## IN DOLES XVII.\* METHOD FOR THE SYNTHESIS OF 2-METHYL-1,7-DI-AND 2-METHYL-1,7-TRIMETHYLENETRYPTAMINES AND HOMOTRYPTAMINES

## I. I. Grandberg and T. I. Zuyanova

UDC 547.75.07

A new one-step method is proposed for the synthesis of 2-substituted 1,7-di- and 1,7-trimethylenetryptamines and homotryptamines by the reaction of N-aminoindoline and N-aminotetrahydroquinoline with 1,4- and 1,5-halocarbonyl compounds by refluxing the components in alcohol solutions.

We previously reported the reaction between arylhydrazines and 1,4- and 1,5-halocarbonyl compounds leading to tryptamines and homotryptamines under quite mild conditions [2-5]. This reaction opens up vast synthetic possibilities in the most interesting and promising field of physiologically active substances.

In a subsequent study of the range of application of this reaction we accomplished the one-step synthesis of various tricyclic 1,7-di- and 1,7-trimethylenetryptamines and homotryptamines in high yields in analogy with the previously proposed scheme by refluxing the corresponding hydrazines and halocarbonyl compounds in aqueous alcohol.



The tryptamine and homotryptamine salts formed in the reaction were converted, without isolation, to the free bases, which were purified by distillation, recrystallization, or sublimation. All of the compounds obtained were identified by paper chromatography and UV spectra. The PMR spectra also indicated the tryptamine structure.

Hydrazines synthesized from tetrahydroquinoline, tetrahydroquinaldine, and indoline were used as the hydrazine component. Nitrosotetrahydroquinoline and nitrosodihydroindole were obtained according to the method described in [6, 7] from the corresponding tetrahydroquinoline and indoline. However, we reduced the nitroso derivatives to hydrazines using lithium aluminum hydride and inverse addition. Reduction by this method is simpler in an experimental respect and has the advantage, as compared with the method described in [6, 7], that it gives consistently high yields of hydrazines.

\*See [1] for communication XVI.

K. A. Timiryazev Moscow Agricultural Academy. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 51-53, January, 1971. Original article submitted November 24, 1969.

© 1973 Consultants Bureau, a division of Plenum Publishing Corporation, 227 West 17th Street, New York, N. Y. 10011. All rights reserved. This article cannot be reproduced for any purpose whatsoever without permission of the publisher. A copy of this article is available from the publisher for \$15.00.

## EXPERIMENTAL

<u>1-Amino-1,2,3,4-tetrahydroquinoline</u>. A solution of lithium aluminum hydride in 300 ml of absolute ether containing 0.25 mole of active hydride was slowly added dropwise with vigorous stirring to a solution of 40 g (0.25 mole) of 1-nitroso-1,2,3,4-tetrahydroquinoline [6] in 200 ml of absolute ether. At the end of the addition, the mixture was stirred for 2 h at room temperature and then carefully decomposed by the addition, in small portions, of 10 ml of water. The ether was decanted, and the residue was refluxed for 1 h with 200 ml of ether, filtered, and washed several times with ether. The combined ether extracts were dried with fused alkali, after which the ether was removed by vacuum distillation with a water aspirator, and the residue was vacuum-distilled under nitrogen to give 27.5 g (74%) of 1-amino-1,2,3,4-tetrahydroquinoline with bp 141-143° (10 mm) and mp 54-55° [6].

<u>1-Nitroso-1,2,3,4-tetrahydroquinaldine</u>. 1,2,3,4-Tetrahydroquinaldine [44,1 g (0.3 mole)] was dissolved in a mixture of 24 g (0.4 mole) of acetic acid and 200 ml of water, and a solution of 22 g (0.32 mole) of sodium nitrite in water was added slowly to it with vigorous stirring at  $0-5^{\circ}$ . The sodium nitrite solution was added at a rate such that the temperature did not rise above  $5^{\circ}$ . The reaction mixture was stirred for 1 h, and the resulting oil was extracted with ether. The ether extract was washed three to four times with water and thoroughly dried with calcined magnesium sulfate. The ether was then removed by distillation with a water aspirator to give a residue of 50.4 g (95%) of crude nitrosotetrahydroquinaldine in the form of a light-yellow oil which darkened rapidly in air.

<u>1-Amino-1,2,3,4-tetrahydroquinaldine</u>. This compound [39.1 g (86%)], like 1-amino-1,2,3,4-tetrahydroquinoline, was obtained from 50.4 g (0.28 mole) of crude nitrosotetrahydroquinaldine and had bp 115-116° (2 mm) and  $n_D^{21}$  1.5860. Found %: C 74.3; H 8.7. C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>. Calc. %: C 74.0; H 8.71.

<u>1-Amino-2,3-dihydroindole</u>. This compound [27.5 g (82%)], like 1-amino-1,2,3,4-tetrahydroquinoline, was obtained from 37 g (0.25 mole) of nitrosoindoline [8] and had bp 109-110° (11 mm) and  $n_D^{20}$  1.5917 [7].

