SYNTHESIS AND PROPERTIES OF PYRIMIDINYLALKYLSULFONAMIDES

4. REACTION OF THE Na SALT OF p-TOLUENESULFONAMIDE WITH MONO-N-(ω-HALOALKYL)URACILS

Yu. S. Shvetsov, A. N. Shirshov, and V. S. Reznik

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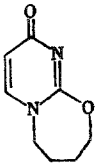
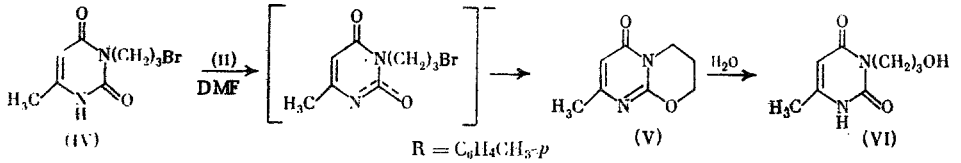
In [1], we showed that the reaction of 1-(ω-bromobutyl)uracil (I) with the Na salt of p-toluenesulfonamide (II) proceeds via the formation of 2-oxopyrimido[1,2-b]perhydro-5,10-oxazepine (III), the oxazepine ring of which is easily opened by nucleophilic reagents



(III)

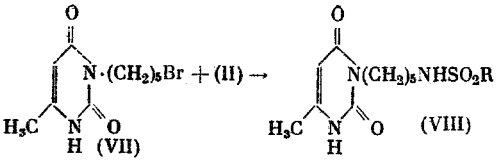
In the present work, we have studied the reaction of (II) with a number of other N-(ω-bromoalkyl)uracils and found that the direction of the reaction depends chiefly on the length of the alkyl chain in the starting N-(ω-bromoalkyl)uracil. Thus, when 3-(ω-bromopropyl)-6-methyluracil (IV) is reacted with (II) in abs. DMF, (IV) undergoes intramolecular cyclization to form 2-oxo-4-methylpyrimido[2,3-b]perhydro-7,1-oxazine (V), the oxazine ring of which is quite stable and can only be hydrolyzed to form 3-(ω-hydroxypropyl)-6-methyluracil (VI) by prolonged boiling



(IV) R = $C_6H_4CH_3$-p (V) (VI)

The IR spectrum of a solution of (V) in CCl_4 has one band at 1691 cm^{-1} in the $\nu_{C=O}$ region and no absorption in the ν_{N-H} region. The position of λ_{max} (278.5 nm) in the UV spectrum of a solution of (V) in $CHCl_3$ is characteristic of 3-alkyl-2-alkoxy-3,4-dihydro-4-pyrimidones [2]; this confirms the structure of (V). In the IR spectrum of a solid sample of (VI), $\nu_{C=O}$ bands appear in the 1630-1715 cm^{-1} region, ν_{N-H} bands in the 3100-3180 cm^{-1} region, and ν_{O-H} bands at 3335 cm^{-1}.

Intramolecular cyclization does not take place if the N-alkyl chain in the starting haloalkyluracil contains 5 CH_2 groups. When 3-(ω-bromopentyl)-6-methyluracil (VII) is reacted with (II) in n-butanol, the only product isolated is 3-[ω-(p-toluenesulfonamido)pentyl]-6-methyluracil (VIII)



(VII) (VIII)

In the IR spectrum of (VIII), the $\nu_{C=O}$ absorption bands appear at 1645 and 1715 cm^{-1}; the ν_s and ν_{as} bands of the SO_2 group appear at 1160 and 1321 cm^{-1}, respectively; and ν_{NH} appears at 3100-3280 cm^{-1}.

The most complicated reaction is that between (II) and the mono-N-(ω-bromobutyl)uracils, which, in anionic form, can undergo intramolecular cyclization to form a labile oxazepine ring. In this case, the composition and yield of the reaction products depends both on the reaction conditions and on which N atom in the

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. 9, pp. 2079-2084, September, 1978. Original article submitted May 16, 1977.

