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SYNTHESIS AND CONVERSIONS OF 2-ARYL DERIVATIVES OF s-TRIAZOLO[4,3-a]PYRIMIDINE

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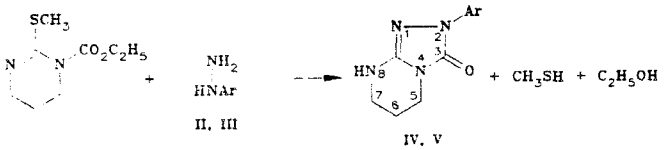
The reaction of arylhydrazines and 1-ethoxycarbonyl-2-methylthio-1,4,5,6-tetrahydropyrimidines forms 2-aryl-3-oxo-2,3,5,6,7,8-hexahydro-s-triazolo[4,3-a]pyrimidines. The reaction of 2-phenyl substituted triazolo[4,3-a]pyrimidine with various acylating agents to give 8-acyl derivatives and the effect thereon of hydrogen chloride were studied. The amine-imine tautomerism of these compounds was studied by PMR spectroscopy.

Among guanidine derivatives there are substances that have a wide spectrum of pharmacological activities [1, 2]. We have previously synthesized derivatives containing guanidine residues [3] and isothioureide residues bioisosteric with guanidines [4, 5]. In a further search for new biologically active compounds, the present work undertakes to synthesize compounds containing a guanidine grouping in a cyclic system.

The starting material was 1-ethoxycarbonyl-2-methylthio-1,4,5,6-tetrahydropyrimidine (I) [6]. The reaction of compound I with phenyl- or 4-sulfonamidophenylhydrazines (II, III) forms materials of cyclic structure; on the basis of elemental analysis and IR and PMR spectra these were assigned the structures of 2-aryl-3-oxo-2,3,5,6,7,8-hexahydro-s-triazolo[4,3-a]pyrimidines (IV, V).



II, IV Ar = C_6H_5; III, V Ar = p-$C_6H_4SO_2NH_2$

When compared with the spectrum of I, the IR spectra of crystalline IV and V are characterized by the disappearance of the valence vibration band of the ether bond (1730 and 1130 cm^{-1}), and the appearance of valence and deformation vibration bands of the NH group in the 3300-3100, 1510, and 1535 cm^{-1} regions and of the amide C=O valence vibration bands in the 1690-1720 cm^{-1} region. The PMR spectra of IV and V also show the disappearance of the SCH_3 and OCH_2CH_3 proton signals and the appearance of aryl proton and NH proton signals. In connection with the presence of the amide group, these compounds can exist in the tautomeric forms A and B.

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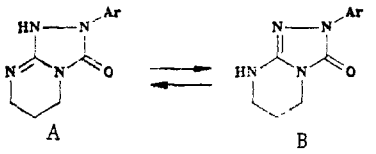
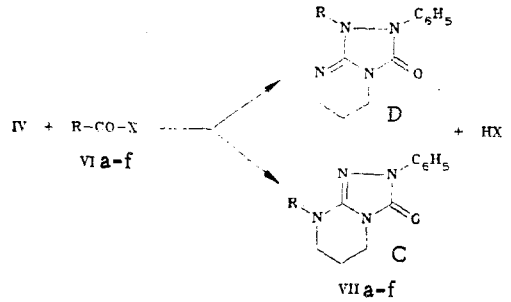


A B

The conclusion concerning the form in which IV and V exist enables us to analyze the PMR spectra obtained in $CDCl_3$ (IV) and DMSO-D_6 (V). The high field portion of the spectra shows two signals: a multiplet in the 3.02-3.40 ppm region, and a triplet in the 3.45-3.80 ppm region. On the basis of binary homonuclear resonance and deuterium exchange these were assigned to the protons at $C_{(7)}$ and $C_{(5)}$, respectively. Upon suppression of the broadened signal in the 5.99-6.16 ppm region (in the case of IV) (NH—C=N) the multiplet signal at 3.02-3.40 ppm is converted to a triplet; this shows the spin-spin coupling of the $C_{(7)}H_{(2)}$—$N_{(8)}H$ protons. When D_2O is added to the sample, the NH—C=N proton signal disappears, while the $C_{(7)}H_{(2)}$ multiplet is also converted to a triplet. From these data, allowing for the integrated signal intensities, it can be presumed that these compounds exist (at least predominantly) as one tautomeric form, viz., form B.

