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REACTION OF THE SODIUM SALTS OF SOME HYDROXYPYRIMIDINES WITH α,ω-DIHALOALKANES. COMMUNICATION 4. SYNTHESIS OF N-(ω-HALOALKYL)URACILS

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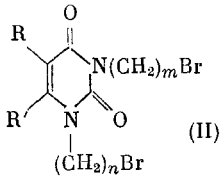
UDC 542.91:547.854-38:547.412.11

We have shown previously [1] that under some conditions uracil salts react with α,ω-dihaloalkanes to give 1,3-bis(ω-haloalkyl)uracils (I). We describe here the preparation of 1-(ω-alkyl)-3-(ω-bromoalkyl')uracils (II), in which the nitrogen atoms of the pyrimidine ring carry alkyl radicals with methylene chains of different lengths, and some other N-(ω-bromoalkyl)-uracils.

In order to synthesize (II), a study was made of the reaction between the sodium salts of 1(3)-(ω-bromoalkyl)uracils (III) with α,ω-dibromoalkanes (IVa-e) in which n = 3-6 and 10. Anions (III) containing four or less methylene groups in the side chain readily undergo intramolecular cyclization to bicyclic compounds [2, 3]. The synthesis of (II) therefore requires the use of strictly controlled conditions which prevent the occurrence of cyclization. Considerable decreases in the yields of bicyclic and oligomeric products are achieved when the sodium salts (III) are obtained in dry n-butanol at 10-15°C, followed by rapid precipitation of the salt with a mixture of light petroleum and ether, and azeotropic removal of the n-butanol. Furthermore, in the reaction of the salt (III) with (IV) it is necessary to use a 6-7 molar excess of (IV), DMF as solvent, and the observance of a temperature regime. Under these conditions, hitherto unknown compounds (II) were obtained in 62-85% yields. These compounds were obtained as clear liquids which were readily soluble in ether, benzene, and chloroform. They were purified by chromatography on alumina columns. The IR spectra of (II) showed two strong absorption bands in the νC=O region (1650-1680 and 1700-1710 cm^{-1}) characteristic of all 1,3-disubstituted uracils.



(II)

R = H, R′ = Me, $m = 4$, $n = 5$ (a); R = H, R′ = Me, $m = 5$, $n = 4$ (b); R = R′ = H, $m = 3$, $n = 5$ (c); R = H, R′ = Me, $m = 4$, $n = 3$ (d); R = NO_2, R′ = Me, $m = 4$, $n = 5$ (e); R = H, R′ = Me, $m = 4$, $n = 6$ (f).

Studies of the reaction of the sodium salts of uracils with (IV) have afforded several new (I) and (III). For instance, alkylation of the disodium salt of 5-fluorouracil with 1,4-dibromobutane (IVb) has given 1,3-bis(ω-bromobutyl)-5-fluorouracil (Ia). Reaction of the disodium salt of 6-methyluracil (V) with 1,6-dichlorohexane has given 1,3-bis-(ω-chlorohexyl)6-methyluracil (Ib) and 6-methyl-3-(ω-chlorohexyl)uracil (IIIa). Reaction of the monosodium salt of (V) with an excess of (IVe) in DMF results in the formation of 3-(ω-bromodecyl)-6-methyluracil (IIIb) and 1,3-bis(ω-bromodecyl)-6-methyluracil (Ic) in yields of 32 and 17%, respectively. Reaction of the disodium salt of (V) with (IVe) gave the same products, but with the ratios of yields reversed (10 and 50%, respectively). The synthesis of N-(ω-bromodecyl)-6-methyluracils by the reaction between (IVe) and 2,4-bis(trimethylsilyloxy)-6-methylpyri-

A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Branch of the Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 5, pp. 1173-1177, May, 1986. Original article submitted December 24, 1984.

