

3. These transitions may all be regarded as successive stages of melting, the phases intermediate between crystal and liquid being of a

mesomorphic nature.

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Fluorenones and Diphenic Acids. VI.¹ Ring Cleavage of 2-Chloro-, 2-Hydroxy-, 2-Amino- and 2-Sulfofluorenones with Potassium Hydroxide in Diphenyl Ether

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In connection with studies of the action of concentrated sulfuric acid upon substituted diphenic acids which has for some time³ been in progress in this Laboratory the use of alkali as a means of fission of the ketonic linkage of substituted fluorenones has been examined. Since the preparation of *o*-phenylbenzoic acid by potassium hydroxide fusion of fluorenone⁴ affords excellent yields and since alkali fusion of unsymmetrical ketones recently has been shown to proceed smoothly in certain other cases,⁵ we have examined this process to determine whether the conditions could be so modified that fission of the fluorenone ring would occur without (serious) action on nuclear substituents. The demonstrated necessity (see Experimental Part) of absolutely avoiding reducing solvents compelled us to try inert materials even though the alkali was thus merely suspended, and after some attempts with biphenyl we discovered that the desired ketonic cleavage could be effected by using potassium hydroxide in diphenyl ether at about 180°. A large excess (*e. g.*, *ca.* 15 mols.) of fused potassium hydroxide vigorously stirred at 180–200° with fluorenone dissolved in diphenyl ether gave a quantitative yield of *o*-phenylbenzoic acid of excellent purity. The present paper reports the results obtained with several fluorenones substituted in the 2-position.

(1) Presented at the Rochester meeting of the American Chemical Society, September, 1937.

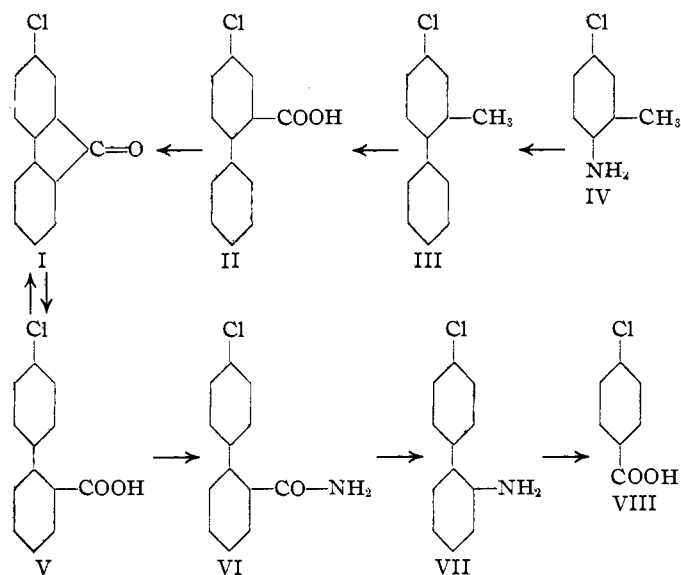
(2) From a dissertation submitted by Miss Seikel to the Faculty of the Massachusetts Institute of Technology, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1938.

(3) Previous papers: (a) I, Huntress, Hershberg and Cliff, *THIS JOURNAL*, **53**, 2720–2724 (1931); (b) II, Huntress and Cliff, *ibid.*, **54**, 826–828 (1932); (c) III, Huntress and Cliff, *ibid.*, **55**, 2559–2567 (1933); (d) IV, Huntress, Cliff and Atkinson, *ibid.*, **55**, 4262–4271 (1933); (e) V, Huntress and Atkinson, *ibid.*, **58**, 1514–1518 (1936).

(4) Fittig and Ostermayer, *Ann.*, **166**, 374 (1873).

(5) Bachmann, *THIS JOURNAL*, **57**, 737–738 (1935).

2-Chlorofluorenone (I).—Upon heating this compound with potassium hydroxide in diphenyl ether a nearly quantitative yield of 4'-chlorobiphenyl-2-carboxylic acid (V) was obtained. The identity of this acid was attested in several ways.



First, upon treatment with concentrated sulfuric acid it was reconverted to the original 2-chlorofluorenone. Second, the cleavage acid (V) was converted with phosphorus pentachloride to the corresponding acid chloride (not isolated) and thence with ammonia (in benzene) to the corresponding 2-(4'-chlorophenyl)benzamide (VI) which was then degraded by application of the Hofmann reaction to the corresponding amine, *viz.*, 4'-chloro-2-aminobiphenyl (VII). The acetyl derivative of this amine melted in accordance with the recorded value and the amine itself on oxidation with alkaline potassium permanganate gave *p*-chlorobenzoic acid (VIII). This formation of *p*-chlorobenzoic acid is consistent only with that formulation (V) of the two conceivable

cleavage acids in whose structure the chlorine atom and the carboxyl group are in different nuclei.

