[CONTRIBUTION FROM AVERY LABORATORY OF THE UNIVERSITY OF NEBRASKA]

The Synthesis of Some Phenanthridine Derivatives

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Some phenanthridine derivatives possess marked chemotherapeutic activity, particularly the quaternary phenanthridine compounds prepared by Walls.[2] The purpose of this investigation was to prepare 4-substituted-phenanthridines which would have a close structural relationship to acridine and quinoline derivatives, such as Quinacrine and Pamaquine.

A number of phenanthridine syntheses are known, but most of them use high temperatures or other drastic conditions which greatly restrict their usefulness. We have found that 4-nitro-6-methylphenanthridine (II) is obtained readily by the cyclization of 3-nitro-2-acetamidobiphenyl (I) in the presence of phosphorus oxychloride, using the general procedure of Morgan and Walls.[3]

Although Walls[4] reduced nitrophenanthridine derivatives to the corresponding amines by the use of powdered iron and water, it was found that 4-amino-6-methylphenanthridine (III) could be readily obtained in good yields by catalytic reduction of II. Condensation of III with β-chlorethyldiethylamine hydrochloride proceeded smoothly to give 4-(β-diethylaminoethylamino)-6-methylphenanthridine (IV). By using the method of Hodgson and Walker,[5] III was converted to 4-chloro-6-methylphenanthridine (V) in good yields. The acetylation of III proceeded smoothly to give the desired product.

Oxidation of II with dichromate solution gave the corresponding 4-nitrophenanthridone (VI), while condensation of II with formaldehyde followed by oxidation of the intermediate gave phenanthridine-6-carboxylic acid.

Experimental

3-Nitro-2-acetamidobiphenyl (I).—A mixture of 105.5 g. of 2-acetamidobiphenyl[6] and 150 ml. of acetic anhydride was maintained at 20° while being treated with a solution of 65 ml. of concentrated nitric acid (sp. gr., 1.42) and 70 ml. of acetic anhydride. The nitrating mixture was added rapidly at first until about one-fifth of the solution had been added, then at such a rate as to maintain the temperature between 20 and 25°. After stirring for five hours the solution was placed in the refrigerator overnight. The cold solution was poured over crushed ice, filtered, and the solid dissolved in hot benzene from which the product separated as yellow needles. A second crop of material was recovered by washing the benzene extract with a 10% sodium carbonate solution; total yield 39 g. (30%); m. p. 185–187°.

4-Nitro-6-methylphenanthridine (II).—A solution of 10.2 g. of I in 50 ml. of hot nitrobenzene was added portionwise to 30 ml. of phosphorus oxychloride heated to 130°. After three hours of refluxing at 130–140° the mixture was poured into water and the nitrobenzene was removed by steam distillation. The residual solution was treated with charcoal, filtered, and made basic to yield 5.7 g. (60%) of product; m. p., after recrystallization from 95% ethanol, 167–167.5°.

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.20; N, 11.76. Found: C, 70.62; H, 4.35; N, 11.57.

4-Amino-6-methylphenanthridine (III).—A solution of 3.7 g. of II dissolved in 120 ml. of dry acetone containing a small amount of Raney nickel was placed on a hydrogenerator at room temperature under a hydrogen pressure 40 to 45 pounds. After eight hours the solution was removed, filtered, and the filtrate saturated with dry hydrogen chloride gas to yield the hydrochloride. The free base was obtained in buff colored plates; m. p. 111–112°.

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.77; H, 5.77; N, 13.44. Found: C, 80.55; H, 5.90; N, 13.30.

4-(β-Diethylaminoethylamino)-6-methylphenanthridine (IV).—A mixture of 1 g. of III, 2 g. of β-diethylaminoethyl chloride hydrochloride, 2 g. of sodium acetate and 50 ml. of absolute ethanol was refluxed for seven hours. After removal of the solvent, the residue was taken up in acid, then slowly made basic to yield 1.2 g. (80%) of material; m. p. 56–57°.

Anal. Calcd. for $C_{20}H_{25}N_3$: C, 78.17; H, 8.14; N, 13.68. Found: C, 78.30; H, 8.36; N, 13.68.

