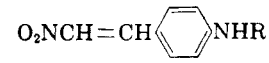
duced. The specificity of this reaction for morpholine and piperidine has already been observed.[4]

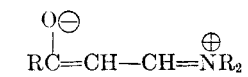
While all of the evidence cited supports the aminonitroethylene structure, there is another possible structure which should be considered. If reaction occurred in the aromatic nucleus rather than on the nitrogen atom,[5] the product would be a 4-alkylamino-β-nitrostyrene (IV). Since aromatic amines are known to undergo nuclear substitution



IV

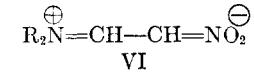
by carbonyl compounds under acidic conditions, the production of this type of compound is not impossible. However, three pieces of evidence argue against this formulation. First, the infrared spectrum of the materials obtained show no bands attributable to an NH group. No NH group is present in the aminonitroethylene structure (II) but there is one in the nitrostyrene structure (IV). Secondly, alkaline hydrolysis of the product of the nitromalonaldehyde - methylaniline reaction produced methylaniline, the product to be expected from the aminonitroethylene, and not *p*-methylaminobenzaldehyde, the hydrolysis product of the nitrostyrene. Finally the ultraviolet spectrum of 4-dimethylamino-β-nitrostyrene, a good model of the nitrostyrenes, has been measured[6] and is quite different from the spectra of the products obtained in this study: λ_{max} 262, 435 mμ; ϵ_{max}. 10,250, 28,500 resp. (This nitrostyrene is bright red as compared to the yellow products obtained here.)

An interesting feature of the infrared spectra of all these compounds is the complete absence of any band in the 1500–1600 cm^{-1} region which might be assigned to the nitro group. A similar situation has been encountered with the infrared spectra of β-amino-α,β-unsaturated ketones[7] in which the carbonyl frequency was lowered considerably. This lowering was attributed to the contribution of structures such as V to the ground state of the



V

molecule. In the present case a similar structure (VI) may be written for the aminonitroethylenes.



VI

The contribution of structures such as VI to the ground state of the aminonitroethylene molecule renders unambiguous assignment of the 1625 cm^{-1} band impossible. It may be associated with the carbon-carbon double bond or a carbon-nitrogen double bond. A detailed spectroscopic study of compounds containing this unique structural unit has been made and will be reported.[8]

(5) This possibility was suggested by a referee.

(6) Drain and Wilson, *J. Chem. Soc.*, 767 (1949).

(7) Cromwell, Miller, Johnson, Frank, and Wallace, *J. Am. Chem. Soc.*, **71**, 3337 (1949).

EXPERIMENTAL

1-(N-Phenyl-N-methylamino)-2-nitroethylene. A solution of 5.4 g. (0.05 mole) of N-methylaniline in 17 ml. of 3 *N* hydrochloric acid was added all at once to a solution of 8.3 g. (0.053 mole) of sodium nitromalonaldehyde[9] in 50 ml. of water. The mixture was warmed on the steam-bath to hasten the separation of a brown oily product. When separation was complete (30–60 minutes), the mixture was cooled and extracted with 50 ml. of benzene. This extract was dried over sodium sulfate and then was treated with Norit to give a yellow solution which was concentrated to 20 ml. Addition of petroleum ether to this solution while it was immersed in an ice-bath caused crystallization of the product; yield 4.3 g. (48%),[10] m.p. 93–94°. Recrystallization from benzene-petroleum ether gave an analytical sample, m.p. 93.5–94.5°.

Anal. Calc'd for $C_9H_{10}N_2O_2$: C, 60.67; H, 5.62; N, 15.73. Found: C, 61.10; H, 5.72; N, 15.57.

When dissolved in 10% sodium hydroxide, this compound liberated methylaniline.

1-(N-Phenyl-N-ethylamino)-2-nitroethylene. Using the same procedure 4.8 g. (0.04 mole) of N-ethylaniline and 6.4 g. (0.04 mole) of sodium nitromalonaldehyde produced 2.3 g. (30%)[10] of the corresponding aminonitroethylene, m.p. 63–65° (from ether).

Anal. Calc'd for $C_{10}H_{12}N_2O_2$: C, 62.50; H, 6.25; N, 14.58. Found: C, 62.66; H, 5.90; N, 14.49.

The reaction was also carried out using N-propylaniline and N-butylaniline. In both cases reaction occurred but the oily products could not be induced to crystallize.

Infrared and ultraviolet spectra. The infrared spectra were measured as Nujol mulls on a Perkin Elmer Model 21 infrared spectrophotometer with a rock salt prism. The ultraviolet spectra were measured in absolute ethanol with a Beckman DK-1 ultraviolet spectrophotometer.

