A Method for the Rapid Cleavage of Sulfonamides

H. R. Snyder, and Richard E. Heckert

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Studies of Acid Stability.—1-γ amounts of isolated and synthesized biocytin in 1-ml. volumes of water were autoclaved for 1 hour at 120° with 1-ml. portions of 0.2, 0.4, 2.0 and 6.0 N H_2SO_4. Following autoclaving each hydrolysate was neutralized, diluted and assayed for microbiological activity with *Lactobacillus arabinosus*.[16] The results are summarized in Table V.

TABLE V

ACID STABILITIES OF ISOLATED AND SYNTHESIZED BIOCYTIN

Normality	Per cent. availability to *Lactobacillus arabinosus* after hydrolysis with acid of the indicated normality: Isolated biocytin	Synthesized biocytin
0	0	0
.1	23	21
.2	43	51
1	91	102
3	100	100

Studies of Enzymatic Stability.—1-γ amounts of isolated and synthesized biocytin were digested under benzene at 37° for 18 hours with 10-mg. quantities of various commercial enzyme preparations in 10 ml. of menstruum considered appropriate for the action of the particular enzyme. Appropriate controls without added biocytin also were prepared. The amount of free biotin, as determined by direct assay with *Lactobacillus arabinosus*, found in each sample containing added biocytin less the amount of free biotin found in the appropriate enzyme control was taken as a measure of the extent to which a particular enzyme hydrolyzes biocytin. The following enzymes, under the conditions used, did not hydrolyze over 1% of the added biocytin: pepsin in 0.1 N HCl, papain or takadiastase in pH 4 phosphate buffer, polidase, mylase or trypsin in pH 7 phosphate buffer.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A Method for the Rapid Cleavage of Sulfonamides[1]

BY H. R. SNYDER AND RICHARD E. HECKERT[2]

A mixture of 48% hydrobromic acid and phenol is an excellent reagent for the rapid cleavage of a sulfonamide when the object is the recovery of the constituent amine. The cleavage is not a simple hydrolysis; an oxidation–reduction reaction between the sulfur-containing fragment and the hydrobromic acid is involved. The phenol serves not only to remove bromine from the reaction mixture, thereby preventing its reaction with the liberated amine, but also to increase the solubility of the sulfonamide.

The foremost objection to the Hinsberg method[3] for the separation of primary, secondary and tertiary amines has been the difficulty with which the intermediate sulfonamides are hydrolyzed. Although a number of attempts have been made to find conditions under which this hydrolysis would proceed rapidly and in good yield, none has been entirely satisfactory. In the present investigation, a mixture of 48% hydrobromic acid and phenol has been found to be an excellent reagent for cleaving sulfonamides when the object is the recovery of the constituent amines.

The reagents commonly employed in the acid hydrolysis of sulfonamides are hydrochloric and sulfuric acids. Whereas sulfonamides are sparingly soluble in hydrochloric acid, they are usually soluble in strong sulfuric acid. Various concentrations of sulfuric acid[4] and sulfuric and acetic acids[5] have been used at moderate temperatures. Although satisfactory hydrolysis rates are normally observed, when aryl amines are produced in the hydrolysis the reaction is complicated by sulfonation. In concentrated sulfuric acid, the rearrangement of sulfonamides to amino-sulfones may also occur.[4b,6]

Concentrated hydrochloric acid was first thought effective only in sealed tubes at temperatures near 150°,[7,8] but Schreiber and Shriner[9] found refluxing 25% hydrochloric acid to be useful. Aniline and N-methylaniline were recovered from benzene and substituted benzenesulfonanilides in excellent yields by this method, but reflux periods of from 12 to 36 hours are normally required, and some o- and p-substituted arylsulfonamides react very slowly or not at all. There appear to be no examples of alkaline hydrolysis of sulfonamides involving, as a first step, cleavage of the sulfur–nitrogen bond.

