compounds X-XIII, which contain halogen atoms in the 5 and 6 positions, exhibit the lowest antitubercular activity. The concentration of the majority of the compounds (except compounds V, VIII, and XIII) which suppress the growth of tubercular microbacteria did not change in the presence of 10% normal horse serum.

Some of the compounds studied (X-XIII) possess antifungal activity. Compound XII at a concentration of 2.4 μg/ml retards the growth of *Candida albicans*, and compounds X, XI, and XIII suppress the growth of this fungus at concentrations of 32-250 μg/ml.

2-Halogenacetylindoles are antimicrobial agents with a wide spectrum of activity (including activity towards antibiotic-resistant strains of staphylococcus) and in our view may be of practical value.

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SYNTHESIS AND ANALGETIC AND PSYCHOTROPIC PROPERTIES OF PIPERIDINE AND DECAHYDROQUINOLINE DERIVATIVES.

IV. STEREOISOMERS OF 2-(α-FURYL)-4-OXODECAHYDROQUINOLINE

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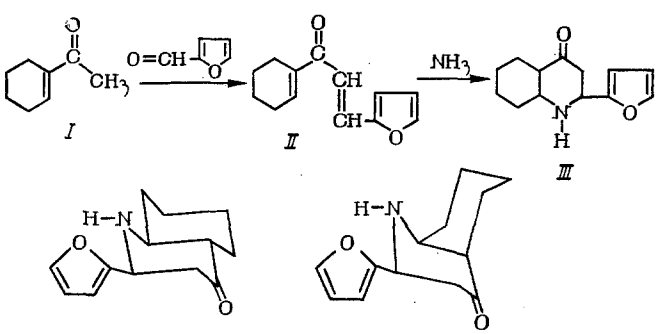
A detailed examination of the isomerism of 2-methyl-4-oxodecahydroquinoline [1] and the corresponding alcohols [2-4] has been carried out in our laboratory, leading to the synthesis of certain pharmacologically active substances (anesthetics and analgetics), and to important conclusions concerning the relationship of structure to biological activity [5, 6]. These synthetic products did not include oxygen-containing decahydroquinolines, containing an α-furyl substituent in the 2 position.

We have obtained a representative of this new group of heterocyclic compounds by the following route:



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The condensation of 1-acetylcyclohexene (I) [7] with furfural proceeds smoothly to form β-(α-furyl)vinyl-Δ^1-cyclohexenyl ketone (II) in 80% yield. Cyclization of the divinyl ketone II with ammonia leads to extensive resinification, the yield of 2-(α-furyl)-4-oxodecahydroquinoline (III) consequently not exceeding 40%.

Thin-layer chromatography of the aminoketone III on alumina showed it to be a mixture of two isomers, instead of the four expected theoretically. Both isomer racemates were readily isolatable as their hydrochlorides, m.p. 189-190° (43% of the total bases) and 175-176° (20%). The hydrochlorides on treatment with aqueous base gave the base racemates, m.p. 59-60 and 65-66°, respectively, designated by analogy with ketones of the decahydroquinoline series [1] as the γ and β forms. The presence of secondary amino and keto groups was shown by the preparation of crystalline oxime hydrochlorides and benzamides, and by their IR spectra. The calculated molecular weights of the base racemates were in agreement with the mass spectroscopic values.

Examination of the IR spectra of carbon tetrachloride solutions of the γ and β isomers of III showed the presence of hydrogen bonding in both isomers. This was shown by absorption bands at 3340-3350 and 3420-3425 cm^{-1} which did not change in intensity on successive dilution of the solutions (0.1, 0.05, and 0.01 mole/liter). An intramolecular N—H....O hydrogen bond can only be formed in these compounds if the furan ring is oriented equatorially.

Examination of the PMR spectra of the stereoisomers of III in terms of the resonance of the proton at C_2 alone can lead to erroneous results. Thus, if the spectrum of the β isomer of III in benzene is regarded as an A_2X system on the basis of the triplet splitting of the X resonance with J = 4.5 Hz, it is easy to draw the conclusion that this isomer has an axial furyl group.

However, in all the spectra (see Fig. 1), the resonances of two protons are observed clearly at C_3, thus making it possible to establish more correctly the nature of the resonating system (Table 1) and to carry out in a more reliable way the stereochemical analysis of the isomers of III. From the stereochemical point of view, in the three-spin system in question two variants are possible for the disposition of the C_2—H bond with respect to the protons of the C_3 methylene group: 1) axial, and 2) equatorial.

