[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE]

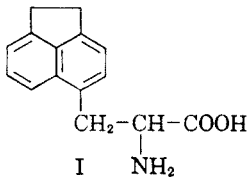
Synthesis of DL-*beta*-(5-Acenaphthenyl)alanine[1]

D. C. MORRISON

Received July 19, 1957

The analog of phenylalanine, DL-*beta*-(5-acenaphthenyl)alanine, was synthesized from 5-acenaphthoic acid. Its properties were studied and its *N*-benzenesulfonyl derivative and hydrochloride were prepared. An improvement in the Grignard synthesis of 5-acenaphthoic acid is reported.

The preparation of DL-*beta*-(5-acenaphthenyl)-alanine (I) was undertaken for studies in cancer chemotherapy. This amino acid is an analog of phenylalanine containing the polyploidy-inducing acenaphthene group. It was obtained from 5-



I

acenaphthoic acid as starting material. This acid was esterified and reduced by lithium aluminum hydride to 5-acenaphthenylcarbinol,[2] which was treated with phosphorus tribromide in benzene to yield the corresponding bromide. It was also possible to prepare the carbinol by lithium aluminum hydride reduction of the corresponding aldehyde,[3] but the reduction of the ester is probably to be preferred. The bromide was used to alkylate the sodium derivative of diethyl acetamidomalonate and the intermediate ester was hydrolyzed and decarboxylated by refluxing with hydrochloric acid to give the amino acid hydrochloride. This, with ammonia, formed the amino acid which was a very sparingly soluble substance and was difficult to purify. It was characterized as the hydrochloride salt and as the *N*-benzenesulfonyl derivative.

EXPERIMENTAL

Melting points are uncorrected.

The 5 acenaphthoic acid was obtained from 5-bromoacenaphthene[4] by a Grignard reaction and carbonation. The acid has been prepared by carbonation of the lithium derivative[2] and also from the Grignard reagent.[5] In the present work, the use of ethyl bromide as entrainer improved the yield to about 90%.

5-Acenaphthoic acid. A solution of 25 g. of 5-bromoacenaphthene in 150 ml. of anhydrous ether was mixed with excess magnesium turnings and then treated dropwise during 1 hr. with a solution of 20 ml. ethyl bromide in 100 ml. of ether. The addition was regulated so that moderately vigorous refluxing occurred. After the addition, the brownish solution was refluxed an additional 20–30 min. and then cooled and poured slowly onto a slurry of Dry Ice in toluene. After several hours, dilute hydrochloric acid was added and the organic layer together with any precipitated acid was separated and washed with water. It was then extracted with 3 portions of potassium carbonate solution, and the carbonate extracts acidified to precipitate the acid. When washed and dried, the crude acid weighed 20.1 g. (94.6%) and melted at 207–211°. Richter[2] gives m.p. 214–218° corr. for his crude acid from the lithium derivative. This was the best yield obtained but other runs gave about 90%. Prolonged refluxing of the solution after the addition of the ethyl bromide seemed to reduce the yield. In spite of the fact that all of the aryl bromide was present at the start of the reaction, no coupling to the biaryl was noticed.

5-Acenaphthenylcarbinol. This was obtained by lithium aluminum hydride reduction of ethyl 5-acenaphthoate, similarly to Richter's procedure[2] except that an ether or benzene solution of the ester was employed in place of the solid acid. The acid was esterified in the usual way with ethanol and sulfuric acid. The much greater solubility of the ester in organic solvents was an advantage over use of the free acid.

The 5-acenaphthene aldehyde[3] was likewise reduced by lithium aluminum hydride in ether solution giving a quantitative yield of carbinol. When recrystallized from aqueous acetone it had m.p. 155–157° with previous softening (lit.[2] 156–157°).