4-Chloro-6-methylphenanthridine (V).—A solution of 2 g. of III in 24 ml. of glacial acetic acid was slowly added to an ice-cold nitrite solution prepared by adding 0.8 g. of sodium nitrite to 6 ml. of cold concentrated sulfuric acid. The diazonium solution was added to a mixture of 2 g. of cuprous chloride in 20 ml. of concentrated hydrochloric acid in the cold. After standing a short time, it was added to water, the solid suspended in water and made basic with ammonium hydroxide to yield 2.2 g. (95%) of material; m. p., after recrystallization from alcohol–water, 113–114°.

Anal. Calcd. for $C_{14}H_{10}NCl$: C, 73.84; H, 4.39; N, 6.14. Found: C, 73.64; H, 4.46; N, 6.25.

4-Acetamido-6-methylphenanthridine.—A solution of 1 g. of III in excess acetic anhydride was warmed for five minutes, then poured into water to yield 1.15 g. (91%) of product; m. p., after recrystallization from benzene, 142–143°.

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 74.33; H, 6.19; N, 12.39. Found: C, 74.30; H, 6.27; N, 12.42.

4-Nitrophenanthridone (VI).—A solution of 2 g. of II in 20 ml. of hot glacial acetic acid was treated slowly with 3.5 g. of powdered sodium dichromate, then refluxed for four hours. When poured into water, 2 g. of crude product was obtained; m. p., after recrystallization from nitrobenzene, 257–258°.

Anal. Calcd. for $C_{13}H_8N_2O_3$: N, 11.67. Found: N, 11.73.

4-Nitrophenanthridine-6-carboxylic Acid (VII).—A mixture of 2.5 g. of II, 100 ml. of 95% alcohol and 5 ml. of formalin was refluxed two hours, then a second 5-ml. portion of formalin added and refluxing continued for nine more hours. After concentrating the solution, it was added to a large volume of ether, washed several times with water, and the ether dried. Evaporation of the ether yielded 2.1 g. of material; m. p. 145–150°. No attempt was made to purify this material since the crude product was readily oxidized to the acid.

A solution of 2.1 g. of the crude material in 20 ml. of hot 2 *N* sulfuric acid was treated dropwise with 35 g. of

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[2] Walls, *J. Chem. Soc.*, 67 (1947).

[3] Morgan and Walls, *J. Chem. Soc.*, 2447 (1931); British Patent 520,273; *C. A.*, **36**, 495 (1942).

[4] Walls, British Patent 577,990; *C. A.*, **41**, 2449 (1947).

[5] Hodgson and Walker, *J. Chem. Soc.*, 1620 (1933).

[6] Sako, *Bull. Chem. Soc. Japan*, **9**, 55 (1934).

Kiliani's dichromate mixture. After the final addition the mixture was refluxed for two hours, then poured into water to give 1.9 g. of material. Recrystallization from alcohol yielded yellow needles; m. p. 247–248°.

Anal. Calcd. for $C_{14}H_8N_2O_4$: C, 62.68; H, 2.98; N, 10.44. Found: C, 62.60; H, 3.16; N, 10.54.

Summary

1. An improvement in the yield of 3-nitro-2-acetaminobiphenyl was accomplished.

2. The synthesis of 4-nitro-6-methylphenanthridine is described. This compound was used to prepare 4-amino-6-methylphenanthridine by reduction, 4-nitrophenanthridone by oxidation and phenanthridine-6-carboxylic acid by condensation with formaldehyde followed by oxidation.

3. 4-Amino-6-methylphenanthridine was converted to 4-acetamino-6-methylphenanthridine, 4-(β-diethylaminoethylamino)-6-methylphenanthridine, and 4-chloro-6-methylphenanthridine.

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The Rearrangement of Allyl 9-Fluorenecarboxylate

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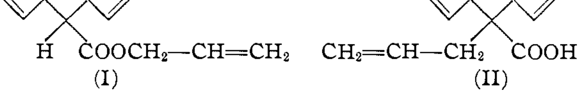
The rearrangement of allyl, *n*-crotyl, and isocrotyl diphenylacetates to the respective α-substituted diphenylacetic acids by means of mesitylmagnesium bromide or sodium hydride has recently been reported.[1] This reaction has now been extended to allyl 9-fluorenecarboxylate.