2-Methyl-1,7-trimethylene-3-( $\beta$ -aminoethyl)indole [9-Methyl-10-( $\beta$ -aminoethyl)-9-lilolidene]. A solution of 4.45 g (0.03 mole) of 1-amino-1,2,3,4-tetrahydroquinoline in 30 ml of 90% methanol was heated to the boiling point, and a solution of 3.65 g (0.03 mole) of  $\gamma$ -chloromethyl propyl ketone [8] in 10 ml of methanol was added immediately. The reaction mixture was refluxed for 8 h. The residue remaining after removal of the methanol on a rotary evaporator was dissolved in 100 ml of 0.1 N hydrochloric acid, and the solution was extracted twice from the neutral impurities with ether. It was then filtered through 1 g of activated charcoal, cooled, and made strongly alkaline. The oil which separated was extracted with benzene, and the benzene extract was vacuum-distilled to give 4 g (66%) of 2-methyl-1,7-trimethylene-3-( $\beta$ -aminoethyl)indole with bp 218-220° (12 mm), mp 54° (from benzene-petroleum ether), and Rf 0.76.\* PMR spectrum: † 9-CH<sub>3</sub> (2.25 s), NH<sub>2</sub> (1.05 s), 7-CH<sub>2</sub> (3.85 t, J=5 Hz), 6-CH<sub>2</sub> (2.15 qu, J=6 Hz), 5-CH<sub>2</sub> (2.88 t, J=7 trum: † 9-CH<sub>3</sub> (2.25 s), NH<sub>2</sub> (1.05 s), 7-CH<sub>2</sub> (3.85 t, J=5 Hz), 6-CH<sub>2</sub> (2.15 qu, J=6 Hz), 5-CH<sub>2</sub> (2.88 t, J=7 trum: † 9-CH<sub>3</sub> (2.25 s), NH<sub>2</sub> (1.05 s), 7-CH<sub>2</sub> (3.85 t, J=5 Hz), 6-CH<sub>2</sub> (2.15 qu, J=6 Hz), 5-CH<sub>2</sub> (2.88 t, J=7 trum: † 9-CH<sub>3</sub> (2.25 s), NH<sub>2</sub> (1.05 s), 7-CH<sub>2</sub> (3.85 t, J=5 Hz), 6-CH<sub>3</sub> (2.15 qu, J=6 Hz), 5-CH<sub>2</sub> (2.88 t, J=7 trum: † 9-CH<sub>3</sub> (2.15 qu, J=6 Hz), 5-CH<sub>2</sub> (2.88 t, J=7 trum: † 9-CH<sub>3</sub> (2.15 qu, J=6 Hz), 5-CH<sub>2</sub> (2.88 t, J=7 trum: † 9-CH<sub>3</sub> (2.88 trum: † 9-CH<sub>3</sub> (2. Hz),  $10\alpha$ ,  $\beta$ -CH<sub>2</sub> (2.81 t, J=5 Hz), aromatic ring protons (H<sub>1</sub> 7.15 q, J<sub>1,2</sub>=7 Hz, J<sub>1,3</sub>=2 Hz; H<sub>2</sub> 6.78 t, J=7 Hz) Hz, H<sub>3</sub> 6.73 d, J=7 Hz). UV spectrum:  $\lambda_{max}$  227, 276 nm (inflection), 285, 295 nm (inflection), log  $\varepsilon$  4.55, 3.89, 3.94, and 3.86. Found %: C 78.2, 78.2; H 8.2, 8.2. C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>. Calc. %: C 78.5; H 8.5. The picrate was obtained in absolute ether with a molar amount of picric acid and was recrystallized from methanol to give a product with mp 197-198° (dec.). Found %: C 54.4; H 4.7. C<sub>14</sub>H<sub>18</sub>N<sub>2</sub> · C<sub>6</sub>H<sub>3</sub>N<sub>3</sub>O<sub>7</sub>. Calc. %: C 54.2; H 4.8. The acid tartrate was obtained in a minimum amount of absolute methanol with a molar amount of tartaric acid and was recrystallized from methanol to give a product with mp 127-128°.

\*Here and elsewhere the paper used was "rapid" paper from the Volodarskii factory, the system used was pyridine-water-butanol (1:1:1), and Ehrlich's reagent was used to develop the chromatograms. †Here and elsewhere s is singlet, d is doublet, t is triplet, q is quartet, qu is quintet, m is multiplet, and the chemical shifts in parts per million in the  $\delta$  scale relative to tetramethylsilane are given in parentheses.

The PMR spectra of 10% solutions in  $CCl_4$  were obtained with a JNM-60 spectrometer with an operating frequency of 60 MHz.

In all cases the UV spectra in ethanol were obtained with a "Hitachi" EPS-3T spectrometer.

## LITERATURE CITED

- 1. I. I. Grandberg and S. N. Dashkevich, Khim. Geterotsikl. Soedin., 1631 (1970).
- I. I. Grandberg, T. I. Zuyanova, N. I. Afonina, and T. A. Ivanova, Dokl. Akad. Nauk SSSR, <u>176</u>, 583 (1967).
- 3. I. I. Grandberg and T. I. Zuyanova, Khim. Geterotsikl. Soedin., 875 (1968).
- 4. I. I. Grandberg, N. I. Afonina, and T. I. Zuyanova, Khim. Geterotsikl. Soedin., 1038 (1968).
- 5. I. I. Grandberg and T. I. Zuyanova, Khim. Geterotsikl. Soedin., 1495 (1970).
- 6. A. N. Kost, L. G. Yudin, and A. P. Terent'ev, Zh. Obshch. Khim., 29, 3820 (1959).
- 7. A. N. Kost, L. G. Yudin, Yu. A. Berlin, and A. P. Terent'ev, Zh. Obshch. Khim., 29, 3820 (1959).
- 8. A. P. Meshcheryakov and V. G. Glukhovtsev, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 780 (1958).
- 9. A. Sachs, Ber., 32, 61 (1899).