In connection with the presence in compounds IV and V of a tautomeric amidine segment, two series of isomeric derivatives, C and D, can form in the reaction with acylating reagents (acid chlorides, acid anhydrides, chlorocarbonic esters). The ability of the synthesized compounds to undergo acylation is exemplified by compound IV. Investigation showed that acylation yields only the compound with structure C.



VI, VII a $R=C_6H_5$, b $R=C_6H_5CH=CH$, c $R=4\text{-}ClC_6H_4$, d $R=3\text{-}CH_3C_6H_6$, e $R=CH_3$, f $R=C_2H_5$, VIa–d $X=Cl$, e $X=CH_3COO$, f $X=OCl$

The structures of these compounds were established by IR and PMR spectroscopy. In the IR spectra of acylation products VIIa-f, as compared with the spectra of starting material I, the typical bands of NH-bond valence and deformational vibrations disappear. In the spectra of VIIa-f a new band appears in the 1660-1690 cm^{-1} region that corresponds to the valence vibrations of amide C=O. The PMR spectra of the acyl derivatives lack the NH signals, but contain the proton signals of the aryl and alkyl substituents. The question as to whether acylation took place at $N_{(1)}$ or $N_{(8)}$ of compound IV was decided by PMR spectroscopy using model compounds (starting materials I and IV) in the consideration of the chemical shifts of the protons bonded at $C_{(7)}$ and $C_{(5)}$. In the spectrum of compound I, with a fixed C=N bond in the pyrimidine ring the methylene protons at $C_{(5)}$ and $C_{(7)}$ form a single multiplet in the 3.32-3.80 ppm region. In the spectrum of IV with the deshielded C=N bond in the triazole ring, the methylene protons at $C_{(7)}$ and $C_{(5)}$ form two different multiplets (see above); in this case the protons at $C_{(7)}$ are located in the stronger field in the 3.02-3.40 ppm region. In the spectra of all the acyl derivatives the methylene protons at $C_{(5)}$ and $C_{(7)}$ form one multiplet in the 3.55-4.17 ppm region. Such a shift of methylene proton signals at $C_{(7)}$ in the acyl compounds toward the weak field as compared with compounds I and IV indicates the deshielding effect of the acyl residue, which is located at $N_{(8)}$ and not at $N_{(1)}$.

Compound IV reacts with HCl to form the hydrochloride. In the IR spectrum of the hydrochloride (in KBr) the C=O band of the N—CO—NPh ureide grouping is shifted toward the high frequency region up to 1760 cm^{-1}, as compared with the C=O frequency (1720 cm^{-1}) of unprotonated IV; this is evidence for weakened conjugation in the N—CO—NPh system.

In the PMR spectrum of the hydrochloride the signal of the methylene protons at $C_{(7)}$ appears as a triplet, and not as a multiplet as in IV; this is evidence for the absence of a proton at $N_{(8)}$. In the weak field in the 8.45-8.90 ppm region there is a broadened signal of two protons that disappears when D_2O is added to the sample. The equivalence of the NH

protons appears in the PMR spectrum of the hydrochloride, while the IR spectra are evidence for the formation of a cationic system that includes all the nitrogen atoms in the molecule.

EXPERIMENTAL

Melting points were determined in a Boetius microblock. PMR spectra were obtained in Varian EM-360 and Tesla 487 (80 MHz) instruments, in $CDCl_3$ with TMS as internal standard. IR spectra were recorded on a Unicam SP-200G spectrometer in KBr tablets. The course of the reaction and the individuality of the compounds obtained were monitored by TLC on Silufol UV-254 plates in 7:3 chloroform—acetone, with development by iodine vapor.

Starting compounds 1-ethoxycarbonyl-2-methylthio-1,4,5,6-tetrahydropyrimidine (I) and 4-sulfonamidophenylhydrazine (III) were synthesized according to [6] and [7], respectively.

