TABLE I

N-BENZOYLAMINO ACIDS FROM BENZONITRILE AND UNSATURATED ACIDS AND ESTERS, AND HYDROXY ESTERS

Starting compound	Formula of product	M. p., °C.[a]	Yield, %	Nitrogen, % Calcd.	Found
β,β-Dimethylacrylic acid	$C_{12}H_{15}O_3N$	141–142[b]	72	6.33	6.49
Ethyl β-hydroxy-β-methylbutyrate	$C_{12}H_{15}O_3N$	141–142.5	62	..	..
Ethyl β-hydroxy-β-methylvalerate	$C_{13}H_{17}O_3N$	103–104.5	76.5	5.99	5.82
Ethyl β-hydroxy-β-methylcaproate	$C_{14}H_{19}O_3N$	76–78	72	5.62	5.77
Ethyl β-hydroxy-β-methylcaprylate	$C_{17}H_{25}O_3N$[c]	113.5–114	67	4.81	4.49
Ethyl β-ethyl-β-hydroxyvalerate	$C_{14}H_{19}O_3N$	125–126.5	78	5.62	5.66
Ethyl α-ethyl-β-methylbutenoate	$C_{14}H_{19}O_3N$	108–109.5	72	5.62	5.70
Ethyl β-hydroxy-α-isopropyl-β-methylbutyrate	$C_{17}H_{25}O_3N$[d]	99–100	62	4.81	4.65
Ethyl β-hydroxy-α,α,β-trimethylbutyrate	$C_{14}H_{19}O_3N$	150–152	80	5.62	5.47
Ethyl 1-hydroxycyclopentylacetate	$C_{14}H_{17}O_3N$	185–187	40	5.66	5.51
Ethyl α-(1-hydroxycyclopentyl)-propionate	$C_{15}H_{19}O_3N$	133–134	44	5.36	5.47
Ethyl 1-hydroxycyclohexylacetate	$C_{15}H_{19}O_3N$	167–168	65	5.36	5.37
Ethyl α-(1-hydroxycyclohexyl)-propionate	$C_{16}H_{21}O_3N$	160–161.5	58	5.09[e]	4.94
Ethyl β-hydroxy-β-methyl-γ-phenylbutyrate	$C_{18}H_{19}O_3N$[f]	179–181	9	4.71	4.32
Ethyl cinnamate	$C_{16}H_{15}O_3N$[g]	195–196	26	5.20	5.23
Methyl undecylenate	$C_{18}H_{27}O_3N$[h]	103–105	16	4.59	4.56

[a] All melting points uncorrected. [b] Slimmer[4a] reported m. p. 141.5°. [c] *p*-Tolunitrile used in place of benzonitrile in this experiment. Calcd.: C, 70.1; H, 8.7. Found: C, 70.6; H, 8.7. [d] Isolated as the ethyl ester since standard alkaline hydrolysis failed. Calcd.: C, 70.1; H, 8.7. Found: C, 70.3; H, 8.9. [e] Calcd.: C, 69.8; H, 7.7. Found: C, 69.7; H, 7.6. [f] Crude acid dissolved in benzene and reprecipitated with hexane. Recrystallized from benzene–ethanol. Calcd.: C, 72.7; H, 6.4. Found: C, 72.7; H, 6.6. [g] Posner[4b] reported m. p. 194–196°. Excess cinnamic acid removed by dissolving in hot benzene. Residue dissolved in alkali, reprecipitated with acid and recrystallized from water. [h] Saponification mixture acidified with acetic acid; crude acid recrystallized twice from diisopropyl ether–acetone and finally from benzene. Calcd.: C, 70.8; H, 8.9. Found: C, 70.9; H, 8.7.

orated to dryness under reduced pressure. The residue was washed from the flask with 30 ml. of absolute ethanol and allowed to stand overnight. The mixture was filtered and the precipitate dried for two weeks under vacuum, then two hours at 110°; yield 0.50 g. (32%), m. p. 215–217°. Slimmer[4a] reported the melting point of β-valine to be 217° (cor.).

Anal. Calcd. for $C_5H_{11}O_2N$: N, 12.0. Found: N, 12.0.

The absolute alcohol filtrate was diluted with 200 ml. of ether, allowed to stand overnight and filtered. The white solid obtained after drying and heating melted at 205–207° and weighed 0.47 g.