The first variant will possess two widely differing splitting constants J_{aa} and J_{ae}, while in the second there will be two approximately equal constants J_{ae} and J_{ee} [8]. In a three-spin system of the ABX type the sum of $(J_{AX} + J_{BX})$ is equal to the width of the X resonance. On this basis, the γ isomer of III may be confidently assigned a structure with an equatorial furyl group, since the width of the corresponding signal in both solvents is ~16 Hz, i.e., at least one of the constants is not less than 8 Hz, in accordance with axial-axial interaction of the vinyl protons.

The analysis of the PMR spectrum of the β isomer in benzene as an ABX system gives one of the vicinal constants as 7.1 Hz, which is also an unambiguous indication of the equatorial orientation of the furyl radical. The reduced values for J_{aa} and J_{ae} (see Table 1) as compared with the usual values (10-12 and 3-4 Hz, respectively) show a substantial deformation of the chair form of the piperidine ring. It does not appear to be possible to arrive at any conclusions concerning the mode of linkage of the rings in the isomers of III on the basis of these PMR spectra.

Thus, both the isomers of III, according to their IR and PMR spectra, have equatorially orientated furan rings, and must therefore differ in the way in which the piperidine and cyclohexane rings are linked.

We have examined the toxicity, neurotropic and analgetic activity of the hydrochlorides of the β and γ isomers of III (Table 2). The acute toxicities were determined in tests on white mice by intraperitoneal administration of the compounds. There were no marked differences in toxicity between these isomers. The LD_{50} of the β isomer was 500 mg/kg, and of the γ isomer, 425 mg/kg. At the same time, the configurational characteristics of the compounds influenced some of their pharmacological properties. Thus, in a dose of 1.5 LD_{50} the β isomer of III, which does not possess the 4-phenyl and 4-propionyloxy groups which are usual in analgesics, has slight analgesic properties, raising the threshold of pain sensitivity in mice on electrical pain stimulation. In contrast, the γ isomer of III exhibits no analgesic properties. Both compounds show a depressive effect on the central nervous system. They reduce the body temperature in mice by ~3°. The γ isomer also disturbs motor coordination in 85% of the animals.

TABLE 1. Chemical Shifts and Splitting Constants for the C_2 and C_3 Protons in Isomers of 2-(α-Furyl)-4-oxodecahydroquinoline

Compound	Solvent	Spin system	Protons at C_2 and C_3	
			chemical shift, ppm	splitting, Hz
III-β	Carbon tetrachloride	ABX	$2H_a$ 4,64 $3H_a$ or $3H_e$ 2,78 $3H_a$ or $3H_e$ 2,72	J_{3a3e} 15 J_{2a3a} 7,1 J_{2a3e} 1,5
	Benzene	Degenerate ABX	$2H_a$ 4,28 $3H_a$, $3H_e$ 2,50	$(J_{2a3a}+J_{2a3e})$ 8,5
III-γ	Carbon tetrachloride	Degenerate ABX	$2H_a$ 4,0 $3H_a$, $3H_e$ 2,47	$(J_{2a3a}+J_{2a3e})$ 16
	Benzene	AB_2	$2H_a$ 3,78 $3H_a$, $3H_e$ 2,48	$(J_{2a3a}+J_{2a3e})$ 16 J_{3a3e} 8

TABLE 2. Neurotropic Activity of Isomers of 2-(α-Furyl)-4-oxodecahydroquinoline on Intraperitoneal Administration

Compound	LD_{50}, mg/kg	Dose, mg/kg	Change in pain sensitivity threshold		Change in body temperature, deg	Disturbance of coordination of movement, %
			on electrical pain stimulation, mA	on thermal stimulation, sec		
III-β	500	100	+1,26± 0,28*	+7,1± 2,09*	—3,4± 0,64*	50
		50	+0,33± 0,09*	+5,7± 0,83*	—3,7± 0,42*	50
III-γ	425	85	+0,17± 0,07	—	—2,7± 0,49*	85*

*Statistically significant differences.

