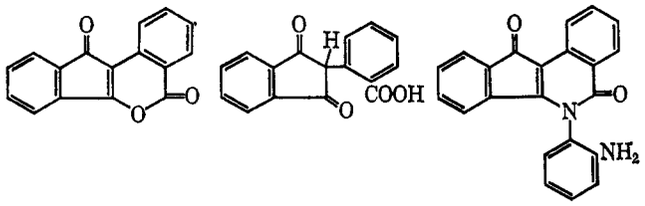
was converted by alkali to 3-(2-carboxybenzoyl) phthalide which can be also made by the action of alkali on diphthalyl.[6]



I II III

Alkylation of 2-(2-carboxyphenyl-)-1,3-indandione with methyl iodide in alkaline solution gave 2-(2-carbomethoxyphenyl)-1,3-indandione which was identical with the ester obtained by direct esterification.[4]

Refluxing the isocoumarin I with *o*-phenylenediamine produced 5,11-diketo-6-(2-aminophenyl)indeno[1,2-*c*]-isoquinoline (III). This compound formed a N,N-diacetyl derivative with acetic anhydride and was reported in the earlier work[3] as a hydrated phenazine.

Experiment Section[7]

2-(2-Carboxyphenyl)-1,3-indandione(II).—The isocoumarin I (0.5 g) when dissolved in alkali gave a deep red solution. Acidification with dilute acid gave a theoretical amount of a white solid. Recrystallization from ethyl acetate and benzene gave 2-(2-carboxyphenyl)-1,3-indandione(II) which was identical with an authentic sample.[4]

Oxidation of 2-(2-Carboxyphenyl)-1,3-indandione.—An alkaline solution (35 ml of 20% KOH) of the isocoumarin (I) (0.2 g) containing methanol (10 ml) was treated with bromine in methanol until the red color disappeared. Acidification gave 2,2′-benzildicarboxylic acid (0.19 g) melting at 271–273° dec. Identification was made by comparison with an authentic sample.[8]

11-Ketoindeno[1,2-*c*]-isocoumarin (I).—2-(2-Carboxyphenyl)-1,3-indandione (0.5 g) was refluxed with concentrated hydrochloric acid until no more of the orange isocoumarin I was formed. The isocoumarin I (0.45 g) was recrystallized from benzene and gave orange crystals melting at 261–262°. A mixture with a sample prepared in the earlier work[3] melted at the same point.

Oxidation of 11-Ketoindeno[1,2-*c*]isocoumarin (I).—The isocoumarin I (1 g) in acetic acid (250 ml) was treated with a solution of chromium trioxide (1 g) in water (100 ml), and the resulting mixture was heated at 100° until all the solid dissolved and a color change was observed. Dilution with water and allowing the solution to stand for 2 days at 10° gave a white solid which was filtered and washed with cold benzene. Purification by crystallization from benzene gave white crystals (0.5 g) melting at 297–298° and identical with the lactone of 2-hydroxy-2-(*o*-carboxyphenyl)-1,3-indandione.[5]

1-(*o*-Carboxybenzoyl)phthalide.—The lactone of 2-hydroxy-2-(*o*-carboxyphenyl)-1,3-indandione (0.1 g) when dissolved in dilute potassium hydroxide gave a green color. Immediate acidification with dilute hydrochloric acid gave, after standing for 24 hr, a white solid (0.1 g). Recrystallization from benzene gave crystals melting at 246° followed by resolidification and remelting at 330°. This compound was identical with a sample prepared by the action of alkali on diphthalyl.[6]

2-(2-Carbomethoxyphenyl)-1,3-indandione.—The isocoumarin I (0.2 g) was dissolved in methanol (50 ml) treated previously with sodium (0.021 g), and treated with methyl iodide (3 ml); the solution was allowed to stand for 24 hr. Acidification gave a quantitative yield of a white solid which, after recrystallization from a mixture of benzene and hexane, melted at 154–155°. Continued heating at this point gave the isocoumarin I. This ester was identical with the product formed by the esterification of 2-(*o*-carboxyphenyl)-1,3-indandione.[5]

5,11-Diketo-6-(2-aminophenyl)indeno[1,2-*c*]isoquinoline (III).—The isocoumarin I (1 g) was refluxed with excess *o*-phenylenediamine and a trace of acetic acid in absolute ethanol (125 ml) for 3 hr. The red solid (1.25 g) which crystallized upon cooling melted at 289–290° after crystallization from benzene.

Anal. Calcd for $C_{22}H_{14}O_2N_2$: C, 78.11; H, 4.14; N, 8.28. Found: C, 78.30; H, 4.30; N, 8.30.