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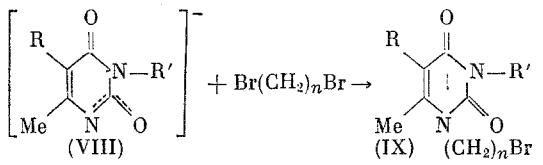
midine (VI) is temperature-dependent. For example, (VI) reacts with a four- to fivefold excess of (IVe) at 145-160°C to give (IIIb), (Ic), and 6-methyl-3-(ω-hydroxydecyl)-uracil (VII) in yields of 19.5, 10, and 1.5%, respectively. At 110°C, this reaction gives (Ic) and a product isomeric with (IIIb), viz., 1-(ω-bromodecyl)-6-methyluracil (IIIc), in yields of 9 and 16%.

Alkylation of the sodium salts of a number of 3,6-disubstituted uracils (VIII) with dibromoalkanes in DMF gives the 1-(ω-bromoalkyl)-6-methyluracils in yields of 35-86%. Similarly, reaction of the sodium salt of 1,6-dimethyl-5-nitrouracil (X) with (IVb) gives 3-(ω-bromobutyl)-1,6-dimethyl-5-nitrouracil (XI). Separation of the reaction mixture obtained in the alkylation of (VIIId) with dibromodecane (IVe) also gave 3,6-dimethyl-1-(ω-hydroxydecyl)uracil (XII) in 4.7% yield.



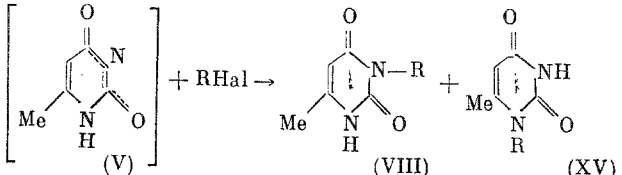
(VIII) (IX)

(VIII): R = H, R′ = CH_2Ph (a); R = H, R′ = Pr-*i* (b); R = H, R′ = Bu-*i* (c); R = H, R′ = Me (d); R = NO_2, R′ = Me (e); R = H, R′ = $CH_2CH=CH_2$ (f).
(IX): R = H, R′ = CH_2Ph, *n* = 4 (a); R = H, R′ = Pr-*i*, *n* = 4 (b); R = H, R′ = Bu-*i*, *n* = 4 (c); R = H, R′ = Me, *n* = 10 (d); R = NO_2, R′ = Me, *n* = 4 (e); R = H, R′ = $CH_2CH=CH_2$, *n* = 4 (f).

Compounds (Ia-c), (IXa-f), and (XI) were clear, viscous oils or crystalline solids which were usually readily soluble in ether, benzene, and chloroform. The IR spectra of these compounds showed strong absorption for νC=O at 1660-1680 and 1695-1720 cm^{-1}, but no absorption at 3100-3600 cm^{-1}. The IR spectra of solid samples of (IIIa-c) showed νNH absorption for the pyrimidine ring (maxima at 3090 and 3100-3200 cm^{-1}) in accordance with their structure. Assignment of substitution to N^1 or N^3 of the pyrimidine ring in monosubstituted uracils was made from the presence or absence of a bathochromic shift of the long-wavelength maximum in the UV spectra of these compounds on changing from an acidic to a basic medium (see the Experimental section) [4-6].

The IR spectra of solid samples of (VII) and (XII) showed νOH absorption at 3520 cm^{-1}. In the case of (VII), the picture at 1600-1750 cm^{-1} was complex. However, the spectrum of a solution of (VII) in chloroform showed only two νC=O bands for the uracil ring (1680 and 1720 cm^{-1}).

Compounds (VIIIb, c) were synthesized by the reaction between the sodium salt of (V) and isopropyl iodide (XIII) or isobutyl bromide (XIV) in DMF at 80-135°C. A mixture of N^1- and N^3-alkylation products was obtained, which was separated by chromatography. No 1,3-bisalkyluracils were detected in the reaction products. It is interesting that in the IR spectra of crystalline samples of (VIIIb, c) doublet bands are seen in the region of CO stretching vibrations (1600-1610, 1640-1645 and 1690-1700, 1720-1725 cm^{-1}), such as has been observed in one modification of 3-(ω-bromoalkyl)-6-methyluracils [2], which are apparently due to differing types of hydrogen bonds in the crystalline lattices of solid samples, since in the IR spectra of solutions of these compounds in dichloromethane no such doublets are seen.