β-Amino-α-ethyl-β-methylbutyric Acid.—This material was obtained from 3.0 g. (0.0120 mole) of β-benzoylamino-α-ethyl-β-methylbutyric acid by hydrolysis with barium hydroxide as described above; yield, 0.40 g. (23%), m. p. 228–229°.

Anal. Calcd. for $C_7H_{15}O_2N$: N, 9.65. Found: N, 9.41.

Summary

The preparation of a number of benzoylamino acids by the interaction of benzonitrile with certain unsaturated acids and esters and hydroxy esters, has been described.

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[CONTRIBUTION FROM THE P. R. INDUSTRIAL DEVELOPMENT LABORATORY AT THE UNIVERSITY OF PUERTO RICO]

Nitric Acid Oxidation of 2,4:3,5-Dimethylene-D-gluconic Acid; Some Derivatives of 2,4-Methylene-D-glucarolactone-3,6

BY I. A. COLÓN, R. FERNÁNDEZ-GARCÍA, LUIS AMORÓS AND HILDA BLAY

In a previous communication[1] from this Laboratory a modification of Zief and Scattergood's preparation of 2,4:3,5-dimethylene-D-gluconic acid was recorded. This paper deals with the nitric acid oxidation of dimethylene-D-gluconic acid as well as with the preparation and properties of derivatives of monomethylene glucarolactone, the oxidation product.

The oxidation of 2,4:3,5-dimethylene-D-gluconic acid was carried out with concentrated nitric acid. No spontaneous reaction could be noticed when dilute nitric acid was used at room temperature. Using the minimum amount of concentrated nitric acid required to dissolve all the dimethylene gluconic acid, a yield of 56% of the theoretical amount was obtained. A higher proportion of concentrated nitric acid led to slightly higher yields (67%).

The oxidation product crystallized directly from the reaction solution on cooling. The physical properties of this substance and of its monoethyl ester, dimethyl ester, monomethyl ester and diamide agreed with the values reported[2,3] for 2,4-methylene-D-glucarolactone-3,6 and its corresponding derivatives.

The stability of the 2,4-methylene acetal ring

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(1) Colón, Fernández, Amorós and Blay, THIS JOURNAL, **71**, 1493 (1949).

(2) Henneberg and Tollens, *Ann.*, **292**, 40 (1896).

(3) Haworth and Jones, *J. Chem. Soc.*, 66 (1944).

TABLE I

PHYSICAL AND ANALYTICAL DATA FOR THE N,N'-SUBSTITUTED 2,4-METHYLENE-D-GLUCARODIAMIDES

Amide	Yield, %	M. p., °C.	$[\alpha]_D$	Temp., °C.	c	Formula	Analyses, %					
							Carbon		Hydrogen		Nitrogen	
							Calcd.	Found	Calcd.	Found	Calcd.	Found
Diamide	77	226 (dec.)	+52.0	30.4	2.16	$C_7H_{12}N_2O_6$	...	..	...	...	12.7	12.4
Methyl	69	224 (dec.)	+59.2	29.2	1.22	$C_9H_{16}N_2O_6$	43.5	43.5	6.4	6.4	11.3	11.0
Ethyl[a]	87	177.2–177.8	+54.1	26.8	1.78	$C_{11}H_{22}N_2O_7$	44.9	44.7	7.5	7.1	9.5	9.4
Isopropyl	73	213.4–214.6	+49.7	27.2	1.24	$C_{13}H_{24}N_2O_6$	51.2	51.3	7.9	8.0	9.2	9.0
Butyl[b]	48	202.8–203.4	+48.1	30.6	0.90	$C_{15}H_{30}N_2O_7$	51.4	51.7	8.6	8.3	8.0	8.1
Isobutyl	37	227.2–229.4	+51.5	27.2	0.80	$C_{15}H_{28}N_2O_6$	54.2	54.4	8.4	8.2	8.4	8.1
Allyl	68	169.5–170.0	+43.5	28.2	1.97	$C_{13}H_{20}N_2O_6$	52.0	51.7	6.7	6.5	9.0	8.9
β-Hydroxyethyl	68	163.0–164.6	+53.7	29.2	2.53	$C_{11}H_{20}N_2O_8$	42.9	42.5	6.5	6.6	9.1	8.5
Cyclohexyl	40	243.2–244.4	+49.7	27.4	0.55	$C_{19}H_{32}N_2O_6$	59.4	59.3	8.3	8.2	7.3	7.5

