Compound IV was obtained analogously (see Table 4).

2-(1'-Hydroxyethyl)-4,5,6,7-tetrahydroisoindole (V). A mixture of 5.6 g (0.03 mole) 1,3-dimethoxyoctahydrobenzofuran, 3.6 g (0.06 mole) freshly distilled monoethanolamine, and 15 ml propionoic acid were heated at 120-125°C for 6 h on a glycerin bath. The methanol formed in the reaction is driven off during the heating. On cooling, the contents of the flask were decanted in crushed ice and sodium hydroxide was added until attainment of a strongly basic reaction. The oil which separated was extracted with ether. After removal of the ether, the product was heated to boiling with 5 ml methanol and 0.5 g potassium hydroxide for 4 h. The ester impurities are saponified in this manner. The methanol was further driven off and the residue was treated with water (20 ml). A yellow oil separated and was extracted with ether. The ether extracts were dried with calcined magnesium sulfate. After removal of the ether, the product was vacuum distilled and the fraction with bp 137-138°C/2mm was collected. Yield 3.4 g (67%).

Compound VI was prepared analogously (see Table 4).

Hydrogenation Method. A rotary autoclave with a capacity of 150 ml was charged with 0.015-0.03 mole tetrahydroisoindole, 50-80 ml solvent, and an appropriate amount of catalyst (1-2% $PtO_2$, $RuO_2$, and $Rh/Al_2O_3$ or 10-15% Raney nickel, based on quantity to be hydrogenated). The hydrogenation was conducted at initial hydrogen pressure of 100 atm and at temperature necessary for saturation. At the end of saturation the hydrogen of the autoclave was discharged and the catalyst was filtered off. After solvent removal at reduced pressure, the liquid products were vacuum distilled; the crystalline products were recrystallized from ethanol.

Compounds VII-XII were obtained in this manner (see Table 2).

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# SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF N-ARYL FURAN-SUBSTITUTED AMINES AND THEIR DERIVATIVES


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UDC 615.28:547.722.6


Many aryl-substituted furanoamines possess biological activity [1-2]. In addition, amines containing functional groups three carbons from the furan ring are of interest as intermediates in the synthesis of heterocyclic bases such as pyrrolidylalkanols [3]. Finally, they can be used in the synthesis of possible neurotropic preparations [4].

Simple methods for the preparation of aryl substituted furanoamines are not available in the literature.


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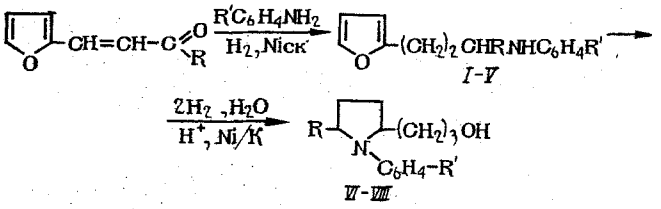
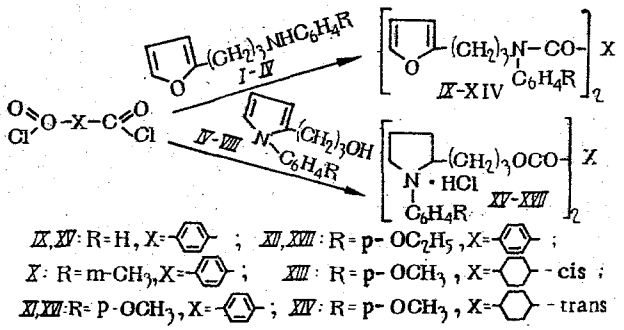
Our method involved the reduction of aminoarylated unsaturated carbonyl side chains of the furan nucleus to aromatic amines in the presence of Raney nickel under hydrogen pressure to give N-arylfurylpropyl amines (I-V).

Earlier, we reported obtaining alkylpyrrolidine alcohols of interest for the synthesis of medicinal preparation [3]. In a further study of this reaction, we succeeded in hydrogenating N-arylfurylpropylamines to obtain a series of previously-unknown N-arylpyrrolidyl propanols.



I, VI R=R'=H ; III, VII: R=H, R'= p-$OCH_3$, V: R=$CH_3$, R=H
II R=H, R'= m-$CH_3$, IV, VIII: R=H, R'= p-$OC_2H_5$

In order to study their antimicrobial activity, we synthesized a series of N- and O-acyl derivatives of compounds I-VIII. Thus, we acylated amines I-IV and alcohols VI-VIII with the acid chlorides of terephthalic and of cis- and trans-1,4-cyclohexane dicarboxylic acids to give amides IX-XIV and esters XV-XVII. (Table 1).



