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SYNTHESIS AND PROPERTIES OF PYRIMIDINYLALKYLSULFONAMIDES.

COMMUNICATION 1. INTERACTION OF CERTAIN ω-HALOALKYLURACILS WITH p-TOLUENESULFAMIDE

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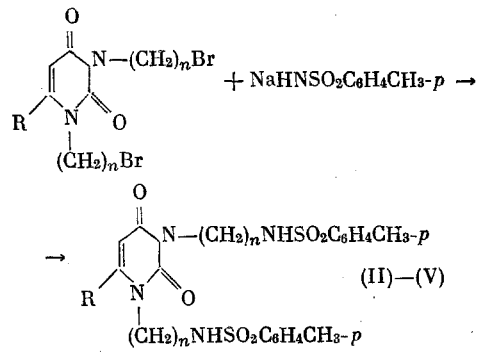
To study N-alkyl derivatives of uracil containing the sulfonamide grouping in the alkyl chain we investigated the interaction of certain N-(ω-bromoalkyl)uracils with p-toluenesulfamide (I). The corresponding 1,3-bis[ω-(p-toluenesulfonamido)alkyl]uracils (II)-(V) in yields of 45-80% are formed upon reaction of 1,3-bis(ω-bromoalkyl)uracils with the Na salt of (I).



R = H; $n = 4$ (II); R = CH_3, $n = 4$ (III); R=H, $n = 3$ (IV); R = CH_3, $n = 3$ (V)

Compounds (II)-(V) are stiff oils or crystalline materials having limited solubility in $CHCl_3$ and being insoluble in water. IR Spectra of (II)-(V) have intense bands in the region of stretching vibrations of the C=O group (1627-1665 and 1682-1710 cm^{-1}). Stretching vibration

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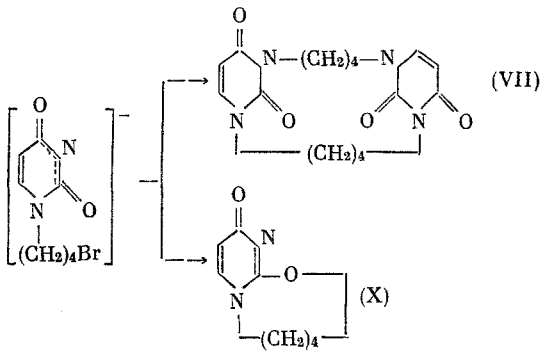
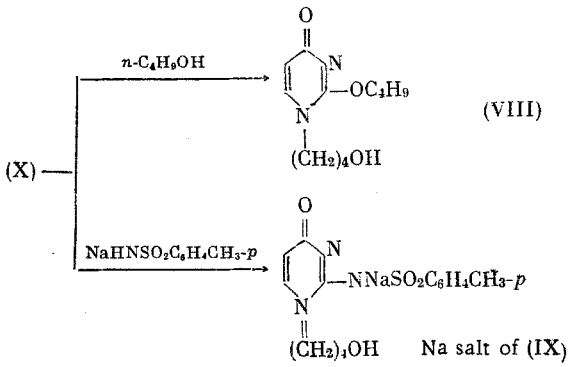
bands of the sulfonamide group are displayed at 1321-1340 (ν_{as} SO_2), 1120-1170 (ν_s SO_2), and 3165-3270 cm^{-1} (ν_{NH}).

Reaction of 1-(ω-bromobutyl)uracil (VI) with the Na salt of (I) under these same conditions proceeds entirely differently. 9,18,19,20-Tetraoxo-1,6,10,15-tetraazatricyclo[13.3.1.-$1^{6,10}$]eicosa-7,16-diene (VII), 1-(ω-hydroxybutyl)-2-butoxypyrimid-4-one (VIII), and 1-(ω-hydroxybutyl)-2-p-toluenesulfonamidopyrimid-4-one (IX) were isolated instead of the expected 1-[ω-(p-toluenesulfonamido)butyl]uracil. Such results can be explained if it is considered that acidic properties of uracils and sulfamides are similar (pK_a are correspondingly 9.5 [1] and ~9 [2]) and consequently, an equilibrium between the anionic forms of (VI) and (I) is possible in solution. Interaction of two ionized molecules of compound (VI) leads to formation of (VII) and intramolecular cyclization of the anion of (VI) leads to 2-oxopyrimido[1,2-b]perhydro-5,10-oxazepine (X).