To support still further the preceding evidence for the structure (V) assigned to the cleavage acid, we have also synthesized the isomeric 4-chlorobiphenyl-2-carboxylic acid (II). This was effected by coupling diazotized 5-chloro-2-aminotoluene (IV) with benzene, by a process analogous to that employed by Gomberg⁶ for the corresponding bromo analog, to yield 4-chloro-2-methylbiphenyl (III). The structure of this intermediate was certified by its oxidation with chromic trioxide in glacial acetic acid to the known 4-chloro-2-methylbenzoic acid. Upon oxidation with alkaline permanganate, however, it yielded the desired 4-chlorobiphenyl-2-carboxylic acid (II). This product was characterized by its conversion with concentrated sulfuric acid to 2-chlorofluorenone (I). Although the absolute values of the melting points of the cleavage acid (V), m. p. 165.5–166°, and the synthetic isomer (II), m. p. 157–158°, are not far apart, yet the melting point of their mixture showed profound lowering (125–145°).

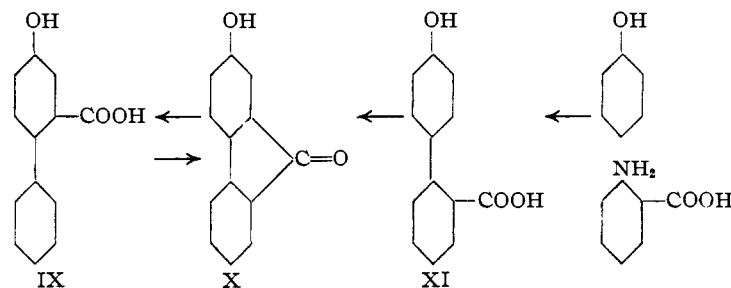
These experiments definitely establish the identity of both of the acids to be expected from the alkaline fission of the ketonic ring of 2-chlorofluorenone. The high melting point (159–161°) and nearly quantitative yield of the actual crude fission product both indicate, however, that 4'-chlorobiphenyl-2-carboxylic acid composes by far its main constituent. A bond connecting the ketonic linkage of the fluorenone series to the nucleus is weakened by the presence of a nuclear chlorine in meta relationship. This effect is opposite to that observed by Bachmann⁵ for a meta methyl group in benzophenones. The excellent yield of chloro acid shows, moreover, that opening of the fluorenone ring can be accomplished without replacement of the halogen by a phenolic group.

2-Hydroxyfluorenone (X).—Cleavage of 2-hydroxyfluorenone gave a 50% yield of 4-hydroxybiphenyl-2-carboxylic acid (IX).

The identity of this compound was established by analysis, by its conversion with concentrated sulfuric acid to 2-hydroxyfluorenone,

(6) (a) Gomberg and Bachmann, *THIS JOURNAL*, **46**, 2339–2343 (1924); (b) Gomberg and Pernert, *ibid.*, **48**, 1372–1384 (1926).

and by its non-identity with the isomeric 4'-hydroxybiphenyl-2-carboxylic acid (XI).⁷



Of the two hydroxybiphenyl-2-carboxylic acids which might be expected from alkaline fusion of 2-hydroxyfluorenone it is evident that only one, *i. e.*, 4-hydroxybiphenyl-2-carboxylic acid (IX) is conveniently isolatable from the crude product. The large yield of this isomer obtained despite losses due to adverse solubility relationships shows that as compared with 2-chlorofluorenone alkaline ring fission occurs mainly in the opposite sense.

This appears to be the first preparation of true 4-hydroxybiphenyl-2-carboxylic acid (IX) (m. p. 202°). Compounds alleged to have this constitution have, however, twice been reported in the previous literature. By the alkaline fusion of fluorene-2-sulfonic acid (XII) Courtot⁸ (and also Hodgkinson and Matthews⁹) obtained a compound, m. p. 180°, which he assumed must possess the structure (IX). Later Dzięwoński and Reicher¹⁰ obtained by alkaline fusion of the sodium salt of 2-benzoylfluorenone-7-sulfonic acid, both 2-hydroxyfluorenone (X) and a hydroxybiphenylcarboxylic acid, m.p. 172°, to which they ascribed the structure of 4-hydroxybiphenyl-2-carboxylic acid (IX).

It will be noted that both the Courtot and the Dzięwoński acids were obtained by alkali fusions of salts of sulfonic acids. Our 4-hydroxybiphenyl-2-carboxylic acid was obtained merely by opening of the fluorenone ring under much milder circumstances. We have found (see below) that alkali fusion of fluorenone-2-sulfonic acid cleaves the fluorenone ring within a few moments but that several hours are required for the replacement of the sulfonic acid group by hydroxyl. It seems possible, therefore, that both the Courtot

(7) Graebe and Schestakow, *Ann.*, **284**, 317, 323 (1895).

(8) (a) Courtot and Geoffroy, *Compt. rend.*, **180**, 1665–1667 (1925); (b) Courtot, *Ann. chim.*, [10] **14**, 17–31 (1930).

