nite depression is observable it appears that an attempted identification by the use of these solids might lead too frequently to inconclusive results.

All melting points reported are corrected.

Experimental

Preparation of Olefins.—The olefins were prepared by coupling allyl bromide with the Grignard reagent prepared from the appropriate alkyl bromide, following the procedure of Wilkinson.[6] The olefins were ultimately purified by fractionation through a total condensation partial take-off column packed with glass helices.[7] The fraction boiling at the point tabulated by Doss[8] was retained for use. The styrene used was Eastman White Label quality, used without further treatment.

Preparation of 4-Mercaptobiphenyl.—The mercaptobiphenyl was obtained by the reduction of 4-biphenylsulfonyl chloride, prepared from biphenyl by previously recorded procedures.[9] Since we found no adequate description of the preparation of the mercaptan the details follow. In a one-liter Claisen flask were placed 120 g. of mossy zinc, 200 cc. of water, 12 g. of mercuric chloride, and 6 cc. of concentrated hydrochloric acid. The mixture was allowed to stand for a few minutes and the supernatant liquid decanted. To the amalgamated zinc were added 30 g. of biphenylsulfonyl chloride and 200 cc. of concentrated hydrochloric acid. The Claisen flask was attached to a 2-liter flask filled with constant boiling hydrochloric acid, serving as a steam generator, and to a 2-liter distilling flask cooled with a stream of water, serving as a condenser. Both the steam generator and the Claisen flask were heated to vigorous boiling. In this way the mercaptan distilled over as rapidly as it was formed. When the condenser flask became filled the heating was discontinued, the mercaptobiphenyl was filtered from the acid solution, 10 cc. of concentrated hydrochloric acid was added to the filtrate and the latter was used to recharge the steam generator. This reduced greatly the amount of acid used and simplified the purification of the mercaptan. Without any purification save washing free of acid, a pale yellow crystal, m. p. 107–110°, was obtained; yield of crude mercaptan 13.5 g., 61%. We found this product entirely satisfactory for the addition reactions. On recrystallization from alcohol or acetone a white crystal, m. p. 111°, can be obtained.

The Preparation of Alkylbiphenyl Sulfides: (a) Alkylation of 4-Mercaptobiphenyl.—A mixture of 0.5 g. of pure alkyl bromide, a slight excess of theoretical mercaptobiphenyl, and 3 cc. of alcohol were placed in a test-tube. To this was added a slight molar excess of 1 *N* alcoholic potassium hydroxide. The tube was heated in a beaker of water on a steam-bath for six hours. At the end of this time 5 cc. of boiling water was added to the test-tube. This mixture was heated to boiling for a few minutes and then chilled with vigorous shaking in a stream of water. This produced fine crystals which were removed by filtration and recrystallized from aqueous alcohol twice. The melting points are recorded in Table I.

(b) Addition of 4-Mercaptobiphenyl to Olefins.—The olefin (0.5–1 cc.) and the mercaptan (0.5 g.) and a few crystals of benzoyl peroxide were sealed in a soft glass semi-micro test-tube. The tube was placed in a flask of nitrobenzene and the nitrobenzene boiled under reflux for ten hours. The tube was removed, cooled, broken, and extracted with ether. The ether solution was washed with 20% sodium hydroxide. The ether was removed under reduced pressure and the residue dissolved in a minimum of acetone. The sulfide was precipitated by the dropwise addition of water. Two crystallizations from acetone usually were sufficient to give white crystals with a sharp melting point.

Summary

1. A satisfactory synthesis of 4-mercaptobiphenyl is described.

2. A series of biphenylalkyl sulfides has been prepared (a) by the addition of the mercaptan to an olefin, (b) by the reaction of the mercaptan with an alkyl bromide.

3. The melting points of these sulfides are given.

EMORY UNIV., GA. RECEIVED JUNE 28, 1944

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(6) Wilkinson, *J. Chem. Soc.*, 3057 (1931).

(7) Whitmore and Lux, THIS JOURNAL, **54**, 3451 (1932).

(8) Doss, "Physical Constants of the Hydrocarbons," fourth edition, The Texas Co., 1943.

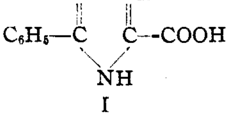
(9) Pollak, Heimberg-Krauss, Katscher and Lustig, *Monatsh.*, **55**, 358–378 (1930).