(V) (VIII) (XV)

(VIII): R = Pr-*i* (b); R = Bu-*i* (c); (XV): R = Pr-*i* (a); R = Bu-*i* (b).

EXPERIMENTAL

The IR spectra were obtained on UR-10 and Specord IR-75 spectrophotometers, in the case of solids as suspensions in Vaseline oil, and liquids as films between KBr plates. The UV spectra were obtained on a Specord UV-VIS spectrophotometer. Column chromatography was carried out on grade II neutral alumina. The constants of the compounds obtained are shown in Table 1.

3-(ω-Bromobutyl)-1-(ω-bromopentyl)-6-methyluracil (IIa). To a solution of 0.35 g of sodium in 50 ml of dry n-butanol was added at 10-15°C 4 g of 3-(ω-bromobutyl)-6-methyluracil

TABLE 1

Compound	Yield, %	mp, °C, or n_D^{20}	Found/Calculated, %				Empirical formula
			C	H	N	Br, Cl	
(Ia)	59	1,5520	36,02 36,00	4,44 4,25	6,88 7,00	39,66 40,00	$C_{12}H_{17}FBr_2N_2O_2$
(Ib)	52	1,5206	56,01 56,20	8,06 7,71	7,64 7,71	19,25 19,56	$C_{17}H_{28}Cl_2N_2O_2$
(Ic)	17 * 50 †	Viscous oil	53,49 53,18	7,80 7,86	4,88 4,96	27,93 28,34	$C_{25}H_{44}Br_2N_2O_2$
(IIa)	80	1,5536	41,40 40,92	5,40 5,38	6,66 6,82	38,68 39,02	$C_{14}H_{22}Br_2N_2O_2$
(IIb)	87	1,5495	41,29 40,92	5,26 5,38	6,67 6,82	38,90 39,02	$C_{14}H_{22}Br_2N_2O_2$
(IIc)	79	1,5519	37,92 37,69	4,72 4,76	7,27 7,33	41,76 41,88	$C_{12}H_{18}Br_2N_2O_2$
(IId)	75	1,5589	37,80 37,69	4,74 4,76	7,16 7,33	41,62 41,88	$C_{12}H_{18}Br_2N_2O_2$
(IIe)	62	1,5470	36,94 36,92	4,68 4,61	9,11 9,23	34,96 35,18	$C_{14}H_{21}Br_2N_3O_4$
(IIf)	85	1,5371	42,92 42,45	5,95 5,66	6,46 6,60	37,52 37,73	$C_{15}H_{24}Br_2N_2O_2$
(IIIa)	3,6	121–123	53,68 53,99	6,62 6,95	11,36 11,45	14,45 14,52	$C_{11}H_{17}ClN_2O_2$
(IIIb)	32 * 10 †	118–120	51,79 52,16	7,34 7,30	7,81 8,11	22,81 23,16	$C_{15}H_{25}BrN_2O_2$
(IIIc)	16	89–91	52,47 52,16	7,15 7,30	8,29 8,11	22,86 23,16	$C_{15}H_{25}BrN_2O_2$
(VII)	1,5	142–145	63,97 63,80	9,80 9,28	9,82 9,91	–	$C_{15}H_{26}N_2O_3$
(VIIIb)	8	186–188	57,14 57,14	7,16 7,14	16,87 16,67	–	$C_8H_{12}N_2O_2$
(VIIIc)	9	199–200	59,66 59,34	7,56 7,69	15,19 15,38	–	$C_9H_{14}N_2O_2$
(IXa)	71	65–67	55,02 54,70	5,67 5,41	8,26 7,98	22,62 22,79	$C_{16}H_{19}BrN_2O_2$
(IXb)	79	80–82	47,72 47,52	6,36 6,20	9,14 9,24	26,31 26,40	$C_{12}H_{19}BrN_2O_2$
(IXc)	75	1,5374	48,99 49,21	6,35 6,24	8,77 8,83	25,38 25,24	$C_{13}H_{21}BrN_2O_2$
(IXd)	36	72–74	53,35 53,47	7,99 7,57	8,09 7,79	21,36 22,26	$C_{16}H_{27}BrN_2O_2$
(IXe)	77	79–80	37,51 37,50	4,56 4,38	13,26 13,13	25,30 25,00	$C_{10}H_{14}BrN_3O_4$
(IXf)	77	Viscous oil	47,84 48,70	5,64 5,82	9,30 9,51	–	$C_{12}H_{17}BrN_2O_2$
(XI)	87	1,5702	37,43 37,50	4,36 4,38	12,87 13,13	25,16 25,00	$C_{10}H_{14}BrN_3O_4$
(XII)	4,7	119–124	64,98 64,83	9,46 9,52	9,64 9,44	–	$C_{16}H_{28}N_2O_3$
(XVa)	25	160–162	57,28 57,14	7,23 7,14	17,00 16,67	–	$C_8H_{12}N_2O_2$
(XVb)	35	118–120	59,64 59,34	7,65 7,69	15,32 15,38	–	$C_9H_{14}N_2O_2$

