[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

Fluorinated Aromatic Amino Acids. I. *o*-, *m*-, and *p*-Trifluoromethylphenylalanines[1]

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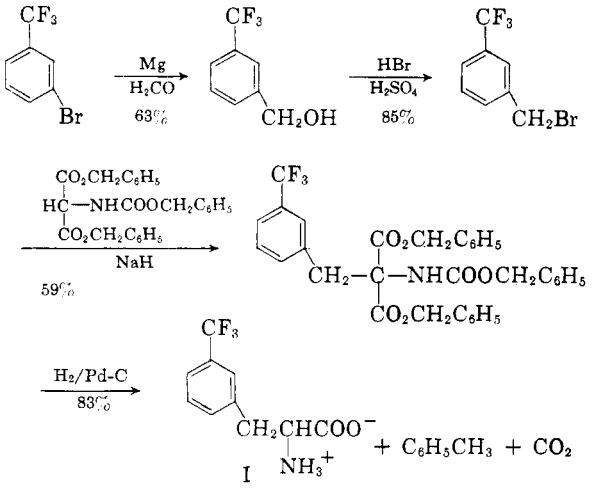
o-, *m*-, and *p*-Trifluoromethyl-*dl*-phenylalanines have been synthesized as part of a study of the effect of the trifluoromethyl group on the physical properties and physiological activity of aromatic amino acids. The *m*-amino acid was prepared in an over-all yield of 25% from *m*-bromobenzotrifluoride using the carbobenzyloxyaminomalonate method. This route failed for the preparation of the *o*-trifluoromethyl amino acid. All three amino acids were obtained *via* the corresponding unsaturated azlactones. The trifluoromethyl group exhibited remarkable hydrolytic stability under the strongly acidic conditions employed during these procedures.

Aromatic amino acids substituted with fluorine atoms in the aromatic nucleus have been prepared previously and have been shown to possess significant physiological activity. Thus, Schiemann and Winkelmuller[2] and later, English, Mead, and Niemann,[3] synthesized 3-fluoro-*dl*-tyrosine. May and Litzka[4] reported that this compound inhibited tumor growth in animals in which carcinoma had been experimentally induced. The three fluoro-*dl*-phenylalanines and 5-fluoro-*dl*-tryptophan, have also been prepared.[5-7]

We now wish to report the synthesis of the *o*-, *m*-, and *p*-trifluoromethyl-*dl*-phenylalanines as part of a study of the physical properties and physiological activity of trifluoromethyl aromatic amino acids.

m-Trifluoromethyl-*dl*-phenylalanine (I) was obtained in 25% overall yield *via* the method outlined in Chart A:

Chart A



m-Trifluoromethylbenzyl alcohol, prepared from the readily available *m*-bromobenzotrifluoride, was smoothly converted in 85% yield to the benzyl bromide by refluxing with 48% hydrobromic acid and concentrated sulfuric acid for six hours. There was no evidence of any hydrolysis of the trifluoromethyl group to carboxyl under these conditions. This is in contrast to several reports that the trifluoromethyl group is labile under strongly acid conditions.[8] It has been our experience that longer reflux periods are often required to effect this hydrolysis. The nature of other nuclear substituents also plays an important role.

m - Trifluoromethylbenzyl bromide was then treated with dibenzyl carbobenzyloxyaminomalonate[9] in refluxing toluene in the presence of sodium hydride to give a 59% yield of the condensation product. This material was readily converted to I in 83% yield by hydrogenolysis using palladium on charcoal. This debenzylation and decarboxylation step was similar to that described by Kissman and Witkop.[10]

o-Trifluoromethylbenzyl bromide was prepared from *o*-chlorobenzotrifluoride[11] *via* the benzyl al-

(1) This work was supported by a grant (CY-2879) from the National Cancer Institute, National Institutes of Health, USPHS. Presented in part at the 136th National Meeting of the American Chemical Society, Atlantic City, N. J., September 1959.

(2) G. Schiemann and W. Winkelmuller, *Ber.*, **66B**, 727 (1933).

