INDOLE DERIVATIVES

LXXXII.* SYNTHESIS OF N^{15}-INDOLE DERIVATIVES

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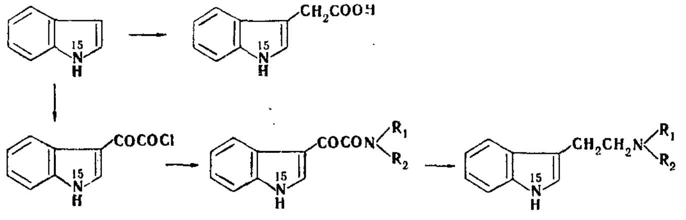
The synthesis of N^{15}-3-indolylacetic acid, 1-N^{15}-tryptamine, and 1-N^{15}-N,N-dimethyltryptamine was accomplished.

The synthesis of N^{15}-indole by cyclization of 1-N^{15}-phenylhydrazone under heterogeneous catalysis conditions on γ-aluminum oxide [2] opens up a convenient route to the preparation of biologically active indole derivatives with a labeled nitrogen.

In the present study we have accomplished the synthesis of N^{15}-3-indolylacetic acid, 1-N^{15}-tryptamine, and 1-N^{15}-N,N-dimethyltryptamine.



I, II

I $R_1=R_2=H$; II $R_1=R_2=CH_3$

N^{15}-3-Indolylacetic acid was obtained by heating N^{15}-indole with chloroacetic acid at 245-250°C in the presence of KOH in an autoclave, while 1-N^{15}-tryptamine (I) and 1-N^{15}-N,N-dimethyltryptamine (II) were obtained by reduction of the corresponding 1-N^{15}-3-indolyloxalylamides with lithium aluminum hydride.

The substances were analyzed for their N^{15} content by combustion to nitrogen by the Dumas method [3] with subsequent mass-spectrometric determination of the percentage of N^{15} (Table 1).

EXPERIMENTAL

The isotopic analysis for the percentage of N^{15} was performed with an MI-1305 mass spectrometer.

N^{15}-3-Indolylacetic Acid. A 100-ml autoclave was charged with 1.2 g (0.01 mole) of N^{15}-indole, 1.44 g (0.015 mole) of chloroacetic acid, 6.15 g of KOH, and 30 ml of water. The autoclave was then evacuated and filled with argon to 5 atm. The mixture was then heated at 245-250° with shaking for 12 h, after which it was filtered, and the filtrate was cooled to 6° and acidified (with respect to Congo Red) with 16% HCl. The resulting precipitate was removed by filtration and recrystallized from water to give 1.14 g (64%) of a product with mp 164-165° (mp 164-165° [4]).†

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*See [1] for communication LXXXI.

†Here and elsewhere, the physical constants of the corresponding compounds with a natural isotopic composition are presented for comparison.

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TABLE 1. Results of the Determination of the Percent N^{15}

Substance	N^{15}, %
N^{15}-Indole	10.9
N^{15}-3-Indolylacetic acid	10.7
1-N^{15}-Tryptamine	5.33
1-N^{15}-N,N-Dimethyltryptamine	5.46

N^{15}-3-Indolyloxalyl Chloride. A 1.2-g (0.01 mole) sample of N^{15}-indole was dissolved in 25 ml of absolute ether, the solution was cooled to − 5°, and 1.3 g (0.01 mole) of oxalyl chloride was added slowly by drops. The mixture was then stirred for 30 min, and the precipitate was removed by filtration and washed with ether to give 1.8 g (90%) of a product with mp 136° (dec.) (mp 135-136° (dec.) [5]).

1-N^{15}-3-Indolyloxalylamide. A 1.8-g (8.7 mmole) sample of 3-indolyloxalyl chloride was added to 30 ml of a saturated aqueous solution of ammonia, and the mixture was stirred at 60-70° for 1.5 h. The precipitate was removed by filtration to give 1.55 g (94%) of a product with mp 251° (dec., from alcohol) (mp 251-252° (dec.) [5]).

1-N^{15}-N,N-Dimethyl-3-indolyloxalylamide. This compound was similarly obtained in 90% yield and had mp 158-159° (from benzene) (mp 160-162° [6]).

1-N^{15}-Tryptamine. A solution of 0.7 g (3.7 mmole) of 1-N^{15}-3-indolyloxalylamide in 20 ml of absolute tetrahydrofuran was added by drops to 1 g (0.026 mole) of $LiAlH_4$ in 30 ml of absolute tetrahydrofuran, after which the mixture was stirred and refluxed for 4 h. It was then cooled, and 1 ml of water, 1 ml of 15% NaOH, and 3 ml of water were added successively. The mixture was then stirred for 3 h, and the precipitate was removed by filtration and washed with tetrahydrofuran. The filtrate was dried with $MgSO_4$, the solvent was removed by vacuum distillation, and the residue was dissolved in methylene chloride and acidified with 5% HCl in alcohol. The precipitated hydrochloride of I was removed by filtration and washed on the filter with ether to give 0.4 g (55%) of a product with mp 240-242° (mp 243-244° [7]).

1-N^{15}-N,N-Dimethyltryptamine. This compound was similarly obtained except that the amine was isolated as the oxalate. The yield of product with mp 148-149° (mp 151-152° [6]) was 60%.

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