[a] A sample of 80.42 mg. lost on heating *in vacuo* at 100°, 4.96 mg.; calculated for such sample of $C_{11}H_{20}N_2O_6 \cdot H_2O$, 4.87 mg. [b] A sample of 87.93 mg. lost on heating *in vacuo* at 100°, 4.52 mg.; calculated for such sample of $C_{15}H_{28}N_2O_6 \cdot H_2O$, 4.52 mg.

in boiling concentrated nitric acid was surprising even though the limited acetolysis of methyl 2,4:3,5-dimethylene-D-gluconate has been shown[4] to result in the cleavage of only the 3,5-methylene acetal ring. The acetolysis reaction was tried on methyl 2,4-methylene-D-glucarolactone-3,6 and on dimethyl 2,4-methylene-D-glucarate at 0° for forty-five minutes. The monomethyl ester was subjected to a similar treatment with propionic acid–propionic anhydride mixture. The 2,4-methylene acetal ring was not cleaved in any of the three cases as shown by the formation of N,N'-dimethyl-2,4-methylene-D-glucarodiamide.

Some N,N'-disubstituted 2,4-methylene-D-glucarodiamides have been prepared which appear to be new; their properties are listed in Table I.

Experimental

Oxidation of 2,4:3,5-Dimethylene-D-gluconic Acid.—The reaction was carried out in a fume hood. In a 1.5-l. beaker 408 g. (1.86 moles) of dimethylenegluconic acid[1] was placed and 650 ml. of concentrated nitric acid added. After ten–fifteen minutes the mixture started to react and the temperature increased steadily to about 100°; a violent evolution of oxides of nitrogen was produced. The solid did not dissolve completely and the temperature started to decrease; 70 ml. of concentrated nitric acid was added and after a few minutes the solid dissolved so that a clear solution was obtained at the end of the reaction (one hour). On cooling a white crystalline precipitate was formed. The crude product was filtered, washed with 100 ml. of cold water, and dried under reduced pressure; m. p. 170–172°. The yield of the partially hydrated substance was (232 g.) 56% of the theoretical amount. The acid was recrystallized from methanol and dried *in vacuo* at 100°; m. p. 177.6–178.2; neutral equivalent found 201, calculated for $C_7H_8O_7$: 204; $[\alpha]^{28.6}_D$ + 121 (*c*, 2.22; water), in close agreement with the values reported by Henneberg and Tollens[2] and by Haworth and Jones[3] for 2,4-methylene-D-glucarolactone-3,6. The monoethyl, monomethyl and dimethyl esters were prepared and their physical properties found to be in close agreement with the values reported.[3] The diamide was obtained from the ethyl ester.

Anal. Calcd. for $C_7H_{12}O_6N_2$: N, 12.7. Found: N, 12.4.

Using essentially the same procedure, 440 g. of dimethylenegluconic acid treated with 1260 ml. of concentrated nitric acid produced 297 g. (67%) of monomethylene glucarolactone.

N,N'-Disubstituted 2,4-Methylene-D-glucarodiamides.—Through a suspension of 0.02 mole of ethyl ester of monomethylene glucarolactone in methanol at 0° was passed enough of the freshly distilled amine to dissolve the ester. Any undissolved residue was filtered out and the solution allowed to stand at 5–10° for twenty-four hours. The first crop of crystalline amide was filtered out and washed with ether; on adding ether to the mother liquor further crops were obtained. The crude amides were recrystallized from methanol–ether except the N,N'-di-β-hydroxyethyl amide which was recrystallized from methanol. Specific rotations were determined in methanol as solvent for all the diamides except the unsubstituted diamide and N,N'-di-β-hydroxyethyl amide in which cases water was used as solvent. The specific rotations as well as concentrations and temperatures are indicated in Table I. All the diamides were found to be insoluble in benzene and ether but soluble in methanol except the unsubstituted diamide and N,N'-di-β-hydroxyethyl amide. All were found to be insoluble in water except N,N'-di-β-hydroxyethyl amide. The N,N'-diethyl and N,N'-dibutyl amides were obtained as hydrates.

