without appreciably affecting the rate of formation of benzene. Biphenyl seems to be formed by coupling of adsorbed phenyl radicals on a specific surface in the absence of a more adequate source of hydrogen.

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Arsenoso Derivatives of Phenyl-substituted Fatty Acids[1]

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The substitution of an acidic group in arsenosobenzene or its derivatives generally inhibits the activity and decreases the potential therapeutic utility of this class of compound.[4] An exception has been found in γ-(*p*-arsenosophenyl)-butyric acid which possesses marked trypanocidal activity and has undergone extensive therapeutic trial.[5] This unusual activity is not shown by the homologous *p*-arsenosophenylacetic and β-(*p*-arsenosophenyl)-propionic acids.

The present paper describes the preparation and properties of two higher homologs, one isomer and one derivative of γ-(*p*-arsenosophenyl)-butyric acid, as well as two other acid-substituted derivatives of arsenosobenzene.

For the preparation of several of these compounds, the *p*-nitro- and *p*-aminophenyl derivatives of the corresponding fatty acids were required as intermediates. The method of Van der Scheer[6] was previously used in this Laboratory for the preparation of γ-(*p*-nitrophenyl)- and γ-*p*-aminophenyl)-butyric acids, necessary for the synthesis of γ-(*p*-arsenosophenyl)-butyric acid.[7] The nitration procedure gave poor yields, probably due to oxidation of the side chain at the temperature employed. In an attempt to improve the yield, γ-phenylbutyric acid was nitrated under a variety of conditions. The most satisfactory yield was obtained by a procedure described in the Experimental Part. This procedure was also used for the nitration of δ-phenylvaleric acid. An improved method for the reduction of these nitro compounds to the desired amino compounds is also described.

For the preparation of *m*-arsonocinnamic acid the Scheller reaction was used.[8] The remaining arsonic acids were synthesized by the method of Palmer and Adams.[9] Since *p*-arsonomandelic acid was obtained as a sirup, which could not be crystallized, it was converted to the disodium salt which was readily crystallized from alcohol.

The arsenoso compounds were prepared by reduction of the corresponding arsonic acids with sulfur dioxide and hydriodic acid in the presence of hydrochloric acid, followed by hydrolysis of the resulting dichloroarsines with sodium bicarbonate. We were unable to isolate *p*-arsenosomandelic and γ-(2-amino-4-arsenosophenyl)-butyric acids because of their solubility in water. Therefore these two compounds were isolated as the dichloroarsines and neutralized in solution just prior to therapeutic testing.

The chemotherapeutic activity of these compounds has been reported previously.[5,10] δ-(*p*-Arsenosophenyl)-valeric acid was one-half as active against *T. equiperdum* as γ-(*p*-arsenosophenyl)-butyric acid, while none of the remaining compounds possessed any appreciable activity.

Experimental Part

δ-Phenylvaleric Acid.—This compound has previously been described by Ali, *et al.*,[11] but no yield was reported. Using a somewhat similar procedure[12] we reduced γ-benzoylbutyric acid to the desired compound, which was purified by distillation under reduced pressure. The yield was 63%; b. p. 164–168° (5 mm.); m. p. 51–53° (cor.).

ε-Phenylcaproic Acid.—The method used for the preparation of this compound differed from that previously described by Grateau[13] in that δ-benzoylvaleric acid, rather than the corresponding ethyl ester, was reduced by the Clemmensen method.[12] The yield was 86%; b. p. 165° (1 mm.); f. p. 10–11°.

Nitration of γ-Phenylbutyric Acid.—γ-Phenylbutyric acid (140 g.) was added in small portions to 250 ml. of fuming nitric acid (d. 1.50) which was maintained at a temperature between −20 and −30° by means of an alcohol-Dry Ice-bath. The time of addition was two to three hours and the mixture was stirred mechanically throughout this period. A further 10 ml. of acid was then used to wash down the sides of the reaction vessel and the temperature was kept at −10° for a further one-half hour. The clear solution was poured into a four-liter beaker filled with cracked ice. The oil which precipitated solidified on standing for fifteen minutes. The mixture was allowed to stand in the ice-box overnight after which the solid was removed by filtration and washed with cold water.

