The rapidity of the overall reaction $A + B + C$ led us to investigate its kinetics. Under conditions of constant total cyanide concentration, the rate of proton release, corrected for the extent of ionization of the products, increased with increasing pH. Since, in the *p*H range of these experiments the rate of solvolysis of ninhydrin is negligible, the major catalytic species is established to be CN^-. The reaction was found to follow *pseudo* first order kinetics at *p*H 3.0. Deviations from first order plots were apparent at *p*H 4.0 and continually increased to *p*H 7.0. Part of this deviation was traced to the loss of cyanide from the reaction mixture. The value of the apparent second order rate constant at *p*H 3.0 and 30° (in 0.2 N aqueous KCl) was found to be approximately 30 l mol^{-1} min^{-1} giving a value of k_c for CN^- of the order of magnitude 10^7 l mol^{-1} min^{-1}. Reliable initial rate constants could not be obtained above *p*H 4.0, though at this pH the approximate initial rate gave a value of k_c in agreement with that determined at *p*H 3.0.

EXPERIMENTAL

Cyanide in catalytic concentration. With constant mechanical stirring, 0.5 ml. of a 0.01*N* KCN solution (0.005 mmole) was added to 50 ml. water containing 0.5 g. (2.8 mmole) of ninhydrin. The solution was contained in a 100 ml. beaker equipped for automatic maintenance of pH by addition of standard NaOH using an automatic buret and recorder. The reaction was allowed to go to completion at pH 6.0 (approximately 40 min. at room temperature) when 2.1 protons per 3.0 molecules of ninhydrin were released (105% of theory) as measured by base uptake.

The reaction solution was acidified with HCl and the hydrindantin collected, washed with water, and dried *in vacuo* over P_2O_5 (0.29 g.; 97% based on the production of one molecule of II per 3 molecules of III), m.p. 249° dec. (lit. 249° dec.).[1] The filtrate and washings were taken to dryness *in vacuo*, the residue taken up in 4 ml. of 1*N* HCl and filtered to remove a small quantity of II (10 mg.).

The identification of phthalonic acid in the filtrate was carried out by the formation of its dianiline salt and 1-carboxy-3-phenyl-2,3-naphthyridone-4.

(*a*) The filtrate was saturated with aniline and heated on a steam bath for 30 min. After cooling, the black residue was collected, washed with CCl_4 and the tan product recrystallized from a mixture of ethanol and chloroform by addition of carbon tetrachloride to yield colorless needles (20 mg.), m.p. 164°. The dianiline salt of phthalonic acid is reported to melt at 165°.[8]

(*b*) The filtrate was saturated with NH_3, taken to dryness *in vacuo*, the residue taken up in ethanol and collected. After being washed free of color, the salt was dissolved in 2 ml. concentrated HCl and taken to dryness and the residue dissolved in 2 ml. water. The aqueous solution was saturated with phenylhydrazine hydrochloride, heated on the steam bath for 30 min., and chilled; the resulting orange crystals were collected and recrystallized from ethanol and water to yield 60 mg. of 1-carboxy-3-phenyl-2,3-naphthyridone-4, m.p. 219° (lit. 214°).[9]

High cyanide concentration. A warm solution of 0.5 g. (2.8 mmole) of ninhydrin in 15 ml. water was added dropwise with constant mechanical stirring to 25 ml. of an aqueous solution containing 1 g. of sodium acetate dihydrate, 1 g. of KCN (0.0156 mole) and about 18 ml. of 0.1*N* HC (pH 6.0). When this addition was completed, the solution was immediately adjusted to *p*H 2.0 by addition of 6*N* HCl. The resulting white flocculent precipitate was collected, washed with water, and dried over P_2O_5 *in vacuo;* yield 0.20 g. (40%) of *o*-carboxymandelic acid lactone, m.p. 153–154° (lit. 152–153°).

Kinetics. The rate of proton release was determined from the record obtained with a Radiometer TTT 1a Titrator equipped for graphical recording of base uptake. The reaction was carried out in 0.2*N* KCl at 30 ± 0.1° at various *p*H values. At low *p*H the reaction was followed to at least 80% completion and above *p*H 4 to 20 or 30% completion.