Dimethyl 3,5-Diacetyl-2,4-methylene-D-glucarate.—To an ice-cold mixture of 35 ml. of acetic anhydride, 15 ml. of glacial acetic acid and 1 ml. of concentrated sulfuric acid, 4.7 g. (0.019 mole) of dimethyl 2,4-methylene-D-glucarate[3] was added. The mixture was shaken for forty-five minutes at 0°. It dissolved completely when shaken at room temperature for fifteen minutes. The solution was poured into a beaker containing 400 g. of ice. Seventy grams of sodium bicarbonate was added to nearly neutralize the solution; the precipitate was filtered and upon recrystallizing from benzene–petroleum ether it melted at 87.8–89.2°. The solid was soluble in benzene in which it showed a specific rotation $[\alpha]^{25.6}_D$ −15.5° (*c*, 2.67; benzene). The yield was (2.8 g.) 44% of the theoretical amount.

Anal. Calcd. for $C_{13}H_{18}O_{10}$: C, 46.7; H, 5.4. Found: C, 47.1; H, 5.4.

N,N'-Dimethyl-2,4-methylene-D-glucarodiamide from Dimethyl 3,5-Diacetyl-2,4-methylene-D-glucarate.—Methylamine was bubbled through a solution of 0.5 g. of dimethyl 3,5-diacetyl-2,4-methylene-D-glucarate in 25 ml. of methanol at 0° until the theoretical amount had dissolved. The solution was left overnight at 5–10°. A white precipitate was formed when ether was added; m. p. 219–220° (dec.) and a specific rotation $[\alpha]^{28.2}_D$ + 62.3 in methanol (*c*, 1.13), these data being in agreement with those previously found for the N,N'-dimethyl-2,4-methylene-D-glucarodiamide obtained by the action of methylamine on ethyl ester of monomethyleneglucarolactone. A mixed melting point determination with N,N'-dimethyl-2,4-methylene-D-glucarodiamide from this source showed no depression.

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[4] Mehltretter, Mellies and Rist, THIS JOURNAL, **70**, 1064 (1948).

Methyl-5-acetyl-2,4-methylene-D-glucarolactone-3,6.—To an ice-cold mixture of 20 ml. of acetic anhydride, 8 ml. of glacial acetic acid and 0.5 ml. of concentrated sulfuric acid, 2.6 g. (0.012 mole) of methyl 2,4-methylene-D-glucarolactone-3,6[3] was added. The mixture was shaken for forty-five minutes at 0°. The solid dissolved and almost immediately a white precipitate was formed. It was filtered, washed with water and recrystallized from hot water. The yield was (2.1 g.) 68% of the theoretical amount; m. p. 190.6°–192°; $[\alpha]^{27.2}\mathrm{D}$ + 133 (c, 1.99; acetone).

Anal. Calcd. for $C_{10}H_{12}O_8$: C, 46.1; H, 4.6. Found: C, 46.1; H, 4.7.

N,N'-Dimethyl-2,4-methylene-D-glucarodiamide from Methyl-5-acetyl-2,4-methylene-D-glucarolactone-3,6.—In 30 ml. of ice-cold methanol 2.1 g. (0.008 mole) of methyl-5-acetyl-2,4-methylene-D-glucarolactone-3,6 was suspended. Methylamine was passed through the mixture until the solid dissolved. The solution was allowed to stand at 5–10° overnight. A white precipitate (0.5 g.) was formed; m. p. 217–218° (dec.). The filtrate was evaporated to dryness and crude product was recrystallized from methanol–ether. The yield was (2.1 g.) 95% of the theoretical amount; m. p. 223–224° (dec.) and a specific rotation $[\alpha]^{26.6}\mathrm{D}$ + 60.0° in methanol (c, 0.69), these data being in agreement with those previously found for the N,N'-dimethyl-2,4-methylene-D-glucarodiamide obtained by the action of methylamine on ethyl ester of monomethyleneglucarolactone. A mixed melting point determination with N,N'-dimethyl-2,4-methylene-D-glucarodiamide from this source showed no depression.

Methyl-5-propionyl-2,4-methylene-D-glucarolactone-3,6.—To an ice-cold mixture of 35 ml. of propionic anhydride, 15 ml. of propionic acid and 1 ml. of concentrated sulfuric acid, 5.0 g. (0.023 mole) of methyl 2,4-methylene-D-glucarolactone-3,6 was added. The mixture was shaken for forty-five minutes at 0°. The solid dissolved and almost immediately a white precipitate was formed. It was filtered, washed with water and ether and recrystallized from hot water. The yield was (5.0 g.) 79% of the theoretical amount; m. p. 164.6–165.8°; $[\alpha]^{28.6}\mathrm{D}$ + 153° (c, 2.06; chloroform).