Acknowledgment. We are indebted to Dr. M. F. Hawthorne for helpful discussions concerning the ultraviolet spectra, to Dr. Keith S. McCallum for infrared interpretations, and to Dr. W. D. Emmons for carrying out several of the experiments.

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(8) Freeman and Emmons, *J. Am. Chem. Soc.*, In Press.

(9) Fanta, *Org. Syntheses*, **32**, 95 (1952).

(10) These experiments were carried out before the course of the reaction and thus its stoichiometry had been established. After the identity of the aminonitroethylene had been established, an experiment was made using a 2:1 ratio of amine to aldehyde and the formanilide was isolated. Thus the yields reported here do not represent a maximum as the amount of amine employed was insufficient.

A Synthesis of *o*-Carboxyphenyl β-D-Glucopyranosiduronic Acid

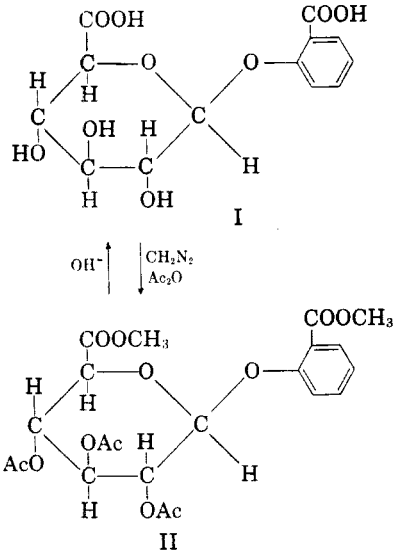
CARL D. LUNSFORD AND ROBERT S. MURPHEY

Received January 12, 1956

Much biological interest has been expressed in the glucuronides of salicylic acid, but no characteri-

zation or synthesis of the compounds have been reported. The available evidence suggests that there exist at least two such metabolites in which the ratios of glucuronic acid to salicylic acid are two and one respectively.[1] There are countercurrent[1c] and chemical[1a] indications of two glucuronic acid conjugates in human urine; however, only one such conjugate has been detected in the dog[1c] and this appears to be linked through the phenolic hydroxyl group. Quick[1b] has reported the isolation of a crystalline product, which reduced Benedict's solution, from the urine of one dog which had been fed salicylic acid but failed to characterize the substance. Repeated attempts to duplicate his experiment in this laboratory have been unsuccessful.

Reported here is the synthesis of the glucuronide of salicylic acid (I) coupled through the phenolic hydroxyl group. The synthesis was accomplished by the basic hydrolysis of methyl (*o*-carbomethoxyphenyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosid)uronate (II) which was prepared by the condensation of methyl 1-bromo-2,3,4-tri-O-acetyl-α-D-glucuronate[2] and methyl salicylate. Evidence for the retention of structure during the basic hydrolysis was obtained by resynthesizing II from I by methylation with diazomethane followed by acetylation.



The mode of synthesis suggests that the glycosidic linkage of I is the β-type.[3] Both compounds I and II gave negative ferric chloride tests, but after mild acid hydrolysis the tests became positive which is evidence that the phenolic hydroxyl is involved in the glycosidic bond.

Arrendondo, *et al.*[4] have reported the synthesis of the intermediate II by the fusion of methyl (1,2,3,4-tetra-O-acetyl-β-D-glucopyranosid)uronate with methyl salicylate in the presence of *p*-toluenesulfonic acid. The compound which they obtained had the melting point 176–178° and $[\alpha]_D^{20}$ +35.7°, while the compound which we have prepared melts at 111.5–113° and has $[\alpha]_D^{23}$ −41.8° (*c*, 6, chloroform). They reported no analysis but stated that the number of acetyl and methyl groups was determined. Following their procedure we have been able to isolate only the starting material, methyl (1,2,3,4 - tetra - O - acetyl - β - D - glucopyranosid)-uronate with melting point 178°.

A study of the possible interference of I with the fluorometric determination of salicylic and salicyluric acids in urine and plasma has shown that it does not fluoresce and therefore does not interfere.[5]

There is also reported here the synthesis of methyl (salicyloyl 2,3,4-tri-O-acetyl-β-D-glucopyranosid)uronate which is the triacetylated methyl ester of the glucuronide of salicylic acid coupled through the salicylic carboxyl group. This was prepared from methyl 1-bromo-2,3,4-tri-O-acetyl-α-D-glucuronate and silver salicylate and gave a positive ferric chloride test showing a free phenolic group. We have been unsuccessful in converting this compound to the simple glucuronide.