The maximum proton release at completion was known from the initial stoichiometry studies. Using these values as α_∞ the graphical data obtained were replotted as $\ln \alpha_\infty/\alpha_\infty - \alpha$ *vs. t.* The first order constants were obtained as the slopes of the best straight lines. Where marked deviations from the first order kinetics occurred, the rate for the initial 5% or less of reaction was estimated.

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(8) R. C. Fuson, *J. Am. Chem. Soc.*, **48**, 1096 (1926).
(9) R. Henrique, *Ber.*, **21**, 1610 (1888).

Concerning a Preparation of Tryptamine[1]

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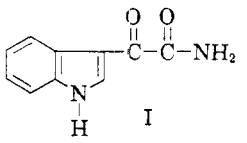
Although numerous methods for the synthesis of tryptamine have been reported, there existed none which fully satisfied the authors as a practical source, even though in this laboratory the gramine method[2] was observed to be a dependable alternate route. The Upjohn method[3] for the preparation of 5-benzyloxy tryptamine and several other substituted tryptamines appeared to be desirable even though little investigation into the preparation of the parent compound was reported. The last step of Woodward's 6-methoxy tryptamine synthesis[4] further prompted use of this method for the preparation of tryptamine.

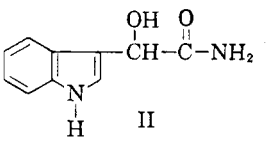
The preparations of 3-indoleglyoxylyl chloride and 3-indoleglyoxylamide (I) which have been previously reported[3,5] have been carried out in this laboratory in 99 and 96 per cent yields respectively in an over-all time of three to four hours. The only

(1) This investigation was supported by a fellowship (number MF-6776 from the National Institute of Mental Health, Public Health Service (W.D.V.). A DuPont Summer Faculty Fellowship is gratefully acknowledged (F.V.B., Jr.).
(2) G. Stork and R. K. Hill, *J. Am. Chem. Soc.*, **79**, 495 (1957).
(3) N. E. Speeter and W. C. Anthony, *J. Am. Chem. Soc.*, **76**, 6209 (1954).
(4) R. B. Woodward, *et al.*, *J. Am. Chem. Soc.*, **78**, 2025 (1956).
(5) M. S. Kharasch, S. S. Kane, and H. C. Brown, *J. Am. Chem. Soc.*, **62**, 2242 (1940).

difficult reaction was the lithium aluminum hydride reduction of the amide.[3] A ten-to-one mole ratio of the hydride was found to be desirable. After trying several solvents (Table I), we found dioxane to afford the highest yield of tryptamine. A by-product of the reduction was 3-indoleglycolamide (II) which



I



II

can also be produced in nearly quantitative yield by the sodium borohydride reduction of I. Reduction of II with lithium aluminum hydride produced tryptamine in yield approximating that of the reduction of I under the same conditions, indicating that II is an intermediate in the formation of at least some of the tryptamine.

TABLE I

REDUCTION OF 3-INDOLEGLYOXYL AMIDE WITH LITHIUM ALUMINUM HYDRIDE IN VARIOUS SOLVENTS

Mole Ratio, $LiAlH_4$/ Amide	Solvent	Reaction Time	Yield, % Tryptamine hydrochloride	Yield, % II
5/1	Ether,[a] b.p. 34.6°	48 Hr.	Trace	Undetermined
10/1	Tetrahydrofuran, b.p. 64–66°	120 Hr.	41.5	11.2
10/1	Dioxane, b.p. 101–102°	48 Hr.	64.0	Trace
10/1	Dioxane	91 Hr.	65.0	Trace
5/1	*n*-Butyl ether,[a] b.p. 142°	46 Hr.	8.1	Undetermined

[a] Amide not soluble.