(9) Hodgkinson and Matthews, *J. Chem. Soc.*, **43**, 167 (1883).

(10) Dzięwoński and Reicher, *Bull. intern. acad. Polon. Sci.*, (A) **643–652** (1931).

and the Dziewoński acids were mixtures of the authentic 4-hydroxybiphenyl-2-carboxylic acid (m. p. 202°) with authentic 4'-hydroxybiphenyl-2-carboxylic acid (m. p. 206°). We observed that artificial mixtures melt very sharply in the vicinity of 175°.

2-Aminofluorenone.—Attempts to isolate aminobiphenylcarboxylic acids by the usual treatment of 2-aminofluorenone led only to dark-colored gummy precipitates melting over a wide temperature range. Attempts to facilitate isolation of the desired products by acetylation of the crude mixture were unsuccessful. However, when the aqueous extract from the diphenyl ether alkaline fusion was diazotized (any insoluble matter being removed) and the resultant solution boiled with water to effect conversion of any cleavage acids to the corresponding hydroxybiphenyl carboxylic acids, there was obtained readily a mixture of colorless materials from which the beautiful characteristic white needles of 4'-hydroxybiphenyl-2-carboxylic acid (XI), m. p. 205–206° (uncorr.), could be isolated. That the crude product from diazotization also contained the isomeric 4-hydroxybiphenyl-2-carboxylic acid (IX) was evidenced by the values obtained for its neutralization equivalent and by reconversion of the mixture with sulfuric acid to 2-hydroxyfluorenone, but all attempts to isolate the other isomer were fruitless.

2-Sulfofluorene (XII) and Potassium Fluorenone-2-sulfonate (XIII).—Upon fusion of the fluorene (XII) with potassium hydroxide in diphenyl ether in the usual fashion, there was iso-

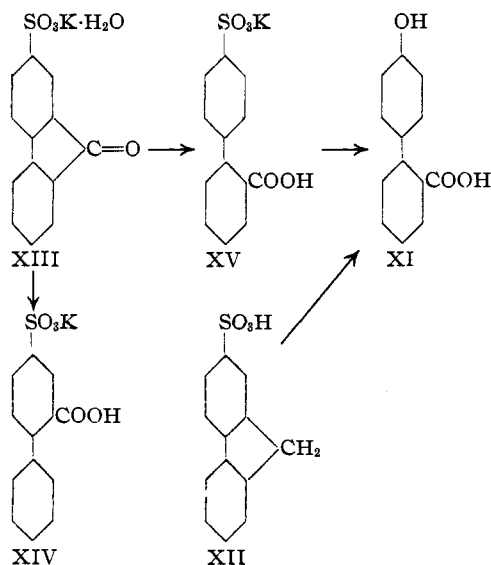
lated a crude product which after purification proved to be 4'-hydroxybiphenyl-2-carboxylic acid (XI).

The result of heating the ketone (XIII) with potassium hydroxide in diphenyl ether was found to vary according to the length of treatment. If heated for only a short time there could be obtained in excellent yield a mixture of the hydrated acid salts of 4-sulfobiphenyl-2-carboxylic acid (XIV) and 4'-sulfobiphenyl-2-carboxylic acid (XV). Due to insuperable experimental difficulties these isomers could not be separated but their nature was indicated by the neutralization equivalent of their mixture, and finally by reconversion of the mixture to the potassium salt of fluorenone-2-sulfonic acid and the corresponding acid chloride. On subjecting potassium fluorenone-2-sulfonate (XIII) to the action of the potassium hydroxide-diphenyl ether mixture for five hours, however, there was obtained in addition to acids (XIV) and (XV) a smaller yield of a compound which proved to be 4'-hydroxybiphenyl-2-carboxylic acid (XI). It thus becomes evident that the opening of the ketonic ring of 2-sulfofluorenone occurs with great ease as compared with the replacement of the sulfonic acid group by hydroxyl.

Experimental

All melting points reported in this paper were taken by the method described in Mulliken's "Identification of Pure Organic Compounds," Vol. I, page 218, on a 360° rod-form melting point thermometer immersed in the sulfuric acid to the 0° point. All melting points are uncorrected.

Study of Use of Solvents for Alkaline Cleavage of Fluorenone.—Fusion of fluorenone with potassium hydroxide at 180°^{4,11} gave good yields of (crude) *o*-phenylbenzoic acid.¹² In attempting to find milder conditions for effecting this same ring cleavage various solvents for the alkali were tried without success. After refluxing fluorenone with 20 *N* potassium hydroxide solution for five hours, 90% of the ketone was recovered unchanged. After fluorenone was dissolved in saturated ethyl alcoholic potassium hydroxide and the dark solution boiled for two and one-half hours, addition of water precipitated large quantities of unchanged ketone and from the residual alkaline solution there was obtained a small quantity of solid which proved to be fluorenylacetic acid, m. p. 128° (rec. 129–130°). On refluxing fluorenone with 5 *N* potassium hydroxide in methanol for three days, precipitation of the product by dilution with water gave a gelatinous yellow precipitate. Extraction with benzene removed a small quantity of fluorenone and left a good yield (95%) of



(11) Graebe and Rateanu, *Ann.*, **279**, 259 (1894).