(3) J. English, J. J. Mead, and C. Niemann, *J. Am. Chem. Soc.*, **62**, 350 (1940).

(4) N. May and G. Litzka, *Z. Krebsforsch.*, **48**, 376 (1939); *Chem. Abstr.*, **33**, 4662 (1939).

(5) G. Schiemann and M. Roselius, *Ber.*, **65**, 1439 (1932).

(6) H. K. Mitchell and C. Niemann, *J. Am. Chem. Soc.*, **69**, 1232 (1947).

(7) H. Rinderknecht and C. Niemann, *J. Am. Chem. Soc.*, **72**, 2296 (1950).

(8) (a) M. Hauptschein, E. A. Nodiff, and A. J. Saggiomo, *J. Am. Chem. Soc.*, **76**, 1051 (1954); (b) H. Gilman and D. Blume, *J. Am. Chem. Soc.*, **65**, 2467 (1943); (c) G. M. LeFave, *J. Am. Chem. Soc.*, **71**, 4148 (1949); (d) P. M. Maginnity and C. A. Gaulin, *J. Am. Chem. Soc.*, **73**, 3579 (1951).

(9) We wish to thank Dr. Marcel Harnik of Chemetron Corp., Newport, Tenn., for a sample of this material which was prepared from the diethyl ester by refluxing with excess benzyl alcohol in the presence of sodium hydride. Kissman and Witkop (ref. 10) prepared the dibenzyl ester by the reaction of dibenzylaminomalonate with benzyl chlorocarbonate.

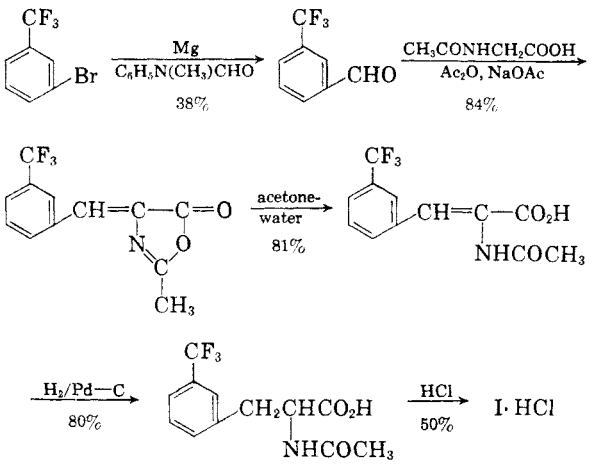
(10) H. M. Kissman and B. Witkop, *J. Am. Chem. Soc.*, **75**, 1967 (1953).

(11) *o*- and *p*-Chlorobenzotrifluoride were generously supplied by Hooker Electrochemical Co.

cohol. Attempted condensation of this bromide with dibenzyl carbobenzyloxyaminomalonate under several reaction conditions failed to yield an isolable product. It seems possible that the *o*-trifluoromethyl group may cause steric retardation of the condensation. No attempt was made to prepare *p*-trifluoromethyl-*dl*-phenylalanine by this procedure.

The successful synthesis of all three isomeric trifluoromethyl-*dl*-phenylalanines as their hydrochlorides was accomplished *via* the azlactone route which has been employed for *dl*-phenylalanine.[12] The free amino acids were then obtained by passing the hydrochloride salts through a column containing Dowex-3, a weakly basic ion-exchange resin. The method used is illustrated for the *m*-trifluoromethyl isomer (I) in Chart B.

Chart B



The preparation of *m*-trifluoromethylbenzaldehyde from the bromo Grignard reagent and *N*-methylformanilide has been described.[13] Our yield of 38% of pure aldehyde however, was considerably lower than the 52–59% previously reported.[13] It should be mentioned that autoxidation of this aldehyde to *m*-trifluoromethylbenzoic acid occurred within several hours at room temperature, so that the reaction with aceturic acid to form 2-methyl-4-(*m*-trifluoromethylbenzylidene)-5(4H)-oxazolone was carried out as soon as the aldehyde had been distilled. The azlactone ring was readily opened by refluxing with an acetone-water mixture to form α-acetamido-β(*m*-trifluoromethylphenyl) acrylic acid in 81% yield. Catalytic hydrogenation gave α-acetamido-β(*m*-trifluoromethylphenyl)propionic acid. The acetamido group was then hydrolyzed by refluxing with concentrated hydrochloric acid for ten hours to form the amino acid I as its hydrochloride. The trifluoromethyl group once again remained intact throughout the procedure.

