SYNTHESIS AND TUBERCULOSTATIC ACTIVITY OF N-PHENYL-N'-(QUINAZOLYL-6)-THIOUREAS

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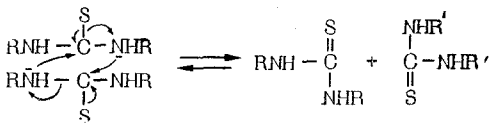
UDC 615.761.61-012 + 615.761.61-017.248

The condensation of 4-ethoxy-6-aminoquinazoline with p-substituted phenylisothiocyanates was studied. Methiodides of the N-phenyl-N'-(4-ethoxyquinazolyl-6)-thioureas isolated were produced.

It is well known that thiocarbanilides include a number of compounds possessing high antitubercular activity. Some of them have found use in medical practice [1].

In a search for substances with antitubercular activity, we were interested in replacing one phenyl residue in the thiocarbanilide with a quinazoline residue. In view of the fact that the presence of an alkoxyl group in compounds of the thiocarbanilide series promotes an intensification of the biological activity in the interaction of 4-ethoxy-6-aminoquinazoline (II) with p-methoxy(ethoxy-, propoxy-, butoxy-, or chloro-)-phenylisothiocyanates (III), N-(4-ethoxyquinazolyl-6)-N'-phenylthioureas (I) were obtained (see Table 1). It was found that the reaction of II with III proceeds ambiguously. In the reaction mixture, N,N'-(4,4-diethoxyquinazolyl-6)-thiourea (IV), the corresponding thiocarbanilides (V), the amine (II), isothiocyanates (III), p-substituted anilines (VI) corresponding to the original isothiocyanates, as well as a spot with R_f value close to that of compound III, evidently 4-ethoxyquinazolyl-6-isothiocyanate (VII), were found together with I by thin-layer chromatography on aluminum oxide in the system chloroform – 1.5% methanol. The mixture was separated preparatively on plates with development in ultraviolet or iodine vapors. The substances were eluted from the aluminum oxide with methanol. In an attempt to conduct the condensation of II and III at room temperature, II and III were isolated in quantitative yield. All the reactions were monitored by chromatography in a thin layer of aluminum oxide.

The formation of symmetrical thioureas in the production of nonsymmetrical N,N'-disubstituted thioureas was noted earlier by a number of authors [2-5] and has been explained either by "exchange of radicals" [2] or by cleavage of the nonsymmetrically disubstituted thioureas into the isothiocyanate and amine and their recombination into symmetrical thioureas [3], or by steric hindrance [4], or according to the scheme proposed by Kappe [5]:



The detection of two symmetrical thioureas (IV, V), two isothiocyanates (III, VII), and two amines (II, VI) in the reaction mixture shows that the N-(p-alkoxy-or chlorophenyl-)-N'-(4-ethoxyquinazolyl-6)-thiourea (I) obtained breaks down during the reaction in two directions, and two amines (II, VI) and two isothiocyanates (III, VII) are formed, which interact with one another to form one nonsymmetrical substituted thiourea (I) and two symmetrical ones (IV, V):

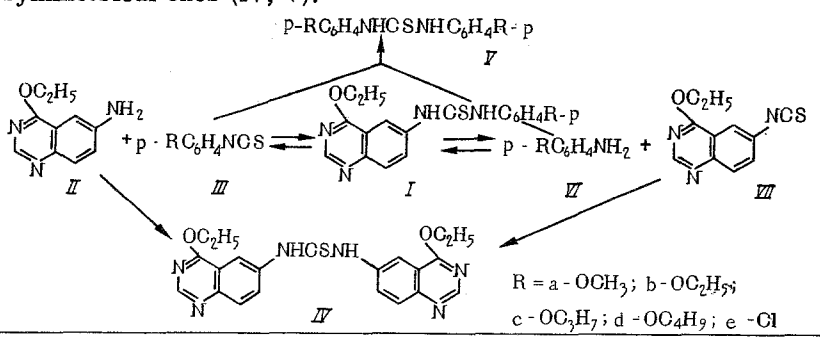


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TABLE 1. Chemical Constants and Tuberculostatic Activity of the Compounds

