LITERATURE CITED

1. K. Fujikawa-Yamamoto, T. Ota, S. Odashima, H. Abe, and S. Arichi, Cancer J., 1, No. 8, 349 (1987).
2. T. Ota, K. Fujikawa-Yamamoto, Z. Zong, M. Yamasaki, S. Odashima, I. Kitagawa, H. Abe, and S. Arichi, Cancer Res., 47, No. 14, 3863 (1987).
3. Japanese Patent No. 58 57,399, Chem. Abstr., 99, 76852u (1983).
4. L. N. Atopkina, V. A. Denisenko, N. I. Uvarova, and G. B. Elyakov, Carbohydr. Res., 177, 101 (1988).
5. F. G. Fischer and N. Seiler, Ann. Chem., 626, 185 (1959).
6. M. Nagai, N. Tanaka, O. Tanaka, and S. Ishikawa, Chem. Pharm. Bull., 9, 2061 (1973).

AROMATIC AMINO-CLAISEN REARRANGEMENT IN THE SYNTHESIS OF ELLIPTICINE

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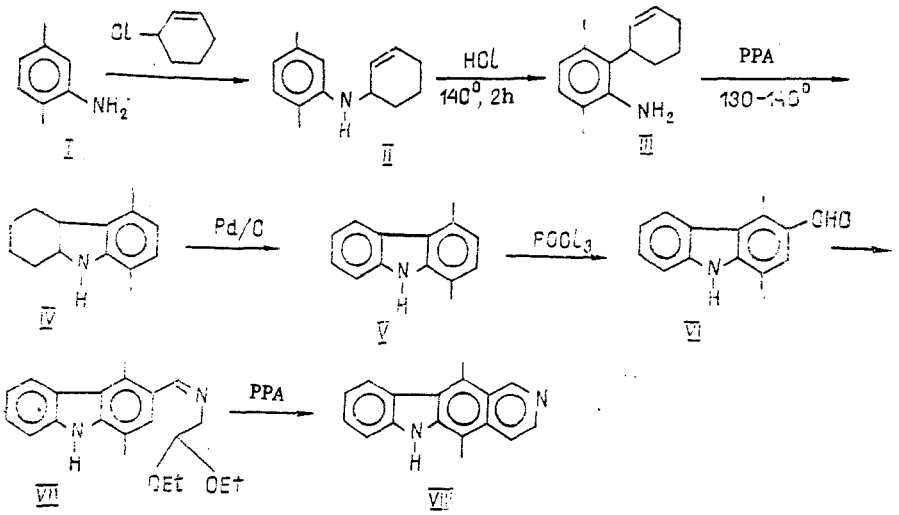
UDC 547.94.759.32

A convenient route is described for the preparation of 1,4-dimethylcarbazole – the key compound in the synthesis of the antitumoral alkaloid ellipticine. The interaction of 2,5-xylidine with 3-chlorocyclohexene led to N-(cyclohex-2-enyl)-2,5-xylidine (I), the two-hour heating of which at 140-150°C gave the product of an amino-Claisen rearrangement, 6-(cyclohex-2-enyl)-2,5-xylidine (II) with a yield of 82%. The intramolecular cyclization of compound (II) in polyphosphoric acid (130-140°C, 5 h) led to 5,6,7,8,12,13-hexahydro-1,4-dimethylcarbazole (III) in a yield of 75%. The dehydrogenation of substance (III) by boiling in trimethylbenzene in the presence of Pd/C gave 1,4-dimethylcarbazole (IV) with a yield of 87%. The conditions for performing the reactions and the physicochemical constants of the compounds obtained are given.

The alkaloid ellipticine from the leaves of the plant Ochrosia elliptica, family Apocynaceae, and also some of its synthetic analogues possess a high antitumoral activity [1, 2]. The synthesis of these substances has attracted the attention of many chemists in the last few years [2-5].



In this paper we describe a convenient method for obtaining 1,4-dimethylcarbazole – the key compound in the synthesis of ellipticine (scheme). When 3-chlorocyclohexene was heated with a fourfold excess of 2,5-xylidine (I), N-(cyclohex-2-enyl)-2,5-xylidine (II) was formed, and this was then subjected to aromatic amino-Claisen rearrangement with the formation of 6-(cyclohex-2-enyl)-2,5-xylidine (III), the yield of which amounted to 82% [6].

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The intramolecular cyclization of compound (III) in polyphosphoric acid (PPA) led to the hexahydrocarbazole (IV) with a yield of 75% [7]. The dehydrogenation of substance (IV) with Pd/C [8] gave 1,4-dimethylcarbazole (V) with a yield of 87%.

The formation of the carbazole (V), the interaction of substance (VI) with 2,2-diethoxyethylamine, and the cyclization of compound (VII) with the formation of ellipticine (VIII) [1] took place fairly smoothly. The physicochemical characteristics of the alkaloid obtained agreed well with those given in the literature [1, 9].