5-Acenaphthenylmethyl bromide. A solution of 1 ml. of phosphorus tribromide in 7.5 ml. of benzene was treated gradually, in portions, with 2 g. of the carbinol. The latter dissolved readily, without heating, leaving a small amount of brown sludge. This solution was left overnight and the solution decanted from the sludge. The latter was extracted with several portions of benzene and the combined benzene solutions were diluted with ether and extracted 4 times with water. The organic solvents were removed under vacuum, leaving a pale tan or cream colored solid. The yield was 2.68 g. (quantitative) and the product had m.p. 117–119°. The bromide was recrystallized 3 times from ether–petroleum ether but the m.p. was not raised. The white crystalline solid had an irritating effect on nasal mucosa, especially when warmed.

Anal. Calcd. for $C_{13}H_{11}Br$: C, 63.16; H, 4.45. Found: C, 62.92; H, 4.57.

On standing, the bromide readily darkens to greenish-gray and evolves HBr. When left for 3–4 days at room temperature, only about half could be recovered by solvent extraction and rebromination with phosphorus tribromide.

Diethyl (5-acenaphthenylmethyl)acetamidomalonate. A solution of 0.82 g. (0.0356 mole) of sodium and 7.8 g. (0.0356 mole) ethyl acetamidomalonate in 300 ml. anhydrous ethanol was treated gradually with 8.8 g. (0.0356 mole) of solid, freshly prepared 5-acenaphthenylmethyl bromide, added in portions to the warm solution. On heating, all of the bromide dissolved, and the resulting mixture was refluxed for 15 hr. Five ml. of acetic acid were added, and the

(1) The work described in this paper was carried out under a research grant (No. C-327) to D. M. Greenberg, from the National Cancer Institute, United States Public Health Service.

(2) H. J. Richter, *J. Am. Chem. Soc.*, **75**, 2774 (1953).

(3) L. F. Fieser and J. E. Jones, *J. Am. Chem. Soc.*, **64**, 1666 (1942).

(4) C. Graebe, *Ann.*, **327**, 77 (1903).

(5) V. Grignard, E. Bellet, and Ch. Courtot, *Ann. Chim.*, **4**, Ser. 9, 53 (1915).

solution was distilled to dryness, finally under vacuum. Aqueous sodium carbonate and a large amount of water were added, and the suspension was steam distilled at 70 mm. to remove steam-volatile material. The mixture was cooled and left to stand for some time, and the solid product filtered, washed with water, and dried. The weight of crude ester was 11.61 g. (85.1%). A 12-hr. reflux period also gave 85%. The material was recrystallized from acetone-water 6 times and formed a white powder of m.p. 139–141°.

Anal. Calcd. for $C_{22}H_{25}NO_5$: C, 68.94; H, 6.53. Found: C, 68.77; H, 6.60.

DL-*beta*-(*5-Acenaphthenyl*)*alanine hydrochloride.* A solution of 2.77 g. of the ester in 25 ml. of ethanol was mixed with 20 ml. of concentrated hydrochloric acid and the solution refluxed 15 hr. It was then cooled and diluted with 8 volumes of water and left several hours. A white substance and some tar separated and these were removed by filtration. The filtrates were now boiled to a small volume and cooled to yield a crystalline deposit weighing 1.23 g. The filtrates from this, on further concentration, gave an additional 0.23 g. The total of 1.46 g. represents a 73% yield of hydrochloride. The amino acid hydrochloride was recrystallized by adding an excess of petroleum ether to the solution in a minimum of hot ethanol, and cooling. The first and last portions to crystallize were removed and the center fraction crystallized again. After 5 recrystallizations, a white powder was obtained.

Anal. Calcd. for $C_{15}H_{16}NO_2Cl$ (monohydrochloride): C, 64.86; H, 5.77. Found: C, 64.45; H, 5.80.

The hydrochloride and the free amino acid were difficult to purify. The best sample of hydrochloride, on heating, sintered above 190° with beginning discoloration, and melted indefinitely at 220–232° to a brownish-orange melt.

