INTRODUCTION OF DIHYDROPYRAN FRAGMENTS INTO CERTAIN HETEROCYCLES

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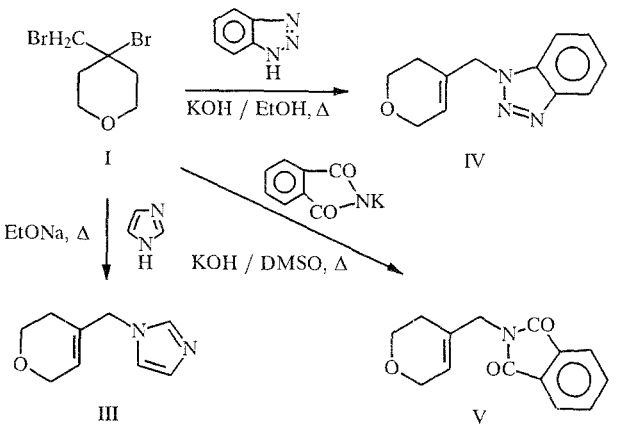
By reaction of 4-bromo-4-bromomethyltetrahydropyran and 3,4-dibromo-4-methyltetrahydropyran with certain heterocyclic compounds, dihydropyran derivatives have been obtained.

4-Bromo-4-bromomethyltetrahydropyran (I) and 3,4-dibromo-4-methyltetrahydropyran (II), which are readily obtained by the bromination of the accessible 4-methylenetetra- and 4-methyl-5,6-dihydro-2H-pyrans, are convenient synthones for the introduction of dihydrogenated rings into phenols [1] and also into aliphatic [2] and aromatic [3, 4] amines.

In the work reported here, we utilized the synthetic possibilities of the bromides I and II for the modification of various heterocyclic compounds. We found that when N- or S-nucleophilic centers are present in the side chain of these compounds, the reaction proceeds just as readily as with aniline, upon refluxing in excess triethylamine [3, 4] or in a mixture with DMF to improve solubility.



For the interaction of the dibromide I or II with compounds in which such a nucleophilic center is located directly in the ring, stronger bases must be used, in particular alcoholates or solid caustic in alcohol (for example, in the reaction of I or II with benzotriazole).

The first stage in the convenient synthesis of primary amines by the Gabriel reaction includes nucleophilic substitution of the halogen atom by the action of potassium phthalimide. In the case of the bromides I and II, in carrying out this reaction we used various solvents (DMF, EtOH, MeCN, MEK, DMSO) and various basic reagents (K_2CO_3, AcONa, Et_3N, KOH). The expected imides V and X were obtained successfully in the DMSO/KOH system, with respective yields of 41% and 19%.

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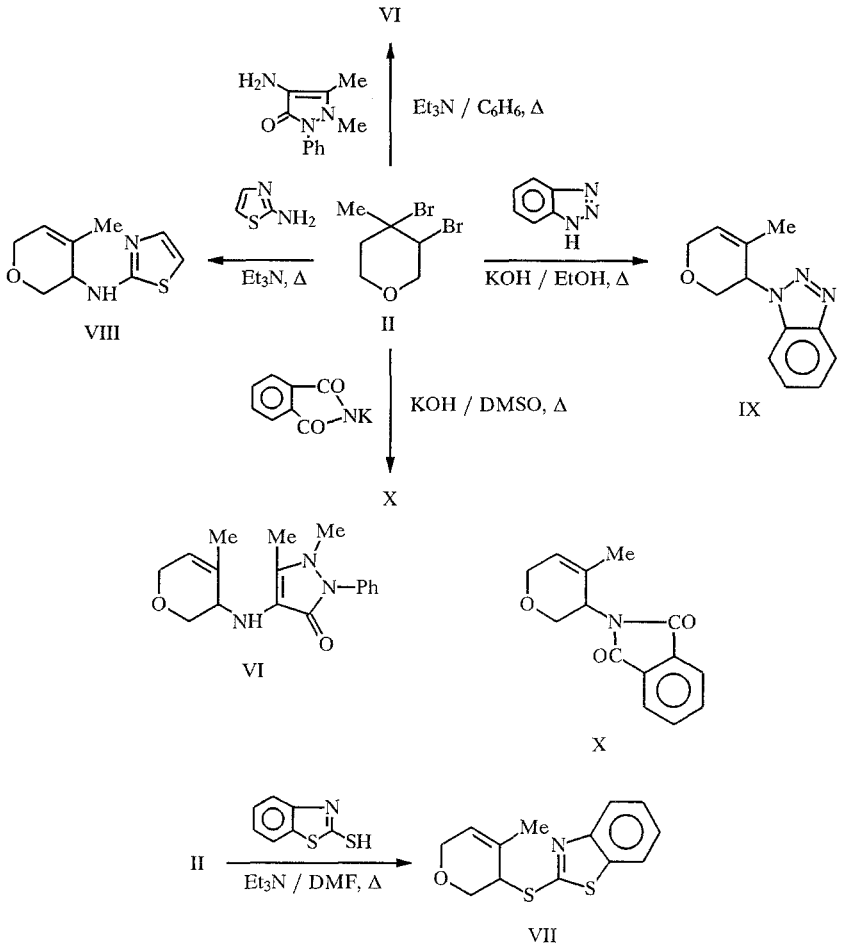

Since phenothiazine derivatives are of great interest in the search for new biologically active substances, we investigated the possibility of synthesizing new compounds of this series, containing pyran fragments, by using the bromides I and II and also by cyclization of 4-methyl-5-(N,N-diphenylamino)-5,6-dihydro-2H-pyran by sulfur in the presence of iodine (known conditions for obtaining phenothiazines); however, these attempts were unsuccessful.