Hydrobromic acid is often a more effective hydrolytic agent than hydrochloric acid, and it seemed desirable to test its action on a simple substance of this class. When benzenesulfonanilide was heated under reflux with freshly distilled 48% hydrobromic acid, p-bromoaniline rather than aniline was found as the principal constituent of the amine fraction. The reaction, further characterized by reduction of the sulfonyl group, undoubtedly is related to the cleavage of arylsulfonamides by hydriodic acid (d. 1.96), first described by Fischer.[10] At temperatures of 70 to 100° benzene- and p-toluenesulfonamides were cleaved in 25 to 30 minutes with the formation of the amines, the aryl disulfides and iodine. When phosphonium iodide was added to reduce the iodine, the thiophenols rather than the disulfides were obtained. Schönheimer[11] made use of this reductive cleavage of sulfonamides in the synthesis of polypeptides from amino acids and p-toluenesulfonamido acid chlorides. Under the

(1) After the completion of this work a similar method has been disclosed by D. I. Weisblat, B. J. Magerlein and D. R. Myers [U. S. Patent 2,562,222, July 31, 1951; see also D. Weisblat, Abstracts of Papers at XII International Congress of Pure and Applied Chemistry, p. 76 (Sept. 1951)].

(2) Minnesota Mining and Manufacturing Co. Fellow, 1948–1949.

(3) O. Hinsberg, *Ber.*, **23**, 2962 (1890).

(4) (a) O. Witt and H. Truttwin, *ibid.*, **47**, 2786 (1914); (b) O. Witt and D. Uermenyi, *ibid.*, **46**, 296 (1913); (c) G. Schroeter and O. Eisleb, *Ann.*, **367**, 157 (1909).

(5) F. Ullmann and H. Bleier, *Ber.*, **35**, 4273 (1902).

(6) J. Halberkann, *ibid.*, **54**, 1665 (1921); **54**, 1833 (1921); **55**, 3074 (1922). Halberkann has recommended 60% sulfuric acid for the optimum balance between rate of hydrolysis and extent of sulfonation and rearrangement.

(7) T. B. Johnson and J. A. Ambler, THIS JOURNAL, **36**, 372 (1914).

(8) C. Schotten and W. Scholmann, *Ber.*, **24**, 3687 (1891).

(9) R. S. Schreiber and R. L. Shriner, THIS JOURNAL, **56**, 1618 (1934).

(10) E. Fischer, *Ber.*, **48**, 93 (1915).

(11) R. Schönheimer, *Z. physiol. Chem.*, **184**, 203 (1926).

TABLE I

CLEAVAGE OF SULFONANILIDES WITH 25% HYDROCHLORIC ACID (PROCEDURE A) AND WITH A MIXTURE OF 48% HYDROBROMIC ACID AND PHENOL (PROCEDURE B)

Sulfonyl group in sulfonanilide	Weight of sulfonanilide, g.	Procedure A: Time of reflux, hr.	Procedure A: Aniline·HCl isolated, Weight, g.	Procedure A: Aniline·HCl isolated, Yield, %	Procedure A: Sulfonanilide recovered, %	Procedure B: Time of reflux, hr.	Procedure B: Aniline·HCl isolated, Weight, g.	Procedure B: Aniline·HCl isolated, Yield, %
$C_6H_5SO_2-$	10.0	7	1.45	26	71	1/3	3.83	69
$2,4,6-(CH_3)_3C_6H_2SO_2-$	10.0	7	2.90	61	16	1/3	4.34	93
$2,3,5,6-(CH_3)_4C_6HSO_2-$	10.0	7	0.29	6	92	1/3	4.13	92
$(CH_3)_5C_6SO_2-$	10.0	7	.03	1	97	1/3	4.04[14]	94
$2,4-(CH_3O)_2C_6H_3SO_2-$	5.0	7	.00	0	100	1/3	1.97	89

conditions employed, carboxamide groups were unaffected. Recently, Challenger and co-workers[12] employed hydriodic acid (d. 1.95) and hydrobromic acid (d. 1.49) in conjunction with sodium sulfite solutions to reduce arylsulfonyl chlorides to the disulfides. Sulfonic acids and their esters are not affected by these reagents.[10] A similar cleavage of sulfonamides by hydrogen bromide and acetic acid has been described.[13]