When hippuric acid was substituted for aceturic acid in the azlactone synthesis and the subsequent steps carried out, it was found that the final hydrolysis of the benzamido group to give I could not be readily effected. Therefore, the *ortho*- and *para*-substituted amino acids were also obtained from the acetamido compounds.

The *ortho*-isomer was prepared by analogous reactions starting with *o*-chlorobenzotrifluoride.[11] The preparation of the Grignard reagent required the use of tetrahydrofuran in place of ether and the yield of aldehyde was only 20–25%.

An attempt to form this aldehyde from *o*-trifluoromethylphenyllithium was unsuccessful, although carbonation gave a good yield of *o*-trifluoromethylbenzoic acid, in agreement with Roberts and Curtin.[14] *p*-Trifluoromethylphenylmagnesium chloride was even more difficult to prepare although many sets of reaction conditions were tried. The difficulties may be due in large measure to the passivity of the surface of magnesium. Results were inconsistent, although we were successful in several small runs in isolating small amounts of *p*-trifluoromethylbenzoic acid after carbonation. These results are in agreement with those reported previously.[15] Attempts to form the organolithium compound using lithium dispersion or *n*-butyllithium, failed, however. The *para*-aldehyde was satisfactorily prepared from the Grignard reagent formed from *p*-bromobenzotrifluoride,[16] and the amino acid subsequently obtained *via* the azlactone.

The physical properties of these new "unnatural" amino acids are being examined and will be reported separately. The possibility that these compounds may exhibit physiological activity as amino acid antimetabolites is also being explored.

EXPERIMENTAL[17]

m-Trifluoromethylbenzyl alcohol. *m*-Bromobenzotrifluoride (112.5 g., 0.5 mole) in 100 cc. of dry ether was added dropwise to a mixture of 18 g. of magnesium in 200 cc. of dry ether. After the reaction subsided, stirring was continued for 1 hr. Paraformaldehyde (30 g.) was introduced into the system according to the procedure of Gilman[18] to produce 55 g. of product. The alcohol distilled at 86° (3 mm.) n_D^{21} 1.4597, yield 63% (lit.,[19] b.p. 100° (10 mm.), n_D^{25} 1.4574, yield 38%).

Anal. Calcd. for $C_8H_7OF_3$: C, 54.55; H, 4.01. Found: C, 54.63; H, 3.93.

m-Trifluoromethylbenzyl bromide. *m*-Trifluoromethylbenzyl alcohol (35.2 g.) was heated under reflux with 88 g. of 48%

(12) *Org. Synthesis*, Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y. (1943), p. 491.

(13) H. Gilman, L. Tolman, F. Yeoman, L. A. Woods, D. A. Shirley, and S. Avakian, *J. Am. Chem. Soc.*, **68**, 426 (1946).

(14) J. D. Roberts and D. Y. Curtin, *J. Am. Chem. Soc.*, **68**, 1658 (1946).

(15) H. E. Ramsden, A. E. Balint, W. R. Whitford, J. J. Walburn, and R. Cserr, *J. Org. Chem.*, **22**, 1202 (1957).

(16) M. Markarian, *J. Am. Chem. Soc.*, **74**, 1858 (1952).

(17) Melting points are uncorrected. Analyses by Micro-Tech Laboratories, Skokie, Ill.

(18) *Org. Synthesis*, Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y. (1941), p. 188.

(19) H. H. Szmant, J. F. Anzenberger, and R. Hartle, *J. Am. Chem. Soc.*, **72**, 1419 (1950).

aqueous hydrobromic acid and 13 cc. of concd. sulfuric acid for 6 hr. Evidence of reaction could be observed since the alcohol layer was less dense and the organic bromide layer more dense than the aqueous layer. The bromide layer was separated, washed with concd. sulfuric acid to remove unchanged benzyl alcohol, washed twice with water, and dried. Distillation gave 41 g. (85%) of bromide, b.p. 69° (4 mm.) n_D^{25} 1.4895. This compound is a strong lachrymator.