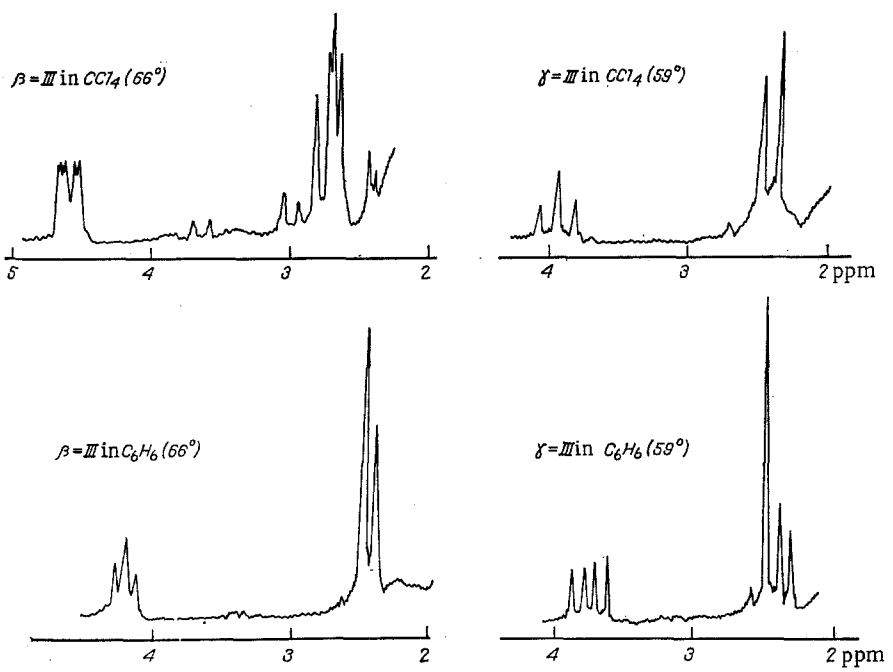

Fig. 1. PMR spectra of isomers of 2-(α-furyl)-4-oxodecahydroquinoline (III).

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument in carbon tetrachloride, and the PMR spectrum on a ZKP-60 instrument of working frequency 60 MHz in carbon tetrachloride and benzene at room temperature, using hexamethyldisiloxane (HMDS) as internal standard. Thin-layer chromatography was carried out using grade III alumina with iodine vapor as the developing agent.

β-(α-Furyl)vinyl-Δ^1-cyclohexenyl Ketone (II). To a mixture of 24.9 g of I and 27 g of freshly distilled furfural was added dropwise 4 ml of saturated potassium hydroxide solution in methanol, and the mixture was stirred for 2 h at 20-30°. The reaction mixture was taken up in ether, dried with calcined magnesium sulfate, and distilled *in vacuo* to give 32.4 g (80%) of II as a mobile, yellowish liquid, bp 170-172° (5 mm), n_D^{20} 1.6090.

2-(α-Furyl)-4-oxodecahydroquinoline (III). A mixture of 20.2 g of the divinyl ketone II, 50 ml of a 24% ethanolic solution of ammonia, and 30 ml of alcohol was heated in a steel vessel at 95-100° for 10 h. The alcohol and the excess of ammonia were removed *in vacuo* at 40-45°, and the residue was diluted with 30 ml of water, neutralized with dilute hydrochloric acid, and the hydrocarbons extracted with ether. The aqueous solution of the hydrochlorides was treated with potassium carbonate, and the upper layer of the free bases was taken up into ether, dried over magnesium sulfate, and distilled *in vacuo* to give 8.8 g (40%) of mixed isomers of III, bp 140-142° (2 mm), n_D^{20} 1.5289.

Preparation of the Hydrochlorides of the γ and β Isomers of 2-(α-Furyl)-4-oxodecahydroquinoline (III). The liquid mixture of isomers of III (46 g) was dissolved in 200 ml of absolute ether, and neutralized in the cold with an ethereal solution of dry hydrogen chloride. Repeated recrystallization of the mixed hydrochlorides from acetone afforded two crystalline fractions. The first fraction (21.5 g; 43% of the mixed isomers) was the hydrochloride of the γ isomer, mp 189-190°. Found, %: N 5.65, 5.82. $C_{13}H_{17}NO_2 \cdot HCl$. Calculated, %: N 5.48. The second fraction (10.75 g; 20%) was the hydrochloride of the β isomer, a white crystalline powder, mp 175-176°. Found, %: N 5.69, 5.26. $C_{13}H_{17}NO_2 \cdot HCl$. Calculated, %: N 5.48.