(12) (a) Graebe and Aubin, *Ber.*, **20**, 845–848 (1887); (b) Weger and Döring, *ibid.*, **36**, 881 (1903).

white fluorenol, m. p. 151–152°, identified by mixed melting point with an authentic sample prepared¹³ by reduction of fluorenone with zinc dust and ammonia. The use of 5 *N* methyl alcoholic alkali for five hours or of 0.7 *N* alkali for one hour was without effect, and the ketone was recovered quantitatively.

Attempts to use mixtures of dioxane and water or morpholine and water as mutual solvents for the alkali and the ketone failed to bring about cleavage and the fluorenone was recovered quantitatively.

Since the use of higher temperatures appeared to be essential for successful alkaline cleavage of the ketone, ethylene glycol was studied as solvent. When fluorenone was heated with 1.5 *N* potassium hydroxide in ethylene glycol at 170–180° the yellow solution turned dark red. Addition of water precipitated fluorenol (60–70% yield) contaminated with unchanged fluorenone (removed by benzene extraction). From the mother liquor there was recovered (by ether extraction) a small yield (13%) of fluorenylacetic acid. This was identified by its melting point of 130.5–131°, by its neutralization equivalent, its molecular weight (Rast), analysis, and by failure to depress the melting point of an authentic sample prepared¹⁴ by the Reformatsky reaction from fluorenone. This fluorenylacetic acid presumably resulted by condensation (under the alkaline conditions) of fluorenone with acetaldehyde followed by reduction (potassium alcoholate) of the unsaturated linkage and oxidation of the aldehyde group to carboxyl. With ethylene glycol from which every trace of aldehyde had been removed the yield of fluorenylacetic acid remained the same, showing that the acetaldehyde was formed from the ethylene glycol by the action of alkali.

Inasmuch as the use of alcohols as a means of moderating the action of alkali had proved impossible because of the reducing, condensing or dehydrating conditions which result, the effect of inert solvents (or diluents) was examined. A solution of fluorenone in melted biphenyl, after a few moments of heating at a temperature sufficient to melt the suspended potassium hydroxide, gave *o*-phenylbenzoic acid. Since the rather high melting point of biphenyl rendered the procedure slightly inconvenient, we finally turned to the use of diphenyl ether.

General Procedure for Cleavage of Fluorenonenes with Potassium Hydroxide in Diphenyl Ether.—The reactants generally consisted of 0.5 g. of ketone, 2 g. of potassium hydroxide (*ca.* 15 mols.) and 15–40 ml. of diphenyl ether. The mixture was placed in a 20-cm. wide-mouthed Pyrex test-tube suspended in an oil-bath (at 160–180°) and vigorously stirred by means of a motor-driven glass stirrer.

With such small quantities of material the use of this large proportion of alkali is necessary to obtain adequate emulsification and provide sufficient reaction surface. With larger quantities of ketone the proportion of alkali may be greatly diminished. The amount of diphenyl ether does not appear to be critical, but must suffice to dissolve neutral ketones at the reaction temperature, or to form a protective layer around the salts of phenolic ketones or ketone acids.

The method of mixing the reactants varied according to the solubilities of the ketones, the tendency toward salt formation, and the reactivity of the components. With the more soluble ketones a cold (or slightly warm) solution of the compound in diphenyl ether was prepared, the alkali added in the form of pellets and the system brought to reaction temperature. Stirring was then begun and continued until the color of the solution disappeared and a white precipitate of potassium salt appeared. With ketones yielding colorless solutions the time required for reaction was determined by experience. With more difficultly soluble fluorenonenes, the ketone was dissolved in a small quantity of hot diphenyl ether (160–180°) and this solution added rapidly to a previously heated and well-stirred emulsion of alkali in diphenyl ether. Fluorenonenes which because of phenolic or carboxylic acid substituents showed a tendency to precipitate uncleaved potassium salts were added to the prepared alkaline emulsion in powdered form or dissolved in hot diphenyl ether in such a manner as to cause the precipitation of the alkaline salts in finely divided condition.

After completion of the cleavage reaction, the mixture was cooled and stirred with about half its volume of water until both the resultant salts and excess alkali were dissolved. The two layers were then separated and the aqueous layer filtered. The diphenyl ether layer was further extracted with water. From the original alkaline aqueous layer and subsequent aqueous extracts insoluble acids were precipitated by acidification with concd. hydrochloric acid. Soluble acids were taken out of the water layer by extraction with ether.

Preparation of 2-Chlorofluorenone.—Purified 2-nitrofluorenone was reduced to 2-aminofluorenone with sodium sulfide in alcoholic sodium hydroxide,¹⁵ the amine being obtained in 89–93% yields, m. p. after recrystallization from alcohol 156–157° (recorded, sinters at 156°, m. p. 160°). For the preparation of 2-chlorofluorenone the 2-aminofluorenone hydrochloride was diazotized and subjected to the Sandmeyer reaction.