The infrared spectrum in Nujol had major peaks at 2.95, 5.91, 6.01, 6.14, and 6.48 mμ.

This compound was identified in earlier work[3] as a hydrated phenazine.

5,11-Diketo-6-(2-diacetylaminophenyl)indeno[1,2-*c*]isoquinoline.—The aminoisoquinoline III (0.34 g) was refluxed in excess acetic anhydride containing sodium acetate (0.5 g) for 24 hr. Dilution with water gave a red solid which melted at 265–266° after recrystallization from benzene to yield 0.32 g.

Anal. Calcd for $C_{26}H_{18}O_4N_2$: C, 73.93; H, 4.27; N, 6.64. Found: C, 73.74; H, 4.16; N, 6.77.

The infrared spectrum in Nujol had major peaks at 5.89, 5.99, 6.19, 6.68, and 8.11 mμ.

(6) C. Grabe and H. Schmalzigang, *Ann.*, **228**, 126 (1885).

(7) Melting points are corrected. Infrared spectra were determined on an Infracord spectrophotometer.

(8) C. Graebe and P. Juillard, *Ann.*, **242**, 214 (1887).

Synthesis of 3-Sulfopropionimide[1]

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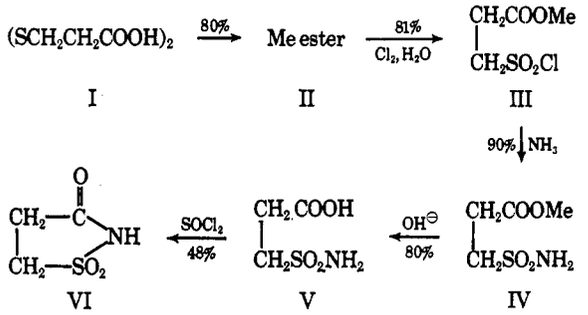
Received April 11, 1966

The synthesis of 3-sulfopropionimide (VI), a ring system similar to saccharin, is reported. This work culminated from efforts to prepare 4-amino-3-ketobutanesulfonamide as an analog of δ-aminolevulinic acid suggested earlier[2] for use as an anticancer agent. The synthetic pathway which resulted in 3-sulfopropionimide (VI) is outlined in Scheme I.

SCHEME I



After esterification of 3,3′-sulfopropionic acid, the sulfonyl chloride (III) was prepared by chlorine oxidation using water as an oxygen source and solvent instead of the acetic acid–water mixture which is customarily employed.[3]

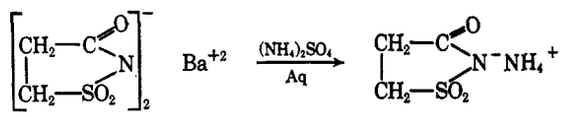
By careful titration of the carbomethoxy sulfonyl chloride (III) with ammonia in ether, conversion to IV proceeded in 90% yield. Hydrolysis of the ester, methyl 3-sulfamoylpropionate (IV) with acid was accompanied by sulfonamide hydrolysis under surprisingly mild conditions (6 *N* HCl, 1 hr, reflux). When 1 *N* sodium hydroxide under carefully controlled con-

(1) This investigation was supported by U. S. Public Health Service Research Grant CAO 6520.

(2) C. C. Price and M. L. Beck, *J. Org. Chem.*, **27**, 210 (1962).

(3) S. W. Lee and G. Dougherty, *ibid.*, **5**, 81 (1940).

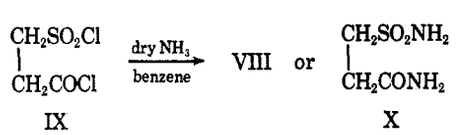
ditions was employed, followed by exact neutralization with acid, the carboxy sulfonamide V was prepared in 80% yield. Upon treatment with thionyl chloride, 3-sulfamoyl propionic acid (V) did not convert to the acid chloride, 3-sulfamoylpropionyl chloride. The product actually obtained was 2-sulfopropionimide (VI) resulting from dehydration of V. Its structure was assigned on a basis of analysis, infrared spectrum, and conversion into the barium (VII) and ammonium (VIII) salts.



VII VIII

The infrared spectrum of VI shows a band at 1670 cm^{-1} corresponding to the first amide band of a cyclic imide.[4] One of the characteristic amide bands for a cyclic imide, which arises from the second carbonyl group was not present having been replaced by the sulfone group. The NH stretching frequencies reported[5] for the aromatic saccharin, are at 3405 and 3350 cm^{-1} for the aliphatic analog IX. Bands corresponding to those for the sulfonyl group occurred at 1140 and 1350 cm^{-1}; the SO stretching frequencies reported[5] for saccharin are at 1164 and 1377 cm^{-1}.