2-Phenyl-3-oxo-2,3,5,6,7,8-hexahydro-s-triazolo[4,3-a]pyrimidine (IV). A mixture of 1.01 g (5 mmole) of compound I and 0.54 g (5 mmole) of phenylhydrazine in 5 ml of absolute ethyl alcohol was boiled for 7 h. The reaction mixture was evaporated to dryness in vacuum and the residue was triturated with ether (10 ml). The precipitate was filtered off and crystallized from an ethyl alcohol—ether mixture. Yield, 0.76 g (70%); mp, 176-178°. IR spectrum: 3300, 3260, 1535 (NH), 1720 (N—CO—N), 1640 cm^{-1} (C=N). PMR spectrum: 1.85-2.42 (m, 2H, 6-CH_2); 3.02-3.40 (m, 2H, 7-CH_2); 3.43-3.8 (t, 2H, 5-CH_2); 5.99-6.16 (br. s, 1H, NH); 6.93-8.0 ppm (m, 5H, Ar). Found, %: C 61.0; H 5.5; N 25.8. $C_{11}H_{12}N_4O$. Calculated, %: C 61.1; H 5.6; N 25.9.

2-(4-Sulfonamidophenyl)-3-oxo-2,3,5,6,7,8-hexahydro-s-triazolo[4,3-a]pyrimidine (V). A mixture of 0.5 g (2.5 mmole) of compound I and 0.47 g (2.5 mmole) of compound III in 10 ml of dry pyridine was boiled for 1 h. The pyridine was distilled off in vacuum and the residue was washed with ether (10 ml) and ethanol (2 × 10 ml). After recrystallization from ethyl alcohol the yield was 0.32 g (74%); mp, 322-324°. IR spectrum: 3300, 3200 (NH_2, NH), 1690 (N—CO), 1640 (C=N), 1340, 1160 cm^{-1} (SO_2). PMR spectrum (DMSO-D_6): 1.7-2.2 (m, 2H, 6-CH_2); 3.16-3.4 (m, 2H, 7-CH_2); 3.42-3.88 (t, 2H, 5-CH_2); 6.82-7.1 (br. s, 3H, SO_2NH_2, NH=C=N); 7.67-8.22 ppm (m, 4H, Ar). Found, %: C 44.6; H 4.3; N 23.6. $C_{11}H_{13}N_5O_3$. Calculated, %: C 44.7; H 4.4; N 23.7.

2-Phenyl-3-oxo-8-benzoyl-2,3,5,6,7,8-hexahydro-s-triazolo[4,3-a]pyrimidine (VIIa). A mixture of 1.08 g (5 mmole) of IV and 0.7 g (5 mmole) of benzoyl chloride VIa was boiled for 1 h in 5 ml of pyridine. After cooling, 20 ml of dry ether was poured into the reaction mixture and the whole was left for 12 h. The precipitate was filtered off, dried, and recrystallized from ethyl alcohol. Yield, 1.25 g (78%); mp, 222-224°. IR spectrum: 1715, 1660 (N—CO—N—Ph, N—CO—C), 1615 cm^{-1} (C=N). PMR spectrum: 1.91-2.38 (m, 2H, 6-CH_2); 3.68-4.17 (m, 4H, 5-CH_2, 7-CH_2); 7.0-7.72 ppm (m, 10H, Ar). Found, %: C 67.3; H 4.9; N 17.3. $C_{18}H_{16}N_4O_2$. Calculated, %: C 67.5; H 5.0; N 17.5.

2-Phenyl-3-oxo-8-cinnamoyl-2,3,5,6,7,8-hexahydro-s-triazolo[4,3-a]pyrimidine (VIIb) was synthesized by the procedure described above from IV and cinnamoyl chloride VIb in 68% yield; mp, 212-214°. IR spectrum: 1712, 1670 (N—CO—N, N—CO—C), 1625 cm^{-1} (C=N). PMR spectrum: 1.82-2.31 (m, 2H, 6-CH_2); 3.6-4.11 (m, 4H, 5-CH_2, 7-CH_2); 7.01-8.07 ppm (m, 12H, CH=CH, Ar). Found, %: C 69.2; H 5.2; N 16.0. $C_{20}H_{18}N_4O_2$. Calculated, %: C 69.3; H 5.2; N 16.2.

2-Phenyl-3-oxo-8-(4-chlorobenzoyl)-2,3,5,6,7,8-hexahydro-s-triazolo[4,3-a]pyrimidine (VIIc) was synthesized analogously from IV and 4-chlorobenzoyl chloride VIc in 74% yield; mp, 171-172°. IR spectrum: 1725, 1675 (N—CO—N, N—CO—C), 1615 cm^{-1} (C=N). PMR spectrum: 1.91-2.41 (m, 2H, 6-CH_2); 3.58-4.04 (m, 4H, 5-CH_2, 7-CH_2); 7.00-7.95 ppm (m, 9H, Ar). Found, %: C 60.8; H 4.2, N 15.6. $C_{18}H_{15}ClN_4O_2$. Calculated, %: C 60.9; H 4.3; N 15.7.