*From (V) monosodium salt.
†From (V) disodium salt.

(XVI). The resulting salt was precipitated from the clear solution with a mixture of light petroleum and ether, and the solid was filtered off, washed with ether, and dried azeotropically with benzene. To the dry salt was added a solution of 21 g of (IVc) in 60 ml of dry DMF, and the mixture was stirred at 45-70°C until the pH reached 7. The solution was filtered, and the DMF and excess (IVc) were distilled off under reduced pressure. The residue was treated with boiling benzene and filtered hot, and the filtrate was concentrated and chromatographed. The column was eluted successively with light petroleum, ether, and benzene. From the ether fractions there was obtained 4.4 g (80%) of (IIa).

Obtained similarly were: 1-(ω-bromobutyl)-3-(ω-bromopentyl)-6-methyluracil (IIb) by the reaction between 3.3 g of 3-(ω-bromopentyl)-6-methyluracil sodium salt and 16.5 g of (IVb), yield 3.5 g (87%), n^{20}_D 1.5495; 1-(ω-bromopentyl)-3-(ω-bromopropyl)uracil (IIc) from 4 g of 1-(ω-bromopentyl)uracil sodium salt and 17 g of (IVa), yield 3.7 g (79%), n^{20}_D 1.5519; 1-(ω-bromopropyl)-3-(ω-bromobutyl)-6-methyluracil (IId) from 3 g of the sodium salt (XVI) and 13 g of (IVa), yield 3 g (75%), n^{20}_D 1.5589; 1-(ω-bromopentyl)-3-(ω-bromobutyl)-6-methyl-5-nitrouracil (IIe) from 8 g of 3-(ω-bromobutyl)-6-methyl-5-nitrouracil sodium salt and 40 g of (IVc), yield 5 g (62%), n^{20}_D 1.5470; and 1-(ω-bromohexyl)-3-(ω-bromobutyl)-6-methyluracil (IIf) from 4 g of (XVI) sodium salt and 21 g of (IVd), yield 5 g (85%), n^{20}_D 1.5371.