In the present work it was necessary to add to the sulfonamide–hydrobromic acid mixture a bromine acceptor active enough to protect the amine. As expected, phenol served this purpose admirably and, in addition, its solvent action resulted in increased rate of reaction. In a mixture of 48% hydrobromic acid and phenol under reflux, most of the benzene- and substituted benzenesulfonanilides were cleaved in 20 to 60 minutes. Aniline, isolated as the hydrochloride from ether extracts of the mixtures after the addition of alkali, was recovered in yields of 90 to 95%. When the technique was applied to ortho or para electronegatively substituted arylsulfonamides, which resist the action of boiling hydrochloric acid, the cleavage was complete in 1 to 2 hours.

To compare the rates of cleavage by hydrochloric acid and by the new reagent, benzene-, mesitylene-, durene-, pentamethylbenzene- and 2,4-dimethoxybenzenesulfonanilides were tested in timed reactions. The results are summarized in Table I. After 7 hours, benzene- and mesitylenesulfonanilides were hydrolyzed by hydrochloric acid to the extent of 26 and 61%, respectively. Durene-, pentamethylbenzene- and 2,4-dimethoxybenzenesulfonanilides, the first two of which might reasonably be expected to react at a rate comparable with that of mesitylenesulfonanilide, were hydrolyzed 6, 1 and 0%, respectively, in this period. The slow hydrolysis of durene- and pentamethylbenzenesulfonanilides probably results from their low solubility in the aqueous acid. When 5.00- and 10.00-g. samples of these five sulfonamides were refluxed for 20 minutes in 10 g. of phenol and 75 ml. of 48% hydrobromic acid, the aniline from all but benzenesulfonanilide was recovered in yields of about 92%. In 20 minutes, benzenesulfonanilide released 69% of its aniline. It is of interest that during the warming-up period a number of phenol–sulfonamide–hydrobromic acid mixtures pass through a temperature range of complete miscibility recalling the pattern of the phenol–water phase-temperature diagram.

TABLE II

CLEAVAGE OF SOME SULFONAMIDES BY REFLUXING ONE HOUR WITH HYDROBROMIC ACID AND PHENOL

Sulfonamide: Formula	Sulfonamide: Weight, g.	Amine hydrochloride: Weight, g.	Amine hydrochloride: Yield, %	Amine recovered[a]: M.p. or b.p., °C. Obsd.	Lit.	Ref.
$C_6H_5SO_2NH_2$	9.0	..	50[b]	.....		
$CH_3SO_2NHC_6H_5$	5.0	3.16	83	194–196[h]	198	14
$C_6H_5SO_2NH(CH_2)_2C_6H_5$	5.0	1.67	55	198[f]	198	15
$C_6H_5SO_2NH(C_{10}H_7)-(\alpha)$	5.0	2.67	84	47–48[f]	50	15
$C_6H_5SO_2NHC_6H_4NO_2-(o)$	5.0	0.70	22	70–71[f]	71	15
$C_6H_5SO_2NHC_6H_4NO_2-(p)$	5.0	2.82	90	146–147[f]	147	15
$p-NO_2C_6H_4SO_2NHC_6H_5$	5.0	2.11	90	194–196[h]	198	14

[a] In most instances the amine was isolated and weighed as the hydrochloride. [b] Determined by titration of the ammonia distilled from an aliquot portion of the reaction mixture following the addition of alkali. [h] Amine hydrochloride. [f] Free amine.

To determine the scope of the method, sulfonamides of a variety of types were examined (Table II). Methanesulfonanilide, benzenesulfon-*p*-nitroanilide, benzenesulfon-α-naphthylamide and *p*-nitrobenzenesulfonanilide were cleaved to the amines in yields of about 85 to 90% after one hour at reflux. The rapid cleavage of *p*-nitrobenzenesulfonanilide is of particular interest because this substance was recovered unchanged[9] after a 36-hour treatment with 25% hydrochloric acid. Less easily cleaved were benzenesulfon-*p*-nitroanilide, benzenesulfonamide and benzenesulfon-β-phenylethylamide. The bases from these were isolated in yields of 22, 50 and 55%, respectively, after refluxing for one hour with the new reagent. The slow reaction of the *o*-nitroanilide evidently results from the combination of steric factors and electron-withdrawal by the nitro group. In the application of the cleavage to sulfonyl derivatives of unknown amines, in which similar adverse structural influences might be present, a reflux period of 2 to 3 hours should give generally good results.

