[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DUKE UNIVERSITY]

AROMATIC CYCLODEHYDRATION. XXIV. CYCLIZATION OF DERIVATIVES OF (2-BIPHENYLYL)PYRUVIC ACID[1]

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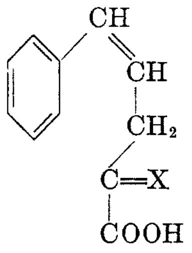
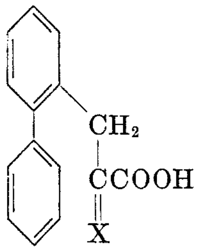
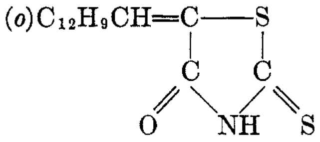
It is reported (1, 2) that α-benzimino-β-(β-styryl)propionic acid (I), in the presence of hydrochloric acid, undergoes cyclization to yield α-naphthoic acid, presumably (2) through (β-styryl)pyruvic acid as an intermediate. This suggests that (2-biphenylyl)pyruvic acid (III), or substances yielding this keto acid in strongly acid solutious, might be expected to yield 9-phenanthroic acid. It has been postulated (3) that the cyclization of ethyl α-keto-β-(2-biphenylyl)succinate (4) to yield 9-phenanthroic acid is an example of such a cyclization. The present communication records the results of some preliminary experiments directed toward the synthesis and cyclization of some derivatives of (2-biphenylyl)pyruvic acid.



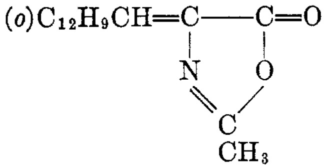
I, X = $NCOC_6H_5$
II, X = O



III, X = O
IV, X = S
V, X = NOH



VI



VII

The first derivative selected was α-oximino-β-(2-biphenylyl)propionic acid (V). The required *o*-phenylbenzaldehyde, conveniently prepared (68% yield) by the method of Zaheer and Fahsee (5), was condensed with rhodanine, essentially as described by Julian and Sturges (6). The resulting product (VI) underwent cleavage in alkali slowly, but on acidification, α-thioketo-β-(2-biphenylyl)-propionic acid (IV) was obtained in excellent yield. Conversion to the oximino acid (V) was effected by the action of hydroxylamine.

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[1] For the preceding communication of this series see Bradsher and Kittila, *J. Am. Chem. Soc.*, **72**, 277 (1950).

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Cyclization of the oximino acid (V) in a hydrobromic-acetic acid mixture, gave a small quantity of 9-phenanthroic acid. More remarkable was the behavior of the thioketo acid (IV), which, under the same conditions, cyclized with the evolution of hydrogen sulfide to produce 9-phenanthroic acid in 23–25% yield. Since the yields were excellent for both steps in the preparation of the thioketo acid (IV) from the *o*-phenylbenzaldehyde, the over-all yield (22% in one instance) is large enough to give the method some preparative significance.

Another compound of the type expected to yield biphenylylpyruvic acid (III) on hydrolysis is the azlactone of α-acetamino-*o*-phenylcinnamic acid (VII). It was found that when this product was added to hydrobromic-acetic acid, no isolable amount of phenanthroic acid was produced.

EXPERIMENTAL

5-(o-Phenylbenzylidene)rhodanine (VI). To a hot solution containing 5.5 g. of *o*-phenyl benzaldehyde (5) and 4 g. of rhodanine in 20 ml. of glacial acetic acid, 7.5 g. of fused sodium acetate was added. The mixture was refluxed for thirty minutes, cooled, and poured into water. The solid was collected and washed with water and ethanol. The yield of yellow needles was 7.8 g. (87%), m.p. 243–244°. An analytical sample prepared by recrystallization from benzene melted at 245–246°.

Anal. Calc'd for $C_{16}H_{11}NOS_2$: C, 64.62; H, 3.73.
Found: C, 64.95; H, 3.77.

α-Thioketo-β-(2-biphenylyl)propionic acid (IV). The crude rhodanine derivative above (VI, 3.5 g.) was suspended in 15 ml. of 15% sodium hydroxide solution and heated in a water-bath until a clear solution had been formed and had again become cloudy (one hour). The solution was cooled in an ice-salt bath and 15 ml. of cold 10% hydrochloric acid was added with stirring. The amorphous material which precipitated, slowly solidified on stirring. It was collected, washed, and dried in a desiccator. The yellow crystals, m.p. 154–167°, weighed 3 g. (100%) and were pure enough for further reactions. An analytical sample was obtained as orange needles from chloroform, m.p. 172.5–173°.