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

The Preparation of Certain Acids and Esters which Contain Phenylpyrryl Nuclei[1]

BY F. F. BLICKE, R. J. WARZYNSKI, J. A. FAUST AND J. E. GEARIEN

Some time ago we began a study of certain amines and amides which contained phenylpyrryl nuclei because it seemed that these substances might be of pharmacological interest. Among the intermediates required for the preparation of these compounds, which will be described in a later publication, were the following acids and their esters: 5-phenylpyrrole-2-carboxylic acid (I), 2-(5-phenyl)-pyrrylacetic acid (II), β-[2-(5-phenyl)-pyrryl]-propionic acid (III), the 1-methyl and 1-phenyl derivative of compound III, and 2-(4-phenyl)-pyrrylacetic acid (IV); 2-(3-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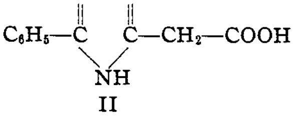
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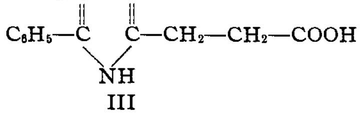
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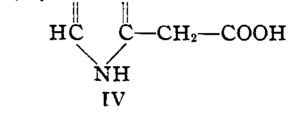
IV

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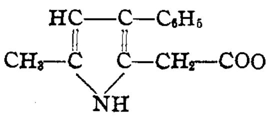
[1] We wish to express our indebtedness to the Board of Governors of the Horace H. Rackham School of Graduate Studies, Parke, Davis and Company and Eli Lilly and Company for their joint support of this project. Original manuscript received January 28, 1944.

phenyl-5-methyl)-pyrrylacetic acid was prepared only in the form of its ethyl ester (V).



V

Compound I was obtained by interaction of 5-phenylpyrrylmagnesium bromide with ethyl chloroformate, and subsequent hydrolysis of the ethyl 5-phenylpyrrole-2-carboxylate.

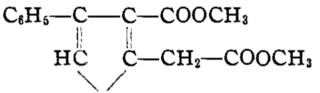
Ethyl 2-(5-phenyl)-pyrrylacetate was produced when 5-phenylpyrrole was allowed to react with ethyl diazoacetate; hydrolysis of the ester yielded compound II.

When phenacyllevulinic acid, $C_6H_5COCH_2CH_2$-$COCH_2CH_2COOH$, was heated on a steam-bath with ammonia water, and the mixture then acidified, compound III was obtained[2]; Robinson and Todd[3] synthesized this substance from phenacyllevulinic acid and ammonium acetate.

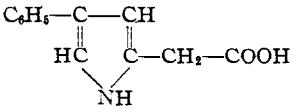
Phenacyllevulinic acid was prepared by hydrolysis of crude ethyl phenacyllevulinate, a black oil.[4] We found that when the crude ester was subjected to distillation under 4 mm. pressure, in an attempt to purify it, the oily distillate was not the original ester but was ethyl β-[2-(5-phenyl)-furyl]-propionate.

Reaction of phenacyllevulinic acid with methylamine and aniline, respectively, produced the 1-methyl and the 1-phenyl derivative of compound III.

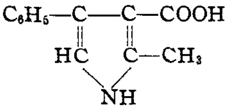
It was discovered that the dicarboxylic acid formed by hydrolysis of methyl 2-(3-carbomethoxy-4-phenyl)-pyrrylacetate[5] (VI), underwent partial decarboxylation during the hydrolytic process. The monocarboxylic acid obtained melted at 165–166°, and must possess structure IV since Knorr and Lange[6,7] found that the isomeric acid (VII) melted at 115°.



