6. N. N. Kundo and N. P. Keier, Kinet. Katal., 11, 91 (1970).
7. V. F. Borodkin, V. E. Maizlish, V. A. Fomin, and A. M. Mazgarov, Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol., 22, 413 (1979).
8. A. D. Simonov, N. N. Kundo, E. K. Mamaeva, and L. A. Akimova, Zh. Prikl. Khim., 50, 307 (1977).
9. V. E. Maizlish, T. A. Anan'eva, V. F. Borodkin, A. M. Mazgarov, and V. A. Foman, USSR Inventors' Certificate No. 687,065; Byull. Izobret., No. 35 (1979).
10. V. E. Maizlish, V. F. Borodkin, R. D. Komarov, and A. M. Mazgarov, in: Questions of Kinetics and Catalysis [in Russian], Ivanovo (1978), p. 82.
11. Y. Masao, S. Fukamatsu, A. Yoshio, and T. Hajime, Kogyo Kagaku Zasshi, 67, 1147 (1964); Chem. Abstr., 61, 15895 (1964).
12. M. L. Khidekel' and V. E. Vasserberg, Zh. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol., 22, 73 (1977).
13. I. Dolanský, D. Wagnerová, and I. Veprěk-Šiška, Collect. Czech. Chem. Commun., 41, 2326 (1976).
14. B. D. Berezin, V. N. Klyuev, and A. B. Korzhenevskii, Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol., 20, 170 (1977).

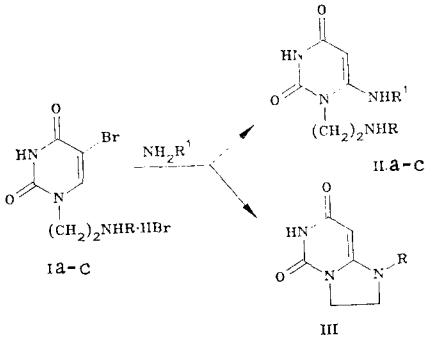
kine-SUBSTITUTION IN THE N-[ω-(5-BROMOURACIL-1-YL)ALKYL]ALKYLAMINE SERIES

I. Zh. Lulle, R. A. Paégle, and M. Yu. Lidak

UDC 547.854.4.859.3

In the reaction of N-[2-(5-bromouracil-1-yl)ethyl]alkylamines with alkylamines at 40°C kine-substitution takes place with the formation of N-[2-(6-alkylaminouracil-1-yl)ethyl]alkylamines.

As we have reported, the reaction of N-[ω-(5-bromouracil-1-yl)alkyl]alkylamines (Ia-c) with amines of different nucleophilicities (propylamine, butylamine, morpholine) at the boiling point of the reaction mixture takes place with the formation of bicyclic systems [1, 2]. The aim of the present investigation was to study the influence of the temperature on the course of the reaction. After mixtures of compound (Ia) with propylamine and butylamine and of (Ib) with butylamine had been kept at 40°C for 2 h, the main reaction products isolated were the N-[2-(6-alkylaminouracil-1-yl)ethyl]alkylamines (IIa-c), respectively.



I a) $R=C_3H_7$; b) $R=C_4H_9$; c) $R=CH_2C_6H_5$;
II a) $R=R^1=C_3H_7$; b) $R=C_3H_7$, $R^1=C_4H_9$;
c) $R=R^1=C_4H_9$

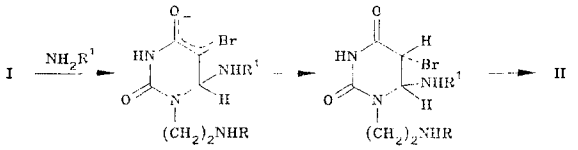
Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1260-1261, September, 1984. Original article submitted November 9, 1983.

In the PMR spectrum of each of compounds (IIa-c) a narrow signal was observed in the 4.5-4.6 ppm region due to the 5-H proton of the pyrimidine ring, while signals at 7.8 and 6.5 ppm could be assigned to the protons of the 6-NH group of the pyrimidine ring and to the amine group of the alkyl chain at $N_{(1)}$ of the pyrimidine ring, respectively. The ratio of the integral intensities of the signals of the 5-H protons and of those of the methylene groups indicated the presence of two aliphatic chains in each molecule.