Anal. Calc'd for $C_{15}H_{12}O_2S$: S, 12.51.
Found: S, 12.54.

α-Oximino-β-(2-biphenylyl)propionic acid (V). Sodium (0.56 g.) was dissolved in 16 ml. of ethanol and to this was added a warm solution of 1.7 g. of hydroxylamine hydrochloride in 2 ml. of water. The filtered solution was poured on 2 g. of crude thioketo acid (IV, m.p. 150–160°). The resulting solution was heated for twenty minutes on a steam-bath, hydrogen sulfide being evolved. The solvent was removed under reduced pressure. The residue was dissolved in 10% sodium hydroxide solution, filtered, cooled in an ice-salt bath, and acidified with 10% hydrochloric acid. The amorphous product which crystallized on standing, was dried over potassium hydroxide in a vacuum desiccator, yielding 1.7 g. of coarse white crystals suitable for the cyclization reaction.

An analytical sample was obtained by twice repeating the reprecipitating process; a white powder, m.p. 143.5–144°. A sodium fusion test showed sulfur to be absent.

Anal. Calc'd for $C_{15}H_{13}NO_3$: C, 70.57; H, 5.13.
Found: C, 70.20; H, 5.24.

The azlactone of α-acetamino-o-phenylcinnamic acid (VII). A mixture of 9.1 g. of *o*-phenylbenzaldehyde, 8.2 g. of acetylglycine, 2.9 g. of sodium acetate and 12.8 g. of acetic anhydride was warmed on the steam-bath until solution was almost complete and then refluxed for one and one-half hours (7). The mixture was extracted with benzene and the solution washed, dried, and concentrated. Yellow crystals, 4.2 g. (32%), were deposited, m.p. 234–236°. An analytical sample was prepared by repeated recrystallization from methyl ethyl ketone as orange crystals, m.p. 241–242° (with decomposition).

Anal. Calc'd for $C_{17}H_{13}NO_2$: N, 5.32. Found: N, 5.54.

CYCLIZATION EXPERIMENTS

With α-oximino-β-(2-biphenylyl)propionic acid (V). Two grams of the crude acid was dissolved in 50 ml. of acetic acid and added slowly to refluxing 48% hydrobromic acid (30 ml.) over a period of 45 minutes. After refluxing for a total of three hours, the mixture was cooled, diluted with water, and the solid collected. The product, purified by vacuum sublimation and by crystallization from ethanol, melted at 254–255°. This material did not depress the melting point of an authentic sample of 9-phenanthroic acid, (m.p. 253.5–254.5°) obtained by hydrolysis of 9-phenanthronitrile.

With α-thioketo-β-(2-biphenylyl)propionic acid (IV). One gram of the crude thioketo acid was dissolved in 25 ml. of acetic acid and added dropwise to 15 ml. of boiling 48% hydrobromic acid. The mixture was refluxed for two hours during which hydrogen sulfide was evolved. The mixture was cooled and the product collected and washed with 50% acetic acid. The white needles (0.5 g.) melted at 238–250°. This material was completely soluble in alkali, and, on reprecipitation, showed no improvement in melting point. Recrystallization from ethanol yielded 0.2 g. (23%) of phenanthroic acid, m.p. 254–255°. Essentially the same results were obtained in larger scale reactions, 9 g. of crude thioketo acid yielding 2 g. of phenanthroic acid, m.p. 254–255°.

In another experiment, phenanthroic acid was obtained in 23% yield when (*o*-phenylbenzylidene)rhodanine (2 g.) was heated in 75 ml. of 15% sodium hydroxide for 1½ hours and the alkaline solution run directly into a refluxing mixture of hydrobromic and acetic acids.

With the azlactone of α-acetamino-o-phenylcinnamic acid (VII). The azlactone was suspended in acetic acid and added to hydrobromic acid and the mixture refluxed for seventeen hours. On dilution of the mixture and recrystallization of the resulting product, an unidentified red solid was obtained, m.p. 258–263°. This was not studied further.

SUMMARY

It has been shown that α-oximino- and α-thioketo-β-phenylpropionic acids are cyclized to 9-phenanthroic acid by the action of boiling hydrobromic and acetic acids.

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