Dibenzyl m-trifluoromethylbenzylcarbobenzyloxyaminomalonate. In a dry 250-cc. 3-necked flask, fitted with a stirrer and reflux condenser connected to a mercury-filled bubble counter, and swept with dry nitrogen, was placed 9.0 g. of *m*-trifluoromethylbenzyl bromide and 0.9 g. of sodium hydride to which was added a hot solution of 16.3 g. of dibenzyl carbobenzyloxyaminomalonate[10] in dry toluene. The mixture was heated under reflux for 45 min., the solution cooled and a few cc. of glacial acetic acid added, followed by 3 cc. of ethanol (to dissolve the unchanged sodium hydride). Fifty cc. of water and 50 cc. of ether were added, the mixture shaken, and the organic layer was separated, washed with water, and taken to dryness *in vacuo* to give 13.1 g. (59%) of a white solid, recrystallized from petroleum ether, m.p. 88–88.5°.

Anal. Calcd. for $C_{33}H_{28}NO_6F_3$: C, 67.00; H, 4.77. Found: C, 67.27; H, 4.96.

m-Trifluoromethylphenylalanine. The hydrogenolysis of the condensation product using palladium on charcoal in glacial acetic acid yielded the amino acid. Two recrystallizations from 95% ethanol gave a slightly impure product. The final purification was effected by sublimation at 160° and 1 mm. pressure. The amino acid, obtained in 83% yield, decomposed at 219–222°.

Anal. Calcd. for $C_{10}H_{10}HO_2F_3$: C, 51.50; H, 4.32; N, 6.01. Found: C, 51.40; H, 4.28; N, 6.25.

o-Trifluoromethylbenzyl alcohol. *o*-Chlorobenzotrifluoride[11] (91 g., 0.5 mole), 13 g. of dry magnesium turnings, 5 cc. of ethyl bromide (used as an "entrainer"), and 200 cc. of tetrahydrofuran were stirred vigorously. The exothermic reaction proceeded smoothly after an induction period. One hour after the tetrahydrofuran stopped refluxing, paraformaldehyde (30 g.) was introduced into the system to produce 30 g. (34%) of product, b.p. 82–83° (3.5 mm.), $n_D^{25.5}$ 1.4657; α-naphthyl urethan, m.p. 129.5–130.5°.

Anal. Calcd. for $C_{19}H_{14}NO_2F_3$: C, 66.08; H, 4.09. Found: C, 66.03; H, 4.18.

3,5-Dinitrobenzoate, m.p. 73–73.5°.

Anal. Calcd. for $C_{15}H_9N_2O_6F_3$: C, 48.66; H, 2.45. Found: C, 48.24; H, 2.55.

o-Trifluoromethylbenzyl bromide. *o*-Trifluoromethylbenzyl bromide, b.p. 72° (7.5 mm.), n_D^{26} 1.4961 was prepared in 80% yield in a manner similar to that used for *m*-trifluoromethylbenzyl bromide.

Anal. Calcd. for $C_8H_6F_3Br$: C, 40.19; H, 2.53. Found: C, 40.40, H, 2.56.

Attempted condensation of o-trifluoromethylbenzyl bromide with dibenzyl carbobenzyloxyaminomalonate. The procedure described above for the *meta-* analog gave a brown oil in this case. The oil failed to crystallize and similar procedures using dimethylformamide and tetrahydrofuran as solvents were also unsuccessful. An attempt to prepare the α-amino acid by hydrogenolysis of this oily material yielded an oil which gave a negative ninhydrin reaction.

m-Trifluoromethylbenzaldehyde. *m*-Trifluoromethylbenzaldehyde was prepared in 38% yield according to the procedure of Gilman and co-workers,[13] b.p. 80–82° (21 mm.), n_D^{20} 1.4659 (lit.,[13] b.p. 64–66° (10 mm.), n_D^{20} 1.4660, yield 52–59%).

