STRUCTURE OF CHEMICAL COMPOUNDS, METHODS OF ANALYSIS AND PROCESS CONTROL

IDENTIFICATION OF IMPURITIES IN THE PRODUCTION OF TERBINAFINE HYDROCHLORIDE

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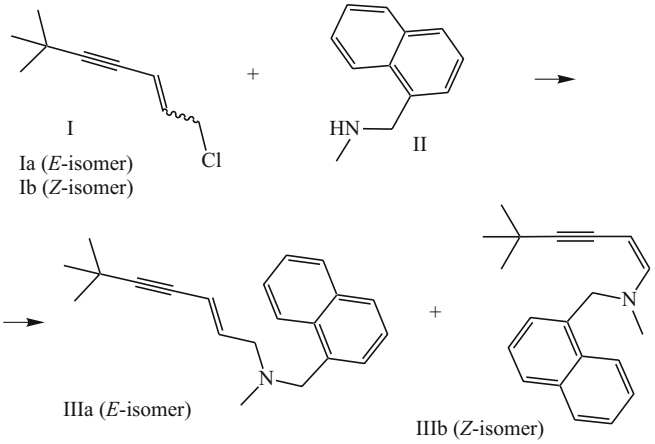
The purity of the parent substance of (*E*)-N-(6,6-dimethylhept-2-en-4-ynyl)-N-methylnaphth-1-ylmethylamine (terbinafine) is evaluated via TLC identification of the main impurities appearing during its synthesis via alkylation of N-methylnaphth-1-ylmethylamine with 1-chloro-6,6-dimethyl-2-hept-2-en-4-yne The possible formation of impurities including N-methyl-N,N-di(methylnaphth-1-yl)amine, N-methylnaphth-1-ylmethylamine, N-methylnaphth-2-ylmethylamine, (*E*)-N-(6,6-dimethylhept-2-en-4-ynyl)-N-methylnaphth-1-ylmethylamine, (*Z*)-N-(6,6-dimethylhept-2-en-4-ynyl)-N-methylnaphth-1-ylmethylamine, (*E*)-N-(6,6-dimethylhept-2-en-4-ynyl)-N-methylnaphth-2-ylmethylamine, and (*Z*)-N- (6,6-dimethylhept-2-en-4-ynyl)-N-methylnaphth-2-ylmethylamine was confirmed by means of countersynthesis.

The discovery of antimycotic properties of terbinafine, a compound belonging to the class of allylamines, was undoubtedly one of the most important recent achievements in pharmacology, which made possible the complete recovery from fungal disorders without numerous side effects. However, terbinafine is still among most expensive drugs and, hence, the development of more readily accessible methods for the synthesis of this compound is an urgent problem. The most important task is to obtain a high-purity parent substance, which is necessary for the preparation of effective ready-to-use medicinal forms. In order to provide for the reliable control over the parent drug purity, it is necessary to identify all possible by-products that can appear in the course of synthesis.

Previously, we proposed to synthesize (*E*)-N,6,6-trimethyl-N-(naphth-1-ylmethyl)hept-2-en-4-yn-1-amine hydrochloride (terbinafine hydrochloride) using condensation of 1-chloro-6,6-dimethyl-2-hept-2-en-4-yne (I) with N-methylnaphth-1-ylmethylamine (II) [1].

It was established that, in addition to yielding the target *E*-isomer (IIIa), this process is accompanied by the formation of minor amounts of *Z*-isomer (IIIb) [1]. The ratio of these products, IIIa/IIIb, depends on the isomer composition (Ia/Ib) of the initial chloroheptenyne.



In order to ensure the complete consumption of chloroheptenyne Ia (which is the most expensive precursor) during the synthesis of terbinafine, the corresponding amine II is taken is excess. Therefore, as is naturally expected, the final reaction mass also contains this excess amine II which, after acidification with hydrochloric acid, mostly passes to the aqueous phase so that the rough target product (terbinafine) contains only trace amounts of amine II.