In the UV spectrum of each of compounds (IIa-c), an absorption maximum (pH 7, in water) was observed at 275 nm, i.e., shifted in the short-wave direction by 5 nm in comparison with the initial compounds (Ia, b).

The reaction of N-[2-(5-bromouracil-1-yl)ethyl]benzylamine (Ic) with propylamine and butylamine led to intromolecular cyclization with the formation of 6-benzyl-4,5-dihydroimidazo[1,2-c]pyrimidine-2,8-dione (III), which we have isolated previously [2]. Apparently, the benzyl group sterically opposes the nucleophilic attack of the amine on $C_{(6)}$ of the uracil ring.

Compounds (Ia-c) did not react with morpholine under the same conditions, and in all cases the initial compound was recovered.



It may be assumed that the initial act of the reaction is an attack of the nucleophile — the amine — on $C_{(6)}$ of the pyrimidine the addition of a proton to $C_{(5)}$, and the formation of a 5,6-dihydropyridine from which, after the splitting out of hydrogen bromide, a N-[-2-(6-alkylamino-uracil-1-yl)ethyl]alkylamine is produced.

The kine-substitution reaction, consisting of the addition of a nucleophile in the ortho position with respect to the leaving group, has been littled studied among the 5-halopyrimidine bases of nucleic acids. There are a few reports that in the reactions of 5-bromo-1,3-dimethyluracil, 5-bromocytidine, and 5-bromouridine with potassium cyanide in DMFA at room temperature the corresponding 6-cyano derivatives are formed [3-5]. It must be recalled that, on being heated with potassium cyanide in DMFA, 5-bromouridine and 5-bromocytidine form the corresponding 5',6'-cyclonucleosides as the result of the nucleophilic attack of the 5'-OH group of the $C_{(6)}$ atom of the pyrimidine ring [6]. The cyclization of N-[ω-(5-bromouracil-1-yl)alkyl]alkylamines [2] and of (5-bromouracil-1-yl)-α-alanine that we have observed [1], in which, under the influence of the amines of the medium, on heating there is a nucleophilic attack of the amino group of the aliphatic chain of the 5-bromouracil derivative on the $C_{(6)}$ atom of the pyrimidine ring, may be regarded as a peculiar case of kine-substitution in the pyrimidine series.

EXPERIMENTAL

PMR spectra were taken on a Bruker instrument (360 MHz) in DMSO-D_6 with HMDS as internal standard. UV spectra were recorded on a Spectromom 204 spectrophotometer. Melting points were determined on a Boëtius microstage. The individuality of the compounds obtained was checked with the aid of TLC on Silufol UV-254 plates in the isopropanol—25% ammonia—water (7:1:2) system.

N-[2-(6-Propylaminouracil-1-yl)ethyl]propylamine (IIa). A mixture of 0.39 g (0.011 mmole) of the hydrobromide (Ia) and 6 ml of propylamine was kept at 40°C for 2 h. The reaction mixture was evaporated in vacuum to dryness and the residue was washed with ether. The resinous residue obtained was treated with cold water, and the precipitate was filtered off, washed with cold acetone, and recrystallized from water. Yield 0.17 g (60%), mp 206-207°C; R_f 0.55. UV spectrum (in water); λ_{max} 275 nm (log ε 5.6). PMR spectrum, ppm: 10.95 (3-H, s, 1 H); 7.8 (N''H, m, 1 H); 6.5 (N'H, m, 1 H); 4.51 (5-H, s, 1 H); 0.86 (CH_3, m 6 H). Found, %: C 56.3, H 8.9, N 21.9. $C_{12}H_{22}N_4O_2$. Calculated, %: C 56.2, H 8.7, N 22.1.

N-[2-(6-Butylaminouracil-1-yl)ethyl]propylamine (IIb) was obtained from the amine (Ia) and butylamine in a similar manner to compound (IIa). Yield 65%. mp 203-204°C; R_f 0.50. UV spectrum (pH 7): λ_{max} 275 nm (log ε 5.4). PMR spectrum, ppm: 2.95 (3-H, s, 1H), 7.7 (N''H,

m, 1H), 6.5 (N'H, m, 1 H), 4.54 (5-H, s, 1 H), 0.89 (CH_3, m, 6H). Found, %: C 57.9, H 9.1, N 20.7. $C_{13}H_{24}N_4O_2$. Calculated, %: C 58.2, H 9.0, N 20.9.