IX, XV: R=H, X= ; XII, XVIII: R= p-$OC_2H_5$, X= ;
X: R= m-$CH_3$, X= ; XIII: R= p-$OCH_3$, X= - cis ;
XI, XVI: R= p-$OCH_3$, X= ; XIV: R= p-$OCH_3$, X= - trans

The structure of the compounds obtained was confirmed by IR spectroscopy. The IR spectra of I-XVII showed intense bands at 3150-3130 and 3050-3040 $cm^{-1}$, characteristic of $\nu_{C-H}$ of furans and aromatic rings, respectively. In the IR spectra of I-V there is an intense absorption in the 3410-3385 and 1630-1610 $cm^{-1}$ regions, characteristic of the stretching and bending vibrations of secondary amine groups. Stretching vibrations associated with the hydroxyl group in compounds VI-VIII were characteristically wide intense bands in the 3400-3200 $cm^{-1}$ region with maxima at 3380-3390 $cm^{-1}$. The amides IX-XIV showed intense absorptions in the 1670-1630 $cm^{-1}$ region and overtones in the 3400-3200 $cm^{-1}$ region. In the IR spectra of compounds XV-XVII there are intense bands in the 1750-1730 $cm^{-1}$ region characteristic of the $\nu_{C-O}$ of esters.

## EXPERIMENTAL

### Pharmacological

The antimicrobial activity of the N-arylfurylpropyl amines I-V, amides IX-XIV, and esters XV-XVII was determined by double serial culture into Hottinger's broth, pH 7.2, with the following test-microbes: *Staphylococcus aureus*, *Escherichia coli*, *Proteus vulgaris*, *Pseudomonas pyocyaneum*, and *Candida albicans*.

Compounds I-V showed moderate antimicrobial activity, inhibiting growth of the test microbes in concentrations of 37-75 μg/ml (Table 2).

We obtained selective activity for amides IX-XIV and esters XV-XVII against gram-positive microbes. Thus, bacteriostatic concentrations for staphylococci equalled 6-12 μg/ml. Thus, these results indicate our search for prospective new antimicrobial preparations among the amino and oxy derivatives of furans and pyrrolidines.

TABLE 1. Synthesized Compounds

| Compound | Yield, % | bp, °C | $d_4^{20}$ | $n_D^{20}$ | $MR_D$ found | $MR_D$ calc., | Found, % C | Found, % H | Found, % Cl | Found, % N | Formula | Calc.,% C | Calc.,% H | Calc.,% Cl | Calc.,% N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I | 39,6 | 162—4 (7) | 1,062 | 1,5647 | 61,62 | 60,74 | 77,90 | 7,50 | — | 7,01 | $C_{13}H_{15}NO$ | 77,58 | 7,52 | — | 6,97 |
| II | 31 | 135—7 (1) | 1,045 | 1,5610 | 66,42 | 65,63 | 78,28 | 8,15 | — | 6,94 | $C_{14}H_{17}NO$ | 78,20 | 7,97 | — | 6,52 |
| III | 43,2 | 43—3,5 | — | — | — | — | 72,64 | 7,52 | — | 6,33 | $C_{14}H_{17}NO_2$ | 72,79 | 7,42 | — | 6,06 |
| IV | 60 | 67—7,5 | — | — | — | — | 73,40 | 7,62 | — | 5,54 | $C_{15}H_{19}NO_2$ | 73,47 | 7,75 | — | 5,71 |
| V | 22 | 146—8 (2) | 1,038 | 1,5500 | 65,96 | 65,36 | 78,17 | 7,19 | — | 6,24 | $C_{14}H_{17}NO$ | 78,14 | 7,90 | — | 6,51 |
| VI | 20,9 | 175—6 (4) | 1,045 | 1,5698 | 61,99 | 62,70 | 76,96 | 9,34 | — | 6,91 | $C_{13}H_{19}NO$ | 76,16 | 9,34 | — | 6,83 |
| VII* | 27 | 175—80 (2) | — | 1,5695 | — | — | 71,82 | 6,94 | — | 5,84 | $C_{14}H_{21}NO_2$ | 71,45 | 6,38 | — | 5,91 |
| VIII* | 25 | 208—10 (1) | — | 1,5640 | — | — | 72,57 | 7,82 | — | 6,06 | $C_{15}H_{23}NO_2$ | 72,28 | 8,43 | — | 5,62 |
| IX | 45 | 159—60 | — | — | — | — | 76,70 | 6,07 | — | 5,58 | $C_{34}H_{32}N_2O_4$ | 76,69 | 6,03 | — | 5,26 |
| X | 42,5 | 144—5 | — | — | — | — | 77,12 | 6,45 | — | 4,95 | $C_{36}H_{36}N_2O_4$ | 77,01 | 6,42 | — | 5,00 |
| XI | 40 | 171—2 | — | — | — | — | 72,15 | 6,15 | — | 4,70 | $C_{36}H_{36}N_2O_6$ | 72,98 | 6,08 | — | 4,72 |
| XII | 26 | 158—9 | — | — | — | — | 72,94 | 6,57 | — | 4,89 | $C_{38}H_{40}N_2O_6$ | 73,54 | 6,45 | — | 5,51 |
| XIII | 35 | 85—6 | — | — | — | — | 72,48 | 7,27 | — | 5,15 | $C_{36}H_{46}N_2O_6$ | 72,24 | 7,02 | — | 4,68 |
| XIV | 35 | 94—5 | — | — | — | — | 72,01 | 7,00 | — | 4,65 | $C_{36}H_{46}N_2O_6$ | 72,24 | 7,02 | — | 4,68 |
| XV | 40 | 129—31 | — | — | — | — | — | — | 11,2 | 4,69 | $C_{34}H_{40}N_2O_4 \cdot 2HCl$ | — | — | 11,4 | 4,56 |
| XVI | 45 | 190 | — | — | — | — | — | — | 10,72 | 4,58 | $C_{36}H_{44}N_2O_6 \cdot 2HCl$ | — | — | 10,54 | 4,26 |
| XVII | 54 | 139—40 | — | — | — | — | — | — | 10,12 | 4,03 | $C_{38}H_{48}N_2O_6 \cdot 2HCl$ | — | — | 10,12 | 3,99 |