VI



IV (m. p. 165-166°)



VII (m. p. 115°)

Ethyl 2-(3-phenyl-5-methyl)-pyrrylacetate (V) was prepared by action of ethyl diazoacetate on 3-phenyl-5-methylpyrrole.[6]

Experimental Part

5-Phenylpyrrole-2-carboxylic Acid (I).—A mixture of 94 g. of the crude ester, 450 cc. of alcohol, 73.4 g. of potassium hydroxide and 45 cc. of water was refluxed for three hours. The alcohol and water were removed under reduced pressure on a steam-bath. The pasty residue was triturated with 300 cc. of water, and the insoluble 5-phenylpyrrole (31 g.) removed by filtration through a coarse Jena filter. The phenylpyrrole was washed three times with 100-cc. portions of water, filtered and the filtrate added to the original filtrate. The red-brown solution of the potassium salt of the desired acid was cooled and treated with sulfuric acid (1:4) until the solution was only slightly alkaline. The solution was decanted from the black, gummy precipitate (which was discarded), stirred with Norite at room temperature, and filtered. The filtrate was treated again with Norite. The light brown solution was acidified with dilute sulfuric acid, and the precipitated acid filtered, washed with water and dried; yield 27.9 g. The product was stirred with 950 cc. of 2% sodium bicarbonate solution, filtered and the filtrate acidified with dilute sulfuric acid. The precipitated, cream-colored acid weighed 22 g.; m. p. 206–208° (dec.) after several recrystallizations from alcohol.

Anal. Calcd. for $C_{11}H_9O_2N$: N, 7.48. Found: N, 7.31.

Ethyl 2-(5-Phenyl)-pyrrylacetate.—A mixture of 57.3 g. of 5-phenylpyrrole and 1.3 g. of copper powder (copper metal Merck) was placed in a 200-cc. wide-mouth Erlenmeyer flask and heated in a bath to 125° (thermometer in the pyrrole). Then 45.6 g. of ethyl diazoacetate was dropped into the mixture during a two-hour period. As soon as the evolution of nitrogen began, the temperature was lowered to 95–100°. The mixture was shaken occasionally. After all of the nitrogen had been evolved, the material was heated for one hour longer, cooled, 100 cc. of ether added, the material filtered, the ether removed and the residue distilled. The following fractions were collected: 9 g. of phenylpyrrole, b. p. 155–195° (1–2 mm.); 35 g. of ester the major portion of which boiled at 208–213° (1–2 mm.); 28 g. of material, the nature of which was unknown, b. p. 220–280° (1–2 mm.).

The ester, a yellow oil, was analyzed:

Anal. Calcd. for $C_{14}H_{15}O_2N$: N, 6.11. Found: N, 6.19.

2-(5-Phenyl)-pyrrylacetic Acid (II).—A mixture of 34.4 g. of the ester, 175 cc. of alcohol, 17 cc. of water and 25.3 g. of potassium hydroxide was refluxed for three hours, cooled and the partially precipitated potassium salt filtered and washed with alcohol. It was dissolved in 50 cc. of water, the solution acidified with dilute sulfuric acid and the precipitated acid treated with 945 cc. of 2% sodium bicarbonate solution. The solution was stirred with Norite, filtered and the colorless filtrate acidified. The colorless, crystalline acid weighed 8.2 g.; m. p. 144–145° (dec.). The melting point was not changed by recrystallization from 33% alcohol. The acid slowly turns pink when exposed to the air.

A further amount of the acid was obtained from the original filtrate. After removal of the water and alcohol under reduced pressure, the red, pasty residue was triturated with 75 cc. of water and filtered through a Jena filter. The filtrate was acidified with dilute sulfuric acid, the red precipitate treated with 945 cc. of 2% sodium carbonate solution, filtered and the material then treated in the manner described above. There was obtained 6.5 g. of acid which melted at 142–145° (dec.). The total yield was 14.7 g. (49%).

Anal. Calcd. for $C_{12}H_{11}O_2N$: N, 6.96. Found: N, 6.73.

β-[2-(5-Phenyl)-pyrryl]-propionic Acid (III).—A slow stream of ammonia was passed into a solution, prepared from 23.4 g. of phenacyllevulinic acid[8] and 125 cc. of 28%

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[2] Kehrer (*Ber.*, **35**, 2010 (1902)) stated that he prepared compound III in this manner but reported no experimental details.

[3] Robinson and Todd, *J. Chem. Soc.*, 1743 (1939).

[4] Kehrer and Igler, *Ber.*, **32**, 1176 (1899); Kehrer, *ibid.*, **34**, 1263 (1901).

[5] Knorr and Lange, *ibid.*, **35**, 3004 (1902).

[6] Knorr and Lange, ref. 5, p. 3003.

[7] Ehrenstein, *Ber.*, **64**, 1140 (1931); Sonn, *ibid.*, **68**, 151 (1935).