EXPERIMENTAL

IR spectra were taken on a UR-20 instrument ^{1}H NMR spectra on a Tesla BS-567B instrument (working frequency 100 MHz; internal standard tetramethylsilane; solvent $CDCl_3$), and mass spectral on a MKh-13-06 instrument with an energy of ionizing electrons of 70 eV and a temperature of the ionization chamber of 200°C. GLC analysis was conducted on a LKhM-8 MD chromatograph with a 3 mm × 3 m column containing SE-30 on Chromaton N-AW-DMCS at a rate of flow of helium of 30 ml/min.

N-(Cyclohex-2-enyl)-2,5-xylidine (II). A solution of 12.1 g (0.1 mole) of 2,5-xylidine in 50 ml of triethylamine was treated with 11.6 g (0.1 mole) of 3-chlorocyclohexene, and the reaction mixture was heated at 80°C for 2 h. It was treated with water (3 × 20 ml) and with a 30% solution of KOH (3 × 20 ml), and was dried over $MgSO_4$. The solvent was eliminated under reduced pressure, and the residue was rectified in vacuum. This gave 15 g (75%) of product (II), bp 138-140°C/2 mm. IR spectrum (cm^{-1}): 720, 1580, 1610, 3350. ^{1}H NMR spectrum (δ, ppm): 1.62 m (6H, $3CH_2$); 1.98 s (3H, CH_3); 2.22 s (3H, CH_3); 3.23 s (1H, NH); 3.92 s (1H, CH); 5.70 m (2H, HC=CH); 6.16 s (1H, ArH); 6.28 d (1H, ArH, J = 7.5 Hz), 6.75 d (1H, ArH, J = 7.5 Hz). Found, %: C 83.58; H 9.45; N 6.97. $C_{14}H_{19}N$. Calculated, %: C 83.58; H 9.66; N 6.74.

6-(Cyclohex-2-enyl)-2,5-xylidine (III). To 60.5 g (0.5 mole) of 2,5-xylidine was added 11.6 g (0.1 mole) of 3-chlorocyclohexene, and the mixture was heated at 140-150°C for 2 h. The consumption of compound (II) and the accumulation of substance (III) were monitored by GLC. After the end of the reaction, the mixture was treated with a 30% solution of KOH (3 × 100 ml), dried over $MgSO_4$, and distilled under reduced pressure. This gave 16.5 g (82%) of product (III). mp 160-162°C/3 mm. IR spectrum (cm^{-1}): 735, 1620, 3380, 3470. ^{1}H NMR spectrum (δ, ppm): 1.73 m (6H, CH_2); 1.98 s (3H, CH_3); 2.18 s (3H, CH_3); 3.58 s (2H, NH_2); 3.76 m (1H, CH); 5.73 m (2H, HC=CH); 6.28 d (1H, ArH, J = 7.5 Hz); 6.63 d (1H, ArH, J = 7.5 Hz). Found, %: C 83.58; H 9.45; N 6.97. $C_{14}H_{19}N$. Calculated, %: C 83.12; H 9.44; N 6.88.

1,4-Dimethyl-5,6,7,8,12,13-hexahydrocarbazole (IV). A mixture of 10 g of compound (III) and 60 g of polyphosphoric acid (50 g of H_3PO_4 + 10 g of P_2O_5) was heated at 130-140°C in an atmosphere of argon for 5 h. Then it was treated with concentrated KOH solution and was extracted with benzene (5 × 50 ml). The extract was dried over $MgSO_4$, the solvent was driven off under reduced pressure, and the residue was rectified in vacuum. This gave 7.5 g (75%) of substance (IV). bp 130-134°C/2 mm. IR spectrum (cm^{-1}): 800, 1270, 1600, 2930, 2860, 3360. ^{1}H NMR spectrum (δ, ppm): 1.51 m (8H, CH_2), 1.91 s (3H, CH_3), 2.07 s (3H, CH_3); 2.75 m (1H, CH); 3.15 s (1H, NH); 3.57 m (1H, CH); 6.22 d (1H, ArH, J = 7.5 Hz), 6.53 d (1H, ArH, J = 7.5 Hz). M^+ 201.

1,4-Dimethylcarbazole (V). A solution of 5 g of the hexahydrocarbazole (IV) in 20 ml of trimethylbenzene was treated with 1.5 g of 5% Pd/C, and the mixture was boiled for 3 h. After cooling, it was filtered and was washed with hot ethyl acetate (400 ml). The solution was concentrated, and the addition of 50 ml of pentane led to the separation of the crystalline product (V). Yield 4.2 g (87%). mp 94°C. IR spectrum (ν, cm^{-1}): 750, 760, 815, 1270, 1385, 1600, 2870, 2930, 3415. ^{1}H NMR spectrum (δ, ppm): 2.49 s (3H, CH_3); 2.79 s (3H, CH_3); 6.78 d (1H, ArH, J = 7.2 Hz); 6.96-7.17 m (4H, ArH); 7.41 d (1H, ArH, J = 7.2 Hz); 8.10 s (1H, H). M^+ 195.