Reaction of the Disodium Salt of (V) with 1,6-Dichlorohexane. To 50 g of the disodium salt of (V) in dry DMF was added 227 g of 1,6-dichlorohexane, and the mixture was stirred at 80-100°C until the pH reached 7. The solution was filtered, and the filtrate was evaporated. The residue was treated with bezene, and the solid was filtered off to give 7 g of (V). The benzene filtrate was concentrated to 80 ml and chromatographed. From ether fraction I (800 ml) there was obtained 46.2 g (52%) of (Ib), n^{20}_D 1.5206. Ether fraction II (500 ml) gave 2.5 g (3.6%) of (IIIa), mp 121-123°C (benzene–hexane). UV spectrum [pH, λ_{max}, nm (log ε)]: 2.263 (3.96), 12.282 (4.22).

1,3-Bis(ω-bromobutyl)-5-fluorouracil (Ia) was obtained similarly from 20 g of 5-fluorouracil disodium salt and 200 g of (IVb). The ether fractions gave 22 g (59%) of (Ia), n^{20}_D 1.5520.

Reaction of (V) Monosodium Salt with (IVe). To the sodium salt of (V), obtained from 3.1 g of sodium and 17.1 g of (V) in dry n-butanol, was added 250 ml of dry DMF and 144 g of (IVe), and the mixture was stirred at 40-60°C until the pH reached 7. The solution was evaporated, and the residue was treated with benzene, the solid which separated being filtered off to give 7 g of (V). The benzene filtrate was concentrated and chromatographed. The ether fraction gave 13 g (17%) of (Ic) as a viscous oil, and the chloroform fraction 15 g (32%) of (IIIb), mp 118-120°C (from benzene). UV spectrum [pH, λ_{max}, nm (log ε)]: 7.267 (3.89), 12.282 (4.04).

Obtained similarly were (Ic) and (IIIb) in yields of 38 g (50%) and 4.7 g (10%), respectively, by the reaction between the disodium salt of (V) and (IVe).

Reaction of (VI) with (IVe). a) To 40.3 g of (VI) was added 224 g of (IVe), and the mixture was heated in a stream of argon at 145-160°C with simultaneous removal of trimethylbromosilane, until the theoretical amount was obtained. The reaction mixture was treated with 100 ml of water and boiled for 1 h. It was then cooled and extracted with benzene (2 × 150 ml), the extract obtained being dried over sodium sulfate and evaporated under reduced pressure. The residue was treated with light petroleum (1.5 liters), and the oil which separated was dissolved in the minimum amount of benzene and chromatographed. The ether fractions gave 18.3 g (10.2%) of (Ic), the benzene fractions 21.6 g (19.5%) of (IIIb), mp 118-120°C, and the n-propanol fractions 1.4 g (1.5%) of (VII), mp 142-145°C (from benzene–methyl ethyl ketone). UV spectrum [pH, λ_{max}, nm (log ε)]: 7.257 (3.69), 12.283 (3.64).

b) A mixture of 40.3 g of (VI) and 180 g of (IVe) was heated under argon at 110-120°C. The reaction mixture was worked up similarly. The ether fractions gave 16 g (9%) of (Ic), and the benzene fractions 18 g (16.3%) of (IIIc), mp 89-91°C. UV spectrum [pH, λ_{max}, nm (log ε)]: 7.268 (3.95), 12.267 (4.04).

Reaction of (VIIId) Sodium Salt with (IVe). To the sodium salt of (VIIIe), obtained from 3.3 g of sodium and 20 g of (VIIId) in 300 ml of dry n-butanol, was added 200 ml of dry DMF and 215 g of (IVe), and the mixture was stirred at 50-60°C until the pH reached 7. The mixture was evaporated, and the residue was treated with 200 ml of benzene, the resulting solid being filtered off. The filtrate was diluted with 800 ml of light petroleum, and after 1 day the solvent was decanted from the oil which separated (solution A). The oil was dissolved in the minimum amount of benzene and chromatographed. The ether and benzene fractions gave 13 g (25.5%) of (IXd), mp 72-74°C (from benzene). Solution A was diluted to 2 liters with light petroleum, and after 3 days the solid which had separated was filtered off (filtrate B) and recrystallized from light petroleum–benzene to give 2 g (4.7%) of (XII), mp 119-124°C. Filtrate B was evaporated, and the residue was dissolved in the minimum amount of benzene and chromatographed. The ether and benzene fractions gave a further 5.2 g (10%) of (IXd). Total yield of (IXd), 35.5%.