[8] Kehrer, *ibid.*, **34**, 1263 (1901). The required furfuralacetophenone was prepared according to the directions of Drake and Gilbert (This Journal, **52**, 4965 (1930)).

ammonia water, while it was heated on a steam-bath for five hours. After dilution with 100 cc. of water, the mixture was acidified with dilute sulfuric acid (1:4), and the almost colorless, crystalline product filtered and washed with water; yield 20.7 g. (96%). The acid was recrystallized from chloroform; m. p. 140–141°.[9]

Ethyl β-[2-(5-Phenyl)-furyl]-propionate.—When we attempted to purify the crude, oily black ethyl phenacyllevulinate[10] by distillation, a yellow oil, ethyl β-[2-(5-phenyl)-furyl]-propionate, was obtained which boiled at 167–168° (4 mm.).[11] The hydrazide, prepared from the ester, melted at 109–110°[12] after recrystallization from water. The crude β-[2-(5-phenyl)-furyl]-propionic acid, obtained by hydrolysis, melted at 113–115°.[13]

β-[2-(1-Methyl-5-phenyl)-pyrryl]-propionic Acid.—(a) A mixture of 46.8 g. of phenacyllevulinic acid and 100 cc. of aqueous methylamine (40%) was placed in a 500-cc. round-bottom flask fitted with a condenser and a dropping funnel. After the material had been heated for one hour on a steam-bath, an additional 150 cc. of aqueous methylamine was added during the course of two hours. The mixture was heated for seven hours longer, cooled, diluted with 200 cc. of water, and acidified with dilute sulfuric acid. The precipitated propionic acid (45.5 g. or 99%) was washed with water, and recrystallized from alcohol; m. p. 169–170°.

(b) Seven grams of phenylacyllevulinic acid and 41 g. of methylammonium acetate[14] were placed in a flask and heated on a sand-bath for thirty minutes at 140–150° (thermometer in mixture). The clear, red solution was cooled somewhat, poured into 100 cc. of water, the product filtered (6.7 g. or 97%) and recrystallized from alcohol; m. p. 169–170°.

Anal. Calcd. for $C_{14}H_{15}O_2N$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.27; H, 6.64; N, 6.06.

Methyl β-[2-(1-Methyl-5-phenyl)-pyrryl]-propionate.—After 22.9 g. of the propionic acid, 9.8 g. of concd. sulfuric acid and 250 cc. of absolute methyl alcohol had been heated on a steam-bath for six hours, about 175 cc. of alcohol was removed and 400 cc. of water was added. The oily precipitate was extracted with ether, the aqueous layer saturated with salt and also extracted with ether. The combined ether layers were shaken with dilute sodium bicarbonate solution, dried with fused sodium sulfate, and the solvent removed. The crystalline residue weighed 23.3 g. (96%); m. p. 51–52° after recrystallization from methyl alcohol.

Anal. Calcd. for $C_{15}H_{17}O_2N$: C, 74.04; H, 7.04; N, 5.75. Found: C, 74.31; H, 7.10; N, 5.57.

β-[2-(1,5-Diphenyl)-pyrryl]-propionic Acid.—The method described below is simpler than that employed by Holdsworth and Lions.[15]

A mixture of 23.4 g. of phenacyllevulinic acid and 93 g. of aniline was heated at 100° for twenty minutes, cooled and poured into 100 cc. of concd. hydrochloric acid which had been diluted with 600 cc. of water. The material was stirred and the precipitated acid filtered and washed with water; yield 28.5 g. (98%); m. p. 172–173°. After recrystallization from alcohol the acid melted at 173–174°.[16]

The ethyl ester, obtained in 96% yield according to the method described in the literature,[15] melted at 102–103°.

2-(4-Phenyl)-pyrrylacetic Acid (IV).—Methyl 2-(3-carbomethoxy-4-phenyl)-pyrrylacetate was obtained when 17.1 g. of ω-aminoacetophenone hydrochloride,[17] 17.4 g. of dimethyl acetone dicarboxylate,[18] 14.0 g. of sodium acetate ($3H_2O$) and 100 cc. of 75% acetic acid were heated for eight hours on a steam-bath; yield 11.5 g. (42%) after recrystallization from methyl alcohol; m. p. 137–138°.[19]

Seven grams of the ester, 16 g. of potassium hydroxide and 60 cc. of alcohol were refluxed for three hours, the alcohol removed, the residue treated with water, the mixture filtered, and the filtrate acidified with dilute sulfuric acid. The precipitated 2-(4-phenyl)-pyrrylacetic acid was recrystallized from water; yield 3.0 g. (58%); m. p. 165–167°.

