STUDIES IN THE IMIDAZOLE SERIES

LXXXVI.* SYNTHESIS OF DIHYDRO AND TETRAHYDRO DERIVATIVES OF IMIDAZOPYRIMIDONES AND IMIDAZOQUINAZOLINES

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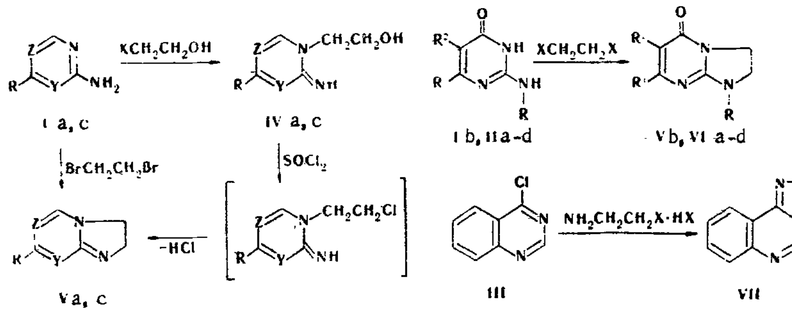
Methods were developed for the synthesis of dihydro and tetrahydro derivatives of imidazo-[1,2-a]- and imidazo[1,2-c]pyrimidine and imidazo[2,1-b]-5-quinazolone from 2-amino- and 4-aminopyrimidines, 2-amino-4-quinazolones, and β-haloethanols or 1,2-dihaloethanes. Dihydroimidazo[1,2-c]quinazoline, which was also obtained by cyclization of 4-(β-hydroxyethylamino)-quinazoline, was synthesized by reaction of 4-chloroquinazoline with β-haloethylamines.

It is known that dihydro and tetrahydro derivatives of imidazopyrimidines and imidazoquinazolines have biological activity [2-4], but the methods used to synthesize them have not been adequately studied.

We have shown that 2-amino- (Ia,b) and 4-aminopyrimidines (Ic) react with ethylene halohydrins to give β-hydroxyethyl-substituted (at the ring nitrogen atom) aminopyrimidines (IVa-c). The latter on heating with thionyl chloride are converted to β-chloroethylpyrimidines, which are readily cyclized in alkaline media to the corresponding derivatives of dihydro- (Va,c) and tetrahydroimidazopyrimidines (Vb). 1-(p-Tolyl)-1,2,3,5-tetrahydroimidazo[2,1-b]-5-quinazolone (VIc) was synthesized under similar conditions from 2-(p-tolylamino)-4-quinazolone. The synthesis of the above systems can also be realized in one step by reaction of aminopyrimidines (Ia-c) and 2-amino-4-quinazolones (IIa-e) with 1,2-dihaloethanes.



X=Cl, Br; Ia, IVa Z=CH, Y=N, R=H; Ib, Vb R=C_6H_5, R^1=CH_3, R^2=H; Ic, IVc Z=N, Y=CH, R=OCH_3; IIa–d, VIa–d R^1R^2=–CH=CH–CH=CH–, a R=H, b R=C_6H_5, c R=p-$CH_3C_6H_4$, d R=p-ClC_6H_4.

4-(β-Chloroethylamino)quinazoline, which is converted to 2,3-dihydroimidazo[1,2-c]quinazoline (VII) on treatment with 10% sodium hydroxide solution, was obtained by heating 4-(β-hydroxyethylamino)quinazoline with thionyl chloride or phosphorus oxychloride. Quinazoline VII is also formed in the reaction of 4-chloroquinazoline (III) and β-haloethylamine hydrohalides in the presence of sodium bicarbonate.

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*See [1] for communication LXXXV.

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The IR spectra of IVa-d contain absorption bands of associated NH and OH groups at 3100-3380 cm^{-1}. The presence of absorption bands at 1670-1720 cm^{-1} in the spectra of IVb,d indicates that they exist in the oxo form in the solid state. Except for VIa, for which a broad absorption band is observed at 3280-3480 cm^{-1} (NH), the characteristic absorption bands of the NH and OH groups are absent in the spectra of V-VII.

EXPERIMENTAL

The IR spectra of mineral oil pastes of the compounds were recorded with a UR-20 spectrometer.

