueous solution of sodium hydroxide for six hours, and the reaction mixture was then acidified and extracted with ether. After evaporation of the ether and recrystallization of the crude product from benzene there were obtained 22.4 g. (59%) of white crystals, which melted at 138–139°. A second recrystallization from benzene raised the m.p. to 139–140° dec.

Anal. Calcd. for $C_8H_8O_4S$: S, 16.01. Found: S, 16.02.

β-3-Thienylpropionic Acid.—3-Thenylmalonic acid (22.4 g., 0.112 mole) was heated at 130 to 141° for one hour, until

(1) Contribution No. 632. For a previous paper in this series see E. Campaigne and P. A. Monroe, THIS JOURNAL, **76**, 2447 (1954).

(2) Taken from part of the thesis submitted by W.C.M. in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Indiana University, August, 1949.

(3) Sterling-Winthrop Fellow in Chemistry, 1948–1949.

(4) M. L. Tainter, *Quart. J. Pharm. Pharmacol.*, **3**, 584 (1930).

(5) F. F. Blicke and J. H. Burckhalter, THIS JOURNAL, **64**, 477 (1942).

(6) G. J. Van Zoeren, U. S. Patent 2,367,702; *C. A.*, **39**, 4195 (1945).

(7) M. R. Warren, D. G. Marsh, C. R. Thompson, R. S. Shelton and T. J. Becker, *J. Pharm. Exptl. Therap.*, **79**, 187 (1943).

(8) G. A. Alles and G. A. Feigen, *ibid.*, **72**, 265 (1941).

(9) *Cf.* R. T. Gilsdorf and F. F. Nord, *J. Org. Chem.*, **15**, 807 (1950).

(10) This reduction was reported recently by W. Herz, THIS JOURNAL, **73**, 351 (1951), in low yield.

(11) H. Decker and P. Becker, *Ann.*, **395**, 362 (1913).

(12) All melting points are uncorrected.

(13) C. S. Marvel, *Org. Syntheses*, **21**, 99 (1941).

(14) E. Campaigne and B. F. Tullar, *ibid.*, **33**, 96 (1953).