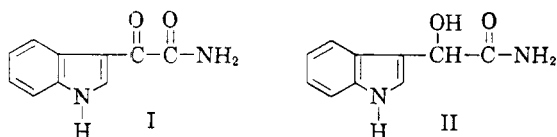


difficult reaction was the lithium aluminum hydride reduction of the amide.³ A ten-to-one mole ratio of the hydride was found to be desirable. After trying several solvents (Table I), we found dioxane to afford the highest yield of tryptamine. A by-product of the reduction was 3-indoleglycolamide (II)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



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	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	<i>n</i> -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 *pH* 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.

EXPERIMENTAL⁶

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 C₁₀H₁₀N₂O₂: 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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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 bromination²⁻⁴ has yielded only ethylene dibromide. Dechlorination of 2,3-dichloro-*p*-dioxane to *p*-dioxane (2,3-dihydro-*p*-dioxin) followed by addition

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(6) All melting points are uncorrected.

of bromine to the double bond is the only method recorded for the synthesis of 2,3-dibromo-*p*-dioxane.⁵

Dry hydrogen bromide converts tetrahydrofuran to 1,4-dibromobutane readily whereas dry hydrogen chloride is unreactive.⁶ The failure to obtain 2,3-dibromo-*p*-dioxane by direct bromination is probably due to a similar opening of the *p*-dioxane ring by the hydrogen bromide coproduct.

A refluxing mixture of *p*-dioxane and carbon tetrachloride, however, can be brominated to give 2,3-dibromo-*p*-dioxane readily in good yield. This is probably due to the low solubility of hydrogen bromide in warm carbon tetrachloride.⁷ Good quality 2,3-dibromo-*p*-dioxane that is considerably more stable than material described previously⁵ can be crystallized readily from the reaction mixture in 75% yield. Simple distillation of the crude reaction mixture gives similar yields of crystalline product that decompose rapidly at room temperature with evolution of hydrogen bromide unless washed well with ether. One possible explanation is that the ether removes traces of hydrogen bromide which trigger the autocatalyzed decomposition if not removed. This is suggested by the fact that in one run in which the ether wash was less thorough the product was considerably less stable than usual and began to decompose on standing at room temperature for one day. At the beginning of the decomposition dark specks appeared throughout the mass of colorless crystals. The specks increased in size with increasing speed and with evolution of heat and hydrogen bromide until the entire mass had decomposed.

Bromination in refluxing carbon tetrachloride has an additional advantage in that halogen loss is minimized since halogen in the off-gas is returned to the reaction mixture dissolved in the condensate. This method might be extended to the halogenation of other compounds (especially ethers) where evolved hydrogen halides produce undesirable side reactions.

EXPERIMENTAL⁸

2,3-Dibromo-p-dioxane. A refluxing solution of 88.1 g. (1.00 mole) of *p*-dioxane (Union Carbide Corp. commercial grade) and 100 ml. of reagent-grade carbon tetrachloride in a 500-ml. round-bottomed flask equipped with all-glass accessories including a dropping funnel, Trubore stirrer, and an efficient condenser connected to an off-gas scrubbing system, was treated with 291.0 g. (1.82 moles, 91% of theory) of bromine over a 4-hr. period with constant irradiation from two Hanovia SC 5041 ultraviolet lamps placed 1 cm. from the flask. Bromine was added at such a rate that the condensate and flask contents remained only slightly colored.

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(8) Melting points are corrected.

The mixture was irradiated for an additional 5 min. The resulting pale yellow solution was cooled, seeded with 2,3-dibromo-*p*-dioxane, and held at 0° for 0.5 hr. The heavy crop of crystals was collected on a sintered glass funnel, washed with cold carbon tetrachloride, and dried on an aspirator with the aid of a rubber dam. To keep the product free from moisture, it was allowed to warm to room temperature before removing the dam. The product was then transferred to a round-bottomed flask and dried further at 12 mm. to give 118.8 g. of colorless, irregular prisms, m.p. 73.0–74.5° (reported⁵ 69–70° with previous softening).

Anal. Calcd. for C₄H₈O₂Br₂: Br, 65.0%. Found: Br, 65.2, 64.9, 64.8%.

A small portion of the product was allowed to react with excess 2,4-dinitrophenylhydrazine in aqueous ethanol containing perchloric acid.⁹ The yield of glyoxal 2,4-dinitrophenylosazone in four runs was 99.6 ± 0.2%.

The mother liquor was concentrated rapidly at aspirator pressure (water bath at 60°) and on working up as described above yielded 37.2 g. of colorless, irregular prisms, m.p. 71.5–73.5°. Repeating this operation gave 11.9 g. of colorless product, m.p. 70.5–73.0°, bringing the total yield to 167.9 g. (0.683 mole; 75.1% based on bromine consumed). The mother liquor was not investigated further.

Samples of product in polyethylene-capped bottles were stored for several weeks at room temperature and for 6 months at –8° with no change in appearance.

When the reaction was repeated exactly as described above and the crude product distilled rapidly through an 8-in. Vigreux column, there was obtained, after a forerun of solvent and unreacted dioxane, 72.4% (based on bromine consumed) of colorless liquid in four fractions, b.p. 123–133° (21 mm.). This material crystallized completely when cooled and seeded. A small portion of the third cut was washed several times with cold ether and dried under vacuum at room temperature to give colorless, irregular prisms, m.p. 73.0–74.5°, having the same stability as the material described above. The remainder of the distilled product turned dark and began to liquify on standing at room temperature for 1 hr.

When *p*-dioxane was brominated and distilled as described above, except that no solvent was employed and the bromination was carried out at 90–110°, none of the seven fractions obtained crystallized on cooling and seeding with 2,3-dibromo-*p*-dioxane.

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Preparation and Properties of Some Aryl Esters of Phosphoric Acid¹

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Diphenyl hydrogen phosphate (I) and its *p*-nitro derivative, bis(*p*-nitrophenyl) hydrogen phosphate (II) are convenient substrates for the investigation of phosphodiesterases. Rapp² has in-

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(2) M. Rapp, *Ann.*, **224**, 156 (1884).