[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

SOME DERIVATIVES OF α-AMYLCINNAMIC ACID

HARRY L. YALE

Received November 30, 1950

Our need for rather large amounts of *p*-amino-α-amylcinnamic acid made it desirable to develop a practical preparative method. The only related work could be found in the report by Blout and Silverman (1) who prepared *p*-amino-α-methylcinnamic acid by the catalytic reduction of *p*-nitro-α-methylcinnamic acid.

Our synthetic approach started with the commercially available α-amylcinnamaldehyde,[1] since the literature afforded a description of its oxidation by silver oxide to α-amylcinnamic acid (2). Preliminary attempts to carry out this oxidation were often unsuccessful; the successful experiments did not give consistently good yields. A detailed study of this reaction showed that the critical factor was the silver oxide. Conditions are now described for the preparation of silver oxide which has repeatedly given good yields (72%) of the acid; about 23% of the aldehyde can be recovered for re-use.

The nitration of α-amylcinnamic acid was carried out in glacial acetic acid with fuming nitric acid at 25°, and gave a 59% yield of *p*-nitro- and a 26% yield of *o*-nitro-α-amylcinnamic acid. The isomers were separated by fractional crystallization from methanol. The structure of the *p*-isomer was established by its oxidation with potassium permanganate to *p*-nitrobenzoic acid. The structure of the *o*-isomer is inferred by the fact that the nitration of cinnamic acid is known to give a mixture of *o*- and *p*-isomers (3). The reduction of the nitro compounds with 20% ammonium sulfide solution gave the corresponding amino derivatives in 85 and 83% yield, respectively. Catalytic reduction with hydrogen at 50 lb. over 5% palladium on charcoal proceeded very rapidly to the aminophenyl-α-amylpropionic acid. It was not possible to stop the reduction to give the desired unsaturated acid.[2]

Acknowledgement: The microanalyses were carried out by Mr. J. F. Alicino.

EXPERIMENTAL PART[3]

Oxidation of α-amylcinnamaldehyde to α-amylcinnamic acid. Preparation of silver oxide. To a solution of 85 g. (0.5 mole) of silver nitrate in 250 ml. of water was added slowly, with vigorous stirring, a solution of 25 g. of sodium hydroxide in 100 ml. of water. After thorough stirring, the silver oxide was allowed to settle and the supernatant liquid decanted. The silver oxide was washed about 7 times with a total of 2 l. of boiling water, decanting the washings in each instance, except the last, when the silver oxide was filtered and dried as well as possible with suction (*ca.* 5 min.). The slightly moist solid was then washed thoroughly with absolute alcohol and sucked dry. At this point, the silver oxide was a

---

[1] Givaudan-Delawanna, Inc., New York, N. Y.

[2] Blout and Silverman (1) used Raney nickel at 20–30° under 2–3 atm. of hydrogen to reduce *p*-nitro-α-methylcinnamic acid to *p*-amino-α-methylcinnamic acid. The reduction required six hours.

[3] All temperatures are uncorrected.

powdery solid, free of any liquid, and dry to the touch. It was important that air be drawn through the silver oxide subsequent to the alcohol washings.

Oxidation. To a 1 l. 3-necked flask equipped with stirrer, condenser, and dropping-funnel was added the dry silver oxide, 300 ml. of absolute alcohol, and 101 g. (0.5 mole) of α-amylcinnamaldehyde. To this stirred suspension was added a few ml. of the hot solution prepared by dissolving 20 g. of sodium hydroxide in 70 ml. of water and diluting with 100 ml. of 95% alcohol. Reaction occurred immediately, the mixture became warm and the silver oxide became light colored. If the reaction failed to start directly, the yield of acid was lowered considerably. The remainder of the sodium hydroxide solution was added dropwise during one hour. The stirred reaction mixture was then refluxed one hour, cooled, the liquid decanted, and the precipitated silver leached four times with 100-ml. portions of boiling water. The combined liquids were distilled from the steam-bath to remove the alcohol, cooled, and extracted with ether. The aqueous layer on acidification gave 78 g. (72% yield) of α-amylcinnamic acid, m.p. 78–79° after recrystallization from hexane. The ether extracts gave 23.5 g. (23% recovery) of unreacted aldehyde.

p-Nitro-α-amylcinnamic acid. To a stirred mixture of 200 ml. each of glacial acetic acid and fuming nitric acid (*d.* 1.5) was added 50 g. (0.229 mole) of α-amylcinnamic acid, in small portions, maintaining the temperature at 25° during the addition and for three hours afterward. The mixture was then poured with stirring on a kilogram of crushed ice. The solid which separated was washed well with water; after drying it weighed 60 g. The crude product was dissolved in 500 ml. of boiling methanol, decolorized with carbon, and filtered. The filtrate gave 35.5 g. (59% yield) of *p*-nitro-α-amylcinnamic acid, yellow needles, m.p. 166–168°. Recrystallization from methanol raised the m.p. to 168–169°.

Anal. Calc'd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32.
Found: C, 63.70; H, 6.17; N, 5.30.

o-Nitro-α-amylcinnamic acid. The methanol filtrate from the first recrystallization of the *p*-nitro isomer was concentrated from the steam-bath. The oily residue was recrystallized from glacial acetic acid to give 15.5 g. (26% yield) of product, yellow plates, m.p. 85–87°. The analytical sample, recrystallized from hexane, melted at 86–87°.