2-Phenyl-3-oxo-8-(3-methylbenzoyl)-2,3,5,6,7,8-hexahydro-s-triazolo[4,3-a]pyrimidine (VIId) was synthesized analogously from IV and 3-methylbenzoyl chloride VId in 82% yield; mp, 175-176°. IR spectrum: 1730, 1675 (N—CO—N, N—CO—C), 1625 cm^{-1} (C=N). PMR spectrum: 1.91-2.40 (m, 5H, 6-CH_3); 3.58-4.09 (m, 4H, 5-CH_2); 6.98-7.62 ppm (m, 9H, Ar). Found, %: C 68.4; H 5.3; N 16.9. $C_{19}H_{18}N_4O_2$. Calculated, %: C 68.2; H 5.4; N 16.7.

2-Phenyl-3-oxo-8-acetyl-2,3,5,6,7,8-hexahydro-s-triazolo[4,3-a]pyrimidine (VIIe). A. A mixture of 0.54 g (2.5 mmole) of IV and 1 g (10 mmole) of acetic anhydride in 5 ml of dry pyridine was boiled for 2 h. The solution was evaporated to dryness in vacuum, and the residue was triturated with ether. The precipitate was filtered off and crystallized from ethyl alcohol. Yield, 0.43 g (67%); mp, 175-177°. IR spectrum: 1690 (N—CO—N, N—CO—C,

broad band), 1612 cm^{-1} (C=N). PMR spectrum: 1.82-2.32 (m, 2H, 6-CH_2); 2.62 (s, 3H, $COCH_3$); 3.62-4.11 (m, 4H, 5-CH_2, 7-CH_2); 7.00-7.91 ppm (m, 5H, Ar). Found, %: C 60.3; H 5.4; N 21.4%. $C_{13}H_{14}N_4O$. Calculated, %: C 60.4: H 5.5: N 21.7%.

B. To a solution of 1.08 g (5 mmole) of IV in 15 ml of dry chloroform containing 3 ml of pyridine, cooled to 0°, was added dropwise with stirring 0.39 g (5 mmole) of acetyl chloride in 5 ml of chloroform. The mixture was stirred at 20° for 2 h, and the solution was evaporated to dryness in vacuum. The residue was washed with 10 ml of water, dried, and crystallized from ethyl alcohol. Yield, 0.88 g (68%).

2-Phenyl-3-oxo-8-ethoxycarbonyl-2,3,5,6,7,8-hexahydro-s-triazolo[4,3-a]pyrimidine (VIIf) was synthesized analogously to VIIe by procedure B from IV and C_2H_5OCOCl (VIf). Yield, 72%; mp, 170-172°. IR spectrum: 1745 (O=C-O), 1715 (N-CO-N), 1605 cm^{-1} (C=N). PMR spectrum: 1.21-1.54 (m, 3H, CH_3); 1.88-2.35 (m, 2H, 6-CH_2); 3.55-4.00 (m, 4H, 5-CH_2, 7-CH_2); 4.12-4.58 (q, 2H, $-OCH_2$); 6.95-8.12 ppm (m, 5H, Ar). Found, %: C 58.1; H 5.5; N 19.3. $C_{14}H_{16}N_4O_3$. Calculated, %: C 58.3; H 5.6; N 19.4.

2-Phenyl-3-oxo-2,3,5,6,7,8-hexahydro-s-triazolo[4,3-a]pyrimidine hydrochloride (VIII). To a solution of 0.22 g (1.03 mmole) of IV in 10 ml of ethyl alcohol was added 5 ml of ether saturated with HCl and the mixture was left at 20° for 18 h. The crystals that separated were filtered off and washed with ether. Yield, 0.16 g (66%); mp, 190-192°. IR spectrum: 1760 (N-CO-N), 1680 (C=N), 3200-3080, 2700-2400 cm^{-1}. PMR spectrum: 1.79-2.20 (m, 5H, 6-CH_2); 3.12-3.41 (m, 2H, 7-CH_2); 3.48-3.76 (t, 2H, 5-CH_2); 7.00-8.04 (m, 5H, Ar); 8.45-8.9 ppm (br. s, 2H, NH). Found, %: C 52.1; H 5.1; N 22.0. $C_{11}H_{13}ClN_4O$. Calculated, %: C 52.3; H 5.2; N 22.2.

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