impossible to determine yields of these sensitive fulvenes so that only these qualitative results can be given at this time. It is hoped that future refinements in technique may make a more quantitative treatment of this method possible.

EXPERIMENTAL

The ion exchange resins used in these reactions were prepared by first generating their basic forms with 20% aqueous potassium hydroxide, followed by thorough washing with distilled water. They were then washed well with methanol and dried under reduced pressure at room temperature. The dried resins were stored under nitrogen.

Dimethyl fulvene. Forty-four grams (0.67 mole) of cyclopentadiene was cooled to 0° in a 250 ml. glass-stoppered flask and 23 g. of Dowex 1-X10 (a strongly basic quaternary ammonium hydroxide type ion exchange resin) and 29 g. (0.5 mole) of acetone were added rapidly. The temperature of the mixture was permitted to rise slowly to room temperature and after 1.5 hr. a vigorous exothermic reaction commenced. The flask was shaken until the temperature began to fall and the reaction subsided (about 10 min. were required). The dark mixture was then allowed to stand at room temperature overnight. The Dowex 1-X10 was removed by filtration and thoroughly washed with ether, and the washings were combined with the original filtrate. The ether and unreacted starting materials were removed at 80 mm. pressure and the residue was kept at 30°/10 mm. for 1.5 hr. Fractionation of the residue through an 8 × 3/4 in. column packed with berl saddles gave 29.7 g. of the bright yellow dimethyl fulvene boiling from 41.5–45.5°/10 mm., yield 46.7%.

Methyl fulvene. A mixture of 22 g. (0.5 mole) of acetaldehyde and 44 g. (0.67 mole) of cyclopentadiene was introduced into the top of a 10 × 270 mm. column of Permutit A (an anionic exchange resin of medium base strength, consisting primarily of tertiary amine exchange sites) surrounded by a jacket containing circulating methanol cooled to −22 to −24° by an external Dry Ice–acetone bath. The rate of addition was adjusted so that the reactants were in contact with the resin for 1.25 hr., about 7 hr. being required to complete the reaction. The unreacted starting materials were removed at room temperature by distillation through a Dry Ice–cooled column at *ca.* 17 mm. The column was then permitted to warm to room temperature, the pressure was lowered to 0.75 mm. and the receiver was cooled in a Dry Ice–acetone bath. Under these conditions 16.3 g. of a bright yellow distillate (a solid at −70°) was collected without applying heat to the distilling flask. The ultraviolet absorption spectrum of this distillate in methanol showed a strong maximum at 255 mμ and a very weak one at 290 mμ. The absorption spectrum of dimethyl fulvene has a strong maximum at 265 mμ and a weak one a 357,[1] while that of fulvene is reported[3] to have maxima at 242 mμ (strong) and 362 mμ (weak). Thus the strong peak should be due to methyl fulvene.

Ethyl fulvene. In a 300-ml. three neck flask equipped with a stirrer, thermometer, reflux condenser, and addition funnel were placed 19.8 g. (0.30 mole) of cyclopentadiene and 10 g. of Dowex 1-X10. The mixture was cooled to 0° under nitrogen in an ice bath, and 14.5 g. (0.25 mole) of propionaldehyde was added over a 15-min. period while the temperature rose to 10–12°. After an additional 10 min. the mixture was warmed to 25° and the ion exchange resin was rapidly removed by filtration. The red-orange filtrate was transferred to a 50-ml. distilling flask, 3 g. of anhydrous magnesium sulfate was added, and the low-boiling material was removed at 20 mm., using a water bath at 40–50° for a heat source. After 3 hr. under these conditions no further boiling occurred and the orange oil was filtered to yield 14 g. of material. Its ultraviolet absorption spectrum showed a strong maximum at 256 mμ and a weak maximum at 360 mμ (see the previous section).

Fulvene. A mixture of 18.7 g. of 40% aqueous formaldehyde (equivalent to 0.25 mole of formaldehyde), 70 ml. of methanol, and 19.8 g. (0.3 mole) of cyclopentadiene was introduced into the top of a 20 × 150 mm. column of Amberlite IRA 400 (a strongly basic quaternary ammonium hydroxide type resin) at a rate such that the contact time with the catalyst was about 30 sec., 1 hr. being required to complete the reaction. The temperature of the column was maintained at *ca.* 5° throughout the reaction by circulating tap water. The orange oil which separated was removed and the aqueous layer was extracted 5 times with 10-ml. portions of ether. The extracts were combined with the original oil layer, dried over magnesium sulfate, and the solvent and other low boilers removed under reduced pressure as described in the previous sections. The yield of the orange product was 5.3 g. A single rather weak maximum occurred at 240 mμ in its ultraviolet absorption spectrum. This agrees quite well with the strong peak reported for fulvene[3] (see the preparation of methyl fulvene described previously). The absence of the second, weaker absorption at 362 mμ is probably due to the low concentration of the fulvene indicating a lack of purity in the product.