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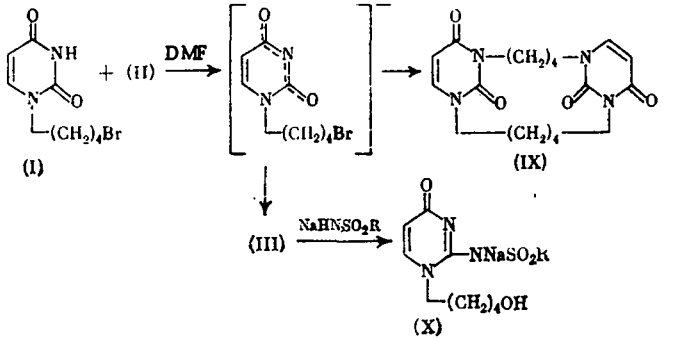
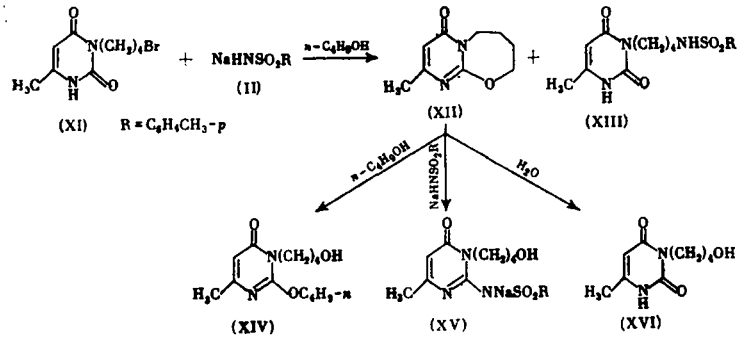
pyrimidine ring carries the haloalkyl substituent in the starting haloalkyluracil. Thus, reaction of (I) with (II) in abs. DMF gives 9,18,19,20-tetraoxo-1,6,10,15-tetraazatricyclo[13.3.1.1^{6,10}]eicosa-7,16-diene (IX) and the Na salt of 1-(ω-hydroxybutyl)-2-(p-toluenesulfonamido)-4-pyrimidone (X) in yields of 79 and 0.3%, respectively. When this reaction is carried out in n-butanol [1], the yields of (IX) and (X) are 10.0 and 5.7%, respectively



The higher yield of (IX) obtained by reaction in DMF is evidently due to the low degree of solvation of the anion by this aprotic solvent, which favors intermolecular reaction between two anions of (I). The IR spectra of (IX) and (X) were identical to those of the samples obtained in [1].

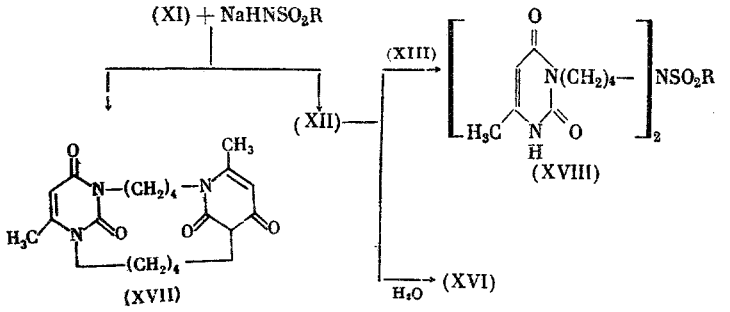
Reaction of 3-(ω-bromobutyl)-6-methyluracil (XI) with (II) in abs. n-butanol gives 3-[ω-(p-toluenesulfonamido)butyl]-6-methyluracil (XIII), 2-butoxy-3-(ω-hydroxybutyl)-6-methyl-4-pyrimidone (XIV), 2-(p-toluenesulfonamido)-3-(ω-hydroxybutyl)-6-methyl-4-pyrimidone (XV), and 3-(ω-hydroxybutyl)-6-methyluracil (XVI):



The intermediate in this reaction is 2-oxo-4-methylpyrimido[2,3-b]perhydro-7,1-oxazepine (XII), the pyrimidine ring of which is in the o-quinone form, which is energetically more favorable than the p-quinone form in (III). Consequently, (XII) will be more inert with respect to nucleophilic reagents and can evidently remain in the reaction mixture in partially unchanged form. During subsequent chromatographic separation of the mixture on Al_2O_3, (XII) is decomposed by water to form (XVI).