γ Isomer of 2-(α-Furyl)-4-oxodecahydroquinoline (III). The hydrochloride (21.5 g) with mp 189-190° in 100 ml of water was decomposed with saturated sodium hydroxide solution, and the free base was dried over magnesium sulfate in ether. After removal of the ether the solid was recrystallized from light petroleum to give 17 g (92%) of the γ isomer of III, mp 59-60°, R_f 0.80 (ether). Found, %: C 70.71, 71.11; H 8.03, 8.18; N 6.69; 6.80. $C_{13}H_{17}NO_2$. Calculated, %: C 71.20; H 7.81; N 6.39.

Picrate — yellow crystals, mp 185-186° (in a sealed capillary tube). Found, %: N 12.66, 12.44. $C_{19}H_{20}N_4O_9$. Calculated, %: N 12.50.

Oxime hydrochloride — colorless crystals, mp 244-245° (in a sealed capillary). Found, %: C 57.61, 57.64; H 7.25, 7.61; Cl 13.09, 13.49; N 10.12, 10.35. $C_{13}H_{18}N_2O_2 \cdot HCl$. Calculated, %: C 57.66; H 7.09; Cl 13.09; N 10.35.

γ Isomer of 1-Benzoyl-2-(α-furyl)-4-oxodecahydroquinoline. To a solution of 1 g of the γ isomer of III in 10 ml of dry benzene at 75° was added 0.316 g of benzoyl chloride, and the mixture was boiled for 1 h. The solid hydrochloride of the γ isomer of III was filtered off, and from the evaporated filtrate there was obtained 0.67 g (91.8%) of a compound, mp 150-151° (from benzene), R_f 0.30 (ether—light petroleum, 1:1). Found, %: C 74.03, 73.81; H 6.97, 7.02; N 4.15, 4.45. $C_{20}H_{21}NO_3$. Calculated, %: C 74.28; H 6.55; N 4.31.

β Isomer of 2-(α-Furyl)-4-oxodecahydroquinoline (III). From 10.75 g of the hydrochloride of the β isomer of III, mp 175-176°, was obtained 8.8 g (95%) of the free base of the β isomer of III as large white crystals, mp 65-66° (from light petroleum), R_f 0.57 (ether). A mixed mp with the γ isomer of III (mp 59-60°) gave a value of 38-42°. Found, %: C 70.82, 71.09; H 7.80, 7.92; N 6.00, 6.64. $C_{13}H_{17}NO_2$. Calculated, %: C 71.20; H 7.81; N 6.39.

Picrate — small yellow crystals, mp 174-175° (in a sealed capillary). Found, %: N 12.00, 12.39. $C_{19}H_{20}N_4O_9$. Calculated, %: N 12.50.

Oxime hydrochloride — small colorless crystals, mp 233-234° (decomp.). Found, %: N 10.35, 10.64. $C_{13}H_{18}N_2O_2 \cdot HCl$. Calculated, %: N 10.35.

β Isomer of 1-Benzoyl-2-(α-Furyl)-4-oxodecahydroquinoline. Obtained in theoretical yield as described above; light colorless crystals, mp 178-180° (from benzene), R_f 0.49

(ether–light petroleum, 1:1). Found, %: C 74.20, 74.30; H 6.40, 6.65; N 4.25, 4.40. $C_{20}H_{21}NO_3$. Calculated, %: C 74.28; H 6.65; N 4.31.

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ANTIMICROBIAL ACTIVITY OF CYCLOALKENYL- AND 4-(α-ARYLCYCLOPENTYL)PHENOLS

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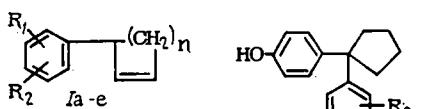
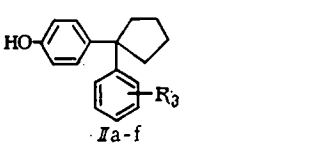
The physiological role of phenolic compounds in living organisms and their pharmacological effects have recently been investigated in detail [1]. There is much interest in the investigation of synthetic phenols of low toxicity, the biological activity of which is due to their antioxidant properties [2]. It was of interest in this connection to examine the biological effects of phenols both with the aim of the directed synthesis of antimicrobial drugs and for their more rational use as antiseptics and disinfectants.

This paper describes an investigation of the antibacterial and antimycological effects of phenols of differing structures which we have synthesized:





The cycloalkenylphenols (Ia-e) were prepared by alkylation of the phenols with 1,3-cyclodienes in the presence of phosphoric acid [3], and the 4-(α-arylcyclopentyl)phenols

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