The formed (X) has a partial positive charge on the 2-C atom of the pyrimidine ring and therefore, analogously to 2-alkoxypyrimidines [3], can undergo attack with nucleophilic reagents. In particular, attack of n-butanol leads to formation of compound (VIII) and attack of p-toluenesulfonamide anion leads to (IX). As a result of the effect of the electronegative pyrimidine ring the acidic properties of the sulfamide nitrogen atom of compound (IX) are higher than in initial (I). This leads to the case that (IX) is separated from the reaction mass as the Na salt. Yield of product (VIII) is significantly higher than the yield of product (IX), which is explained by the use of n-butanol as the solvent.

Compound (VII) is a high melting crystalline product, soluble in boiling $CHCl_3$ and insoluble in water.



The IR spectrum of (VII) has two bands $\nu_{C=O}$ (1665 and 1700 cm^{-1}), analogously to 1,3-bisalkyluracils [4]. Absorption is absent in the region of stretching vibrations of NH and OH groups. The UV spectrum of (VII) is analogous to the UV spectra of 1,3-bisalkyluracils [5] (λ_{max} 267 nm) and does not give a bathochromic shift upon changing the pH of the medium from acidic to basic. Compound (VIII) is a colorless oil, soluble in $CHCl_3$ and insoluble in water. The IR spectrum of (VIII) contains one intense band at 1660 cm^{-1} ($\nu_{C=O}$) and a broad intense band with a maximum at 3380 cm^{-1} (ν_{OH}). A series of bands in the region of 1000-1320 cm^{-1} can be assigned to stretching vibrations of C—O bonds. The position of absorption maxima in

TABLE 1

Compound	mp, °C or n_D^{20}	Yield, %	Found / Calc., %				Empirical formula
			C	H	N	S	
(II)	1,5630 (n_D^{45})	46,5	55,72 / 55,50	6,07 / 6,05	9,62 / 10,00	—	$C_{26}H_{34}N_4O_6S_2$
(III)	85—105	80,0	—	—	9,74 / 9,75	11,22 / 11,10	$C_{27}H_{36}N_4O_6S_2$
(IV)	165—167,5	66,0	—	—	10,98 / 10,50	12,00 / 12,00	$C_{24}H_{30}N_4O_6S_2$
(V)	100—103	80,0	—	—	9,83 / 10,20	10,62 / 11,70	$C_{25}H_{32}N_4O_6S_2$
(VII)	>340 (with dec.)	10,0	57,61 / 57,80	5,81 / 5,85	16,49 / 16,90	—	$C_{16}H_{20}N_4O_4$
(VIII)	1,5255	39,0	59,60 / 60,00	8,17 / 8,30	11,34 / 11,70	—	$C_{12}H_{20}N_2O_3$
(IX)	104—106	5,7	53,02 / 53,40	5,56 / 5,60	—	9,60 / 9,50	$C_{15}H_{19}N_3O_4S$

the UV spectrum of (VIII) (pH 1, λ_{max} 260 nm; pH 14, λ_{max} 260 nm) is characteristic for 1-alkyl-2-alkoxy-1,4-dihydropyrimid-4-ones [6]. Compound (IX) is a crystalline material, soluble in polar solvents and insoluble in water. The IR spectrum of (IX), in accordance with its structure, has one band $\nu_{C=O}$ (1685 cm^{-1}); ν_{OH} and ν_{NH} lie at 3368 and 3170-3220 cm^{-1}, respectively. Stretching vibration bands of the SO_2 groups appear at 1135 (ν_s) and 1370 cm^{-1} (ν_{as}).

EXPERIMENTAL METHODS

IR spectra were taken on a UR-10 spectrophotometer of solid materials as suspensions in mineral oils and of liquids as a film between KBr plates. UV spectra were taken on a Specord UV-VIS spectrophotometer. Column chromatography was carried out on neutral Al_2O_3 (act. II). Constants of the obtained compounds are presented in Table 1.

1,3-Bis[ω-(p-toluenesulfonamido)butyl]uracil (II). To a stirred suspension of 10 g of Na salt of (I) in 250 ml of abs. n-butanol was added a solution of 9.7 g of 1,3-bis(ω-bromobutyl)uracil in 50 ml of n-butanol and the mixture was boiled for 10 h (pH 7.5-8.0). After cooling the precipitate was filtered and the filtrate was evaporated in vacuum. The residue was treated with $CHCl_3$, filtered, evaporated in vacuum, and the residue was chromatographed. The column was washed consecutively with petr. ether, ether, and $CHCl_3$. From the residue after evaporation of the ether fraction was isolated 1.6 g of initial (I). The residue after evaporation of the $CHCl_3$ fraction was dissolved in 500 ml of boiling benzene, evaporated to a volume of 100 ml, treated with act. carbon, filtered, and evaporated in vacuum. We obtained 5.6 g (46.5%) of (II), a stiff colorless oil with n_D^{45} 1.5630.

