(3 × 30 ml), the extracted dried over anhydrous Na_2SO_4, the ether distilled off, and the residue vacuum-distilled. Yield 9 g (67%). Colorless oil, crystallized on cooling. Bp 84–86° (4–5 mm). Colorless needles, mp 41.5–42.5° (ex n-heptane). Found: N 20.32%. Calculated for $C_8H_{12}N_2$. N 20.58%. Picrate., yellow transparent needles, mp 180–182° (ex dil EtOH). Found: N 19.32%. Calculated for $C_8H_{12}N_2 \cdot C_6H_3N_3O_7$: N 19,16%.

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SYNTHESIS OF (1-METHYL-3-PIPERIDYLIDENE)DI(2-THIENYL)METHANE CITRATE (BITHIODINE)

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An improved method of synthesizing (1-methyl-3-piperidylidene)di-(2-thienyl)methane citrate, starting from ethyl pyridine-3-carboxylate (ethyl nicotinate).

(1-Methyl-3-piperidylidene)di(2-thienyl)methane (I) is of great interest, as its salts are powerful antitussives and expectorants, without narcotic action [1–4]. Japanese patents [1–4] give information only about preparation of I salts by treatment with citric, salicylic and other acids in ethanol solution, and there are pharmacological data regarding the preparation "Azverin."

A paper [5] describes the preparation of I by reacting a 2-fold excess of Grignard reagent with ethyl 1-methylpiperidine-3-carboxylate (nipecotate), to give a 35% yield of (1-methyl-3-piperidyl)di(2-thienyl)-carbinol (II), dehydrated to I by a large excess of mixed hydrochloric and sulfuric acids.

By modifying the reaction conditions we were able to effect the synthesis of II in 75% yield. We used 85% formic acid to dehydrate II and obtained a good yield. The starting ethyl 1-methylpiperidine-3-carboxylate (nipecotate) (III) was prepared by hydrogenating the quaternary salt (IV) of ethyl pyridine-3-carboxylate (nicotinate (V) with dimethyl sulfate, over Raney nickel at 50–60°, by analogy with [6].

EXPERIMENTAL

Ethyl 1-methylpiperidine-3-carboxylate (nipercotate) (III). a) 45.3 g (0.3 mole) V in 150 ml benzene was heated to boiling, and to the boiling mixture 40.82 g (0.324 mole) VI added over a period of 40 min, after which the mixture was refluxed for 1 hr. The products were cooled and poured into 100 ml petrol ether. IV was isolated by strongly cooling the mixture, then decanting the solvent. The crude product was used for hydrogenation.

b) A rotating steel autoclave capacity 610 ml was charged with 80 g IV in 200 ml MeOH, 10 g Raney Ni catalyst, and hydrogen introduced at 100 atm. Hydrogenation was effected at 50–60°, in 2–3 hr gas ceased to be absorbed. The autoclave was emptied, the products were poured off, the catalyst in the autoclave was washed with 20 ml MeOH, and the next batch of IV placed with it. The MeOH was vacuum-distilled off from the products, the residue dissolved in 150 ml water, and 60 g K_2CO_3 added. The oil which came out was separated off, and the aqueous solution left extracted with ether. The ether extracts and oil were dried over $MgSO_4$, the ether distilled off, and the residue vacuum-distilled, to give 43.7 g III (85.1%), calculated in V), bp 82—85° (10 mm), n_D^{20} 1.4505; d_4^{20} 0.981; MR_D Found: 46.97. Calculated 46.59.

(1-Methyl-3-piperidyl)di(2-thienyl)carbinol (II). 86.4 g (0.53 mole) bromothiophene was added to 12.72 g (0.53 mole) Mg turnings in 80 ml dry ether, at such a rate that the ether constantly refluxed gently. Then the flask was heated for 2 hr 30 min on a waterbath, until the Mg completely dissolved. The flask was cooled, and 43.7 g (0.255 mole) III in 80 ml dry ether dropped in. Cooling was stopped, the contents of the flask brought to room temperature, heated on a waterbath for 2–3 hr, and left overnight. The products were decomposed with 300 g ice, 250 ml water, and 130 g NH_4C. The crystals which separated out were filtered off with suction, washed with water, then with ethanol, and dried. Yield 56.2 g (75.1%) II, bp 137–139°. Found: C 61.29; 61.00; H 6.69, 6.38; N 5.08%. Calculated for $C_{15}H_{19}NOS_2$. C 61.39; H 6.52; N 4.77%.