1-(β-Hydroxyethyl)-2-imino-1,2-dihydropyrimidine (IVa) Hydrobromide. A solution of 9.5 g (0.1 mole) of amine Ia and 50.7 g (0.11 mole) of ethylene bromohydrin in a mixture of 10 ml of anhydrous dimethylformamide (DMF) and 40 ml of butanol was refluxed for 9 h, after which the solution was cooled, and the resulting precipitate was removed by filtration and washed with ether to give 17.6 g (80%) of the hydrobromide of IVa as colorless crystals with mp 183-185° (dec., from isopropyl alcohol). Found: C 35.2; H 5.1; Br 39.4; N 20.8%. $C_6H_9N_3O \cdot HBr$. Calculated: C 35.3; H 4.9; Br 39.2; N 20.6%.

1-(β-Hydroxyethyl)-2-phenylamino-4-methyl-6-oxo-1,6-dihydropyrimidine (IVb). A solution of 4.02 g (0.02 mole) of 2-phenylamino-4-hydroxy-6-methylpyrimidine (Ib) and 4.0 g (0.05 mole) of ethylene chlorohydrin in 10 ml of anhydrous DMF was refluxed for 6 h, after which the solvent was vacuum evaporated to dryness. The dry residue was dissolved in water, and the solution was made alkaline to pH 7-8 with a saturated sodium bicarbonate solution. The resulting precipitate was removed by filtration and washed with water to give 3.6 g (76%) of colorless crystals with mp 92° (from 20% methanol). Found: C 63.8; H 6.3; N 17.0%. $C_{13}H_{15}N_3O_2$. Calculated: C 63.7; H 6.2; N 17.1%.

3-(β-Hydroxyethyl)-6-methoxy-4-imino-3,4-dihydropyrimidine (IVc) Hydrobromide. This compound was obtained in 84% yield from amine Ic and ethylene bromohydrin by a method similar to that used to prepare the hydrobromide of IVa, but ethanol was used as the solvent. The colorless crystals had mp 122-124° (from dioxane). Found: C 33.3; H 4.8; N 16.7%. $C_7H_{10}N_3O_2 \cdot HBr$. Calculated: C 33.3; H 4.8; N 16.8%.

2-(p-Tolylamino)-3-(β-hydroxyethyl)-4-quinazolone (IVd). A 2.5-g (0.01 mole) sample of 2-(p-tolylamino)-4-quinazolone (IIe) and 0.8 g (0.01 mole) of ethylene chlorohydrin were added to a solution prepared from 0.01 g-atom of sodium metal and 10 ml of methanol, after which the mixture was refluxed for 4 h. The precipitate was removed by filtration and washed with water and ether to give 2.1 g (71%) of colorless crystals with mp 260-261° (dec., from dioxane). Found: N 14.3%. $C_{17}H_{17}N_3O_2$. Calculated: N 14.3%.

2,3-Dihydroimidazo[1,2-a]pyrimidine (Va) Hydrohalides. A) A mixture of 2.2 g (0.01 mole) of hydrobromide IVa and 10 ml of thionyl chloride was refluxed for 2 h, after which the thionyl chloride was removed by vacuum distillation, 40 ml of 10% sodium hydroxide solution was added, and the mixture was refluxed for 2 h. The solvent was removed by vacuum distillation, and the dry residue was extracted twice with 20-ml portions of boiling acetone. The extract was filtered, 1 ml of 35% hydrochloric acid was added to the filtrate, and the precipitate was removed by filtration and washed with ether to give 1.5 g (93%) of colorless crystals of Va hydrochloride with mp 278-280° (mp 280° [5]).

B) A solution of 2.85 g (0.03 mole) of amine Ia and 16.9 g (0.09 mole) of 1,2-dibromoethane in a mixture of 5 ml of anhydrous DMF and 15 ml of butanol was refluxed for 6 h, after which it was cooled, and the precipitate was removed by filtration and washed with ether to give 5.8 g (90%) of Va hydrobromide as colorless crystals with mp 281-282° (dec., from butanol). Found: Br 37.2%. $C_6H_7N_3 \cdot HBr$. Calculated: Br 37.3%.