Anal. Calc'd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32.
Found: C, 63.67; H, 6.36; N, 5.27.

Oxidation of p-nitro-α-amylcinnamic acid. A mixture of 1.0 g. of the higher-melting (168–169°) isomer, 4.0 g. of potassium permanganate, 80 ml. of water, and 2 ml. of 10% aqueous sodium hydroxide was refluxed for two hours, cooled and filtered. The filtrate was acidified with 10% hydrochloric acid and the precipitated acid recrystallized from 50% methanol, m.p. 235–237°. A mixture m.p. with an authentic sample of *p*-nitrobenzoic acid was 235–237°.

p-Amino-α-amylcinnamic acid hydrochloride. A mixture of 37.5 g. (0.13 mole) of *p*-nitro-α-amylcinnamic acid and 265 ml. of 20% ammonium sulfide solution was heated at the boiling point for three hours, keeping the volume constant by the addition of water. The hot mixture was filtered and the insoluble material was washed with hot 5% aqueous ammonia. The combined filtrates were cooled and acidified with acetic acid. The crude acid weighed 35 g., m.p. 134–136°. For purification it was boiled with 5 l. of 5% hydrochloric acid, decolorized with carbon, and filtered hot. On cooling, the filtrate gave 29.1 g. (85% yield) of crude product, m.p. 187–189°. It was observed that the hydrochloride hydrolyzed partially even in 5% hydrochloric acid; it hydrolyzed completely in boiling water. For analysis, a sample was recrystallized from 2 *N* alcoholic hydrogen chloride; m.p. 200–202°.

Anal. Calc'd for $C_{14}H_{20}Cl\ NO_2$: N, 5.20; Cl, 13.14.
Found: N, 5.13; Cl, 13.55.

The *free base* was obtained by dissolving the hydrochloride in 10% aqueous sodium hydroxide solution and acidifying with acetic acid. The solid was recrystallized from 25% isopropanol to give *p*-amino-α-amylcinnamic acid as fine, pale yellow needles, m.p. 147–148°.

Anal. Calc'd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.01.
Found: C, 72.07; H, 8.02; N, 6.06.

o-Amino-α-amylcinnamic acid hydrochloride. The reduction of 73.5 g. (0.28 mole) of *o*-nitro-α-amylcinnamic acid was carried out as with the *p*-isomer; yield, 61 g. (83%). After recrystallization from 2 *N* alcoholic hydrogen chloride the product melted at 208–210° (with decompn.).

Anal. Calc'd for $C_{14}H_{20}ClNO_2$: N, 5.20; Cl, 13.14.
Found: N, 5.19; Cl, 12.97.

o-Amino-α-amylcinnamic acid was obtained as described above for the *p*-isomer and recrystallized from hexane to give yellow plates, m.p. 114–116°.

Anal. Calc'd for $C_{14}H_{19}NO_2$: N, 6.01. Found: N, 6.07.

β-(p-Aminophenyl)-α-amylpropionic acid. A mixture of 5 g. (0.002 mole) of *p*-nitro-α-amylcinnamic acid, 150 ml. of isopropanol, and 0.5 g. of 5% palladium on charcoal was hydrogenated at 50 lb. Four equivalents of hydrogen were absorbed in 16 minutes. The product was isolated in the usual manner; yield, 4 g. (85%), m.p. 142–143°. A mixture m.p. with *p*-amino-α-amylcinnamic acid was 122–123°.

Anal. Calc'd for $C_{14}H_{21}NO_2$: N, 5.12. Found: 5.11.

β-(o-Aminophenyl)-α-amylpropionic acid. This compound was obtained in a manner similar to that employed with the *p*-isomer. The yield was 87%, m.p. 112–113°, after recrystallization from benzene-hexane.

Anal. Calc'd for $C_{14}H_{21}NO_2$: N, 5.95. Found: N, 5.95.

The *hydrochloride* melted at 200–202° (with decompn.).

Anal. Calc'd for $C_{14}H_{22}ClNO_2$: N, 5.12. Found: N, 5.18.

Ethyl p-amino-α-amylcinnamate. A mixture of 20 g. (0.086 mole) of *p*-amino-α-amylcinnamic acid and 150 ml. of saturated alcoholic hydrogen chloride was refluxed three hours and then worked up in the usual manner to give 16 g. (61% yield) of product, b.p.$_{1.5}$ 181°.

Anal. Calc'd for $C_{16}H_{23}NO_2$: N, 5.36. Found: N, 5.44.

SUMMARY

Conditions are described which give consistently good yields of α-amylcinnamic acid by the silver oxide oxidation of α-amylcinnamaldehyde. In addition, there is described the preparation of a number of derivatives of α-amylcinnamic acid.

New Brunswick, New Jersey

REFERENCES

(1) Blout and Silverman, *J. Am. Chem. Soc.*, **66**, 1442 (1944).
(2) Bogert and Davidson, *J. Am. Chem. Soc.*, **53**, 3122 (1931).
(3) Beilstein and Kuhlberg, *Ann.*, **163**, 126 (1872).