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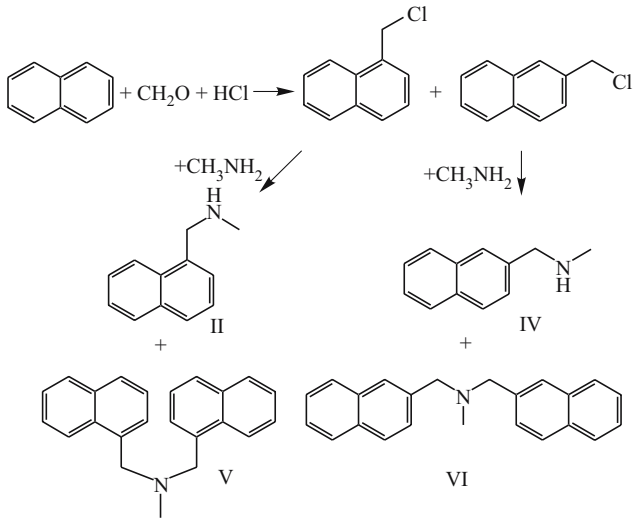
Taking into account the scheme of obtaining amine II [2], the most probable impurities in this precursor are the following three compounds: N-methylnaphth-2-yl-methylamine (IV), N-methyl-N,N-di(methylnaphth-1-yl)amine (V), and N-methyl-N,N-di(methylnaphth-2-yl)amine (VI).



In order to study these possible impurities, we have synthesized amines IV and V and isolated chromatographically pure amine II.

Amine V was obtained under the same conditions as compound II [2]. A significant difference in the boiling points of these compounds allows amine II (b.p., 115 – 120°C/1 Torr) to be readily separated by distillation from amine V (b.p., 231 – 233°C/1 Torr). Nevertheless, the reaction mass formed during the synthesis of terbinafine still showed the presence of traces of amine V. The presence of amine VI is low probable, since the formation of β-chloromethylnaphthalene is a side process. Since amine V was found only in trace amounts, it is practically impossible to detect a compound that is formed with a much smaller yield. For this reason, we did not perform the countersynthesis of amine VI.

Amine IV is formed as a result of the interaction of β-chloromethylnaphthalene with methylamine. Since the boiling points of compounds II and IV are close (b.p., 162 – 165°C/10 Torr and 167 – 170°C/10 Torr, respectively), the presence of amine IV as an impurity in the initial amine II upon distillation is quite probable. Being a nucleophile, amine IV can react with both (*E*)- and (*Z*)-isomers of chloroheptenyne I, which leads to the formation of a mixture of the corresponding (*E*)- and (*Z*)-isomers of N,6,6-trimethyl-N-(naphth-2-ylmethyl)hept-2-en-4-yn-1-amine (VII, VIII).

In order to confirm the possibility of formation of these compounds as impurities in terbinafine, the aforementioned compounds were obtained by countersynthesis. Amine IV was obtained by means of reductive amination, via the interaction of 2-naphthaldehyde with methylamine in methanol, followed by the reduction with sodium borohydride. Then, (*E*)- and (*Z*)-isomers of N,6,6-trimethyl-N-(naphth-2-ylmethyl)hept-2-en-4-yn-1-amine (VII, VIII) were obtained via the interaction of amine IV with chloroheptenynes Ia and Ib, respectively, in the presence of potassium carbonate (as hydrogen chloride acceptor).

The obtained products were used as reference markers for establishing the presence of such impurities in the reaction mass of terbinafine synthesis. Rapid qualitative analysis of the reaction mass formed during the interaction of technical-purity amines I and II under the conditions of terbinafine synthesis showed that compounds indicated in Table I were actually present as detectable impurities. Thus, we have identified the main impurities accompanying the synthesis of terbinafine (IIIa).

EXPERIMENTAL PART

The ^{1}H NMR spectra were recorded on a Bruker AM-370 spectrometer operating at a working frequency of 360.13 MHz. The isomer composition of 1-chloro-6,6-dimethyl-2-hepten-4-yne (Ia, Ib) was determined by gas chromatography (GC). The GC measurements were performed on an LKhM-80M chromatograph (Russia) equipped with a DTP detector and a 1-m column filled with a 5% SE-30 sorbent on Inerton AW-DMCS. The analyses were performed at an evaporator temperature of 200°C and a detector temperature of 150°C. The system was operated in a programmed mode: initial temperature, 80°C; isothermal regime, 2 min; heating at 25 K/min up to 140°C.

TLC analyses were performed on Merck Silicagel-60 F_{254} plates. The spots were developed by exposure to UV radiation or by treatment with a 1 % ninhydrin solution in an ethanol – carbon tetrachloride (1 : 10) mixture or with a 20 % solution of phosphomolybdic acid in ethanol.