1-Phenyl-5-oxo-7-methyl-1,2,3,5-tetrahydroimidazo[1,2-a]pyrimidine (Vb). A) This compound was obtained from IVb by the method used to prepare imidazopyrimidine Va (method A). The yield of colorless crystals with mp 160-162° (from water) was 90%. Found: C 68.5; H 5.7; N 18.2%. $C_{13}H_{13}N_3O$. Calculated: C 68.7; H 5.8; N 18.5%.

B) A solution of 2.01 g (0.01 mole) of amine Ib and 5.6 g (0.03 mole) of dibromoethane in 10 ml of DMF was refluxed for 3 h, after which it was cooled and poured into water. The aqueous mixture was neutralized with sodium bicarbonate solution, and the liberated oily mass was separated and dissolved by heating in 20% methanol (in the presence of charcoal). The solution was filtered, the filtrate was cooled, and the precipitate was removed by filtration and washed with cold water to give 1.2 g (52%) of product.

7-Methoxy-2,3-dihydroimidazo[1,2-c]pyrimidine (Vc). A) A solution of 1.0 g (3 mmole) of IVc hydrobromide in 5 ml of thionyl chloride was refluxed for 4 h, after which the thionyl chloride was removed by vacuum distillation, 10 ml of 10% alcoholic sodium hydroxide solution was added to the residue, and the mixture was refluxed for 2 h. It was then cooled and diluted with 20 ml of water, and the precipitate was removed by filtration and washed with water to give 0.4 g (66%) of colorless crystals with mp 135-137° (from ethanol). Found: C 55.7; H 6.1; N 27.4%. $C_7H_9N_3O$. Calculated: C 55.6; H 6.0; N 27.8%.

B) A mixture of 2.5 g (0.022 mole) of amine Ic, 9.4 g (0.05 mole) of dibromoethane, 10 ml of butanol, and 2 ml of DMF was refluxed for 5 h, after which it was cooled, and the precipitated Vc hydrobromide was removed by filtration, washed with ether, and dissolved in water. A saturated sodium bicarbonate solution was added, and the precipitate was removed by filtration and washed with water to give 2.26 g (75%) of product.

1,2,3,5-Tetrahydroimidazo[2,1-b]-5-quinazolones (VIa-d). A) A mixture of 2.72 g (0.01 mole) of amine IId, 0.02 mole of dibromo-or dichloroethane, and 3.26 g (0.04 mole) of sodium hydrocarbonate in 10 ml of DMF was refluxed for 4 h, after which it was cooled and diluted with 30 ml of water. The precipitate was removed by filtration and washed with water to give colorless crystals of VId with mp 192-194° [dec., from DMF-water (1 : 1)] in 90% yield. Found: C 64.3; H 3.9; Cl 11.8; N 14.3%. $C_{16}H_{12}ClN_3O$. Calculated: C 64.8; H 3.8; Cl 11.9; N 14.2%.

Compounds VIa-c were similarly obtained as white crystals with mp 226-228, 164-165, and 198.5-199° (in agreement with the literature melting points [6]), respectively, in 89, 87, and 88% yields.

B) A mixture of 2.95 g (0.01 mole) of IVd and 10 ml of thionyl chloride was refluxed for 2 h, after which the thionyl chloride was removed by vacuum distillation. A total of 10 ml of 10% alcoholic sodium hydroxide solution was added to the residue, and the mixture was refluxed for 10 min. It was then cooled, and the precipitate was removed by filtration and washed with water to give 2.07 g (75%) of VIc.

2,3-Dihydroimidazo[1,2-c]quinazoline (VII). A) A mixture of 3.3 g (0.02 mole) of III, 0.02 mole of β-chloro(bromo)ethylamine hydrochloride (hydrobromide), and 5.04 g (0.06 mole) of sodium bicarbonate in 20 ml of absolute ethanol was refluxed for 6 h. The precipitated inorganic salt was removed by filtration, the filtrate was vacuum evaporated, and the residue was recrystallized from water in the presence of activated charcoal to give colorless crystals with mp 128-130° [from water; mp 119-123° (from water) [7]] in 71-79% yield. Found: C 70.0; H 5.4; N 24.2%. $C_{10}H_9N_3$. Calculated: C 70.1; H 5.3; N 24.5%.

B) Compound VII was also obtained in 70-82% yield by treatment of 4-(β-hydroxyethylamino)quinazoline [8] with thionyl chloride or phosphorus oxychloride under the conditions described for the preparation of Va (method A).

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