SYNTHESIS AND FUNGICIDAL ACTIVITY OF SUBSTITUTED 2-α-FURYLBENZIMIDAZOLES AND THEIR PHARMACEUTICAL INVESTIGATION

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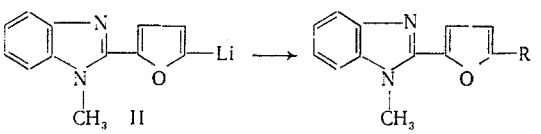
The search for new antifungal compounds is still continuing. At the present time, about 150 drugs and medicinal formulas are used for treating dermatomycoses. These inhibit the growth of fungi in vitro, and are effective during surface afflictions in vivo, but often have no effect on nail mycoses. For treating the latter, systematic antifungal drugs are needed, which have a broad spectrum of activity, low toxicity, and do not cause a resistance in stimulants. Derivatives of imidazole, such as clotrimazole, myconazole, econazole, do not completely satisfy these requirements.

The aim of the present work was to synthesize new compounds in the 2-(2-furyl)-benzimidazole series, and to examine their antifungal activity. The synthesis was carried out by using organolithium compounds in the furan series. Their usefulness in synthetic organic chemistry has been shown in recent years [2-5].

By the reaction of 1-methyl-2-(5-bromo-2-furyl)benzimidazole (I) and butyllithium, we obtained 1-methyl-2-(5-lithium-2-furyl)benzimidazole (II). We were unable to substitute a bromine atom by lithium in 1-methyl-2-[β-5-bromo-2-furyl)-vinyl]benzimidazole (III) because of the low mobility of the halogen atom.

The reaction of organolithium compound II and benzonitrile, benzaldehyde, benzophenone and iodine gave compounds IV–VII, respectively.



IV: R = COC_6H_5; V: R = $CH(OH)C_6H_5$; VI: R = $C(OH)(C_6H_5)_2$; VII: R = I.

The action of carbon dioxide on compounds II leads to the formation of 1-methyl-2-(5-carboxy-2-furyl)-benzimidazole (VIII), but the latter could not be isolated because of its high tendency to decarboxylation with the formation of 1-methyl-2-(2-furyl)-benzimidazole (IX). It should be noted that, as in the case of furylbenzimidazoles containing aceto or nitro groups in the 5 position of the furan ring, compounds IV–VII cannot be quaternized at the pyridine nitrogen atom of the imidazole ring.

The antifingal action of compounds I, IV–VII, and IX was estimated from their influence on the growth of the T. rubrum culture.* For cultivating the dermophyte, we used the solid Saburo medium, which was prepared by the generally accepted method. The inoculation of the fungal material was carried out, as in the case of usual microbiological inoculations, and the fungal culture was cultivated at a temperature of 24-27°C. It was treated with a 0.1% alcoholic solution of the compounds studied at 25°C. The influence of the furylbenzimidazoles on the growth of the T. rubrum culture was determined from its repeated cultivation, by transplantation from a culture subjected to the action of compounds I, IV-VII, and IX, and by comparison with control experiments. The mycological tests have shown (see Table 1) that T. rubrum culture is completely destroyed by the action of 0.1% solutions of I for 24 h and more, and 0.1 solutions of IV for 3 h and more. α-Hydroxybenzyl and α-hydroxybenzhydryl groups, as well as the bromine and iodine atoms in the 5 position of the furan ring of furylbenzimidazole, cause the antifungal activity to be lower than that of compound IX, which was found to be the most active with reference to the T. rubrum culture.

* The tests were carried out at the Novocherkask skin-venerological clinic.

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TABLE 1. Action of Furylbenzimidazoles on the T. rubrum Culture Present in a Pathological Material

Duration of action, h	Compound					
	I	IV	V	VI	VII	IX
1	+	+	+	+	+	—
2	+	+	+sl	+	+	—
3	+	—	+sl	+	—	—
6	+	—	+sl	+	—	—
12	+	—	+sl	+	—	—
24	—	—	+sl	+	+	—
48	—	—	+sl	+	—	—

Note. −) No growth; +) growth; +sl) slight growth.

Although the synthesized compounds show low antifungal activity, the data obtained may be interesting in the further search for more active drugs in this series.

EXPERIMENTAL

The IR spectra were run on the UR-20 spectrophotometer, in chloroform.

1-Methyl-2-(5-lithium-2-furyl)benzimidazole (II). This compound was prepared by a known method [6]. A 5-g (0.036 mole) portion of butyl bromide was added gradually in a nitrogen current at 0°C to 0.51 g (0.072 g-atom) of lithium chips in 30 ml of absolute ether. A suspension of 6.6 g (0.024 mole) of I in 20 ml of absolute ether was added to the butyllithium formed at 20-25°C for 30 min, and the reaction mixture was stirred at this temperature for 1 h. Compound II thus obtained was used for the synthesis of compounds IV-VII.

1-Methyl-2-(5-benzoyl-2-furyl)benzimidazole (IV). A 1.8-g (0.017 mole) portion of benzonitrile in 20 ml of absolute ether was added to a suspension of compound II prepared from 2.8 g (0.01 mole) of I, and the mixture was stirred at room temperature for 2 h. The reaction mixture was then treated with 60 ml of water and 1 ml of acetic acid. The precipitate was filtered and washed by water. Yield 1.6 g (51%), pale-yellow crystals, mp 151-152°C (from aqueous alcohol). IR spectrum, cm^{-1}: 1640 (C=O). Found, %: C 75.6, H 4.8, N 9.3. $C_{19}H_{14}N_2O_2$. Calculated, %: C 75.5, H 4.8, N 9.2.