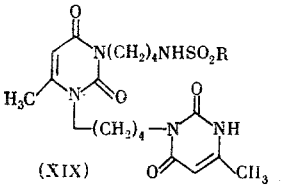
In the IR spectrum of (XIII), the $\nu_{C=O}$ bands appear in the 1630-1705-cm^{-1} region and the ν_{NH} bands of the pyrimidine ring appear at 3120 and 3190 cm^{-1}. The stretching bands of the sulfonamide group appear at 1162 ($\nu_{s\,SO_2}$), 1333 ($\nu_{as\,SO_2}$), and 3290 cm^{-1} (ν_{NH}). The IR spectrum of (XIV), like the spectrum of 1-(ω-hydroxybutyl)-2-butoxy-4-pyrimidone in [1]. has one $\nu_{C=O}$ band at 1665 cm^{-1} and a broad strong band with a maximum at 3450 cm^{-1} (ν_{OH}). The position of λ_{max} (270 nm) in the UV spectrum of (XIV) in $CHCl_3$ is characteristic of 3-alkyl-2-alkoxy-3,4-dihydro-4-pyrimidones [2]. In accordance with its structure, the IR spectrum of (XV) has one $\nu_{C=O}$ band (1712 cm^{-1}) and a ν_{OH} band at 3400 cm^{-1}. The stretching bands of the sulfonamide group appear at 1136 ($\nu_{s\,SO_2}$), 1340-1380 ($\nu_{as\,SO_2}$), and 3240 cm^{-1} (ν_{NH}). In the UV spectrum of a solution of (XV) in 0.1 N HCl, the position of λ_{max} at 251 nm fits in with data for analogous structures in [3,4]. The IR spectrum of (XVI) has $\nu_{C=O}$ bands at 1710 and 1736 cm^{-1}, ν_{NH} at 3100-3250 cm^{-1}, and ν_{OH} at 3355 cm^{-1}.

When we performed this same reaction in DMF, as would be expected, we obtained 7,16-dimethyl-9,18,19,20-tetraoxo-1,6,10,15-tetraazatricyclo[13.3.1.1^{6,10}]eicosa-7,16-diene (XVII) and the product (XVI) described above. As well as (XVI), we also isolated N,N-bis[ω-(2,4-dioxo-6-methyl-1,2,3,4-tetrahydro-3-pyrimidinyl)-butyl]-p-toluenesulfonamide (XVIII)



R = $C_6H_4CH_3$-p

The latter is evidently formed by reaction of the anion of the initially formed (XIII), which is solvated very little in DMF, with the intermediate (XII) through the C^7 atom of the oxazepine ring, since attack at the 2-C atom of the pyrimidine ring is sterically hindered in this case. The $\nu_{C=O}$ bands in the IR spectrum of (XVII) appear in the 1620-1690-cm^{-1} region, which is in accord with the absorption of (IX) and with the data on 1,3-bis-alkyluracils in [5]; there is no absorption in the ν_{NH} and ν_{OH} regions. In the IR spectrum of (XVIII) there are a number of bands in the $\nu_{C=O}$ region (1610-1720 cm^{-1}); the ν_S and ν_{as} bands of the SO_2 group appear at 1166 and 1335 cm^{-1}, respectively; and ν_{HN} bands appear at 3195 and 3250 cm^{-1}. The UV spectra of solutions of (XVIII) in $CHCl_3$ and 0.1 N KOH each have only one long-wave absorption maximum (at 261 and 273 nm, respectively), which rules out the possibility of (XVIII) having the alternative structure (XIX), in which the two pyrimidine rings are nonequivalent. The presence of two ν_{NH} bands in the IR spectrum of a solid sample of (XVIII) is evidently due to different types of hydrogen bonds



EXPERIMENTAL

The IR spectra were recorded with a UR-10 spectrophotometer; solids were used as mulls in mineral oil and liquids were used as films between KBr plates. The UV spectra were recorded with a Specord UV-VIS spectrophotometer. Column chromatography was carried out on neutral Al_2O_3 (activity II). The constants of the compounds obtained are given in Table 1.