EXPERIMENTAL

The PMR spectra were recorded in a Tesla BS-487C instrument (80 MHz), internal standard HMDS. The TLC was performed with Silufol UV-254 plates, eluent 10:1 benzene–alcohol. For the column chromatography we used Al_2O_3, activity grade II according to Brockman.

The elemental analyses of the compounds for C, H, and N were in agreement with the calculated compositions.

4-Methyl-5(benzotriazolyl-1)-5,6-dihydro-2H-pyran (IX). A mixture of 1.43 g (1.2 mmoles) of benzotriazole, 3 g (1.2 mmoles) of the dibromide II, and 1.45 g (20 mmoles) of KOH in 30 ml of absolute alcohol was refluxed for 6 h. After cooling, the reaction mass was treated with ether and dried with $CaCl_2$; the ether was driven off, and the residue was chromatographed (eluent 1:3 ethyl acetate–hexane); obtained 1.1 g (43%) of the product IX, mp 80°C, R_f 0.8. PMR spectrum (δ, ppm, CCl_4): 1.65 (3H, s, CH_3); 4.0-4.3 (4H, m, CH_2-O-CH_2); 5.3 (1H, m, N–CH); 5.9 (1H, s, CH=C); 7.1-8.0 (4H, m, C_6H_4).

Compounds III and IV were synthesized analogously.

4-(Imidazolyl-1)methyl-5,6-dihydro-2H-pyran (III). Oil, R_f 0.42. PMR spectrum (δ, ppm, $CDCl_3$): 2.01 (2H, m, CH_2-N); 3.6-4.16 (6H, m, CH_2-O-CH_2, CH_2); 5.6 (1H, s, CH=C); 7.1 (2H, s, CH=CH); 7.7 (1H, s, CH=N).

4-(Benzotriazolyl-1)methyl-5,6-dihydro-2H-pyran (IV). Yield 18%, mp 83°C, R_f 0.84. PMR spectrum (δ, ppm, $CDCl_3$): 2.0 (2H, s, CH_2-N); 3.78-5.29 (6H, m, CH_2-O-CH_3, CH_2=C); 5.3 (1H, m, CH=C); 7.34-7.99 (4H, m, C_6H_4).

Compounds VI-VIII were obtained by condensation of the dibromide II with amines in benzene or dimethylformamide in the presence of triethylamine, or in triethylamine alone, as described in [4].

4-Methyl-5-(4-antipyryl)amino-5,6-dihydro-2H-pyran (VI). Yield 45%, yellow oil, R_f 0.18. PMR spectrum (δ, ppm, $CDCl_3$): 1.5 (3H, s, $N-CH_3$); 1.8 (3H, s, 3H); 3.0 (3H, s, $CH_3-C=C$); 3.8-4.2 (6H, m, CH, CH_2OCH_2, NH); 5.5 (1H, s, CH=C); 7.0-7.8 (5H, m, C_6H_5).

4-Methyl-5-(benzothiazolyl-2)thio-5,6-dihydro-2H-pyran (VII). Yield 36%, mp 61°C, R_f 0.97. PMR spectrum (δ, ppm, CCl_4): 1.5 (3H, s, CH_3); 4.0-4.4 (4H, m, CH_2OCH_2); 5.3 (1H, m, CH=C); 4.8 (1H, s, CH−S); 7.1-8.0 (4H, m, C_6H_4).

4-Methyl-5-(thiazolyl-2)amino-5,6-dihydro-2H-pyran (VIII). Yield 30%, oil, R_f 0.5. PMR spectrum (δ, ppm, $CDCl_3$): 1.6 (3H, s, CH_3); 3.5-4.1 (5H, m, NH, CH_2OCH_2); 4.6 (1H, m, CH−N); 5.6 (1H, s, CH=C); 6.3-7.1 (2H, m, CH=CH).

4-Methyl-5-phthalimido-5,6-dihydro-2H-pyran (X). A mixture of 20 mmoles of potassium phthalimide, 20 mmoles of the dibromide II, and 40 mmoles of KOH in 40 ml of DMSO was refluxed for 3 h, after which the cooled oil was poured onto ice. The resulting precipitate was filtered off, washed with water, dried, and purified chromatographically. Yield 19%, mp 87°C, R_f 0.82. PMR spectrum (δ, ppm, $CDCl_3$): 1.5 (3H, s, CH_2); 3.8-4.2 (4H, m, CH_2OCH_2); 4.8 (1H, m, CH−N); 5.6 (1H, s, CH=C); 7.6-7.9 (4H, m, C_6H_4).

4-Phthalimidomethyl-5,6-dihydro-2H-pyran (V) was obtained in the same manner as X. Yield 41%, mp 67°C, R_f 0.83. PMR spectrum (δ, ppm, $CDCl_3$): 2.0 (2H, m, CH_2-N); 3.6-4.1 (6H, m, CH_2OCH_2, CH_2); 5.3 (1H, s, CH=C); 7.6-7.9 (4H, m, C_6H_4).

4-Methyl-3-diphenylamino-5,6-dihydro-2H-pyran was obtained by condensation of the dibromide II with diphenylamine in triethylamine. Yield 33%, mp 96°C. PMR spectrum (δ, ppm, $CDCl_3$): 1.56 (3H, s, CH_3); 3.4-4.6 (5H, m, CH_2OCH_2, CH−N); 6.5-7.0 (10H, m, C_6H_5).

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