The crude product (45% yield), melting at 117–119°, was purified by reprecipitation with water from alcohol solution and then similarly from acetone. Final purification was effected by sublimation at ordinary pressure (m. p. 120.5–122°).

Cleavage of 2-Chlorofluorenone.—The ketone (0.5 g.) was heated with potassium hydroxide in diphenyl ether according to the usual procedure. Decolorization of the solvent was complete in half an hour at bath temperatures of 160–165°, and excellent yields (90–100%) of the mixture of the two possible cleavage acids were obtained. The ecru colored crude melted at 160–162° and was purified by several extractions with small amounts of boiling water followed by recrystallization of the insoluble residue from dilute (33%) acetic acid using Norite decolorizing carbon, or successively from 33% acetic acid, 33% dioxane, and water. By either method there was recovered about 62% of colorless transparent needles, m. p. 165.5–166°, uncorr. The mother liquors from the purification were examined for the presence of other cleavage products and a low melting material (m. p. 127–129°) was isolated. Although this

(13) Werner and Grob, *Ber.*, **37**, 2896 (1904).

(14) Sieglitz and Jassoy, *ibid.*, **54**, 2135 (1921).

(15) (a) Korczynski, *Bull. soc. chim.*, [4] **35**, 1191 (1924); (b) Eckert and Langecker, *J. prakt. Chem.*, **118**, 269 (1928).

was not examined in detail, we believe it was a eutectic mixture of the two possible cleavage products.

Identification of Principal Cleavage Product as 4'-Chlorobiphenyl-2-carboxylic Acid¹⁶(V).—The white needles melting 165.5–166° (uncorr.) had the following composition.

Anal. Calcd. for C₁₃H₉ClO₂: C, 67.1; H, 3.89; Cl, 15.25; neut. equiv., 232. Found: C, 67.3; H, 3.89; Cl, 14.55; neut. equiv., 232.

On standing for one hour in cold concentrated sulfuric acid and diluting with water it yielded 2-chlorofluorenone (I), m. p. and mixed m. p. 118–119°. A mixture of this 4'-chlorobiphenyl-2-carboxylic acid (V), m. p. 165.5–166°, with synthetic isomeric 4-chlorobiphenyl-2-carboxylic acid (II), m. p. 157–158° (see below) was depressed to 125–145°. Upon treatment with phosphorus pentachloride it yielded an acid chloride (not isolated) which with ammonia (in benzene) yielded (68%) 2-(4'-chlorophenyl)-benzamide (VI), which after two recrystallizations from 50% alcohol (Norite) melted sharply at 165° (uncorr.).

Anal. Calcd. for C₁₃H₁₀ClNO: N, 6.05. Found: N, 6.08, 6.31.

From this amide the action of sodium hydroxide and bromine¹⁷ yielded 4'-chloro-2-aminobiphenyl (VII) (83% yield) which after reprecipitation from hydrochloric acid (dilute) melted at 47–48°. The melting point of our amine agreed with neither of the two published values, 52°¹⁷ and 71°¹⁸ but its acetyl derivative showed a melting point of 121.5–122.5° in agreement with De Crauw.¹⁸ This amine was oxidized with alkaline potassium permanganate yielding *p*-chlorobenzoic acid (VIII) m. p. 227–231°; this value could not be raised even after two recrystallizations from acetic acid. When mixed with an authentic sample of *p*-chlorobenzoic acid the observed melting point was 232°. Since from the the circumstances, however, the structure of this product could have been only *p*-chlorobenzoic acid (m. p. 236°) or benzoic acid (m. p. 121°), the high melting point clearly indicates the former.

Synthesis of the Isomeric 4-Chlorobiphenyl-2-carboxylic Acid (II).—5-Chloro-2-aminotoluene hydrochloride ("Fast Red TR Base") (89 g. or 0.5 mole) was diazotized and coupled with an alkaline suspension of benzene exactly as described⁶ for the corresponding bromo analogs. After distillation with superheated steam there was obtained 14.4 g. of yellow oil, b. p. 285–295°. Further fractionations at reduced pressure ultimately yielded 4-chloro-2-methylbiphenyl (III) as a pale yellow oil, b. p. 160–162° at 19 mm.

Anal. Calcd. for C₁₃H₁₁Cl: C, 77.02; H, 5.47. Found: C, 77.25; H, 5.63.

When this substance (1 g.) dissolved in glacial acetic acid (15 ml.) was heated one hour with chromic acid (1 g.) and the oxidation product recovered by pouring into 6 *N* hydrochloric acid (200 ml.), extracting the solution

(16) After our work had been completed this acid was also reported by Heilbron, Hey and Wilkinson, *J. Chem. Soc.*, 116 (1938), who obtained it by permanganate oxidation of 4'-chloro-2-methylbiphenyl prepared (together with isomeric compounds) by the alkaline coupling of diazotized *p*-chloroaniline with toluene. Our acid, as obtained by alkaline cleavage of 2-chlorofluorenone, appears to be somewhat purer than their product.