1,3-Bis[ω-(p-toluenesulfonamido)butyl]-6-methyluracil (III). Interaction of 8.1 g of the Na salt of (I) and 8.2 g of 1,3-bis(ω-bromobutyl)-6-methyluracil and treatment of the reaction mass were carried out analogously. Evaporation of the $CHCl_3$ fraction yielded 9.7 g (80%) of crude (III). The purest fractions crystallized after a certain time. They were combined and triturated in benzene; (III) was filtered as a white powder undergoing recrystallization with difficulty. After maintaining under benzene for 30 days the product could be recrystallized from a benzene—$CHCl_3$ mixture; however, it did not have a sharp melting point (melted in the range of 85-105°).

1,3-Bis[ω-(p-toluenesulfonamido)propyl]uracil (IV). To a stirred suspension of 8.7 g of the Na salt of (I) in 250 ml of abs. n-butanol was added a solution of 7.9 g of 1,3-bis(ω-bromopropyl)-uracil in 50 ml of n-butanol and the mixture was boiled for 2.5 h (pH 8.5). Treatment of the mass was carried out analogously to that described in the preceding experiments. The column was washed consecutively with petr. ether, ether, benzene, $CHCl_3$, and n-propanol, collecting four fractions of $CHCl_3$ (2 × 0.4 liter and 2 × 1 liter) and one fraction of n-propanol (1 liter). The residue after evaporation of the second $CHCl_3$ fraction was treated with 10 ml of a mixture of benzene—$CHCl_3$ (3:1) and 1 g of initial (I) was filtered. Evaporation of the third and fourth fractions of $CHCl_3$ and the n-propanol fraction yielded 6.5 g (66.0%) of crude (IV), mp 165-167.5° (from n-propanol).

1,3-Bis[ω-(p-toluenesulfonamido)propyl]-6-methyluracil (V). Reaction of 6.5 g of the Na salt of (I), 6.1 g of 1,3-bis(ω-bromopropyl)-6-methyluracil and treatment of the reaction mixture were carried out analogously to what has been described. Evaporation of the $CHCl_3$ fraction and n-propanol yielded 6.9 g (80.0%) of crude (V) as a stiff oil. The residue after evaporation of the n-propanol fraction was left under benzene until crystallization and triturated in benzene; 0.5 g of crystalline (V) was filtered, mp 100-103°.

Reaction of Na Salt of (I) with (VI). To a stirred suspension of 4.8 g of Na salt of (I) in 250 ml of abs. n-butanol was added a solution of 6.1 g of (VI) in 50 ml of n-butanol and the mixture was boiled for 6 h (pH 7-7.5). After cooling the mixture was filtered and evaporated in vacuum. The residue was treated with CH_2Cl_2; the precipitate was separated on the centrifuge (solution A), dissolved in 5 ml of H_2O, treated with activated carbon, filtered, and evaporated in vacuum. The residue was triturated in acetone and filtered. We obtained 0.5 g (5.7%) of the Na salt of (IX), mp 268-270° from H_2O–n-propanol. The product was dissolved in 5 ml of H_2O, HCl was added to pH 5, the separated oil was extracted with CH_2Cl_2, and dried over anh. Na_2SO_4 with addition of anh. K_2CO_3, the salt was filtered, and the filtrate was evaporated in vacuum. The crystallized residue was triturated in benzene and filtered. We obtained 0.4 g of (IX), mp 104-106°. Solution A was evaporated in vacuum and the residue was chromatographed. The column was washed consecutively with petr. ether, ether, $CHCl_3$ (1 × 0.1 liter and 4 × 0.5 liter). The residue after evaporation of the first $CHCl_3$ fraction was recrystallized from $CHCl_3$. We obtained 0.4 g (10.0%) of (VII), mp >340° (with dec.). From the remaining fractions of $CHCl_3$ after evaporation was obtained 3.0 g (39%) of crude (VIII), which was purified by repeated chromatography; colorless oil with n_D^{20} 1.5255.

CONCLUSIONS

1. The corresponding 1,3-bis[ω-(p-toluenesulfonamido)alkyl]uracils are formed as a result of the reaction of 1,3-bis(ω-bromoalkyl)uracils and the Na salt of p-toluenesulfamide.

2. Interaction of 1-(ω-bromobutyl)uracil with p-toluenesulfamide in a medium of n-butanol leads to formation of 9,18,19,20-tetraoxo-1,6,10,15-tetraazatricyclo[13.3.1.$1^{6,10}$]-eicosa-7,16-diene,1-(ω-hydroxybutyl)-2-butoxypyrimid-4-one, and 1-(ω-hydroxybutyl)-2-p-toluenesulfonamidopyrimid-4-one.

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