The solubilizing effect of phenol is an important factor in the markedly improved rates of cleavage obtained with phenol–hydrobromic acid reagent. When phenol was added to a mixture of benzenesulfonanilide and 25% hydrochloric acid, 20% of the aniline was recovered after refluxing for two hours. This value is only 6% less than that obtained in the absence of phenol after 7 hours. The introduction of phenol may be expected to reduce the time

(12) F. Challenger, S. Miller and M. Gibson, *J. Chem. Soc.*, 769 (1948).

(13) H. Ohle, H. Friedeberg and G. Haeseler, *Ber.*, **69**, 2311, 2324 (1936).

(14) This sample of aniline hydrochloride melted at 188–194°; all other samples melted over a range of not more than 2° within the limits 194–198°. Pure aniline hydrochloride melts at 198° [F. Ullmann, *ibid.*, **31**, 1699 (1898)].

required for the hydrolysis of sulfonamides with hydrochloric acid by half or more and is suggested when hydrobromic acid is undesirable.

Experimental

The previously known sulfonamides employed in this work were prepared in yields of from 35 to 90% from the amine or ammonia and the corresponding sulfonyl chloride. The sulfonamides were purified through their sodium salts and/or by recrystallization from aqueous ethanol. In this manner were obtained: methanesulfonanilide, m.p. 98–99°; benzenesulfonamide, m.p. 152°; benzenesulfonanilide, m.p. 110–111°; benzenesulfon-*o*-nitroanilide, m.p. 103–104°; benzenesulfon-*p*-nitroanilide, m.p. 138–139°; benzenesulfon-α-naphthylamide, m.p. 165–167°[15]; *p*-nitrobenzenesulfonanilide, m.p. 168°; and mesitylenesulfonanilide, m.p. 114°.[16]

Durenesulfonanilide.—Durenesulfonyl chloride was prepared in 64% yield from durene and chlorosulfonic acid in chloroform according to the method of Huntress and Autenrieth.[17]

Twenty-six grams (0.11 mole) of durenesulfonyl chloride was added slowly to 15 g. (0.16 mole) of aniline and 150 ml. of 10% sodium hydroxide. The mixture was stirred for two hours. The reaction mixture was dissolved in hot ethanol, filtered through a fluted filter (Norit) and the durenesulfonanilide was recovered by cooling and adding dilute hydrochloric acid. The yield of air-dried sulfonamide was 27 g. (62%), m.p. 159–161°. One recrystallization from ethanol gave 22 g., m.p. 161°.

Anal. Calcd. for $C_{16}H_{19}NO_2S$: N, 4.84. Found: N, 4.82.

Pentamethylbenzenesulfonyl Chloride.—To 19 g. (0.13 mole) of pentamethylbenzene (crystallized once from ethanol, m.p. 45–49°) was added with stirring 25 ml. (0.38 mole) of chlorosulfonic acid. The addition was carried out at 0°. The mixture was warmed to room temperature and poured over crushed ice. The pentamethylbenzenesulfonyl chloride was collected on a filter and used without purification. The yield was essentially quantitative.

Pentamethylbenzenesulfonanilide.—This method was employed by Smith and Guss[18] to prepare pentaethylbenzenesulfonamide and -anilide. To 32 g. (0.13 mole) of pentamethylbenzenesulfonyl chloride in 300 ml. of dioxane was added 30 g. (0.32 mole) of aniline. The solution was refluxed for 30 minutes and allowed to stand overnight. The sulfonanilide was separated by adding about 1 l. of water. The solid was collected on a filter and crystallized from 1 l. of 95% ethanol (Darco). The yield of white crystals was 28.4 g. (97%), m.p. 203–206°. A sample of this material, recrystallized once from ethanol, melted at 207° and was analyzed.