(17) Raiford and McNulty, *THIS JOURNAL*, 56, 680–681 (1934).

(18) De Crauw, *Rec. trav. chim.*, 50, 776 (1931).

with ether, the ether in turn with sodium bicarbonate solution, and finally precipitating with acid there was obtained a small yield (0.07 g. or 8.3% theoretical) of 4-chloro-2-methylbenzoic acid. After two recrystallizations from dilute acetic acid this was obtained in fine colorless transparent needles, m. p. 170°.¹⁹

Anal. Calcd. for C₈H₇ClO₂: mol. wt., 170; neut. equiv., 170. Found: mol. wt. (Rast), 168; neut. equiv., 165, 167.

Unlike the 4-chlorobiphenyl-2-carboxylic acid obtained by oxidation with potassium permanganate (see below) this 4-chloro-2-methylbenzoic acid could be recovered unchanged from cold concentrated sulfuric acid; with hot sulfuric acid it was destroyed.

After boiling 4-chloro-2-methylbiphenyl (III) (2 g.) for forty-eight hours with 48 ml. of 6.5% aqueous potassium permanganate solution, half the original oil was recovered unchanged, but from the aqueous alkaline liquor, acidification precipitated a small yield (1.8%) of crude acid. After recrystallization from much boiling water (Norite) this 4-chlorobiphenyl-2-carboxylic acid (II) formed heavy opaque white needles, m. p. 157–158° (uncorr.).²⁰

Anal. Calcd. for C₁₃H₉ClO₂: neut. equiv., 232. Found: neut. equiv., 229, 234.

This acid after standing with cold concentrated sulfuric acid for two hours gave on dilution with water pure 2-chlorofluorenone (I), m. p. 122–123°, m. p. of mixture with an authentic sample, 121.5–122°. A mixture of the acid with the isomer obtained from alkaline cleavage of 2-chlorofluorenone, however, melted over a wide range (125–145°) much lower than the melting point of either pure substance.

Cleavage of 2-Hydroxyfluorenone.—This was carried out in the same general way as described above. Addition of the powdered phenolic ketone²¹ to the vigorously stirred suspension of fused potassium hydroxide in diphenyl ether first precipitated its red potassium salt in fine particles, the mass becoming a puffy pink mixture. After two and one-half hours of rapid stirring at 180° all the color had disappeared. On working up the reaction mixture there was obtained a less soluble portion together with an approximately equal amount of gummy substance (from evaporation of the ether extract from the aqueous mother liquor) representing a total yield of 70%.

4-Hydroxybiphenyl-2-carboxylic Acid (IX).—After two recrystallizations from small proportions of boiling water (Norite) the first portion gave 4-hydroxybiphenyl-2-carboxylic acid (IX) as shiny rosetts of branched feathery colorless needles, m. p. 202–202.5° (uncorr.).

Anal. Calcd. for C₁₃H₁₀O₃: C, 72.87; H, 4.71; neut. equiv., 214. Found: C, 72.69; H, 4.70; neut. equiv., 215.5, 215.6.

The structure of this acid was also supported by its reconversion to 2-hydroxyfluorenone (X) (m. p. 206.5°; mixed melting point 204°) by standing in cold concen-

(19) Beilstein, Vol. IX, p. 468.

(20) After our work had been completed this acid was also reported by Heilbron, Hey and Wilkinson, ref. 16, p. 115, who obtained it (m. p. 157°) by saponification of its methyl ester prepared by coupling diazotized methyl 5-chloroanthranilate with benzene.

(21) Diels, *Ber.*, 34, 1767 (1901).

trated sulfuric acid for half an hour and precipitation of the resultant ketone by dilution with water. The melting point (177–180°) of mixtures of this 4-hydroxybiphenyl-2-carboxylic acid (IX) with a synthesized sample of the isomeric 4'-hydroxybiphenyl-2-carboxylic acid (XI)⁷ proved its non-identity with the latter. Despite its phenolic character it gave no coloration with ferric chloride, either in aqueous or alcoholic solution.

Cleavage of 2-Aminofluorenone.—2-Aminofluorenone (1.5 g.) was dissolved in diphenyl ether (25 ml.) and slowly added to a vigorously stirred emulsion of potassium hydroxide (4 g.) in diphenyl ether (20 ml.). The mixture was heated for half an hour with the bath at 160–170°. The usual aqueous extract was neutralized and then treated with 4 cc. of concentrated hydrochloric acid. Warming on the steam-bath caused the flocculent precipitate thrown out by the acid to collect as a black gum which was readily removed, leaving a pale colored solution. This was diazotized with sodium nitrite (required 0.44 g. or 77% of that calculated on the original) and a small quantity of undiazotizable solid removed by filtration. After heating at 100° nitrogen was evolved and a third gummy precipitate filtered from the boiling solution. On cooling the tan colored filtrate (75 ml.) deposited 0.61 g. of pink hydroxy acid and 0.13 g. more was obtained by ether extraction (yield 45%). The total solids recovered represented 99% of the weight of the original aminofluorenone.