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Succinoylation of the Chloro- and Bromonaphthalenes

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Although the four halobenzenes have been converted to the corresponding β-(*p*-halobenzoyl)-propionic acids with succinic anhydride and aluminum chloride,[2] no successful succinoylation of the halonaphthalenes has been reported.[3] It is shown below that the chloronaphthalenes and 2-bromonaphthalene can be succinoylated, although the yields of pure products are low and the products are sometimes rearranged.

When 1-chloronaphthalene was treated with aluminum chloride and succinic anhydride in either tetrachloroethane or carbon disulfide solutions, an 87% and a 10% yield, respectively, of a mixture of difficultly separatable crude acids was obtained. Separation could best be effected by conversion of the acid mixture to the methyl esters and separation of the esters. From the mixture of methyl

(1) From the Senior Honors thesis of Y. Chu (Mrs. Y. C. Meinwald), 1952, and the M.A. thesis of N. Shieh, 1955.

(2) E. Berliner in *Org. Reactions*, V, Chapter 5 (1949).

(3) The succinoylation of 1-bromo-4-methylnaphthalene has been described as unpromising. R. D. Haworth and C. R. Mavin, *J. Chem. Soc.*, 2720 (1932).

esters pure β-(1-chloro-4-naphthoyl)propionic acid and β-(6-chloro-2-naphthoyl)propionic acid could be isolated. The ratio of pure acids was about 93:7 and they were identified by conversion to the known chloronaphthoic acids. The rearrangement, which must have occurred in the formation of the 2,6-isomer, is analogous to the rearrangement observed in the acylation of 1-chloronaphthalene, when a small amount of 2-chloro-6-acetylnaphthalene is obtained, in addition to the 1,4-product.[4] The succinoylation of 2-chloronaphthalene afforded chiefly β-(6-chloro-2-naphthoyl)-propionic acid, identical with the acid obtained in small amount from 1-chloronaphthalene, as well as a very small amount of an unidentified acid.

With 1-bromonaphthalene no bromo acid could be isolated. Instead, a mixture of β-(1-naphthoyl)- and β-(2-naphthoyl)propionic acid was obtained, as well as higher brominated naphthalenes, most likely 2,6-di- and 1,2,6-tribromonaphthalene. The acid mixture is similar to that obtained on succinoylation of naphthalene, and the formation of the naphthoylpropionic acids probably constitutes a succinoylation of naphthalene, rather than a debromination of bromonaphthoylpropionic acids. That is, it is assumed that the removal of the bromine atom from the 1-position is faster than the possible succinoylation of 1-bromonaphthalene. The formation of naphthalene and of polybromonaphthalenes from bromonaphthalene, as well as the isomerization of the chloro- and bromonaphthalenes, on treatment with aluminum chloride has been known for many years.[5] With 2-bromonaphthalene, a very small amount of β-(6-bromo-2-naphthoyl)propionic acid, identified by hypohalite oxidation to the known 6-bromo-2-naphthoic acid, was obtained.

EXPERIMENTAL

The succinoylations of 1-chloronaphthalene, as well as of the other halonaphthalenes, were conducted by the general procedures described in the literature.[2] In a typical run, 14 g. of aluminum chloride was added over 1 hr. to an ice-cold solution of 0.05 mole each of 1-chloronaphthalene and succinic anhydride in 100 ml. of tetrachloroethane. After 16 hr. at room temperature, the reaction mixture was worked up as usual. The acid mixture weighed 11.5 g. (87%). Numerous fractional crystallizations did not effect a separation into pure acids, although two main fractions were obtained. The best separation was performed when the crude acid mixture was first recrystallized once from ethanol. From a run conducted on 0.2 mole of 1-chloronaphthalene there was obtained a first crop of 17 g. of crystals, while 26 g. more was obtained by diluting the alcoholic filtrate with ice. The 17 g. was esterified with 150 ml. of methanol and 10 ml. of concentrated sulfuric acid. On cooling, 12.65 g. of brownish crystals, melting at 52–54°, separated. The filtrate of this ester was poured onto ice and the mixture was extracted with ether. After washing with a 10% sodium hydroxide solution and drying, the ether was boiled off and the remaining oil was crystallized from methanol, when 0.5 g. of yellow needles, melting at 110–115°, deposited. Two and one half g. of orange crystals (m.p. 48–50°) was obtained from the mother liquor. The 26 g. was treated in the same way, but the yields of pure product were considerably less. After several more crystallizations and combining of appropriate fractions, the over-all yield was 36.5% of the lower melting pure methyl β-(1-chloro-4-naphthoyl)propionate and 2.5% of pure methyl β-(6-chloro-2-naphthoyl)-propionate.