The ammonium salt of 3-sulfopropionimide (VI) was reported earlier by Bigelow.[6] This resulted from the treatment of 3-chlorosulfopropionyl chloride (IX) with ammonia in an effort to make the corresponding diamide. He suggested two structures for the reaction product, *viz.*, VIII and X.



IX X

Bigelow excluded the diamide X because of the salt-like properties of the product, and the formation of a barium salt which analyzed correctly for the structure VII on a basis of Ba and N analyses.

This is not in accord with this investigation. There is a wide disparity in melting points reported for the ammonium salt of the cyclic imide by Bigelow at 164–168° and resulting from this work at 197–200° dec. All efforts made by Bigelow to prepare the free cyclic imide failed.

To further support the 3-sulfopropionimide structure herein assigned, the barium salt VII was converted to the ammonium salt VIII with aqueous ammonium sulfate. The water was allowed to evaporate at room temperature to afford material melting at 197–200° which upon admixture with that obtained directly from VI showed no depression.

The product, 3-sulfopropionimide, was unsuitable for use as an anticancer agent because of its high toxicity.

Experimental Section

Methyl 3,3′-Dithiodipropionate(II).—A mixture containing 21 g (0.1 mole) of 3,3′-dithiodipropionic acid, 60 ml of chloroform, and 50 ml of methanol (containing 3 g of concentrated sulfuric acid) was heated at reflux temperature for 1 hr in a flask equipped with a condenser.

After standing for 18 hr, the mixture was washed twice with water to remove the acid and excess methanol. The solution was dried over anhydrous sodium sulfate, filtered, and distilled at 125° (3 mm), $n^{20}D$ 1.5060.

Anal. Calcd for $C_8H_{14}O_4S_2$: C, 40.30; H, 5.90; S, 26.90. Found: C, 40.35; H, 5.90; S, 27.24.

Methyl 3-(Chlorosulfonyl)propionate(III).—A flask containing 0.2 mole of methyl 3,3′ dithiodipropionate II and 100 ml of water was equipped with a stirrer and a gas inlet tube. Chlorine gas was passed through the stirring mixture for a total of 4 hr. The excess chlorine was removed with a stream of nitrogen gas. The exit gas was tested for the presence of chlorine with a potassium iodide solution. When free iodine was no longer liberated, the nitrogen stream was removed and the product was extracted with ethyl ether and dried. Upon removal of the ether, there remained 42.6 g (81%) of crude product. After distillation (bp 82° (0.3 mm)) the yield was 34.6 g (61%). An anilide was made and recrystallized from carbon tetrachloride; needles melted at 85.0–86.0° (lit.[7] mp 89°).

Anal. Calcd for $C_{10}H_{13}O_4NS$: C, 49.40; H, 5.35: N, 5.76; S, 13.20. Found: C, 49.37; H, 5.42; N, 6.02; S, 13.36.

Methyl 3-Sulfamoylpropionate (IV).—An ethereal solution of ammonia gas was prepared by bubbling gaseous ammonia into ethyl ether. An aliquot was removed and added to a known amount of hydrochloric acid. The excess acid was titrated against standard base. The solution, which contained exactly 0.0534 equiv of ammonia was cooled in a flask equipped with a stirrer to 0–5° in an ice–salt bath. An 80-ml ethereal solution containing 5.0 g (0.0268 mole) of methyl 3-(chlorofulfonyl)propionate, which had been precooled to 5° was added at once. The mixture was stirred at 0–5° for 1 hr and then allowed to warm to room temperature overnight. Titration of an aliquot in the manner described above indicated that 0.7% of the ammonia was unreacted. The small amount of unreacted ammonia was removed with a stream of nitrogen gas, and the solution was filtered to give 5.1 g of a mixture of product and ammonium chloride. The solid was extracted with warm chloroform and the chloroform extracts were concentrated under reduced pressure to yield a total of 3.3 g of product melting at 65.5–67°. An additional 0.75 g was recovered from the mother liquor to give a total of 4.05 g or 90% of product. A sample recrystallized from chloroform melted at 67–68.5°.

Anal. Calcd for $C_4H_9O_4NS$: C, 28.73; H, 5.42; N, 8.38; S, 19.18. Found: C, 28.70; H, 5.45; N, 8.27; S, 18.91.

