CARBOLINES

IV.* 1-METHYL-4-(2-BENZYLOXYETHYL)-3,4-DIHYDRO-β-CARBOLINE

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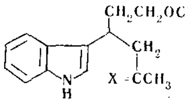
6-Benzyloxy-3-hexen-2-one, which served as the starting compound for the synthesis of 1-methyl-4-(2-benzyloxyethyl)-3,4-dihydro-β-carboline by a previously described method, was obtained by the reaction of β-benzyloxypropionaldehyde with diethylphosphonoacetone.

We have previously described a method for the synthesis of 4-substituted β-carbolines that involved the Beckmann rearrangement of the oximes of β-(3-indolyl) ketones under the influence of phosphorus pentachloride in nitrobenzene [2]. In this paper, we report the use of this method for the preparation of 1-methyl-4-(2-benzyloxyethyl)-3,4-dihydro-β-carboline (VII).

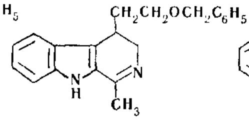
The starting material for the synthesis was β-(benzyloxy)propionaldehyde (I), which was obtained by the addition of benzyl alcohol to acrolein in the presence of triethylamine phosphate according to the instructions contained in a patent [3]. The reaction product was purified in the form of the bisulfite derivative (II). However, the direct isolation of the carbonyl compound from II was impossible, since the liberated I is cleaved to benzyl alcohol and acrolein during acid or alkaline hydrolysis. An alternate pathway consisted in the fact that acetal (III), which could be purified by vacuum distillation, was initially obtained by bubbling dry hydrogen chloride through a suspension of II in anhydrous methanol. Compound I was isolated in sufficiently pure form from III by the action of a 1% solution of HCl in aqueous acetone at room temperature. It was introduced without further purification into the reaction with the sodium derivative of diethylphosphonoacetone in dimethyl sulfoxide, and an α,β-unsaturated ketone (IV) was obtained as a result of PO-olefination [4,5]. A homogeneous mixture of IV and indole was treated by a previously described method [6] with a catalytic amount of perchloric acid to give V. The oxime (VI) of V was then subjected to the action of phosphorus pentachloride in nitrobenzene, and the hydrochloride of VII was isolated from the reaction mixture. It was observed that, in contrast to the other examples described in [2], in which heating was required, the cyclization of VI proceeds best at room temperature. The facilitation of the reaction in this case is possibly explained by the stabilization of the intermediate cation (VIII) through the participation of the free electron pair of the oxygen atom of the benzyloxy group.

$C_6H_5CH_2OCH_2CH_2CH\quad CHCOCH_3$

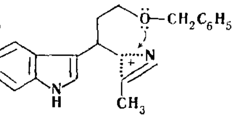
IV



V, VI



VII



VIII

V X=O; VI X=NOH

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[*] See [1] for communication III.

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EXPERIMENTAL

The melting points, none of which were corrected, were determined with a Koffler block. The IR spectra of KBr pellets and liquid films were recorded with a UR-10 spectrometer.

3-Benzyloxypropionaldehyde Dimethylacetal (III). A mixture of 140 g (1.3 mole) of benzyl alcohol, 32 g (0.57 mole) of acrolein, and 7 g of triethylamine monophosphate was heated at 38-40 deg for 160 h. The cooled reaction mixture was washed with aqueous NaCl and dissolved in 500 ml of ether. The ether solution was shaken for 1 h with 170 ml of saturated aqueous sodium bisulfite, and the crystals that formed were removed by filtration, washed with ether, and crystallized from methanol to give 64.2 g (42%) of the bisulfite derivative (II). A dry ether solution of hydrogen chloride was added to a suspension of II in anhydrous methanol with cooling and stirring for 5-6 h, and the mixture was neutralized with sodium methoxide, poured into water, and extracted with ether. The solvent was removed, and the residue was vacuum distilled to give 64% of III with bp 101-105 deg (1-1.5 mm) and n^{20}_{D} 1.4890. Found: C 68.8; H 8.5%. $C_{12}H_{18}O_3$. Calculated: C 68.5; H 8.6%. IR spectrum, cm^{-1}: 1100-1120 (C–O–C).