Chromatographic purification was performed on a 300 × 50 mm column filled with Merck Silicagel 60 (0.040 – 0.063 mm) at an eluent pressure of 200 – 300 kPa.

TABLE 1. TLC Mobilities R_f of Impurities in the Reaction Mixture of Terbinafine Synthesis and Reference Markers Obtained by Countersynthesis

Compound	R_f		Solvent system *
	reaction mixture	reference marker	
V	0.84	0.84	A
IIIa	0.77	0.77	A
IIIb	0.61	0.61	A
VII	0.46	0.46	A
VIII	0.35	0.35	A
II	0.64	0.64	B
IV	0.52	0.52	B

* (A) hexane – diethyl ether – 2-propanol – 25% aqueous ammonia (300 : 50 : 20 : 2); (B) chloroform – methanol – 25% aqueous ammonia (10 : 1 : 0.1).

Amine V was synthesized as described elsewhere [2]; terbinafine IIIa was obtained using an original method described in [1].

(*E*)- and (*Z*)-1-chloro-6,6-dimethyl-2-hepten-4-ynes (Ia, Ib). Rough 1-chloro-6,6-dimethyl-2-hepten-4-yne obtained according to [4] comprising a mixture of (*E*)- and (*Z*)-isomers, was separated by distillation at a reduced pressure in a rectification column. The fraction collected at b.p., 53 – 55°C/8 Torr contained (GC data) 95% of (*Z*)-1-chloro-6,6-dimethyl-2-hepten-4-yne (Ib) and 2% of *E*-isomer (Ia), while the fraction collected at b.p., 71 – 73°C/8 Torr contains 95% of (*E*)-1-chloro-6,6-dimethyl-2-hepten-4-yne (Ia) and 4% of *Z*-isomer (Ib).

Chromatographically pure N-methylnaphth-1-ylmethylamine (II). Rough amine II (7.3 g) synthesized according to [2] was additionally purified by flash chromatography in a gradient system chloroform – methanol – 25% aqueous ammonia (10 : 1 : 0.1). the purity of fractions was checked by TLC. Pure fractions were combined, solvents were distilled off under vacuum, and the residue was dissolved in 100 ml of diethyl ether, the solution was dried over calcined sodium sulfate. Finally, the solvent was distilled off to obtain 6.1 g (83.6%) of chromatographically pure amine II.

^{1}H NMR spectrum in $CDCl_3$ (δ, ppm): 1.45 (s, 1H, H–N), 2.61 (s, 3H, CH_3–N), 4.25 (s, 2H, CH_2N), 7.47 – 7.65 (m, 4H, arom H), 7.84 – 7.88 (m, 1H, arom H), 7.93 – 7.97 (m, 1H, arom H), 8.21 – 8.25 (m, 1H, arom H)

N-Methylnaphth-2-ylmethylamine (IV). To a solution of methylamine hydrochloride (1.9 g, 0.028 mole) and triethylamine (2.85 g, 3.9 ml, 0.028 mole) in 25 ml of methanol at room temperature was added a solution of 2-naphthaldehyde (4.0 g, 0.025 mole) in 20 ml of the same solvent and the mixture was stirred for 8 h. To the resulting solution was gradually added by small portions sodium borohydride (1.1 g, 0.028 mole) and the suspension was stirred for 4 h. Then, the solvent was distilled at a reduced pressure, the residue was dissolved in 20 ml water, and the solution was triply extracted with ethyl ether. The organic phases were combined, the solvent was distilled off, and the residue was purified by flash chromatography as described above for compound II. Yield of chromatographically pure amine IV, 34 g (78%).

^{1}H NMR spectrum in $CDCl_3$ (δ, ppm): 1.72 (s, 1H, HN), 2.51 (s, 3H, CH_3N), 3.93 (s, 2H, CH_2N), 7.44 – 7.52 (m, 3H, arom H), 7.77 (s, 1H, arom H), 7.81 – 7.87 (m, 3H, arom H).