*Viscous liquid.

TABLE 2. Antimicrobial Activity of Compounds Tested (minimal bacteriostatic concentration in μg/ml)

| Compound | Microorganism | | | | |
|---|---|---|---|---|---|
| | St. aureus | E. coli | Pr. vulgaris | Ps. pyocyaneum | Candida albicans |
| I | 37 | 37 | 75 | 75 | 37 |
| II | 37 | 37 | 37 | 75 | 37 |
| III | 37 | 37 | 37 | 75 | 37,5 |
| IV | 37 | 37 | 37 | 75 | 37,5 |
| V | 37 | 37 | 75 | 75 | 37 |
| IX | 6 | 50 | 100 | 100 | 50 |
| X | 6 | 50 | 100 | 50 | 50 |
| XI | 6 | 50 | 100 | 100 | 50 |
| XII | 6 | 50 | 50 | 50 | 50 |
| XIII | 12 | 50 | 50 | 50 | 50 |
| XIV | 12 | 50 | 50 | 50 | 50 |
| XV | 12 | 50 | 100 | 50 | 50 |
| XVI | 6 | 50 | 100 | 50 | 50 |
| XVII | 6 | 50 | 50 | 25 | 50 |

Chemical

IR spectra of the compounds were obtained on a UR-20 spectrophotometer using potassium bromide plates, capillary films, Vaseline oil, and hexafluorobutadiene.

Amines I-V were obtained by reduction of aminoarylated furan carbonyl compounds to the corresponding aromatic amines by the literature method [3].

Physicochemical constants and yields of the compounds obtained are given in Table 1.

3-(1-Phenyl-2-pyrrolidyl)propan-1-ol (VI) was prepared according to [3].

3-(1-p-Methoxyphenyl-2-pyrrolidyl)propan-1-ol (VII). A solution of 20 g of III in a mixture of 20 ml dioxane and 15 ml of 1:1 hydrochloric acid (pH 4.0) was hydrogenated in a 250 ml autoclave in the presence of 15% (based on weight of amine) previously reduced nickel on kieselgur. The initial pressure of hydrogen was 60 atm, and the temperature was 80-90°C. After completion of the hydrogenation, the catalyst was removed by filtration and the solvent was distilled under reduced pressure. The residue was extracted with ether and neutralized with an aqueous solution of $K_2CO_3$. The aqueous layer was extracted with ether, and dried over potassium hydroxide pellets. Distillation under vacuum gave VII, bp 175-180°C/2mm, yield 27%. Spectroscopically pure material was separated by column chromatography on $Al_2O_3$ with hexane and ether.

VIII was obtained analogously.

N,N-Terephthaloyl-bis-[N(p-ethoxyphenyl)]-3-(furyl)-propylamine (XI). Obtained by mixing equimolar ethereal solutions of amine IV and terephthaloyl dichloride. Yield 26%.

Compounds IX, X, XII-XIV were obtained analogously.

Esters XV-XVIII were prepared by the literature method [4].

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