The crude material melted over the range 168–173°. That it consisted exclusively of a mixture of the two hydroxybiphenylcarboxylic acids (IX + XI) was shown by the neutralization equivalents (found: 214, 218, 218 on various samples; calculated 214) and by reversion of the crude with cold concentrated sulfuric acid to 2-hydroxyfluorenone, m. p. 204–205°, which did not depress the melting point of an authentic sample. Recrystallization from hot water raised but did not sharpen this range. Finally a series of water extractions left a small residue, m. p. 201.5–204.5°, but two final recrystallizations were required to obtain from a clear (not cloudy) solution the 6–7 mm. long pointed single transparent needles with *no fernlike structure* characteristic of 4'-hydroxybiphenyl-2-carboxylic acid (XI), m. p. and mixed m. p. 205–206°. All attempts to isolate the isomeric hydroxy acid (m. p. 202°) from the remaining low-melting mixtures were unsuccessful.

Cleavage of 2-Sulfofluorene and of 2-Sulfofluorenone.—When 2-sulfofluorene (XII)^{8b} was added to the emulsified potassium hydroxide-diphenyl ether mixture in the usual way, a thick black mass immediately precipitated. This gradually disintegrated and after three and one-half hours at 180° suddenly faded in color to a light tan. On working up the material a 47% yield of crude product, m. p. 178–202°, was obtained. After three recrystallizations from boiling water (using Norite) the melting point was sharpened to 205.0–205.5°, the acid separating in the distinctive separate long shiny transparent needles characteristic of 4'-hydroxybiphenyl-2-carboxylic acid (XI). This product gave negative tests for sulfur (sodium fusion). It dissolved in sodium bicarbonate solution with evolution of carbon dioxide and on titration with alkali gave a neutralization equivalent of 215 (calcd. = 214). Cold sulfuric acid converted it to 2-hydroxyfluorenone, m. p. 202–204°.

When mixed with a sample of authentic 4'-hydroxybiphenyl-2-carboxylic acid (m. p. 206°), prepared by synthesis, the mixture melted at the same temperature. When mixed with a sample of 4-hydroxybiphenyl-2-carboxylic acid, m. p. 202° (IX), from the fission of 2-hydroxyfluorenone (X) the observed melting point of the mixture was depressed to 173–176°.

The finely powdered potassium salt of the sulfofluorenone (XIII)^{8b} (3.0 g.) was slowly added to the well-stirred emulsion of fused potassium hydroxide (10 g.) in diphenyl ether (30 ml.). A pink melt resulted, from test portions of which aqueous extraction showed no yellow color of unchanged ketone, and the reaction mixture was immediately worked up. From the aqueous extracts of the main reaction product only a trace of ether-soluble hydroxy acids could be obtained. The main ether-insoluble water-soluble product was isolated by salting out with potassium chloride, yielding 2.5 g. (80%) of crude material. Purification of this mixture was tedious and not very satisfactory. After extractions with very limited volumes of cold glacial acetic acid (to remove traces of unreacted yellow ketone) the insoluble residue was treated with warm glacial acetic acid. The insoluble potassium chloride was filtered off and the mixture of monopotassium salts of 2-carboxy- and 2'-carboxybiphenyl-4-sulfonic acids (XIV + XV) reprecipitated from the filtrate by addition of chloroform. The product obtained after several such treatments formed a white powder with a very indefinite melting point range.

Anal. Calcd. for $C_{13}H_9KO_5S \cdot H_2O$: neut. equiv., 334; K, 11.7; for $C_{13}H_9KO_5S \cdot 2H_2O$: neut. equiv., 352; K, 11.1. Found: neut. equiv., 339, 345, 349; K, 11.2–11.6.

On warming with concentrated sulfuric acid for one hour at 100° and diluting with water, the yellow potassium salt of 2-sulfofluorenone was salted out of the diluted solution and converted with phosphorus pentachloride into fluorenone-2-sulfonyl chloride. After two recrystallizations from benzene this melted at 192–193° and did not depress the melting point of an authentic sample.

In several experiments 2-sulfofluorenone was fused with potassium hydroxide in diphenyl ether for several hours. Even after five hours the fusion mixture was pink colored as before but the solid appeared more gummy, having a tendency to stick to the glass, leaving clear solvent. Upon working up the product, in addition to some 47% yield of ether-insoluble mixed acid salts (XIV + XV) there was also isolated a 20% yield of ether-soluble hydroxy acids. Although the crude melted over a range (162–175°) two recrystallizations from boiling water (using Norite) gave 4'-hydroxybiphenyl-2-carboxylic acid (XI), m. p. 203°, which did not depress the melting point of the corresponding material from 2-sulfofluorene (above).