3-Sulfamoylpropionic Acid (V). Base Hydrolysis.—A solution of 1.0 g of methyl 3-sulfamoylpropionate (IV) in 150 ml of standard 1 *N* potassium hydroxide was allowed to reflux for 1 hr. The flask was cooled to 5–10° and acidified slowly with 15.0 ml of standard 1 *N* hydrochloric acid, maintaining the temperature below 10°. The solution was concentrated to about 3–5 ml under reduced pressure. Upon the addition of an equal volume of acetone, potassium chloride precipitated and was filtered. The remaining solution was again concentrated to yield 0.75 g of a waxy solid having a melting point of 95–100°. A sample weighing 0.3 g was recrystallized from absolute ethanol to which 10% chloroform and 10% carbon tetrachloride were added to effect crystallization. After standing at 5° platelets appeared which were filtered and dried in a vacuum at 60°. A solid weighing 0.25 g and having a melting point of 110–111° was obtained.

Anal. Calcd for $C_3H_7O_4NS$: C, 23.50; H, 4.58; O, 41.80; S, 20.90. Found: C, 23.35; H, 4.53; O, 41.63; S, 20.65.

The remainder upon drying had a melting point of 103–111°. The total yield was 0.70 g (80%).

Since recrystallization was difficult, in subsequent preparations the product was not recrystallized. It was found that, after preliminary drying of the crude product, unreacted ester could be removed by washing the solid with chloroform. The acid was then dried for several days in a vacuum desiccator. This procedure afforded a product which melted at 108–110°, sufficiently pure for use in the next step.

3-Sulfopropionimide (VI).—A flask containing 5.8 g of 3-sulfamoylpropionic acid (V) and 18 g of thionyl chloride was allowed to reflux 7 hr. After 2 days at room temperature, solution did not occur, but a change in the appearance of the

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, p 221.

(5) J. Baxter and I. Cymerman-Craig, *J. Chem. Soc.*, 674 (1955).

(6) L. A. Bigelow and H. W. Sigmon, *J. Am. Chem. Soc.*, **57**, 2521 (1935).

(7) R. Adams and J. Campbell, *ibid.*, **72**, 128 (1950).

precipitate was noted. The mixture was heated and filtered to give 4.4 g of material which was washed with chloroform leaving 4.0 g of solid melting at 108–115°. The solid was taken up in 200 ml of ethyl ether in which 1.8 g was dissolved with difficulty. From this there was obtained 1.5 g of product melting at 115.5–117°. In addition, the original thionyl chloride chloroform filtrate yielded 0.6 g of product which upon recrystallization from ethyl ether melted at 115–117.5° to make the total yield 2.4 g (48%).

Anal. Calcd for C, 26.65; H, 3.70; O, 35.60; S, 23.70. Found: C, 26.50; H, 3.69; O, 35.83; S, 23.68.

Registry No.—II, 15441-06-2; III, 15441-07-3; IV, 15441-08-4; V, 15441-10-8; VI, 15441-09-5.

Preparation and Decomposition of 1-Benziloylimidazole

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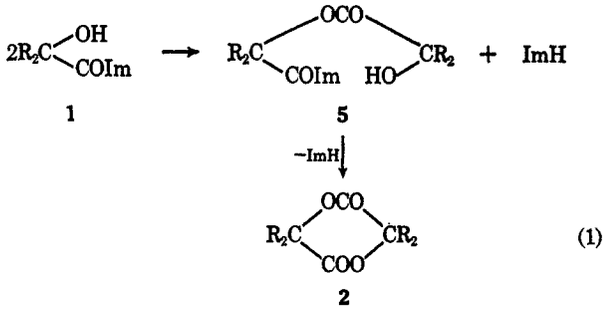
Received September 13, 1967

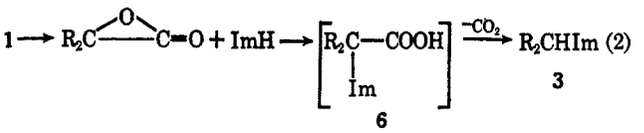
Staab,[1] in his detailed investigations on the synthesis and chemistry of the 1-acylimidazoles, stated that inter- and intramolecular esterification would complicate the isolation of the acylimidazole when a hydroxy acid and 1,1′-carbonyldiimidazole react. Although experimental verification appears to be lacking, such difficulties are given as the reason for the poor yields obtained in reactions involving mandelic and salicylic acids.[2] It has now been found that 1-benziloylimidazole (**1**) can be prepared in satisfactory yield from benzilic acid and 1,1′-carbonyldiimidazole and that **1** displays many of the normal reactions of 1-acylimidazoles. 1-Benziloylimidazole is a crystalline solid which is stable at ambient temperature for an extended period of time and which, in contrast to some of the other acylimidazoles, is moderately resistant to hydrolysis by the moisture in laboratory air.