It was observed that both tryptamine and the hydrochloride defy crystallization unless relatively pure; thus, care had to be taken in the work-up of the reduction. A vital point in this connection is the chilling of the benzene solution of the crude oil prior to filtration. Compound II, which is very insoluble in cold benzene, is removed by this operation. Of equal importance is the addition of ethanolic hydrogen chloride to the point of exact neutrality. At a lower *p*H a less basic substance, probably indole, is precipitated along with the product.

Using this variation of the Upjohn method,[3] tryptamine hydrochloride has been prepared in over-all yields of 55 per cent from indole in two to three days total time.

EXPERIMENTAL[6]

Tryptamine. Lithium aluminum hydride (28.4 g., 0.75 mole) was suspended in 500 ml. of dioxane purified by distillation from lithium aluminum hydride (b.p. 101–102°) and heated to reflux. A solution of crude 3-indoleglyoxylamide (14.10 g., 0.075 mole) in 500 ml. hot dioxane was added dropwise with stirring in about 1 hr. The reaction mixture was stirred and refluxed for 48 hr. Finally, wet dioxane was *cautiously* added to the reaction mixture until a granular, white precipitate of lithium aluminate settled out. This was filtered warm, washed several times with hot dioxane, the combined filtrates dried over anhydrous sodium carbonate, and the solvent stripped off under vacuum to yield an amber oil. This was dissolved in 800 ml. of benzene, boiled with charcoal, chilled, and filtered. To the chilled benzene solution was carefully added a 10 per cent ethanolic solution of hydrogen chloride until the solution was just neutral to moistened Hydrion paper. The precipitated tryptamine hydrochloride was filtered and washed first with benzene and then with petroleum ether (9.58 g., 65.0%). The crude hydrochloride was dissolved in absolute ethanol, boiled with charcoal, filtered, and absolute ether was rapidly added to the hot solution until crystallization commenced; on cooling, the hydrochloride separated as colorless needles (8.50 g., 57.6%), m.p. 250–252° (lit.[7] m.p. 248°). Conversion to the free base by treating a saturated solution of 8.13 g. of tryptamine hydrochloride with strong sodium hydroxide solution resulted in precipitation of white, granular tryptamine. Recrystallization from chloroform and petroleum ether gave 5.92 g. of tryptamine (90%), m.p. 113.5–115.5° (lit.[2] m.p. 115–116°).

3-Indoleglycolamide. To a solution of 3.76 g. (0.02 mole) 3-indoleglyoxylamide in 350 ml. absolute ethanol was added 3.78 g. (0.10 mole) of sodium borohydride. The reaction mixture was allowed to stand at room temperature for 2 hr. with occasional shaking. After approximately 20 ml. of glacial acetic acid was added to destroy the excess borohydride, the volume of the solution was reduced to one half the original and allowed to crystallize in the refrigerator to yield white, granular crystals (3.80 g., 98%). Two recrystallizations from ethanol afforded colorless plates, m.p. 175.5–177° (with decomp.).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.30; N, 14.74. Found: C, 63.13; H, 5.37; N, 14.57.

Tryptamine. 3-Indoleglycolamide (1.48 g., 0.008 mole) was reduced with lithium aluminum hydride by the method described above. The reaction time was reduced to 22 hr. and the yield of crude tryptamine hydrochloride was 0.64 g. (41.8%), m.p. 252–253°.

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(6) All melting points are uncorrected.

(7) R. Manske, *J. Am. Chem. Soc.*, **51**, 1204 (1929).

2,3-Dibromo-*p*-dioxane

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In the absence of a cosolvent, *p*-dioxane can be chlorinated directly to 2,3-dichloro-*p*-dioxane,[1] but bromination[2–4] has yielded only ethylene dibromide. Dechlorination of 2,3-dichloro-*p*-dioxane to *p*-dioxene (2,3-dihydro-*p*-dioxin) followed by addition

(1) J. Böeseken, F. Tellegen, and P. C. Henriquez, *Rec. trav. chim.*, **50**, 909 (1931).

(2) J. van Alphen, *Rec. trav. chim.*, **49**, 1040 (1930).

(3) C. L. Butler and L. H. Cretcher, *J. Am. Chem. Soc.*, **54**, 2987 (1932).

(4) R. K. Summerbell, personal communication.