Anal. Calcd. for $C_{17}H_{21}NO_2S$: N, 4.62. Found: N, 4.86.

2,4-Dimethoxybenzenesulfonyl Chloride.—This is the method of Suter and Hansen,[19] though the yield obtained was considerably higher than claimed. Twenty-seven grams (0.27 mole) of 98% sulfuric acid was added to 25 g. (0.18 mole) of resorcinol dimethyl ether with stirring. The temperature rose to 85°. After standing for one hour, the contents of the flask were neutralized by pouring into a saturated aqueous solution of potassium carbonate. The resulting cake was collected on a filter and washed twice with 100 ml. of concentrated potassium carbonate. The impure potassium salt, dried at 110°, weighed 95 g. (twice the theoretical amount).

The dried crude potassium 2,4-dimethoxybenzenesulfonate was pulverized and treated under reflux with 200 g. of phosphorus oxychloride for 1.5 hours. The excess phosphorus oxychloride was decomposed on crushed ice and the solid sulfonyl chloride was collected on a filter. The product was dissolved in ether, dried over anhydrous calcium chloride and recovered by evaporating the ether under reduced pressure. It melted at 67–69° and weighed 37.5 g., 88% of the theoretical amount. This material decomposes slowly unless kept under refrigeration.

2,4-Dimethoxybenzenesulfonanilide.—Thirty-one grams (0.13 mole) of 2,4-dimethoxybenzenesulfonyl chloride was added slowly to 16 g. (0.17 mole) of aniline and 20 g. (0.5 mole) of sodium hydroxide in 300 ml. of water. The sulfonanilide was purified by treating its alkaline solution with Darco, precipitating it with acid, and crystallizing the product once from aqueous ethanol. The yield of white crystals melting at 178–179° was 25 g. or 65%. A portion of the material recrystallized from ethanol melted at 180° and was analyzed.

Anal. Calcd. for $C_{14}H_{15}NO_2S$: N, 4.78. Found: N, 4.82.

Reaction of Benzenesulfonanilide with Hydrobromic Acid.—Three grams of the sulfonanilide was refluxed for 30 minutes with 25 ml. of water-white 48% hydrobromic acid (free of bromine and hypobromous acid). The acid mixture was extracted once with ether, made alkaline with sodium hydroxide and extracted twice again with 50-ml. portions of ether. The combined ether extracts of the alkaline solution, dried over anhydrous magnesium sulfate, deposited 0.61 g. of amine hydrochloride when treated with dry hydrogen chloride. This material did not melt sharply, but sintered at 200° and above. When treated with 10% sodium hydroxide the salt deposited an oil which solidified on standing. After one recrystallization from aqueous ethanol it melted at 57–62°. A mixed melting point with an authentic sample of *p*-bromoaniline (m.p. 61–64°) was 61–63°. The benzoyl derivative, crystallized from ethanol, melted at 202–203°. Benzo-*p*-bromanilide melts at 204°.[15]

Reaction of Mesitylenesulfonanilide with Hydrobromic Acid.—Mesitylenesulfonanilide, 3.5 g., was refluxed with 25 ml. of pure 48% hydrobromic acid. The amine was isolated as the hydrochloride from dried ether extracts of the mixture after the addition of excess alkali. The hydrochloride weighed 1.65 g. and sintered at 200° and above. When treated with 10% sodium hydroxide it deposited an oil which did not solidify at room temperature. It did crystallize, however, when seeded with a crystal of *p*-bromoaniline.

The General Procedure for Acid Cleavage.—Procedure A, with 25% hydrochloric acid [the method of Schreiber and Shriner[9]]: the hydrolyses were carried out in a single-necked, round-bottomed 100-ml. flask equipped with a 12-in. condenser. Agitation was provided by means of an all-glass stirrer which operated through the condenser. Exactly 5.00 or 10.00 g. of the sulfonamide to be tested and 75 ml. of 25% hydrochloric acid were placed in the flask which in turn was fitted with a pre-heated mantle. The mixture was stirred and refluxed for 7 hours. Five minutes prior to the end of the hydrolysis, heating was discontinued. At the end of the reaction period, timed from the moment at which the mantle was placed in position, the flask was immersed in ice-water.