N-[2(6-Butylaminouracil-1-yl)ethyl] butylamine (IIc) was obtained from the amine (Ib) and butylamine in a similar manner to (IIa). Yield 55%. mp 205-206°C; Rf 0.52. UV spectrum (pH 7): λ_{max} 275 nm (log ε 5.3). PMR spectrum, ppm: 10.98 (3-H, s, 1H), 7.8 (N"H, m, 1 H), 6.54 (N'H, m, 1 H), 4.60 (5-H, s, 1 H), 0.90 (CH_3, m, 6H). Found, %: C 59.3, H 9.5, N 19.5. $C_{14}H_{26}N_4O_2$. Calculated, %: C 59.6, H 9.2, N 19.9.

LITERATURE CITED

1. R. A. Paégle, I. Zh. Lulle, V. É. Krishane, I. B. Mazheika, É. É. Liepin'sh, and M. Yu. Lidak, Khim. Geterotsikl. Soedin., No. 4, 538 (1980).
2. I. Zh. Lulle, R. A. Paégle, M. Yu. Lidak, and I. B. Mazheika, Khim. Geterotsikl. Soedin., No. 4, 535 (1982).
3. A. Matsuda, H. Inoue, and T. Ueda, Chem. Pharm. Bull., 26, 2340 (1978).
4. H. Inoue and T. Ueda, Chem. Pharm. Bull., 26, 2657 (1978).
5. S. Senda, K. Hirota, and T. Asao, J. Org. Chem., 40, 353 (1975).
6. T. K. Bradshaw and D. W. Hutchinson, Chem. Soc. Rev., 6, 43 (1977).

FORMYLATION OF 4-ARYL-2,3-DIHYDRO-1H-1,5-BENZODIAZEPIN-2-ONES

Z. F. Solomko, V. N. Proshkina, V. I. Avramenko, I. A. Plastun, and N. Ya. Bozhanova

UDC 547.892

The formylation of 8-chloro- and 8-methoxy-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-ones with the Vilsmeier reagent leads to 3-dimethylaminomethylene derivatives which, in the case of the 8-chloro derivative, have been converted by hydrolysis in acetic acid into 8-chloro-3-formyl-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-ones.

The formulation of lactams under the conditions of the Vilsmeier reaction takes place with the production of N-formyl [1], chloroformyl [2, 3], or dimethylaminoalkylidene [3, 4] derivatives. A single example of the formylation of 4-phenyl-2,3-dihydro-1-H-1,5-benzodiazepin-2-one (I) with N-methylpyrrolidone and phosphorus oxychloride has been described. It led to 3-(N-methylpyrrolidin-3-ylidene)-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepinone [5].

The present investigation was devoted to a study of the formylation of the benzodiazepinone derivatives (Ia, b) containing substituents of different natures in the fused-on benzene ring.

On reacting with the Vilsmeier complex, 8-chloro-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one formed 8-chloro-3-dimethylaminomethylene-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (IIa), the yield of which rose considerably with an increase in the amount of formylating agent from 1 to 4 moles. The formylation of 8-methoxy-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (Ib) could be achieved only by using 6 moles of the Vilsmeier reagent, and then the yield did not exceed 30%. When a smaller amount of reagent was used, the formation of the 3-dimethylaminomethylene derivative (IIb) was detected only chromatographically, together with the initial substance.

The IR spectra of compounds (IIa, b) had absorption bands of the stretching vibrations of NH and C=O groups in the 3135-3230 and 1667 cm^{-1} regions, and also absorption bands in the 1116, 1060, and 944 cm^{-1} regions that are characteristic for the vibrations of a dimethylamino group [6].

Dnepropetrovsk State University.

Translated from Khimiya Geterotsiklicheskaya Soedinenii, No. 9, pp. 1262-1265, September, 1984. Original article submitted September 19, 1983; revision submitted February 10, 1984.

0009-3122/84/2009-1035$08.50