Summary

1. A new method for opening the ketonic ring in fluorenone derivatives by fusion with potassium hydroxide in the presence of diphenyl ether has been developed.

2. This method has been applied to fluorenone itself and also to 2-chloro-, 2-hydroxy-, 2-amino-, and 2-sulfofluorenes yielding one or the other

(or both) of the expected isomeric biphenyl derivatives without interference with the nuclear substituent.

3. The structures of the various substituted biphenylcarboxylic acids have been established.

CAMBRIDGE, MASS.

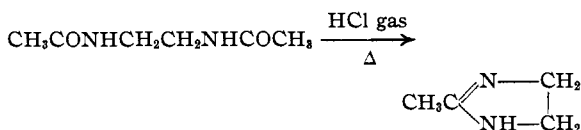
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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF YALE UNIVERSITY]

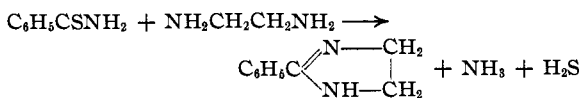
The Preparation and Cyclization of Monoacylethylenediamines¹

BY ARTHUR J. HILL AND SAMUEL R. ASPINALL²

Although 4,5-dihydroimidazoles³ as a class have been known many years, a satisfactory general synthesis for these compounds has not previously been developed. Hofmann⁴ prepared 2-alkyl-4,5-dihydroimidazoles by heating diacyl-ethylenediamines in a stream of hydrogen chloride, and Klingenstein⁵ and Landenberg⁶ carried out a similar type of reaction by heating ethylenediamine hydrochloride with the sodium salt of a low aliphatic acid.



In a recent repetition of this work, Chitwood and Reid⁷ were able to obtain only 10% yields of the 2-methyl derivative. These later workers effectively increased the yields in the low members of the series by a modification of Hofmann's procedure, but the higher alkyl derivatives were produced in rather poor yields, even when the improved method was employed. 2-Phenyl-4,5-dihydroimidazole, first reported by Hofmann,⁴ was made by Forssell⁸ by the interaction of thio-benzamide and ethylenediamine.

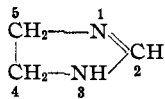


Since it appeared to the writers that appropriately substituted 4,5-dihydroimidazoles might

(1) Constructed from a dissertation presented by Samuel R. Aspinall to the Faculty of the Graduate School of Yale University in candidacy for the degree of Doctor of Philosophy, 1938.

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(3) The 4,5-dihydroimidazole nucleus is numbered as follows:



(4) Hofmann, *Ber.*, **21**, 2332 (1888).

(5) Klingenstein, *ibid.*, **28**, 1176 (1895).

(6) Landenberg, *ibid.*, **27**, 2952 (1894).

(7) Chitwood and Reid, *THIS JOURNAL*, **57**, 2424 (1933).

(8) Forssell, *Ber.*, **25**, 2132 (1892).

possess interesting physiological properties, and because no satisfactory general synthesis for these compounds was known, a study of these cyclic amidines was undertaken. This paper reports work on a simple synthesis which produces uniformly high yields of pure 2-alkyl- and 2-aryl-4,5-dihydroimidazoles starting from readily available materials.

The first step in the synthesis of 2-alkyl-4,5-dihydroimidazoles is the preparation of monoacylethylenediamines by interaction of ethylenediamine and various aliphatic esters⁹ (see Table I).



Acetylethylenediamine.¹⁰—One mole (88 g.) of ethyl acetate and three moles (180 g.) of sodium-dried ethylenediamine were sealed in a glass tube and heated at 100° for thirty-six hours. The reaction mixture was then transferred to a Claisen flask and 170 g. of low boiling material, consisting of ethyl alcohol and excess ethylenediamine, removed under diminished pressure. When the bath temperature was increased to 165°, acetylethylenediamine distilled at 128° (3 mm.). The 11 g. of diacetylethylenediamine which remained as an undistilled residue melted at 175°¹¹ (corr.) after recrystallization from 95% alcohol.

Acetylethylenediamine sets to a very hygroscopic white solid which melts at 51° (corr.) after recrystallization from a dioxane-ether mixture.

The aliphatic monoacylethylenediamines, which are strongly basic, hygroscopic compounds, were converted to a number of derivatives for positive characterization. They react violently with phenyl isocyanate and phenyl isothiocyanate to produce crystalline ureas and thioureas (see Tables VI, VII).



(9) The method used embodies several important extensions and improvements over a similar process outlined in U. S. Patent 1,926,015.

(10) The subsequent paragraphs in this article which are set in small type are descriptive of actual experiments carried out, but are typical of all members of a given class of compounds.

(11) The previously reported m. p. of this compound is 175°, Franchimont and Dubsky, *Rec. trav. chim.*, **30**, 184 (1911).