2-Oxo-4-methylpyrimido[2,3-b]perhydro-7,1-oxazine (V). A solution of 4.2 g of (II) in 100 ml of abs. DMF was treated with 5.4 g of (IV) and stirred at 70-80°C for 8 h. The DMF was distilled off in vacuo; the residue treated with $CHCl_3$; and the solution filtered, evaporated and chromatographed on Al_2O_3. The column was eluted successively with petroleum ether, $CHCl_3$ (0.5 liter), and methanol (0.5 liter). The $CHCl_3$ was evaporated off, the residue treated with ether, and the precipitate filtered off to give 2.2 g of (V), mp 87-89°C (from $CHCl_3$ — petroleum ether). The residue remaining after evaporating off the methanol was treated with benzene — $CHCl_3$ (1 :1), filtered, evaporated, and the residue treated with benzene and filtered to give 0.5 g more of (V). Total yield 2.7 g (74.0 %).

3-(ω-Hydroxypropyl)-6-methyluracil (VI). A 1.2 g portion of (V) was boiled in 30 ml H_2O for 18 h. The solution was evaporated in vacuo and the residue recrystallized from toluene to give 1.1 g (84.5%) of (VI), mp 156-157°C.

3-[ω-(p-Toluenesulfonamido)pentyl]6-methyluracil (VIII). A stirred suspension of 9.7 g of (II) in 400 ml of abs. n-butanol was treated with 13.8 g of (VII) and boiled for 12 h. The butanol was distilled off in vacuo; the residue dissolved in $CHCl_3$; and the solution filtered, evaporated and chromatographed on Al_2O_3. The column was eluted successively with petroleum ether, benzene, $CHCl_3$ (1 × 0.25 liter, 1 × 0.5 liter, and so on until elution ceased), and n-propanol (0.5 liter). The residues remaining after evaporation of the second $CHCl_3$ fraction and the n-propanol fraction were combined and rechromatographed. The column was eluted successively with benzene and $CHCl_3$. Evaporation of the $CHCl_3$ gave 8.3 g (46.0%) of crude (VIII). The purest fractions were crystallized for some time, treated with a minimal amount of $CHCl_3$, filtered off, and carefully washed with benzene; mp 137-139°C.

Reaction of 1-(ω-Bromobutyl)uracil with the Na Salt (II). A solution of 4.5 g (II) in 100 ml of abs. DMF

TABLE 1

Compound	mp, °C	Yield, %	Found/calculated, %				Empirical formula
			C	H	N	S	
(V)	87–89	74,0	58,11 / 57,90	6,13 / 5,70	16,97 / 16,90	–	$C_8H_{10}N_2O_2$
(VI)	156–157	84,5	52,53 / 52,10	6,61 / 6,50	15,20 / 15,20	–	$C_8H_{12}N_2O_3$
(VIII)	137–139	46,0	–	–	12,14 / 11,80	8,50 / 8,80	$C_{17}H_{23}N_3O_4S$
(XIII)	157–158	23,5	54,59 / 54,70	6,01 / 6,00	11,98 / 12,00	9,07 / 9,10	$C_{16}H_{21}N_3O_4S$
(XIV)	Oil	23,0	60,91 / 61,40	8,58 / 8,70	10,82 / 11,00	–	$C_{13}H_{22}N_2O_3$
(XV)	103–104	6,9	54,60 / 54,60	5,95 / 6,00	11,98 / 12,00	–	$C_{16}H_{21}N_3O_4S$
(XVI)	142–143	19,6 (in n-C_4H_9OH) 23,0 (in DMF)	54,45 / 54,50	7,52 / 7,10	14,14 / 14,10	–	$C_9H_{13}N_2O_3$
(XVII)	decomp.>330°	19,00	44,11 / 43,70	5,15 / 5,45	15,68 / 15,60	–	$C_{18}H_{24}N_4O_4$
(XVIII)	172–180	25,6	57,03 / 56,50	6,21 / 6,20	–	6,04 / 6,00	$C_{25}H_{33}N_5O_6S$