Compound	R	Conditions of reaction: duration (in h), anhydrous solvent	Yield (in %)	Melting point (in degrees, from alcohol)	R_f	Found (in %) C	Found (in %) H	Found (in %) N	Found (in %) Cl	Found (in %) S	Gross formula	Calculated (in %) C	Calculated (in %) H	Calculated (in %) N	Calculated (in %) Cl	Calculated (in %) S	Melting point (in degrees, dec.)	Methiodides Iodine (%) found	Methiodides Iodine (%) calculated	Tuberculostatic activity (in μg/ml) strain H_{37}	Tuberculostatic activity (in μg/ml) methiodides
Ia	OCH_3	1, acetone	65.5	139—140	0.51	61.26	5.30	15.30		9.37	$C_{17}H_{16}N_4O_2S$	61.00	5.12	15.81		9.05	195—6	25.34	25.57	250	500
Ib	OC_2H_5	1, alcohol	33	136—7	0.49	61.97	5.66	15.00		8.29	$C_{18}H_{18}N_4O_2S$	61.93	5.47	15.21		8.70	206	25.09	24.86	8	
Ic	OC_3H_7	4, acetone	33.8	131—2	0.50	62.95	5.91	14.34		8.14	$C_{19}H_{20}N_4O_2S$	62.80	5.79	14.65		8.38	189—90	24.06	24.20	4	4
Id	OC_4H_9	1/3 alcohol	80.8	120—1	0.52	63.23	6.02	13.80		8.13	$C_{20}H_{22}N_4O_2S$	63.61	6.10	14.13		8.09	180—1		23.57	8	
Ie	Cl	4, acetone	30	157—8	0.35	56.77	4.45	15.68	10.03	8.82	$C_{17}H_{15}N_4ClO_2S$	56.90	4.21	15.61	9.88	8.94	205—6	25.36	25.34	64	500
IV	—			180—1	0.19	59.67	4.90	19.91		8.82	$C_{21}H_{20}N_6O_2S$	59.98	4.79	19.99		7.62	252	22.00	22.56	32	

The N-phenyl-N'-(4-ethoxyquinazolyl-6)-thioureas (I) that we isolated evidently are energetically more profitable than the symmetrical thioureas (IV, V). Therefore, together with the formation of I at the reaction temperature, there is evidently a cleavage at the C = N bonds, by which we may explain the formation of the symmetrical thioureas IV and V and the amine VI.

The amine II needed for the reaction was produced from quinazolone-4 [6] through 6-nitroquinazolone-4 [7], 6-nitro-4-chloroquinazoline [7], followed by replacement of the chlorine by an ethoxy group and reduction of the 4-ethoxy-6-nitroquinazoline (VIII) obtained in the presence of a nickel catalyst under normal conditions or under pressure at room temperature. In the hydrogenation of VIII under normal conditions, in addition to the amine II, we isolated 4-ethoxy-6-azoquinazoline (IX).

All the compounds obtained were tested for tuberculostatic activity by T. N. Zykova in the Laboratory of Chemotherapy of the All-Union Chemico-Pharmaceutical Scientific Research Institute, headed by G. N. Pershin. The results of the tests indicated that the greatest tuberculostatic activity was possessed by N-(p-propoxyphenyl)-N'-(4-ethoxyquinazolyl-6)-thiourea and its methiodide (4 μg/ml). However, with serum the activity is sharply reduced (250, 1000 μg/ml).

EXPERIMENTAL SECTION

6-Nitro-4-ethoxyquinazoline (VIII). To a solution of sodium ethylate (0.76 g of sodium and 200 ml anhydrous alcohol) we added 6.3 g of 4-chloro-6-nitroquinazoline, produced according to [7], mp 129-130° [7, 8], boiled for 0.5 h, cooled, and poured out into water. The yellow precipitate was filtered off and washed with water to a neutral pH. Yield 4.42 g of VIII (67%) with mp 121-122° (from 50% alcohol), R_f ~0.88 (chloroform—2% methanol), ν_{NO_2} 3100 cm^{-1}, $\nu_{NO_2}^{alk}$ 1500 cm^{-1}. Found, %: C 54.42; H 4.17; N 19.68. $C_{10}H_9N_3O_3$. Calculated, %: C 54.79; H 4.14; N 19.63.

4-Ethoxy-6-aminoquinazoline (II). A. A solution of 3.26 g VIII in 400 ml of alcohol was hydrogenated in the presence of nickel for 1.5 h. After being evaporated under vacuum, the residue was crystallized from alcohol. Yield 0.36 g of 4-ethoxy-6-azoquinazoline (IX) with mp 252-253° (after two crystallizations from alcohol), R_f ~ 0.80 (chloroform—2% methanol), $\nu_{C=C}$ 1630 cm^{-1}, $\nu_{N=N}$ 1580 cm^{-1} $\nu_{C=N}$ 1500 cm^{-1}. Found, %: C 64.24; H 5.00; N 22.52. $C_{20}H_{18}N_6O_2$. Calculated, %: C 64.14; H 4.85; N. 22.46.