(1) Paper X in the series entitled "The Preparation of Phenylarsenoxides"; previous paper, THIS JOURNAL, **67**, 719 (1945).

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(4) Gough and King, *J. Chem. Soc.*, 669 (1930); Eagle, Hogan, Doak and Steinman, *J. Pharmacol.*, **70**, 221 (1940).

(5) Eagle, Hogan, Doak and Steinman, *Pub. Health Rep.*, **59**, 765 (1944); Eagle, *ibid.*, **61**, 1019 (1946).

(6) Van der Scheer, THIS JOURNAL, **56**, 744 (1939).

(7) Doak, Steinman and Eagle, *ibid.*, **62**, 3012 (1940).

(8) Doak, *ibid.*, **62**, 167 (1940).

(9) Palmer and Adams, *ibid.*, **44**, 1356 (1922).

(10) Eagle, *J. Pharmacol.*, **85**, 265 (1945).

(11) Ali, Desai, Hunter and Muhammad, *J. Chem. Soc.*, 1013 (1937).

(12) Martin, Clemmensen method III in "Organic Reactions," Vol. I, John Wiley and Sons, New York, N. Y., p. 166.

(13) Grateau, *Compt. rend.*, **191**, 947 (1930).

TABLE I

ARSONO-, ARSENOSO- AND DICHLOROARSINO- PHENYL SUBSTITUTED FATTY ACIDS

Acid R = Arsono[a]	M. p.,[b] °C.	Yield, %	Formula	As analyses,[c] % Calcd.	Found
p-R-mandelic- (di-sodium salt)		43	$C_8H_9AsNa_2O$	23.4	23.5
α-(*p*-R-phenyl)-butyric	148–149	25	$C_{10}H_{13}AsO_5$	24.5	24.8
m-R-cinnamic	>360	44	$C_9H_9AsO_5$	27.5	27.3
γ-(2-Nitro-4-R-phenyl)-butyric[d]	262	68	$C_{10}H_{12}AsNO_7$	22.5	22.4
γ-(2-Amino-4-R-phenyl)-butyric[e]	309.5 (decomp.)	81	$C_{10}H_{14}AsNO_5.H_2O$	23.3	23.5
δ-(*p*-R-phenyl)-valeric	204	62	$C_{11}H_{15}AsO_5$	24.8	25.2
ε-(*p*-R-phenyl)-caproic	146–150	38	$C_{12}H_{17}AsO_5$	23.7	23.4
R = Arsenoso[f]					
m-R-cinnamic	>360	97	$C_9H_7AsO_3$	31.5	31.0
α-(*p*-R-phenyl)-butyric	Softens at 258	13	$C_{10}H_{11}AsO_3.H_2O$	27.5	27.5
δ-(*p*-R-phenyl)-valeric	>360	53	$C_{11}H_{13}AsO_3$	26.2	26.2
ε-(*p*-R-phenyl)-caproic	>360	66	$C_{12}H_{15}AsO_3.H_2O$	25.0	25.2
R = Dichloroarsino[g]					
p-R-mandelic	167	60	$C_8H_7AsCl_2O_3$	25.2	25.4
γ-(2-Amino-4-R-phenyl)-butyric, hydrochloride[h]	163–164	27	$C_{10}H_{12}AsCl_2NO_2.HCl$	20.8	20.7

[a] Water was used as the solvent in the recrystallization of all arsonic acids. [b] The melting points were determined by the method described in paper VI of this series, Steinman, Doak and Eagle, THIS JOURNAL, 66, 192 (1944), or by the method of Morgan and Hamilton, *ibid.*, 66, 874 (1944). [c] All analyses are the average of two or more determinations. [d] Calcd : N, 4.21. Found: N, 4.21. [e] Calcd.: N, 4.36. Found: N, 4.44. [f] The arsenoso compounds were obtained in an amorphous form and could not be crystallized from common solvents. [g] The dichloroarsines were obtained in crystalline form by solution in water, followed by the addition of concentrated hydrochloric acid. [h] Calcd.: N, 3.89. Found: N, 3.86.