o-Trifluoromethylbenzaldehyde. Method A. The Grignard reagent was formed as before from 0.5 mole of *o*-chlorobenzotrifluoride. One hour after the tetrahydrofuran had stopped refluxing, 68 g. of *N*-methylformanilide were added as rapidly as the rate of reflux would permit. The mixture was stirred for an additional hour. Aqueous sulfuric acid (10%) was carefully added in sufficient quantity to decompose the aldehyde complex and unchanged magnesium. The aqueous layer was separated from the tetrahydrofuran layer, extracted with ether and the extract added to the tetrahydrofuran. The organic layer was neutralized with 10% aqueous sodium bicarbonate, then washed twice with water, dried over anhydrous magnesium sulfate, filtered, and the filtrate concentrated on a steam bath. The liquid residue was distilled to give 18 g. (20%) of amber-colored aldehyde boiling at 61–67° (16 mm.), n_D^{25} 1.4640.

Method B. *o*-Trifluoromethylbenzyl bromide (*vide supra*) (24 g., 0.10 mole) was added to a solution formed from 100 cc. of absolute ethanol, 2.3 g. of sodium and 11.6 g. of 2-nitropropane according to the procedure of Hass and Bender[20] to yield 6 g. (35%) of aldehyde, b.p. 72° (20 mm.), n_D^{25} 1.4640.

p-Trifluoromethylbenzaldehyde. *p*-Bromobenzotrifluoride[16] (40 g.) in 50 cc. of dry ether was added dropwise to a mixture of 10 g. of magnesium in 100 cc. of dry ether after a 3-hr. induction period. After the reaction subsided, stirring was continued for 1 hr. *N*-Methylformanilide (24 g.) was added as quickly as the exothermic reaction would permit and after 1 hr. of stirring the product was isolated in a manner similar to that used for the corresponding *ortho-* aldehyde (Method A), to yield the *para-* aldehyde (40%), b.p. 64.5° (13 mm.), n_D^{20} 1.4630 (lit.[20] b.p. 66–67° (13 mm.), n_D^{20} 1.4630).

(a) *2-Phenyl-4-o-trifluoromethylbenzylidene-5-oxazolone;* (b) *2-phenyl-4-m-trifluoromethylbenzylidene-5-oxazolone.* Freshly distilled *o*-trifluoromethylbenzaldehyde (5 g.), 5.5 g. of hippuric acid, 8.5 g. of acetic anhydride, and 2.4 g. of sodium acetate were treated according to the usual procedure for preparation of unsaturated azlactones[21] to give a 33% yield of the azlactone, yellow crystals, m.p. 132.5–133.5°.

Anal. Calcd. for $C_{17}H_{10}NO_2F_3$: C, 64.35, H, 3.18. Found: C, 64.26, H, 3.24.

The *m*-trifluoromethyl azlactone was prepared similarly, in 79% yield, m.p. 138.5–139°.

Anal. Calcd. for $C_{17}H_{10}NO_2F_3$: C, 64.35; H, 3.18. Found: C, 64.76; H, 3.36.

(a) *α-Benzamido-β(o-trifluoromethylphenyl) acrylic acid;* (b) *α-benzamido-β(m-trifluoromethylphenyl) acrylic acid.* The two oxazolones were hydrolyzed with 10% sodium hydroxide, followed by acidification to give acid a in 79% yield, m.p. 184–185° and acid (b) (74%) m.p. 214–215°. Both compounds were recrystallized from acetone-water mixtures.

Anal. Calcd. for $C_{17}H_{12}NO_3F_3$: C, 60.90; H, 3.61. Found, compound (b): C, 60.81; H, 3.63.