The alcohol mother liquor from the production of IX was evaporated under vacuum and the residue crystallized from benzene. Yield 1.61 g (57.1%) of II with mp 164-165°, R_f ~ 0.51 (chloroform— 2% methanol), ν_{HN_2} 3200 cm^{-1}, $\nu_{C=O}$ 1700, 1590, 1510 cm^{-1}. Found, %: C 63.30; H 5.77; N 22.21. $C_{10}H_{11}N_3O$.
C = N, δ NH
Calculated, %: C 63.47; H 5.87; N 22.21.

Dihydrochloride of II—mp 249-251° (dec.). Found, %: C 26.93. $C_{10}H_{11}N_3O \cdot 2HCl$. Calculated, %: Cl 27.05.

Picrate of II—mp 221-223° (dec.). Found, %:N 20.15. $C_{10}H_{11}N_3O \cdot (NO_2)_3C_6H_2OH$. Calculated, %: N 20.09.

B. A solution of 20.5 g VIII in 18 ml of alcohol was hydrogenated in the presence of Raney nickel at a pressure of 70 atm until the absorption of hydrogen ceased. After evaporation of the solution under vacuum, the dry residue was crystallized from benzene. Yield 14.9 g (84%) II with mp 164-165°.

4-Ethoxy-6-acetylaminoquinazoline (X). To a solution of 0.95 g II in 60 ml of anhydrous benzene, 0.54 g of acetic anhydride was added at room temperature. The solution was boiled for 2.5 h. After cooling the precipitate was filtered off and washed with ether. Yield 0.94 g (81.5%) X with mp 197-198° (from 25%

alcohol), $R_f \approx 0.30$ (chloroform–2% methanol), ν_{NH} 3270 cm^{-1}, δ_{NH} 1540, $\nu C=O$ 1700, $\nu C=C$, $C=N$ 1600-1510 cm^{-1}. Found, %: C 62.38; H 5.57; N 17.96. $C_{12}H_{13}N_3O_2$. Calculated, %: C 62.32; H 5.67; N 18.17.

4-Ethoxy-6-benzoylaminoquinazoline Hydrochloride (XI). To a solution of 1.89 g II in 100 ml of anhydrous benzene we added 1.45 g of benzoyl chloride and heated for 4 h. After cooling, the colorless precipitate was filtered off and washed with benzene. Yield 3 g (91.4%) XI with mp 312.5-314° (dec., from methanol). Found, %: C 62.19; H 4.97; N 12.47; Cl 10.66. $C_{17}H_{15}N_3O_2 \cdot HCl$. Calculated, %: C 61.91; H 4.89; N 12.74; Cl 10.75.

Reaction of 4-Ethoxy-6-aminoquinazoline (II) with p-Methoxyphenyl Isothiocyanate. To a boiling solution of 2.84 g II in anhydrous acetone we added a solution of 2.84 g p-methoxyphenyl isothiocyanate in acetone. The mixture was boiled for an hour, then evaporated to dryness. The oily residue was triturated with anhydrous ether and 4.28 g of a mixture of substances was obtained, then separated preparatively on plates, using chromatography in a thin layer of aluminum oxide in the system chloroform–1.5% methanol with development in ultraviolet or iodine vapors. The substances were eluted from the aluminum oxide with methanol. The solutions were evaporated under vacuum and 3.48 g (65.5%) N-(p-methoxyphenyl)-N'-(4-ethoxyquinazolyl-6)-thiourea (Ia) (see Table 1) was isolated, ν_{NH} 3200, $\nu C=C$, $C=N$, δNH 1585-1515 cm^{-1}, along with 0.1 g N,N'-(4,4-diethoxyquinazolyl-6)-thiourea (IV) with mp 180-181°, $\nu C=C$, $C=N$, δNH 1585-1510 cm^{-1}, ν_{NH} 3420 cm^{-1}, and 0.57 g 4,4-dimethoxythiocarbanilide (Va) with mp 183-185° (according to literature data [9], mp 186-188°).

The amine II, p-methoxyphenylisothiocyanate (IIIa), p-anisidine with mp 58°, and 4-ethoxyquinazolyl-6-isothiocyanate (VII) were isolated from the ether solution. All the substances, with the exception of VII, were compared with reference spots on the chromatogram.

In the condensation of the amine II with other phenylisothiocyanates (III), the isolation and separation of the mixtures formed were performed analogously to the reaction described above.

The constants, yields, and results of analyses and tests of tuberculostatic activity of all the compounds obtained are cited in Table 1.

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