SUMMARY

A convenient method is proposed for obtaining 1,4-dimethylcarbazole — the key compound in the synthesis of the alkaloid ellipticine — by an amino-Claisen rearrangement of N-(cyclohex-2-enyl)-2,5-xylidine and the intramolecular cyclization of the resulting 6-(cyclohexen-2-yl)-2,5-xylidine.

LITERATURE CITED

1. L. K. Dalton, S. Demerac, B. S. Elmes, J. W. Loder, J. M. Swan, and T. Tetei, Aust. J. Chem., 20, No. 12, 2715 (1967).
2. V. K. Kansal and P. Petier, Tetrahedron, 42, No. 9, 2389 (1986).
3. M. Sainsbury, Synthesis, 437 (1977).
4. M. J. Hewlins, A.-M. Oliveira-Campos, and P. V. P. Shannon, Synthesis, 284 (1984).
5. G. W. Gribble and M. G. Saulnier, Heterocycles, 23, No. 5, 1277 (1985).
6. I. B. Abdrakhmanov, G. B. Shabaeva, N. G. Nigmatullin, and G. A. Tolstikov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 6, 1372 (1986).
7. I. B. Abdrakhmanov, A. G. Mustafin, V. M. Sharafutdinov, A. S. Taichinova, and G. A. Tolstikov, Izv. Akad. Nauk SSSR, Ser.Khim., No. 4, 839 (1985).
8. E. C. Horning, M. G. Horning, and G. N. Walker, J. Am. Chem. Soc., 70, No. 11, 3935 (1948).
9. P. A. Cranwell and J. E. Saxton, J. Chem. Soc., 3482 (1962).

STRUCTURE OF PHYTIC ACID AND PHYTATES

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UDC 615.3:541.49

The structure of phytic acid and of cobalt and iron phytates and pharmacopoeial phytin have been studied by diffuse reflection electron spectroscopy and IR spectroscopy. It has been shown that in the structure of the phytates, in contrast to that of phytic acid, there is a pyrophosphate bond formed as the result of the substitution of a proton in the $PO_2(OH)_2$ group by the metal ion.

Phytic acid is the hexaphosphoric ester of the hexahydric cyclic alcohol meso-inositol. Its salts with the alkaline-earth and alkaline metals form the basis of the research of phosphorus compounds in higher plants [1]. The mixed neutral calcium-magnesium salt of phytic acid is used in medical practice under the name of phytin in various diseases of the nervous system, vascular hypotonia, hysteria, neurasthenia, sexual impotence, malnutrition, rickets, anemia, tuberculosis, diatheses, and other conditions [2].

The structures of phytic acid and its salts have been widely studied [3-7], but even at the present time many questions of constitution and structure remain under discussion, which complicates the development of methods for monitoring the quality of the finished product and standardizing industrial forms of raw material.

We have studied the composition and structure of phytic acid and of an industrial sample of phytin and also of phytin obtained from various types of raw material. We have also studied calcium, iron, and cobalt phytates obtained from phytin and from pure phytic acid.

The state of the complex-forming ions and the structure of the compounds formed have been investigated by the methods of diffuse reflection electron spectroscopy and IR spectroscopy.

In the IR spectrum of phytic acid (Fig. 1a) strong absorption bands are observed with maxima at 1060 and 1400 cm^{-1} which we have assigned to ν(P—O—C) and ν(P=O), respectively. A weak absorption band obviously due to the δ(P—OH) vibrations appears at 1020 cm^{-1}, and a band of medium intensity, due, in all probability, to a planar δ(P—OH) not involved in a H-bond [8], at 1218 cm^{-1}, while a band at 1630 cm^{-} can be assigned to δ(O—H) from water molecules of hydration. At the same time, no ν(P—O—P) band was detected in phytic acid.

In contrast to phytic acid, in the spectrum of an industrial sample of phytin (Fig. 1b), a strong absorption band is observed at 980 cm^{-1}, which is characteristic for the stretching vibrations of a pyrophosphate bond [9]. In addition, at 460 cm^{-1}, there is a band of medium intensity due, in all probability, to the Me—O bond and absent, as was to be expected, from the spectrum of phytic acid. It is obvious that the formation of a

All-Union Scientific-Research and Chemical-Technological Institute of the Medical and Microbiological Industry, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, Vol. 6, pp. 818-822, November-December, 1989. Original article submitted January 23, 1989; revision submitted April 7, 1989.

0009-3130/89/2506-0695$12.50