(a) *2-Methyl-4-o-trifluoromethylbenzylidene-5-oxazolone;* (b) *2-methyl-4-m-trifluoromethylbenzylidene-5-oxazolone;* (c) *2-methyl-4-p-trifluoromethylbenzylidene-5-oxazolone.* Freshly prepared *m*-trifluoromethylbenzaldehyde[13] (41 g.), 18.6 g. of aceturic acid, 42 g. of acetic anhydride, and 9.6 g. of sodium acetate were mixed and heated according to a previously described procedure[22] to yield 2-methyl-4-*m*-trifluoromethylbenzylidene-5-oxazolone (b) in 84% yield, m.p. 130–131°. The *ortho-* substituted azlactone (*a*), prepared similarly in 30% yield, melted at 116–117°. The *p*-trifluoromethyl azlactone (*c*) m.p. 113.5–114.5°, was obtained in 80% yield.

Anal. Calcd. for $C_{12}H_8NO_2F_3$: C, 56.48; H, 3.16. Found: *ortho-* compound: C, 56.28; H, 3.14; *meta-* compound: C, 56.90; H, 3.31; *para-* compound: C, 56.39; H, 3.25.

(a) *α-Acetamido-β(o-trifluoromethylphenyl) acrylic acid;* (b) *α-acetamido-β(m-trifluoromethylphenyl) acrylic acid;* (c) *α-acetamido-β(p-trifluoromethylphenyl) acrylic acid.* The oxazolones described above (10 g.) were hydrolyzed in a solvent

(20) H. B. Hass and M. L. Bender, *J. Am. Chem. Soc.*, **71**, 1767 (1949).

(21) *Org. Syntheses*, **Coll. Vol. II**, John Wiley and Sons, Inc., New York, N. Y. (1943), p. 55.

(22) *Org. Syntheses*, **Coll. Vol. II**, John Wiley and Sons, Inc., New York, N. Y. (1943) p. 1.

consisting of 96 cc. of acetone and 38 cc. of water[22] to yield 53% of (*a*), m.p. 180–181°, 81% of (*b*), m.p. 225–226° and 59% of (*c*), m.p. 201.5–202.5°. The acids were recrystallized from acetone-water.

Anal. Calcd. for $C_{12}H_{10}NO_3F_3$: C, 52.75; H, 3.69. Found: *ortho-* compound: C, 53.24; H, 4.02; *meta-* compound: C, 52.51; H, 3.76; *para-* compound: C, 52.83; H, 3.56.

(a) *N-Acetyl-o-trifluoromethylphenylalanine;* (b) *N-acetyl-m-trifluoromethylphenylalanine;* (c) *N-acetyl-p-trifluoromethylphenylalanine;* (d) *N-benzoyl-o-trifluoromethylphenylalanine and* (e) *N-benzoyl-m-trifluoromethylphenylalanine.* In a typical reaction, 10 g. of the substituted acrylic acid was dissolved in 95% ethanol to which was added 1 g. of 5% palladium on charcoal. The mixture was shaken for 3 hr. in the presence of 40 lb. pressure of hydrogen. After filtering the mixture, the colorless filtrate was concentrated *in vacuo* and the solid residue recrystallized from acetone-water to yield 8 g. of product: (*a*) m.p. 179–180°, (*b*) m.p. 132–133°, (*c*) m.p. 178–178.5°, (*d*) m.p. 172–173°, and (*e*) m.p. 167–168°.

Anal. Calcd. for $C_{12}H_{12}NO_3F_3$: C, 52.36; H, 4.40. Found, compound (*b*): C, 52.49; H, 4.42.

Anal. Calcd. for $C_{17}H_{14}NO_3F_3$: C, 60.53; H, 4.18. Found, compound (*e*): C, 60.59; H, 4.05.

(a) *o-Trifluoromethylphenylalanine hydrochloride;* (b) *m-trifluoromethylphenylalanine hydrochloride;* (c) *p-trifluoromethylphenylalanine hydrochloride.* In a typical reaction, 5 g. of the *N*-acetylphenylalanine was hydrolyzed with 100 cc. of concd. hydrochloric acid under reflux for 10 hr. After concentrating the aqueous mixture, a white crystalline solid separated. The pure amino acid hydrochloride was dried *in vacuo*. A second crop of less pure product was obtained on further concentration. The total yield was 2.5 g. (51%). The *N*-benzoyl analogs were much more resistant to hydrolysis under a variety of conditions and no amino acids could be isolated. The decomposition points of the *o-*, *m-*, and *p*-trifluoromethyl amino acid hydrochlorides were 190–195°, 199–202°, and 196–203°, respectively.