1-Methyl-2-[5-(α-hydroxybenzyl)-2-furyl]benzimidazole (V). A 2.1-g (0.2 mole) portion of benzaldehyde in 10 ml of absolute ether was added to a cooled (−10°C) suspension of compound II, prepared from 2.8 g (0.01 mole) of compound I. The mixture was stirred for 2 h at −10°C and 30 min at room temperature, and then 60 ml of water and 3 ml of acetic acid were added. After 1 h, the precipitate was filtered and purified by crystallization from alcohol. Yield 2.3 g (75%), colorless crystals, mp 172-173°C. IR spectrum, cm^{-1} 3600 (OH). Found, %: C 74.6, H 5.6, N 9.3. $C_{19}H_{16}N_2O_2$. Calculated, %: C 74.8, H 5.6, N 9.3.

1-Methyl-2-[5-(α-hydroxybenzhydryl)-2-furyl]benzimidazole (VI). A 1.95-g (0.0105 mole) portion of benzophenone in 25 ml of absolute ether was added at −10°C to the lithium derivative of II, prepared from 2.8 g (0.01 mole) of compound I. The mixture was held at the same temperature for 20 min, and then left to stand for 4 h at room temperature. Then, 50 ml of water was added, the ether layer was separated, and the ether distilled to obtain compound VI. Yield 2 g (55%), colorless crystals, mp 204-205°C (from alcohol). Found, %: C 78.3, H 5.3, N 7.6. $C_{25}H_{20}N_2O_2$. Calculated, %: C 78.9, H 5.2, N 7.4.

1-Methyl-2-(5-iodo-2-furyl)benzimidazole (VII). A 3.2-g (0.025 mole) portion of iodine in 50 ml of absolute ether was added at −28°C to the lithium derivative II, obtained as described above from 0.01 mole of compound I. The mixture was held at this temperature for 40 min, and then left to stand for 3 h at room temperature. It was then treated with 50 ml of water and 3 ml of a saturated solution of sodium bisulfite. The ether layer was separated, the ether distilled, and the residue crystallized from aqueous alcohol. Yield 1.2 g (31%) of yellowish crystals, mp 195-196°C. Found, %: C 44.0, H 3.0, I 39.8, N 8.9. $C_{12}H_9IN_2O$. Calculated, %: C 44.4, H 2.8, I 39.2, N 8.6

1-Methyl-2-(2-furyl)-benzimidazole (IX). A 100-ml portion of water acidified by 0.5 ml of acetic acid was added to the reaction mixture containing II, and the mixture was left to stand for 1 h. A heavy oil was

formed, which was separated and recrystallized from alcohol. Yield 3.9 g (85%), colorless crystals, mp 72-73°C. Found, %: C 72.9, H 5.1, N 14.4. $C_{12}H_{10}N_2O$. Calculated, %: C 72.7, H 5.0, N 14.1.

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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF TROPINE PHENYLGLYOXYLATE AND ITS DERIVATIVES: A NEW METHOD FOR THE PREPARATION OF HOMATROPINE

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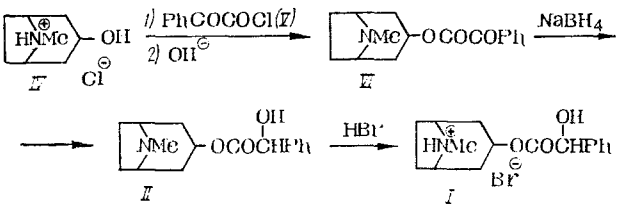
Tropine d,l-mandelate hydrobromide (I, base – II), medically known under the name of homatropine hydrobromide, is used as a mydriatic drug. The known industrial methods used at present for the preparation of homatropine are based on the reaction between tropine (III) or its hydrochloride (IV) and mandelic acid, in the presence of mineral acids [1, 2]. Homatropine is obtained by these methods in low yields, which do not exceed 40%, since the acylation of III with mandelic acid proceeds under drastic conditions and is accompanied by side reactions.

We have developed [3] a new method for the synthesis of I, which ensures its preparation in yields twice as high as those obtained by the previously described methods. According to this method, IV is acylated with phenylglyoxylic acid chloride (V). Tropine glyoxylate (VI) thus formed is reduced with sodium borohydride to II, and the latter is converted by the usual method, i.e., by the action of hydrobromic acid, into I.



In the development of the synthesis of I, definite difficulties arose during the preparation of V from phenylglyoxylic acid (VII), since VII, in the same way as other derivatives of phenylglyoxylic acid, is insufficiently stable [4, 5], and even under relatively mild conditions (~40°C), during its reaction with $SOCl_2$, it is converted into a mixture of V and benzoyl chloride (VIII). The yield of V does not exceed 50% [6]. It should be noted that during the preparation of V by the reaction of VII on oxalyl chloride, the yield of V increases to 75% [7], but in this case the reaction product contains considerable amounts of VIII as an admixture.

We therefore developed a method for the synthesis of V from the ethyl ester of phenylglyoxylic acid (IX) [8, 9], which gives V in a high yield and of high purity. The method consists in the hydrolysis of IX by an aqueous solution of sodium carbonate to the sodium salt of VII, acidification of the reaction mixture by concentrated sulfuric acid, extraction of VII by benzene, and treatment of the partly concentrated extract with a small excess of $SOCl_2$ in the presence of a catalytic amount of dimethylformamide. Compound V is thus obtained in a yield of 82.6%, based on IX.

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