(1-Methyl-3-piperidylidene)di(2-thienyl)methane citrate (bithiodine). 30.72 g citric acid was added to a boiling solution of 44.15 g I in 75 ml MeOH, the whole heated for 7–10 min, then left at room temperature for 2–3 hr. The crystals which separated were filtered off, washed with EtOH, then with ether, and dried. Yield 67.3 g I (90%), mp 135–137° (decomp.). Found: C 53.78; 54.19; H 5.47; 5.81; N 2.97, 3.22%. Calculated for $C_{21}H_{25}NO_7S_2$. C 53,83; H 5,39; N 2,99%. After recrystallizing from EtOH it had mp 139° (decomp.).

(1-Methyl-3-piperidylidene)di(2-thienyl)methane. 56.2 g II was carefully added to 110 ml 85% boiling formic acid and the flask heated for 10 min. 90 ml acid were vacuum-distilled off and the residue carefully poured into saturated Na_2CO_3. The oil which separated was extracted with ether. The ether is evaporated off till dryness and the residue vacuum-distilled. Yield 44.15 g I (83.7%) bp 178–180° (6 mm). Found: C 65.82, 65.55; H 6.54, 6.29%. Calculated for $C_{15}H_{17}NS_2$.C 65.40; H 6.22%; λ_{max} 247 (in EtOH) λ_{min} 218 mμ.

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SYNTHESIS AND ANTITUBERCULAR ACTIVITY OF ISONIAZONES OF SOME ALDEHYDES IN THE FURAN AND THIOPHENE SERIES

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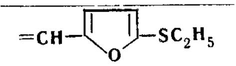
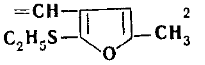
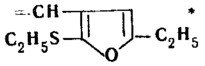
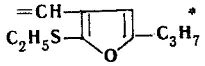
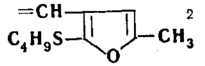
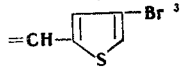
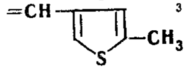
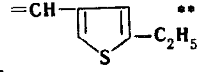
8 Isoniazones of aldehydes of the furan and thiophene series are synthesized; in vitro they all exhibited high antitubercular activity. Two compounds, 5-ethylmercaptofurfural and 2-ethylmercapto-5-n-propyl-3-furanaldehyde isoniazones showed the greatest activity.

At present the most widely used antitubercular preparations are isonicotinic acid hydrazide (isoniazid, tubazid), and its derivatives isoniazones): ftivazid, metazid, saluzid, and larusan.

The rather large number of isoniazones in practical use provides a basis for discovering other, even more effective isoniazid derivatives. In particular, it was of interest to synthesize and test for antitubercular activity, isoniazones of aldehydes of the furan

Isoniazone 

Compound number	R	Mp, °C	N, %		In vitro tuberculostatic activity, dilution 1 : X million		
			Found	Calculated	Academia strain without serum	Academia strain with serum	H 37 RV strain with serum
I		174—175	15.36	15.22	1 : 32	1 : 32	1 : 16
II	 [2]	176—177.5	14.51	14.87	1 : 16	1 : 4	1 : 4
III	 *	157—159	13.47	13.84	1 : 16	1 : 8	1 : 4
IV	 *	113—115	13.29	13.23	1 : 32	1 : 16	1 : 16
V	 [2]	129—130.5	13.13	13.24	1 : 16	1 : 8	1 : 2
VI	 [3]	234—235.5	13.66	13.55	1 : 16	1 : 2	1 : 2
VII	 [3]	175.5—176	16.74	17.17	1 : 16	1 : 8	1 : 8
VIII	 **	185.5—186.5	16.24	16.20	1 : 16	1 : 8	1 : 4

*Prepared similarly to II.

**Prepared similarly to VII.