It was then recrystallized twice from benzene. The yield of pure γ-(*p*-nitrophenyl)-butyric acid was 74 g. (42%); m. p. 93°. From the benzene mother liquors, a solid was obtained which melted at 55–56° after repeated recrystallization from benzene. Oxidation of this fraction with alkaline permanganate gave a mixture of *o*- and *p*-nitrobenzoic acids (52% of the para isomer) which were easily separated by their differential solubility, and were identified by mixed melting points with authentic samples of the two substances. No attempt was made to further separate the two isomeric nitrophenylbutyric acids.

δ-(*p*-Nitrophenyl)-valeric Acid.—δ-Phenylvaleric acid (58.9 g.), nitrated by the above procedure, gave 29.0 g. (40%) of pure δ-(*p*-nitrophenyl)-valeric acid after three recrystallizations from benzene. It was obtained as light-yellow hexagonal needles; m. p. 83.8–84.4° (cor.). The structure was proved by oxidation to *p*-nitrobenzoic acid with alkaline permanganate.

Anal. Calcd. for $C_{11}H_{13}NO_4$: N, 6.28; neut. equiv., 223. Found: N, 6.04; neut. equiv., 224.

ε-(*p*-Nitrophenyl)-caproic Acid.—The above nitration procedure yielded an oil which could not be crystallized; accordingly the procedure of Van der Scheer[6] was used for the preparation of this compound.

γ-(*p*-Aminophenyl)-butyric Acid.—The corresponding nitro acid (20.9 g.) was dissolved in 25 ml. of alcohol and reduced catalytically at 40 lb. gage pressure, using Raney nickel as catalyst. The reduction was rapid and complete. After recrystallization from water, the amino compound (16.1 g., 90%) melted at 130–131° (cor.).

δ-(*p*-Aminophenyl)-valeric Acid.—This compound was prepared in 93% yield by a similar procedure. It crystallized from water in white needles; m. p. 111–112.3° (cor.).

Anal. Calcd. for $C_{11}H_{15}NO_2$: N, 7.25; neut. equiv., 193.2. Found: N, 7.18, 7.04; neut. equiv., 193.4.

ε-(*p*-Aminophenyl)-caproic Acid.[6]—Catalytic reduction of the corresponding nitro acid gave this compound in 67% yield; m. p. 105–107° (cor.).

α-(*p*-Aminophenyl)-butyric Acid.—Catalytic reduction gave the amino compound in 75% yield; m. p. 142° (cor.). It has previously been prepared by Fourneau and Sandulesco who used a different procedure.[14]

***p*-Aminomandelic Acid.**—Catalytic reduction of *p*-nitromandelic acid with Raney nickel as catalyst gave a red product, insoluble in acids, which was not further characterized. The desired amino compound was obtained by the method of Heller.[15]

γ-(2-Nitro-4-arsonophenyl)-butyric Acid.—γ-(*p*-Arsonophenyl)-butyric acid (14.4 g., 0.05 mole) was added in small portions to 16 ml. of concentrated sulfuric acid maintained at −10°. When no undissolved material remained, 3.8 g. of fuming nitric acid (sp. gr. 1.5) were added dropwise. The solution was stirred for one-half hour and then placed in a bath at 36°. The temperature of the mixture rose to 42°, then fell to bath temperature. After being stirred a further fifteen minutes it was poured onto ice. An oil separated which quickly solidified. The crude material as recrystallized from hot water.

γ-(2-Amino-4-arsonophenyl)-butyric Acid.—Catalytic reduction of the above nitro compound, using Raney nickel as catalyst, was not successful. The nitro compound was reduced by the method of Jacobs, Heidelberger and Rolf.[16] The resulting amino compound was recrystallized from alcohol and then from water. It crystallized with one molecular equivalent of water of crystallization.

Summary

Several new arsenoso derivatives of phenyl-substituted fatty acids have been prepared. None of these compounds possess the unusual trypanocidal activity of γ-(*p*-arsenosophenyl)-butyric acid. Improvements in the preparation of the latter compound are also described.

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(14) Fourneau and Sandulesco, *Bull. soc. chim.*, [4] **41**, 450 (1927).

(15) Heller, *Ber.*, **46**, 280 (1913).

(16) Jacobs, Heidelberger and Rolf, THIS JOURNAL, **40**, 1580 (1918).