(*Z*)-N,6,6-Trimethyl-N-(naphth-1-ylmethyl)hept-2-en-4-yn-1-amine (IIIb). To a solution of 2.1 g (0.015 mole) of potassium carbonate in 8.6 ml water was added with intensive stirring 1.71 g (0.01 mole) of N-methylnaphth-1-ylmethylamine and 1.72 g (0.01 mole) of (*Z*)-chloroheptenyne (Ib) and the mixture was stirred at 60°C for 9 h and cooled to room temperature. The reaction mass was extracted with benzene (3 × 30 ml), the organic phases were combined, and the solvent was distilled off at reduced pressure. The residue (2.8 g) was purified by flash chromatography in a hexane – ethyl ether system (3 : 1). The purity of fractions was checked by TLC. Pure fractions were combined and dried over calcined sodium sulfate. Finally, the solvent was distilled off at a reduced pressure to obtain 2.1 g (64%) of *Z*-isomer IIIb.

^{1}H NMR spectrum in $CDCl_3$ (δ, ppm): 1.34 (s, 9H, $C(CH_3)_3$), 2.34 (s, 3H, CH_3N), 3.45 (dd, J 7.3 Hz and 1.5 Hz, 2H, $NC\underline{H}_2CH$=), 4.0 (s, 2H, $NC\underline{H}_2C_{10}H_7$), 5.76 (dt, J 10.8 Hz and 1.5 Hz, 1H, CH=C<u>H</u>–C≡), 6.11 (dt, J 10.8 Hz and 7.3 Hz, 1H, CH_2–C<u>H</u>=CH), 7.45 – 7.61 (m, 4H, arom H), 7.82 – 7.92 (m, 2H, arom H), 8.35 – 8.38 (m, 1H, arom H).

(*E*)-N,6,6-Trimethyl-N-(naphth-2-ylmethyl)hept-2-en-4-yn-1-amine (VII). To a suspension of 2.7 g (0.016 mole) of amine IV and 2.7 g (0.019 mole) of freshly calcined and finely dispersed potassium carbonate in 20 ml of anhydrous DMF was added with intensive stirring at room temperature 2.7 g (0.017 mole) of (*E*)-chloroheptenyne (Ia) in 5 ml of the same solvent and the reaction mixture was stirred for 30 h at 20 – 22°C. Then, the suspension was poured into water (50 ml) and extracted with carbon tetrachloride (3 × 50 ml). The extracts were combined and dried over anhydrous sodium sulfate. The solvent were distilled off at reduced pressure and the residue was purified as described above for compound IIIb; yield of *E*-isomer VII, 3.9 g (74%).

^{1}H NMR spectrum in $CDCl_3$ (δ, ppm): 1.27 (s, 9H, $C(CH_3)_3$), 2.24 (s, 3H, CH_3N), 3.16 (dd, J 6.5 Hz and 1.3 Hz, 2H, $NC\underline{H}_2CH$=), 3.68 (s, 2H, $NC\underline{H}_2C_{10}H_7$), 5.75 (dt, J 15.8 Hz and 1.3 Hz, 1H, CH=C<u>H</u>–C≡), 6.15 (dt, J 15.8 Hz and 6.5 Hz, 1H, CH_2–C<u>H</u>=CH), 7.42 – 7.53 (m, 3H, arom H), 7.74 (s, 1H, arom H), 7.78 – 7.86 (m, 3H, arom H).

(*Z*)-N,6,6-Trimethyl-N-(naphth-2-ylmethyl)hept-2-en-4-yn-1-amine (VIII). To a suspension of 2.7 g (0.016 mole) of amine IV and 2.7 g (0.019 mole) of freshly calcined and finely dispersed potassium carbonate in 20 ml of anhydrous DMF was added with intensive stirring at room temperature 2.7 g (0.017 mole) of (*Z*)-chloroheptenyne (Ia) in 5 ml of the same solvent. Then, the reaction mixture was treated as described above for compound VII; yield of *Z*-isomer VIII, 3.2 g (61%).

^{1}H NMR spectrum in $CDCl_3$ (δ, ppm): 1.27 (s, 9H, $C(CH_3)_3$), 2.29 (s, 3H, CH_3N), 3.32 (dd, J 6.9 Hz and 1.3 Hz, 2H, $NC\underline{H}_2CH$=), 3.70 (s, 2H, $NC\underline{H}_2C_{10}H_7$), 5.67 (dt, J 10.8 Hz and 1.3 Hz, 1H, CH=C<u>H</u>–C≡), 6.11 (dt, J 10.8 Hz and 6.5 Hz, 1H, CH_2–C<u>H</u>=CH), 7.42 – 7.53 (m, 3H, arom H), 7.76 (s, 1H, arom H), 7.79 – 7.85 (m, 3H, arom H).

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