EXPERIMENTAL[6]

Methyl (o-carbomethoxyphenyl 2,3,4-tri-O-acetyl-β-D-glucopyranosid)uronate. (II). A mixture of 12.0 g. (0.03 mole) of methyl 1-bromo-2,3,4-tri-*O*-acetyl-α-D-glucuronate,[2] 9.1 g. (0.06 mole) of methyl salicylate, and 15 ml. of isoquinoline was ground together in a mortar with a pestle while cooling the mortar in an ice-bath. To this mixture 7.62 g. (0.033 mole) of freshly prepared silver oxide was added in small portions with continuous mixing. After complete addition mixing was continued for 20 minutes and the resulting viscous mixture was allowed to stand in a desiccator for two hours and then was extracted with 200 ml. of ether in several portions. The ethereal extract was washed with water, dried over sodium sulfate, and concentrated; and the residual oil was extracted with ligroin (b.p. 60–110°) to remove the isoquinoline and excess methyl salicylate, dried *in vacuo* to remove traces of ligroin, and dissolved in 150 ml. of 95% ethanol. The product was precipitated by the addition of small portions of ice and water and was crystallized from dilute ethanol. Yield, 8.0 g. (57%); m.p. 111.5–113°; $[\alpha]_D^{23}$ −41.8° (*c*, 6, chloroform).

Anal. Calc'd for $C_{21}H_{24}O_{12}$: C, 53.84; H, 5.16; Saponification equivalent, 93.7. Found: C, 54.28; H, 5.09; Saponification equivalent, 91.3.

The compound gives a negative ferric chloride test and does not reduce Fehling's solution. The ferric chloride test is positive after warming in 6 *N* hydrochloric acid.

o-Carboxyphenyl β-D-glucopyranosiduronic acid (I). A

(1) (a) Galimard, *Bull. soc. chim. biol.*, **26**, 185 (1944); (b) Quick, *J. Biol. Chem.*, **97**, 403 (1932); (c) Alpen, Mandel, Rodwell, and Smith, *J. Pharmacol.*, **102**, 150 (1951).

(2) (a) Technical Bulletin JN-2, Corn Products Refining Company, Chemical Division, 17 Battery Place, New York 4, N. Y.; (b) Goebel and Babers, *J. Biol. Chem.*, **111**, 349 (1935).

(3) Huebner, Karjala, Sullivan, and Link, *J. Am. Chem. Soc.*, **66**, 906 (1944).

(4) Arredondo, Paul, and Routh, *Proc. Iowa. Acad. Sci.*, **61**, 217 (1954).

(5) Truitt, Jr., Morgan, and Little, *J. Am. Pharm. Assoc.*, **44**, 142 (1955).

(6) All melting points are corrected. Analyses by Schwarzkopf Microanalytical Laboratory, 56-19 37th Avenue, Woodside 77, New York.

mixture of 3.0 g. (0.0064 mole) of methyl (*o*-carbomethoxyphenyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosid)uronate (II), 3 ml. of ether, 8.16 g. (0.0354 mole) of hydrated barium hydroxide, and 225 ml. of boiled deionized water was shaken for 15 hours and filtered. The filtrate was warmed to 50° and saturated with carbon dioxide; the barium carbonate was filtered and the filtrate was concentrated *in vacuo* to about 100 ml. The barium salts of acetic acid and the glucuronide were precipitated by the addition of several volumes of absolute ethanol, filtered, and dissolved in the minimum volume of cold water. The barium was precipitated as the sulfate with 4 *N* sulfuric acid and centrifuged (*p*H 3). The supernant was concentrated *in vacuo* to about 10 ml., treated with 40 ml. of acetone and filtered. The filtrate was concentrated at reduced pressure, and the gummy residue was crystallized from an acetone-ether mixture. Yield 1.0 g. (50%); m.p. 145–146° (d.); $[\alpha]_D^{23}$ −75.9° (*c*, 6, water). The material is soluble in water, does not reduce Fehling's or Tollen's solution at room temperature, and gives a negative test with ferric chloride.

Anal. Calc'd for $C_{13}H_{14}O_9$: C, 49.69; H, 4.49; Equivalent weight, 157 mg./m. eq. Found: C, 49.61; H, 4.70; Equivalent weight, 160 mg./m. eq.

The conversion of I *to* II. A solution of 2.64 g. (0.0084 mole) of I in 15 ml. of methanol was cooled in ice to 0° and ethereal diazomethane[7] was added until the yellow color persisted. The excess diazomethane was destroyed with a drop of acetic acid and the colorless solution was concentrated to dryness at reduced pressure. The residue was dissolved in 15 ml. of pyridine and cooled to 0°, and 8.0 g. of acetic anhydride was added. The reaction mixture was allowed to warm to 30° and was maintained there until the exothermic reaction was complete. Then it was heated at 80° for three minutes and poured into 100 g. of crushed ice. The gum which separated was extracted with two 50-ml. portions of ether, and the ethereal extract was washed, dried over sodium sulfate, and concentrated. The residual oil was crystallized from aqueous ethanol. Yield 2.6 g. (66%); m.p. 111.5–113°. When mixed with authentic methyl (*o*-carbomethoxyphenyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosid)uronate (II) the melting point was not depressed.