Anal. Calcd. for $C_{10}H_{11}NO_2F_3Cl$: C, 44.54; H, 4.11; N, 5.19. Found: *o*-amino acid: C, 44.32; H, 4.15; N, 5.05; *m*-amino acid: C, 44.56; H, 4.23; N, 5.03; *p*-amino acid: C, 44.76; H, 3.92; N, 4.65.

(a) *o-Trifluoromethylphenylalanine;* (b) *m-trifluoromethylphenylalanine;* (c) *p-trifluoromethylphenylalanine.* In a typical conversion, 1 g. of the amino acid hydrochloride was dissolved in 50 cc. of hot water and the resulting solution passed through a column of Dowex-3 (a weakly basic ion-exchange resin). Hot water was then passed through the column until amino acid could no longer be detected in the eluate (ninhydrin test). The eluate gave a negative test for chloride ion. The solution was distilled *in vacuo* on a steam bath and the resulting solid collected and dried.

CHICAGO 16, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WEST VIRGINIA UNIVERSITY]

Condensation Reactions of a Nitro Group. II.[1] Preparation of Phenanthridine-5-oxides and Benzo(c)cinnoline-1-oxide[2]

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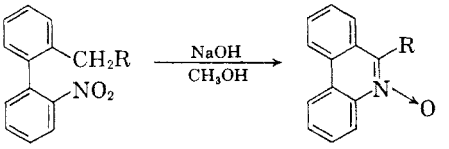
Additional examples in the biphenyl series of the condensation of a nitro group in the 2-position with an activated methylene group in the 2′-position in the presence of methanolic sodium hydroxide have been found. The additional activating groups are benzoyl and benzenesulfonyl; the phenyl group did not serve as an activator. Apparently, the benzoyl and benzenesulfonyl compounds underwent ring closure followed by nucleophilic displacement reactions by hydroxide ion to produce benzoate and benzenesulfinate ions, respectively. 2-Amino-2′-nitrobiphenyl reacted with both sodium hydroxide and sodium methoxide in methanol to yield benzo(c)cinnoline-1- oxide. The intramolecular reaction of a nitro group was not observed in appropriate test compounds outside the biphenyl series.

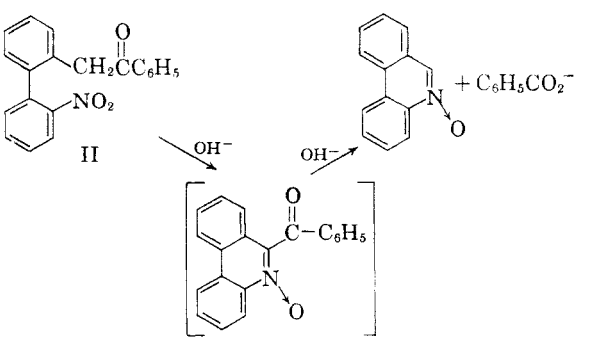
DISCUSSION

Recently it was reported[1] that certain biphenyls of the following type react with methanolic sodium hydroxide to form 6-substituted phenanthridine-5-oxides. The present paper deals with syntheses and testing of additional compounds to determine more about the generality of the foregoing ring closure reaction.



Type I R = CN, CO_2CH_3, $CONH_2$

Three more type I compounds have been treated with methanolic sodium hydroxide. First, with R as benzoyl in 2-(benzoyl)methyl-2′-nitrobiphenyl (II) ring closure occurred to produce phenanthridine-5-



(1) Paper I, C. W. Muth, J. C. Ellers, and O. F. Folmer, *J. Am. Chem. Soc.*, **79**, 6500 (1957).

(2) Supported by the National Science Foundation Research Grant G-4236, whose help we wish to gratefully acknowledge. In part from the master's thesis of R. B. Wotring, 1958, and N. Abraham, 1960, both from West Virginia University.