When **1** is either heated by itself at 145–150° or refluxed in acetonitrile, a rapid and complex decomposition occurs. Carbon dioxide is evolved and imidazole, benzilide (**2**), 1-benzhydrylimidazole (**3**), 1,3-dibenzhydrylimidazolium benzilate (**4**), and a low-molecular weight polyester of benzilic acid are formed. Although no studies have been made to elucidate the mechanism, the routes (eq 1, 2, and 3) to these products are proposed, where R is phenyl and Im is 1-imidazolyl.



(1)

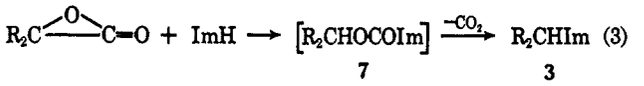
To obtain **3**, a rearrangement of **1** followed by a decarboxylation is necessary. Perhaps imidazole is eliminated in a concerted reaction and diphenylacetolactone is formed; the α-lactone ring is then opened by a nucleophilic attack of imidazole on the carbon atom bearing the phenyl groups to give **6**, which loses carbon dioxide (eq 2). The same hypothetical intermediate is



(2)

implicated in the formation of α-methoxydiphenylacetic acid during the decomposition of di-*t*-butylperoxy-diphenylmalonate in methanol.[3]

A much less favored possibility would involve the formation of 1-carbodiphenylmethoxyimidazole (**7**) by imidazole reattacking the α-lactone at the carbonyl group with ring opening at the carbon–carbon bond rather than through a carbon–oxygen bond (eq 3).



(3)

Staab and Mannschreck[4] have reported that the related compound, 1-carbobenzyloxyimidazole, RCH_2OCOIm, loses carbon dioxide at 100–110° to furnish 1-benzylimidazole in about 70% yield.

Once some of the 1-benzhydrylimidazole, **3**, is formed, it compares with the imidazole in the nucleophilic attack on carbon in the α lactone. Such a reaction would lead to the 1,3-dibenzhydrylimidazolium salt, **4**. Alternatively, benzhydryl benzilate, which might arise through a hydrolysis of the acylimidazole bond in **5**, followed by a decarboxylation, could alkylate **3**. Benzhydryl benzilate, however, was not isolated.

The polyester of benzilic acid could arise by a polymerization of the hypothetical α lactone with imidazole as the initiating nucleophile. Other reactions which suggest the intermediacy of this lactone also gave a polymer.[3]

The 1-benzhydrylimidazole **3** does not arise from a reaction of benzilide (**2**) with imidazole since a 1-hr fusion of these compounds in a 1:3 molar ratio at 145–150° did not yield **3**.

Experimental Section

1-Benziloylimidazole.—Benzilic acid (5.15 g, 0.0226 mole) and 3.7 g (0.0229 mole) of 1,1′-carbonyldiimidazole were mixed in 50 ml of dry acetonitrile; gas was rapidly evolved, and complete solution was obtained. The product, which began to crystallize in about 10 min, was filtered after the solution had stood 2 hr at 25° and then overnight at 5°, and washed twice with 5-ml portions of cold, dry acetonitrile to give 4.0 g (63.5%), mp 143–144°, with vigorous gassing. The decomposition point remained unchanged when the compound was recrystallized rapidly from acetonitrile.

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 72.94; H, 4.83; N, 10.17.

The infrared spectrum shows a carbonyl absorption at 5.78 μ. Since there is no absorption in the 2.8–3.1 μ region, it is concluded that the hydroxyl group is strongly hydrogen bonded, most likely to the unsubstituted nitrogen of the imidazole ring.

The nmr spectrum in $(CD_3)_2SO$ shows a peak at τ 2.81 corresponding to ten protons and four other single protons at 1.8, 2.3, 2.5, and 3.2, respectively.

(1) H. A. Staab, *Angew. Chem., Intern. Ed. Engl.*, **1**, 351 (1962).
(2) H. A. Staab and H. Bräunling, *Ann.*, **54**, 119 (1962).
(3) P. D. Bartlett and L. B. Gortler, *J. Am. Chem. Soc.*, **85**, 1864 (1963).
(4) H. A. Staab and A. Mannschreck, *Chem. Ber.*, **95**, 1284 (1962).