was treated with 5.8 g of (I) and stirred at 60-70°C for 7 h. The precipitate was filtered off (filtrate A); washed with acetone, H_2O (filtrate B), and again with acetone to give 0.2 g of (IX). From filtrate B was isolated 0.03 g (0.3%) of (X). Filtrate A was evaporated, the residue treated with $CHCl_3$, the solution filtered and evaporated, the residue treated with benzene – $CHCl_3$ (1 : 1), and the precipitate filtered off (filtrate C) and recrystallized from $CHCl_3$ – abs. ethanol to give 1.0 g of (IX). Filtrate C was evaporated in vacuo and the residue chromatographed on Al_2O_3. The column was eluted successively with petroleum ether, benzene, and $CHCl_3$. The residue remaining after evaporating off the $CHCl_3$ was treated with ether and the precipitate filtered off and recrystallized from $CHCl_3$ to give 1.9 g of (IX). The total yield of (IX) was 3.1 g (79.0%).

Reaction of 3-(ω-Bromobutyl)-6-methyluracil (XI) with (II) in n-Butanol. A stirred suspension of 9.6 g (II) in 500 ml of abs. n-butanol was treated with 13.0 g of (XI) and boiled for 6 h. The solution was filtered, evaporated, and the residue treated with $CHCl_3$. The precipitate was filtered off (filtrate A), dissolved in 30 ml H_2O, and the solution treated with active charcoal, filtered, and acidified to pH 5 with conc. HCl. The precipitate was filtered off and dissolved in $CHCl_3$. When the $CHCl_3$ was slowly evaporated off, the product crystallized in the form of needles, which were triturated with benzene and filtered off to give 0.2 g of (XV), mp 103-104°C. Filtrate A was evaporated in vacuo and the residue chromatographed. The column was eluted successively with petroleum ether, benzene, $CHCl_3$ (2 × 0.5 liter and so on until elution ceased), and methanol (1 × 0.5 liter and 1 × 1 liter). The residue remaining after evaporation of the second $CHCl_3$ fraction was dissolved in ether – benzene (1 : 1), the solution was filtered and evaporated, and the residue was azeotropically dried with benzene. The benzene solution was treated with 1 g of Al_2O_3, filtered, and evaporated in vacuo to give 2.9 g (23.0%) of (XIV) as a yellowish viscous oil, $n_D^{20} = 1.5376$. The residue remaining after evaporating the second methanol fraction was recrystallized from toluene – n-propanol to give 0.3 g of (XV). The residue remaining after evaporating the first methanol fraction was rechromatographed. The column was eluted successively with $CHCl_3$ and methanol (2 × 0.15 liter and 1 × 0.3 liter). The residue remaining after evaporating the third methanol fraction was treated with $CHCl_3$ and the precipitate filtered off to give 0.8 g of (XV), giving a total yield (XV) of 1.2 g (6.9%). The residue remaining after evaporating the second methanol fraction (residue B) was dissolved in 100 ml $CHCl_3$, washed with water (4 × 100 ml), and the aqueous phase evaporated. The residue was treated with $CHCl_3$ – acetone (1 : 1) and the precipitate filtered off to give 1.9 g (19.6%) of (XVI), mp 142-143°C (from toluene – n-propanol). The chloroform layer was evaporated and the residue chromatographed. The column was eluted successively with $CHCl_3$ and 100 ml of methanol – $CHCl_3$ (1 : 10). The last fraction was evaporated down to ~3 ml in vacuo and the precipitate filtered off to give 0.2 g of (XIII), mp 157-158°C (from hexane – methanol). According to IR spectra, elementary analysis, and TLC on Silufol, residue B contained ~30% of (XVI) and 65% of (XIII), i.e., the yield of (XIII) was ~4.1 g (23.5%).