6-Benzyloxy-3-hexen-2-one (IV). A 61.4 g sample of III was dissolved in 300 ml of acetone, 300 ml of 2% aqueous HCl was added, and the mixture was stirred at 15-20 deg for 1.5 h. The solution was then poured in water, and the mixture was extracted with ether. The ether extract was washed with sodium bicarbonate solution and dried with sodium sulfate. The ether was removed below 50 deg to give 45 g (0.275 mole) of 3-benzyloxypropionaldehyde (I). This was then dissolved in 100 ml of anhydrous dimethyl sulfoxide, and the solution was added in the course of 45 min to a stirred solution of 53.3 g (0.275 mole) of diethylphosphonoacetone [7] and 6.6 g (0.275 mole) of sodium hydride in 350 ml of dimethyl sulfoxide. The temperature during the addition was maintained at 15-20 deg by water cooling. Forty minutes after the completion of the addition, the reaction mixture was poured into water and extracted with ether. After drying and removal of the solvent, the residue was vacuum distilled at 121-124 deg (0.08 mm) to give 39.9 g (70%) of IV. IR spectrum, cm^{-1}: 1700, 1680 (CO), 1640, 1630 (C=C), 1100 (C–O–C). The 2,4-dinitrophenylhydrazone of IV melted at 112-113 deg (from methanol). Found: C 59.7; H 5.3; N 14.5%. $C_{19}H_{20}N_4O_5$. Calculated: C 59.4; H 5.2; N 14.6%.

6-Benzyloxy-4-(3-indolyl)-2-hexanone (V). A total of 42 ml of 70% perchloric acid was added by drops in the course of 10 min with cooling and vigorous stirring to 1.72 g (14.7 mmole) of indole and 3.0 g (14.7 mmole) of IV, after which the cooling bath was removed, and the solution was held at room temperature for 40 min. The markedly thickened reaction mixture was dissolved in ether, and the solution was washed thoroughly with sodium bicarbonate solution. The ether was removed, and the residue was chromatographed on 160 g of activity II aluminum oxide. Benzene eluted 3.92 g (83%) of V as a viscous oil. The 2,4-dinitrophenylhydrazone of V melted at 120-121 deg (from trichloroethylene). Found: C 64.7; H 5.4; N 14.1%. $C_{27}H_{27}N_5O_5$. Calculated: C 64.7; H 5.4; N 14.0%.

1-Methyl-4-(2-benzyloxyethyl)-3,4-dihydro-β-carboline Hydrochloride (VII). A mixture of 2.21 g (7.1 mmole) of V, 0.6 g (8.7 mmole) of hydroxylamine hydrochloride, 11.4 ml of pyridine, and 11.4 ml of methanol was held at room temperature for 20 h to give, after the usual workup, 2.38 g (100%) of the amorphous oxime (VI). A solution of 0.66 g (2.7 mmole) of VI in 6.6 ml of nitrobenzene was added to 1.22 g (5.9 mmole) of phosphorus pentachloride in 6.6 ml of nitrobenzene in the course of 5 min at 20 deg, and the mixture was stirred for another 15 min at the same temperature. The excess PCl_5 was decomposed with ice, water was added, and the mixture was extracted with dilute HCl. The combined aqueous extracts were washed with ether and made alkaline with NaOH solution. The liberated base was extracted with ether, and the extract was dried with sodium sulfate. The addition of an ether solution of HCl to the extract precipitated an oil that began to crystallize during drying in a vacuum desiccator over sulfuric acid. Recrystallization from isopropyl alcohol and then from alcohol–acetone gave 0.125 g (18%) of the hydrochloride of VII with mp 180-182 deg. Found: C 70.7; H 6.7; N 7.8%. $C_{21}H_{22}N_2O \cdot HCl$. Calculated: C 71.1; H 6.5; N 7.9%. IR spectrum, cm^{-1}: 3250 (indole NH), 2500-2800, 2300 ($\equiv\overset{+}{N}-H$), 1635 ($C=\overset{+}{N}-$).

LITERATURE CITED

1. E. P. Styngach and A. A. Semenov, Khim. Geterotsikl. Soedin., 619 (1971).
2. K. I. Kuchkova, A. A. Semenov, and I. V. Terent'eva, Khim. Geterotsikl. Soedin., 197 (1970).
3. J. W. Mecorney and E. R. White, U. S. Patent No. 2,967,890 (1961); Referativnyi Zh. Khim. 11L42 (1962).

4. G. Sturtz, Bull. Soc. Chim. France, 2349 (1964).
5. G. V. Grinev, G. I. Chervenyuk, and A. V. Dombrovskii, Zh. Obshch. Khim., 38, 225 (1968).
6. A. A. Semenov, E. P. Styngach, and G. M. Kuperman, Khim. Geterotsikl. Soedin., 878 (1968).
7. A. N. Pudovik, Zh. Obshch. Khim., 25, 2173 (1955).