Anal. Calcd. for $C_{11}H_{14}O_8$: C, 48.2; H, 5.1. Found: C, 48.2; H, 5.3.

N,N'-Dimethyl-2,4-methylene-D-glucarodiamide from Methyl-5-propionyl-2,4-methylene-D-glucarolactone-3,6.—In 15 ml. of ice-cold methanol 0.6 g. of methyl 5-propionyl-2,4-methylene-D-glucarolactone-3,6 was suspended. Methylamine was passed through the mixture until the solid dissolved and the solution allowed to stand at 5–10° overnight. A white precipitate was formed; m. p. 223° (dec.). The crude product was recrystallized from methanol–ether and the specific rotation determined in methanol $[\alpha]^{27.2}\mathrm{D}$ + 61.7° (c, 1.03); these data are in agreement with those previously found for the N,N'-dimethyl-2,4-methylene-D-glucarodiamide obtained by the action of methylamine on ethyl ester of monomethyleneglucarolactone. A mixed melting point determination with N,N'-dimethyl-2,4-methylene-D-glucarodiamide from this source showed no depression.

Summary

1. The nitric acid oxidation of 2,4:3,5-dimethylene-D-gluconic acid has been shown to yield 2,4-methylene-D-glucarolactone-3,6 in 67% yield.
2. An attempted controlled acetolysis of dimethyl-2,4-methylene-D-glucarate and of methyl 2,4-methylene-D-glucarolactone-3,6 did not remove the 2,4-methylene acetal ring.
3. Some N,N'-disubstituted-2,4-methylene-D-glucarodiamides have been prepared which appear to be new.

RIO PIEDRAS, PUERTO RICO RECEIVED APRIL 7, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF LOUISVILLE SCHOOL OF MEDICINE]

Some N-Aminophenylarsanilic Acids

BY ROBERT L. MCGEACHIN

Since it was found recently that Melarsen,[1,2] a diamino triazino derivative of *p*-arsanilic acid, is an effective trypanocidal agent, it was decided to study the preparation of some N-aminophenylarsanilic acids.

Barber[3] condensed 3-nitro-4-chlorophenylarsonic acid with certain aromatic amines to give N-phenylarsanilic acids but no studies on the condensation of dinitrochlorobenzene with *p*-arsanilic acid have been made. However, Linke[4] condensed dinitrochlorobenzene with *p*-aminobenzoic acid and Kogan, Voronov and Lyubiteleva[5] condensed dinitrochlorobenzene with *p*-aminophenol-3,5-disulfonic acid.

Heating *p*-arsanilic acid and 2,4-dinitrochlorobenzene in 5% aqueous sodium hydroxide for seven hours proved to be an unsatisfactory method since excessive hydrolysis of the 2,4-dinitrochlorobenzene to 2,4-dinitrophenol occurred under these conditions. Sodium acetate and calcium carbonate (in aqueous alcohol medium) were found to be satisfactory condensing agents, however, with the latter the better of the two since it produced less by-products than the sodium acetate and gave better yields of N-2,4-dinitrophenylarsanilic acid. N-2,4-Diaminophenylarsanilic acid was prepared from this dinitro compound.

It was found that 3-nitro-4-chlorophenylarsonic acid would react with *p*-aminodimethylaniline and *p*-aminodiethylaniline under conditions outlined by Barber[3] to give N-4-dimethylaminophenyl-3-nitroarsanilic acid and N-4-diethylaminophenyl-3-nitroarsanilic acid. Attempts to reduce the nitro groups in these compounds to amino groups were unsuccessful, however, presumably due to the instability of the products formed.

Experimental

N-2,4-Dinitrophenylarsanilic Acid (I). **A.**—Six grams of *p*-arsanilic acid, 5 g. of 2,4-dinitrochlorobenzene and

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[1] Friedheim, THIS JOURNAL, **66**, 1775 (1944).

[2] Banks, *et al.*, *ibid.*, **66**, 1771 (1944).

[3] Barber, *J. Chem. Soc.*, 471 (1929).

[4] Linke, *J. prakt. Chem.*, **91**, 202 (1915).

[5] Kogan, Voronov and Lyubiteleva, *Anilinokrasochnaya Prom.*, **3**, 153 (1933).