9-Fluorenecarboxylic acid was prepared from benzilic acid and aluminum chloride by a modification of the method previously described.[2] This modified procedure avoided the intractable emulsions obtained by the published directions and resulted in a better yield and a purer product. An attempt to prepare 9-fluorenecarboxylic acid by the catalytic dehydration of benzilic acid with *p*-toluenesulfonic acid in boiling xylene resulted in the formation of benzilide (the lactide of benzilic acid).

9-Fluorenecarboxylic acid was esterified both by treatment of its acid chloride with allyl alcohol and pyridine and by direct reaction with excess allyl alcohol in the presence of *p*-toluenesulfonic acid. When allyl 9-fluorenecarboxylate (I) was heated under reflux with lithium amide[3] in toluene, a practically quantitative yield of 9-allyl-9-fluorenecarboxylic acid (II) resulted.



(I) (II)

In a similar manner, allyl diphenylacetate was rearranged to allyldiphenylacetic acid by the use of lithium amide.

Preliminary experiments have indicated that, on treatment of benzyl 9-fluorenecarboxylate with lithium amide in toluene, a mixture of acids is obtained. Results from the rearrangement of the benzyl esters will be reported at a later date.

Experimental[4]

9-Fluorenecarboxylic Acid.—A solution of 22.8 g. (0.10 mole) of benzilic acid in 350 ml. of dry, thiophene-free benzene was cooled in ice and the crystalline mass which resulted was treated with 40.0 g. (0.30 mole) of anhydrous aluminum chloride. The mixture was thoroughly shaken, then heated under reflux for three hours. Large quantities of hydrogen chloride were evolved. The resulting dark-red solution was cooled and was cautiously decomposed by the addition of small pieces of ice. The mixture was diluted with 200 ml. of water and 100 ml. of concentrated hydrochloric acid and the benzene was distilled from the reaction. The product was separated by filtration; all the lumps were crushed; then the product was extracted by boiling with 200 ml. of 10% sodium carbonate solution. This extraction was repeated on the undissolved residue with 100 ml. of 10% sodium carbonate solution. The basic filtrates were strongly acidified with concentrated hydrochloric acid, and the resulting suspension was digested on the steam-bath for one-half hour. By filtration 21.0 g. (quantitative yield) of 9-fluorenecarboxylic acid, m. p. 200–225°, was obtained. To purify the product, the dry acid was suspended in 100 ml. of benzene; the mixture was warmed on the steam-bath; the product was recovered by filtration and washed on the filter with 25 ml. of benzene and finally with petroleum ether (b. p. 28–38°). In this way 17.3 g. (82.5%) of 9-fluorenecarboxylic acid, m. p. 226–229°, was obtained. The melting points[2,5] reported for this compound range from 222 to 232°.

Benzilide.—A solution of 10.0 g. of benzilic acid and 2.0 g. of *p*-toluenesulfonic acid in 150 ml. of dry xylene was heated under reflux for two hours and the water which formed was separated by an azeotropic separator. Extraction of the xylene solution with aqueous sodium hydroxide produced only traces of acidic material. The xylene solution was diluted with petroleum ether (b. p. 28–38°). The resulting solution was cooled, and the product was separated by filtration. In this manner, 5.90 g. (64%) of benzilide, m. p. 195–196°, was obtained. The compound is reported to melt at 196°.[6]

Anal. Calcd. for $C_{28}H_{20}O_4$: C, 79.98; H, 4.79. Found: C, 80.07; H, 4.90.

Allyl 9-Fluorenecarboxylate.—A mixture of 17.3 g. of 9-fluorenecarboxylic acid and 50 g. of purified thionyl chloride was heated under reflux for 45 minutes. The excess thionyl chloride was removed *in vacuo*. The residue was dissolved in 75 ml. of dry carbon tetrachloride. The

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[1] R. T. Arnold and S. Searles, Jr., THIS JOURNAL, **71**, 1150 (1949).

[2] D. Vorländer and A. Pritzsche, *Ber.*, **46**, 1793 (1913).

[3] Obtained from the Metalloy Corporation, Rand Tower. Minneapolis, Minnesota.

[4] Microanalyses by Jay Buckley and William Hunter. The melting points were taken on a Fisher-Johns melting point apparatus.

[5] R. Burtner and J. W. Cusic, THIS JOURNAL, **65**, 262 (1943); W. Schlenk and E. Bergmann, *Ann.*, **463**, 98 (1928).

[6] A. Einhorn and C. Mettler, *Ber.*, **35**, 3639 (1902).