1-(ω-Bromobutyl)-3-isopropyl-6-methyluracil (IXb). To a solution of 0.58 g of sodium in 100 ml of dry n-propanol was added 4.2 g of (VIIIb), stirring the mixture for 1 h. The solvent was removed under reduced pressure, and the residue was dried azeotropically with benzene. To the dry sodium salt was added 100 ml of dry DMF and 35 g of (IVb), and the mixture was stirred at 60-70°C until the pH reached 7. The solution was evaporated, and the residue was dissolved in benzene and filtered. The filtrate was concentrated to 25 ml and chromatographed. The ether fractions gave 5.7 g (79%) of (IXb), mp 80-82°C.

Obtained similarly were: 1-(ω-bromobutyl)-3-isobutyl-6-methyluracil (IXc) from 8.4 g of (VIIIc) sodium salt and 40 g of (IVb), yield 9.7 g (75%), $n^{20}D$ 1.5374; 3-benzyl-1-(ω-bromobutyl)-6-methyluracil (IXa) from 7 g of (VIIIa) sodium salt and 35 g of (IVb), yield 6.9 g (71%), mp 65-67°C; 3-allyl-1-(ω-bromobutyl)-6-methyluracil (IXf) from 19.3 g of (VIIIf) sodium salt and 110 g of (IVb), yield 23.6 g (77%), viscous yellow oil; 1-(ω-bromobutyl)-3,6-dimethyl-5-nitrouracil (IXe) from 20.5 g of (VIIIe) sodium salt and 85 g of (IVb), 20.4 g (77%) of (IXe), mp 79-80°C (from n-butanol) being obtained from the benzene–dichloromethane fractions; and 3-(ω-bromobutyl)-1,6-dimethyl-5-nitrouracil (XI) from 20 g of (X) sodium salt and 80 g of (IVb), yield 24.5 g (87%), $n^{20}D$ 1.5702.

Reaction of (V) Sodium Salt with (XIII). A mixture of 35 g of (V) sodium salt with 40 g of (XIII) in 250 ml of dry DMF was stirred at 80-100°C until the pH reached 7. The solution was filtered to give 16 g of (V). The filtrate was evaporated under reduced pressure, and the residue was dissolved in the minimum amount of chloroform and chromatographed. The column was eluted successively with hexane, ether, benzene, chloroform, and a mixture of chloroform and n-propanol. The ether and benzene fractions gave 3.2 g (8%) of 3-isopropyl-6-methyluracil (VIIIb), mp 186-188°C (hexane–benzene) [7]. UV spectrum [pH, λ_{max}, nm (log ε)]: 2.263 (3.67), 12.282 (3.70). On evaporation, the chloroform fraction gave a mixture (1.5 g) of (VIIIb) and (XVa). The chloroform–n-propanol fraction gave 10 g (25%) of 1-isopropyl-6-methyluracil (XVa), mp 160-162°C. UV spectrum [pH, λ_{max}, nm (log ε)]: 2.268 (3.70), 12.269 (3.79).

Obtained similarly from 35 g of (V) sodium salt and 60 g of (XIV) were 4 g (9.2%) of 3-isobutyl-6-methyluracil (VIIIc), mp 199°C, and 15 g (35%) of 1-isobutyl-6-methyluracil (XVb), mp 118-120°C, UV spectra [pH, λ_{max}, nm (log ε)]: (VIIIc) 7.260 (3.50), 12.281 (3.76); and (XVb) 1.267 (3.70), 12.269 (4.15).

CONCLUSIONS

A method has been developed for the preparation of 1,3-bis(ω-haloalkyl)uracils with methylene chains of different lengths in the ω-haloalkyl radicals in the N^1 and N^3 positions of the pyrimidine ring.

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