Methyl (salicyloyl 2,3,4-tri-O-acetyl-β-D-glucopyranosid)uronate.[8] A mixture of 12.0 g. (0.03 mole) of methyl 1-bromo-2,3,4-tri-O-acetyl-α-D-glucuronate[2] and 9 ml. of isoquinoline was ground together in a mortar with a pestle, while cooling the mortar in an ice-bath, and 7.8 g. (0.03 mole) of silver salicylate was added in small portions with continuous mixing. After complete addition mixing was continued for 20 minutes, and the resulting mixture was allowed to stand in a desiccator for two hours and was extracted continuously with 500 ml. of ether for 15 hours. The ether extract was concentrated and the residue was crystallized from 95% ethanol. Yield, 8.6 g. (63%); m.p. 168.5–169°; $[\alpha]_D^{25}$ −31.9° (*c*, 6, chloroform). An alcoholic solution gives a reddish-brown color with ferric chloride.

Anal. Calc'd for $C_{20}H_{22}O_{12}$: C, 52.86; H, 4.88. Found: C, 52.94; H, 4.90.

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(7) Arndt, *Org. Syntheses*, Coll. Vol. II, 165 (1943).

(8) Arredondo, *et al.* (Ref. 4) have reported the synthesis of this compound (m.p. 166–170°) but have reported no analysis. The magnitude of the rotation ($[\alpha]_D^{20}$ +32.5) agrees with that reported here.

Some Derivatives of 5-Hydroxy-1-naphthylamine

PIERRE H. PAYOT[1]

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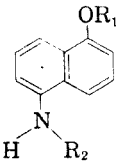
In the course of other work in these laboratories we had the occasion to prepare some derivatives of 5-hydroxy-1-naphthylamine. Since no further work with these compounds is planned in the immediate future it seems appropriate to report their preparation now.



I	R_1 = H	R_2 =	$COCH_3$
II	R_1 = $(CH_2)_5CH_3$	R_2 =	$COCH_3$
III	R_1 = C_2H_5	R_2 =	$COCH_3$
IV	R_1 = $(CH_2)_5CH_3$	R_2 =	H
V	R_1 = $(CH_2)_5CH_3$	R_2 =	$COOC_2H_5$
VI	R_1 = H	R_2 =	H
VII	R_1 = $COOC_2H_5$	R_2 =	$COOC_2H_5$

5-Acetamidonaphthol (I) was etherified with *n*-hexyl bromide using the Claisen method.[2] The homologous ethyl ether (III) was prepared by the same method. Ether II was hydrolyzed to the amine IV, which was acylated with ethyl chloroformate to give V.

Acylation of the unsubstituted 5-hydroxy-1-naphthylamine (VI) with ethyl chloroformate yielded the diacyl product VII.

EXPERIMENTAL

1-Acetamido-5-n-hexoxynaphthalene (II): A solution of 10 g. (*m*/20) of 5-acetamido-1-naphthol (I)[3] in 100 ml. of methyl ethyl ketone, 7.5 g. (slight excess) of anhydrous pulverized potassium carbonate, and 8.75 g. (slight excess) of *n*-hexyl bromide was refluxed (oil bath 110°) with mechanical stirring for 10 hours. After cooling the inorganic material was separated by suction filtration; 12.15 g. (85%) of the ether crystallized from the solution, m.p. 155–158°. The residue from the mother liquor was added to the inorganic material and was extracted with ethyl acetate. After washing the ethyl acetate solution with an ice cold 4% sodium hydroxide solution and water and drying with sodium sulfate a second small crop was obtained. Recrystallization from 96% ethanol after treatment with Norit yielded colorless hexagonal platelets, m.p. 157–158°.

Anal. Calc'd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.60; H, 7.99; N, 5.04.

1-Acetamido-5-ethoxynaphthalene (III). In a similar way, 2 g. (*m*/100) of I was refluxed on a steam-bath during 4.5 hours with 1.5 g. of potassium carbonate and 1.7 g. of ethyl iodide in 50 ml. of acetone. The solvent was distilled off under reduced pressure and the residue was extracted with ethyl acetate and water. The ethyl acetate solution was extracted three times with an ice cold 4% sodium hydroxide solution with water and then was dried with sodium sulfate. After acidification with dil. hydrochloric acid, 400 mg. of starting material (needles, m.p. 176–177°) was recovered from the

(1) Present address: Department of Chemistry and Chemical Engineering, University of California, Berkeley 4, California.

(2) Houben-Weyl, *Methoden der Organischen Chemie*, Vol. III, 3rd ed., p. 144, G. Thieme, Leipzig, 1930.

(3) Lockett and Short, *J. Chem. Soc.*, 787 (1939).