Methyl β-(1-chloro-4-naphthoyl)propionate forms colorless plates from petroleum ether and melts at 53.0–53.5°.[6]

Anal. Calcd. for $C_{15}H_{13}O_3Cl$: C, 65.11; H, 4.74. Found: C, 65.13; H, 4.81.

β-(1-Chloro-4-naphthoyl)propionic acid, obtained from the above ester on basic hydrolysis, was crystallized alternately from benzene and aqueous ethanol, and forms small, colorless needles melting at 161.8–163.3°.

Anal. Calcd. for $C_{14}H_{11}O_3Cl$: C, 64.00; H, 4.22. Found: C, 64.26; H, 4.45.

Oxidation of the above acid with hypochlorite solution[7] afforded 4-chloro-1-naphthoic acid of m.p. 220–222°, after one crystallization from aqueous ethanol (lit.[4] 223–224°). The *p*-bromophenacyl ester, recrystallized from aqueous ethanol, melted at 130.7–131.4° (lit.[8] 130–131°).

Methyl β-(6-chloro-2-naphthoyl)-propionate forms white needles from methanol which melt at 120.0–120.4°.

Anal. Calcd. for $C_{15}H_{13}O_3Cl$: C, 65.11; H, 4.74. Found: C, 65.19; H, 4.89.

β-(6-Chloro-2-naphthoyl)propionic acid, obtained from the above ester, forms white flakes from ethanol, melting at 196.5–197.3°.

Anal. Calcd. for $C_{14}H_{11}O_3Cl$: C, 64.00; H, 4.22. Found: C, 64.09; H, 4.26.

Oxidation of this acid afforded 6-chloro-2-naphthoic acid melting at 280–281°, after two crystallizations from ethanol (lit.[4] 285–286°). The amide was recrystallized from ethanol and melted at 205–206° (lit.[4] 206.5–207°).

The succinoylation of 2-chloronaphthalene (2.5 g.) in tetrachloroethane afforded 3.5 g. (87%) of impure product, melting over a range of 95–133°. Fractional crystallization afforded β-(6-chloro-2-naphthoyl)propionic acid, identical by melting point and mixed melting point with the acid obtained from 1-chloronaphthalene. The residue from the crystallizations contained another acid, but the 0.1 g. of material melting at 145.8–153.2° was not further investigated.

The succinoylation of 1-bromonaphthalene (20.7 g.) in tetrachloroethane afforded in the steam-distillate 9 g. of unchanged starting material, identified by its picrate (m.p. 134–135°), as well as 45 mg. of a solid, m.p. 157.3–158°, from ligroin, which is presumably 2,6-dibromonaphthalene (lit.[9] 160) and 80 mg. of presumably 1,2,6-tribromonaphthalene, m.p. 116.5–117° (lit.[8] 118°). From the acid fraction, about 5–6 g. of yellow material crystallized gradually, from which β-(2-naphthoyl)propionic acid was isolated. It melted at 170.0–172.2° and was identified by a mixed melting point and neutralization equivalent (229.3; calcd. 228.2). The filtrate contained material of neutralization equivalent 231.9, from which the 1-acid was recovered by

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(5) L. Roux, *Bull. soc. chim.*, (2) **45**, 510 (1886); *Ann. chim.*, (6) **12**, 341 (1887). For later references see: C. A. Thomas, *Anhydrous Aluminum Chloride in Organic Chemistry*, Reinhold Publishing Corporation, New York, N. Y., 1941, pp. 692–696, and ref. 4.

(6) Melting points are corrected.

(7) The solution was prepared from commercial "HTH" by the procedure of M. S. Newman and H. L. Holmes in *Org. Syntheses*, **Coll. Vol. 2**, 428 (1948).

(8) D. H. S. Horn and F. L. Warren, *J. Chem. Soc.*, 144 (1946).

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fractional acidification;[10] it was identified by melting point and mixed melting point. Small amounts of unidentified acidic material remained behind. The results in runs in nitrobenzene were similar, except that no di- or tribromonaphthalenes were obtained.

2-Bromonaphthalene (10 g.) was succinoylated in nitrobenzene solution. The crude acid weighed 4.4 g. Repeated recrystallizations from methanol afforded eventually 0.35 g. (2.4%) of yellow crystals of β-(6-bromo-2-naphthoyl)-propionic acid, which started to change color at 198° and decomposed at 207°.

Anal. Calcd. for $C_{14}H_{11}O_3Br$: C, 54.74; H, 3.61. Found: C, 54.82; H, 3.70.