Anal. Calcd. for $C_{11}H_{10}N(COOH)$: neut. equiv., 201. Calcd. for $C_{11}H_9N(COOH)_2$: neut. equiv., 122. Found: neut. equiv., 198.

Methyl 2-(4-Phenyl)-pyrrylacetate.—Ten grams of the acetic acid, 100 cc. of absolute alcohol and 5 cc. of concd. sulfuric acid were refluxed for six hours. Alcohol was distilled from the mixture until a precipitate began to form. The mixture was then cooled, the ester filtered and recrystallized from methyl alcohol; yield 6 g. (56%); m. p. 125–127°.

Anal. Calcd. for $C_{13}H_{13}O_2N$: C, 72.56; H, 6.05; N, 6.51. Found: C, 72.23; H, 6.15; N, 6.35.

Ethyl 2-(3-Phenyl-5-methyl)-pyrrylacetate (V).—The required 3-phenyl-5-methylpyrrole was obtained in the following manner. A mixture of 22.9 g. of 3-phenyl-4-carboethoxy-5-methylpyrrole,[20] 39.5 g. of potassium hydroxide and 200 cc. of alcohol was refluxed for eight hours. The precipitated potassium carbonate was removed by filtration, the alcohol evaporated, and 75 cc. of water added to the residue. The product was extracted with ether, the ether solution dried with magnesium sulfate, and the solvent removed. The pyrrole boiled at 175–177° (18 mm.)[21]; yield 10 g. (63%).

Ten grams of 3-phenyl-5-methylpyrrole and 0.3 g. of copper bronze were heated to 100° (bath temperature) in an oil-bath; 5.5 g. of ethyl diazoacetate was added dropwise while the mixture was stirred. The temperature of the mixture should be kept below 110° during the addition. The material was heated at 100° for one-half hour, cooled, extracted with ether, the solvent removed and the residue distilled. The acetate boiled at 225–227° (4 mm.); yield 4.5 g. (38%).

Anal. Calcd. for $C_{15}H_{17}O_2N$: C, 74.07; H, 6.99; N, 5.76. Found: C, 73.82; H, 7.10; N, 5.89.

Summary

Preparative procedures for the following acids and their esters have been described: 5-phenylpyrrole-2-carboxylic acid, 2-(5-phenyl)-pyrrylacetic acid, β-[2-(5-phenyl)-pyrryl]-propionic acid, the 1-methyl and 1-phenyl derivative of the latter, 2-(4-phenyl)-pyrrylacetic acid, and 2-(3-phenyl-5-methyl)-pyrrylacetic acid; the latter acid was obtained only in the form of its ethyl ester.

ANN ARBOR, MICHIGAN RECEIVED JULY 25, 1944

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[9] Kehrer (ref. 8) reported the same melting point.

[10] Kehrer and Igler, *Ber.*, **32**, 1176 (1899); Kehrer, *ibid.*, **34**, 1263 (1901).

[11] Robinson and Todd (ref. 3) found 165-167° (2-3 mm.).

[12] The reported melting point (ref. 3) is 110°.

[13] The melting point in the literature (ref. 2) is 116°.

[14] Gibbs, THIS JOURNAL, **28**, 1409 (1906).

[15] Holdsworth and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **70**, 431 (1937).

[16] Holdsworth and Lions found 175°.

[17] Mannich and Hahn, *Ber.*, **44**, 1542 (1911).

[18] "Organic Syntheses," Coll. Vol. I, 10 (second edition). The dimethyl ester was prepared according to the procedure described in "Organic Syntheses" (Coll. Vol. I, 237, second edition) for the diethyl ester. See also Haller and Held, *Ann. chim. phys.*, [6] **23**,165 (1891).

[19] Knorr and Lange (ref. 5) were the first to use this procedure. They found the melting point to be 126°, and did not report their yield.

[20] Ref. 5, p. 3003.

[21] Ehrenstein (*Ber.*, **64**, 1140 (1931)) found 175° (25 mm.), and Sonn (*ibid.*, **68**, 151 (1935)) reported 178-181° (15 mm.). See also ref. 5.