When ether-soluble sulfonamides were employed, the contents of the flask were washed with water and ether into a separatory funnel. The condenser and stirrer were rinsed similarly and the washings were added to the mixture. Ether, sufficient to bring the volume of this solvent to 125 ml., was added and the aqueous layer containing the amine hydrochloride was drained slowly into 100 ml. of water and 30 g. of sodium hydroxide, cooled externally with ice. Three 60-ml. ether extracts of the alkaline mixture were combined and dried over anhydrous magnesium sulfate. The amine was precipitated and weighed as the hydrochloride.

The unchanged sulfonamide was recovered from the ether extract of the acid solution by evaporating the ether or by extracting exhaustively with 10% sodium hydroxide and acidifying the combined aqueous layer. In only one instance could less than 96% of the sulfonamide be accounted for.

When ether-insoluble sulfonamides were encountered, the procedure was modified only in that the acid reaction mixture and aqueous and ether washes were filtered to recover the unchanged sulfonamide. Details of the cleavages are shown in Table I.

(15) R. L. Shriner and R. C. Fuson, "Systematic Identification of Organic Compounds," John Wiley and Sons, New York, N. Y., 1948, ed. 3, pp. 234–241, 273–278.

(16) R. S. Schreiber, Thesis, Doctor of Philosophy, University of Illinois, 1935, p. 21.

(17) E. H. Huntress and J. S. Autenrieth, THIS JOURNAL, **63**, 3446 (1941).

(18) L. I. Smith and C. O. Guss, *ibid.*, **62**, 2631 (1940).

(19) C. M. Suter and H. L. Hansen, *ibid.*, **55**, 2080 (1933).

Procedure (B), Employing 48% Hydrobromic Acid and Phenol.—To the 5.00 or 10.00 g. of sulfonamide were added 10 g. of phenol (Merck USP) and 75 ml. of freshly distilled 48% hydrobromic acid. The mixture was refluxed for the specified period (see Tables I and II). In working up the reaction mixture, no attempt was made to isolate unchanged sulfonamide. With these modifications, the techniques employed were those described in detail under (A). The yields obtained in the various cleavages are given in Tables I and II.

The various samples of aniline hydrochloride, isolated from the phenol–hydrobromic acid cleavages, were combined and treated with aqueous alkali to liberate the amine. From 22 g. of the salt 13.8 g. (87%) of distilled aniline was isolated (b.p. 181–182°, $n^{20}D$ 1.5852).

Hydrolysis of Benzenesulfonanilide with Hydrochloric Acid in the Presence of Phenol.—In one experiment a mixture of 10.00 g. of the sulfonanilide, 10 g. of phenol and 75 ml. of 25% hydrochloric acid was refluxed 2 hours. The aniline hydrochloride, isolated as described in Procedure A, weighed 1.09 g. (20%).