Reaction of (XI) with (II) in DMF. A solution of 8.7 g (II) in 400 ml of abs. DMF was treated with 11.7 g of (XI) and stirred at 70-75°C for 8 h and then at 90-100°C for 1 h. After cooling, the precipitate was filtered off (filtrate A), washed with hot water and acetone, and recrystallized from DMF to give 1.3 g of (XVII), mp > 330°C (decomp.). Filtrate A was evaporated in vacuo, the residue treated with $CHCl_3$, the solution filtered

and evaporated, and the residue chromatographed on Al_2O_3. The column was eluted successively with petroleum ether, benzene, $CHCl_3$ and n-propanol. The residue remaining after evaporating off $CHCl_3$ was treated with benzene and the precipitate filtered off to give 3.0 g (25.6%) of (XVIII), mp 172-180°C (from toluene — n-propanol and then dioxane — benzene). The insoluble material from the recrystallization of (XVIII) was carefully washed with acetone to give 0.2 g more of (XVII), giving a total (XVII) yield of 1.5 g (19.0%). The residue remaining after evaporating the n-propanol fraction was treated with benzene — $CHCl_3$ (4 : 1), and the precipitate was filtered off and reprecipitated from n-propanol with ether to give 2.1 g (23.0%) of (XVI), mp 142-143°C (from toluene — n-propanol).

CONCLUSIONS

The direction of reaction and the composition and yields of products obtained by reaction of the Na salt of p-toluenesulfonamide with N-(ω-bromoalkyl)uracils depend primarily on the length of the alkyl chain in the latter: When the Na salt of p-toluenesulfonamide reacts with N-(ω-bromopropyl)-6-methyluracil, the latter undergoes intramolecular cyclization, whereas the Na salt of p-toluenesulfonamide undergoes intermolecular alkylation at the sulfonamide group on reaction with N-(ω-bromopentyl)-6-methyluracil. In analogous reactions, N-(ω-bromobutyl)uracils undergo both intramolecular cyclization, followed by opening of the oxazepine ring by nucleophilic reagents, and intermolecular alkylation.

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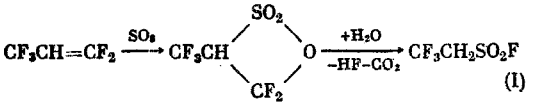
FLUORINE-CONTAINING β-SULTONES

47. DERIVATIVES OF 2,2,2-TRIFLUOROETHANESULFONIC ACID

A. F. Eleev, G. A. Sokol'skii, and I. L. Knunyants

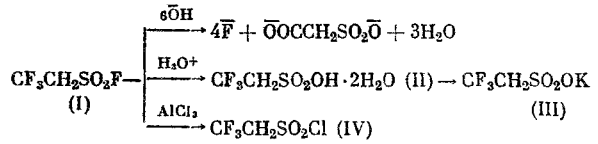
UDC 542.91 : 547.269 : 3'161

Reaction of 2-hydropentafluoropropene with SO_3 followed by hydrolysis of the resulting β-sultone gives 2,2,2-trifluoroethanesulfonyl fluoride in quantitative yield [1]



(I)

It has been found that treatment of sulfonyl fluoride (I) with caustic alkali, and also with dilute $Ba(OH)_2$ solution, results in rapid hydrolysis of the sulfonyl fluoride and trifluoromethyl groups, evidently due to the mobility of the α-H atom. It is possible to isolate one of the intermediate products of hydrolysis only when the reaction is carried out under acidic rather than basic conditions. Thus, heating of (I) with 10% HCl gives 2,2,2-trifluoroethanesulfonic acid, which is isolated in the form of its distillable dihydrate (II), and subsequent neutralization under controlled conditions gives the K salt (III). The yield of acid (II) is not more than 20%. The acid chloride of this sulfonic acid proved to be relatively accessible by heating sulfonyl fluoride (I) with $AlCl_3$ (yield ~ 85%)



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