Small amounts of β-(2-naphthoyl)propionic acid were obtained from the mother liquor. In tetrachloroethane the yields of pure acid were even smaller.

Hypohalite oxidation of the above acid afforded 6-bromo-2-naphthoic acid, which after two crystallizations from ethanol melted with decomposition at 279–286° (lit.[11] 280° dec.). The methyl and ethyl esters, after crystallizations from methanol and ethanol, respectively, melted at 122.0–123.5° and at 66.5–68.0° (lit.[11] 123–124.5° and 67–68°).

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A Reactive Peptide Intermediate Derived from Ethoxyacetylene

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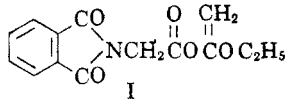
Our studies[2,3] of peptide synthesis in aqueous solution prompted us to investigate the possible utility of ethoxyacetylene[4] under these conditions. An aqueous solution of ethoxyacetylene, phthaloylglycine, and glycine ethyl ester deposited a solid, which was composed of the expected phthaloylglycylglycine ethyl ester[5] and a neutral product in an approximate ratio of 1:8.

The analytical data for the major product supported a structure arising from a 1/1 addition of acid and ethoxyacetylene.

The reaction of the adduct and ethyl glycinate at 60° and at room temperature in anhydrous solvents gave 80% and 75% respectively of phthaloylglycylglycine ethyl ester. These results rule out the symmetrical anhydride of phthaloylglycine, a plausible structure since ethoxyacetylene is known to convert acids to anhydrides,[6]

An infrared spectrum of a chloroform distillate om the reaction of the adduct and ethyl glycinate was identical to that of an ethyl acetate in chloroform solution. The isolation of ethyl acetate is convincing evidence for structure I. Similar results were obtained with phthaloyl-L-phenylalanine.



I

In the examples of peptide synthesis using alkoxyacetylenes published by Arens and coworkers[4] no case was reported in which the possibility of racemization by an azlactonization mechanism existed. We have prepared carbobenzyloxyglycyl-L-phenylalanylglycine ethyl ester[7] from carbobenzyloxyglycyl-L-phenylalanine and glycine ethyl ester with no sign of racemization.

EXPERIMENTAL[8]

1-Ethoxyvinyl phthaloylglycinate (I). A solution of 0.6 g. (2.93 mmoles) of phthaloylglycine[9] and 0.302 g. (2.93 mmoles) of glycine ethyl ester in 6 ml. of water and 0.6 ml. of ethoxyacetylene[10] was stirred at room temperature for 2 hr. The solid, which separated slowly, amounted to 300 mg.; m.p. 102–107°. Recrystallization from benzene and petroleum ether (30–60°) gave as a first crop (yield, 36 mg.) a crystalline product which proved to be identical with phthaloylglycylglycine ethyl ester.[5] The filtrate was evaporated to dryness under reduced pressure and the residue was crystallized from ether, 200 mg., m.p. 108–110°.

Anal. Calcd. for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.36; H, 4.91; N, 5.15.

Phthaloylglycylglycine ethyl ester.[5] *A.* A solution of 50 mg. (0.182 mmole) of the adduct I and 19 mg. (0.182 mmole) of glycine ethyl ester in 1 ml. of dioxane was heated at 50° for 30 min. The dioxane solution was freeze dried and the residue crystallized from ethanol; yield, 42 mg. (80%); m.p. 191–193°. The melting point of a mixture with authentic phthaloylglycylglycine ethyl ester did not show a depression.

B. A solution of 19 mg. (0.182 mmole) of ethyl glycinate and 50 mg. (0.182 mmole) of I in 3 ml. of methylene chloride was stored at room temperature for 4 hr. Removal of the solvent and crystallization from ethanol afforded a product (40 mg.; 75%) which was identical to the product obtained in Run A.

Isolation of ethyl acetate from I. A solution of 400 mg. (1.5 mmole) of I and 152 mg. (1.5 mmole) of glycine ethyl ester in 0.5 ml. of chloroform was heated at reflux for 30 min. The solvent was then distilled until 0.25 ml. was collected. An infrared spectrum of this distillate was identical to one of ethyl acetate in chloroform. The residue yielded 480 mg. of phthaloylglycylglycine ethyl ester; m.p. 191–192°.

Carbobenzyloxyglycyl-L-phenylalanylglycine ethyl ester.[7] A mixture of 0.15 g. (0.42 mmole) of carbobenzoxyglycyl-L-phenylalanine, 43 mg. (0.42 mmole) of glycine ethyl ester, and 0.5 ml. of ethoxyacetylene was heated under reflux for 30 min. The excess ethoxyacetylene was distilled under reduced pressure. The oily residue was dissolved in 6 ml. of

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