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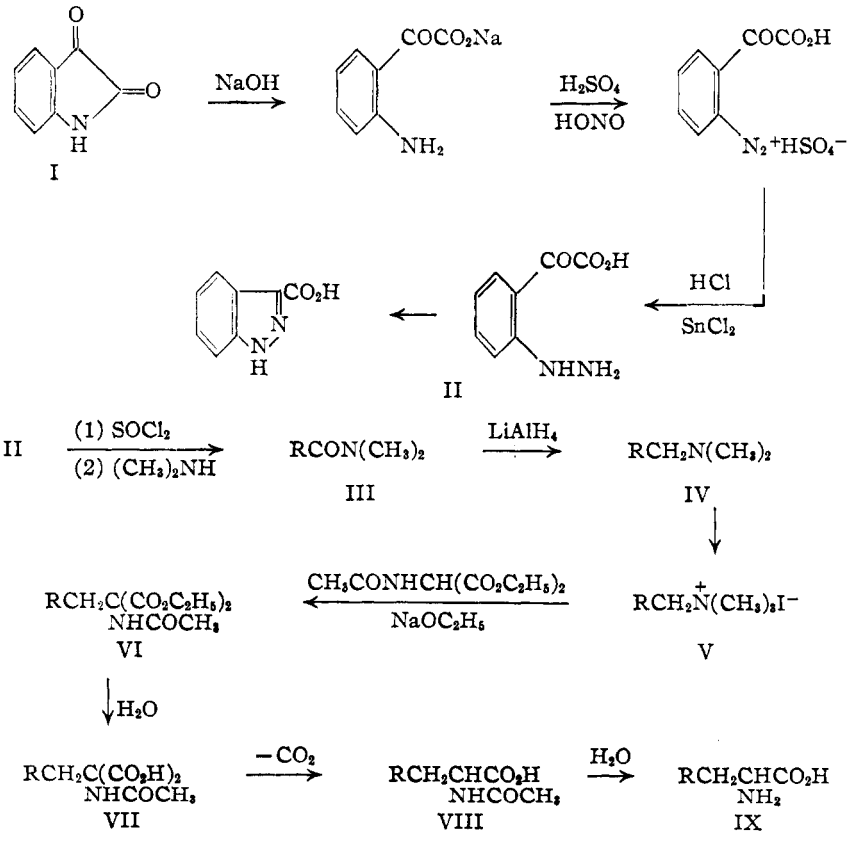
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of an Indazole Analog of DL-Tryptophan

BY H. R. SNYDER, CRAYTON B. THOMPSON AND RICHARD L. HINMAN[1]

DL-α-Amino-β-(3-indazole)-propionic acid, the indazole analog of tryptophan, has been synthesized *via* the sequence: isatin, 3-indazolecarboxylic acid, N,N-dimethyl-3-indazolecarboxylic acid amide, 3-dimethylaminomethylindazole, the corresponding methiodide, ethyl α-acetamino-α-carbethoxy-β-(3-indazole)-propionate, α-amino-β-(3-indazole)-propionic acid. Attempts to induce indazole to undergo the Mannich reaction or chloromethylation were unsuccessful.

Indazole, 4,5-benzopyrazole, bears a close structural resemblance to indole. Since many derivatives of indole are important biochemically, it appeared of interest to study the properties of related compounds which are derivatives of indazole. The present work was devoted to the synthesis of DL-α-amino-β-(3-indazole)-propionic acid (IX), the indazole analog of tryptophan. It was proposed to prepare IX in a manner analogous to the preparation of DL-tryptophan,[2] employing a Mannich base derived from indazole to alkylate acetaminomalonic ester.



I II III IV V VI VII VIII IX

The 3-position of indazole is somewhat reactive, bromination[3,4] and attack by benzenediazonium chloride in basic solution[5] both occurring at this position. This suggested that a dialkylaminomethyl group could be introduced in the 3-position by the Mannich reaction. However, in each of the three procedures tried[6,7,8] either unchanged indazole or unidentified neutral products were isolated. In an attempt to enhance the activity of the 3-position, 5-nitroindazole was prepared. The three methods for the condensation were again tried without success. N-Benzylindazole and N-methyl-5-nitroindazole also failed to undergo the Mannich reaction.

3-Chloromethylindazole undoubtedly could be used to alkylate acetaminomalonic ester. However, attempts to prepare it by chloromethylation of indazole were unsuccessful. From attempted syntheses of 3-halomethylindazoles *via* the corresponding alcohol only high-melting solids were obtained.

The scheme finally selected for the synthesis of

(1) Visking Corporation Fellow, 1951–1952.

(2) H. R. Snyder and C. W. Smith, THIS JOURNAL, **66**, 350 (1944).

(3) E. Fischer and J. Tafel, *Ann.*, **227**, 303 (1885).

(4) K. von Auwers and A. Lohr, *J. prakt. Chem.*, **108**, 297 (1924).

(5) E. Bamberger, *Ann.*, **305**, 289 (1899).

(6) H. Kuhn and O. Stein, *Ber.*, **70**, 567 (1937).

(7) J. van de Kamp and E. Mosettig, THIS JOURNAL, **58**, 1568 (1936).

(8) H. R. Snyder and J. H. Brewster, *ibid.*, **71**, 1062 (1949).