DL-*beta*-(*5-Acenaphthenyl*)*alanine.* The amino acid was best prepared from its hydrochloride by vacuum concentration of its ammoniacal solution. This operation was accompanied by much foaming and had to be done slowly. If concentrated at atmospheric pressure, considerable darkening occurred, while the product obtained by acidifying alkaline solutions with acetic acid was also usually dark and formed slowly in poor yield. If the ammoniacal solution was decolorized by Norit, only small amounts of the latter could be employed due to the ready adsorption of the amino acid on the charcoal. The free amino acid separated as a crystalline powder when the ammonia solution was distilled at 60 mm. to a small volume. This recrystallization was repeated 3 times and the white product dried 4 days in vacuum.

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.69; H, 6.22. Found: C, 74.25; H, 6.38.

The acenaphthenyl alanine is very sparingly soluble in water, even when hot. With ninhydrin in dilute acetic acid, on heating, a purple color was formed. The amino acid darkened (brown) at 218–220° and melted at 228–231° forming a dark brown melt.

N-(*benzenesulfonyl*)-DL-*beta*-(*5-acenaphthenyl*)*alanine.* A solution of 300 mg. of the amino acid hydrochloride in 20 ml. of 1*N* KOH was acylated by stirring at room temperature with benzenesulfonyl chloride and ether, for 3 hr. More KOH was added, and the alkaline solution separated and acidified with hydrochloric acid to yield a partly resinous precipitate of the acid. The acid was collected, washed with water, and dried. The yield was 300 mg. or 72.8%. The product was purified by concentration of its ether solution to a small volume and seeding with scratching. It was recrystallized 3 times and dried in vacuum, m.p. 203–205°.

Anal. Calcd. for $C_{21}H_{19}NSO_4$: C, 66.14; H, 4.99. Found: C, 66.10; H, 5.02.

BERKELEY, CALIF.

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH, U. S. PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Piperidine-Catalyzed Condensation of 1,3-Dicarbonyl Compounds with Ethyl β-Ketoglutarate

GORDON N. WALKER

Received July 3, 1957

Acetylacetone, benzoylacetone, and the hydroxymethylene derivatives of phenylacetone, cyclopentanone, cyclohexanone, and cycloheptanone have been condensed with ethyl β-ketoglutarate in the presence of piperidine to give, after hydrolysis, substituted 2-hydroxyisophthalic acids, III a, b, c, d, e, and f, respectively. With the exception of IIc, a new compound, these products are the same as those obtained in the corresponding reactions carried out earlier using sodium ethoxide as the basic agent. Spectroscopic, degradative, and other data confirming the structures of the products are presented. Generally speaking, α-hydroxymethyleneketones are found to react selectively with one mole of ethylene glycol in the presence of benzenesulfonic acid, giving acetal-ketones IV.

The discovery was made by Prelog and his colleagues[1,2] in 1947, that 2,6-dicarbalkoxyphenols-(II) may be prepared directly by condensation of a variety of 1,3-dicarbonyl compounds with ethyl β-ketoglutarate in the presence of sodium ethoxide. This reaction and related condensation of 1,4-dicarbonyl compounds[3,4] with ethyl β-ketoglutarate appeared to be worthy of further study, in view of the fact that unexpected products are sometimes encountered,[4] and in the hope that the reaction might possibly be extended to condensation of dicarbonyl compounds with ethyl ketipate, EtOOC-CH_2-CO-CO-CH_2COOEt, with consequent formation of tropolones. While the latter idea has not

(1) V. Prelog, O. Metzler, and O. Jeger, *Helv. Chim. Acta*, **30**, 675 (1947).

(2) V. Prelog, L. Ruzicka, and O. Metzler, *Helv. Chim. Acta*, **30**, 1883 (1947).

(3) J. Thiele and J. Schneider, *Ann.*, **369**, 287 (1909).

(4) D. S. Tarbell and B. Wargotz, *J. Am. Chem. Soc.*, **76**, 5761 (1954).