(2H, q, CH_2); 3.44 (3H, s, NCH_3); 3.52 (3H, s, NCH_3); 8.42 (1H, d, 4-H); 8.53 (1H, s, 3'-H); 8.93 ppm (1H, d, 6-H). ^{13}C NMR spectrum (DMSO-D_6): 14.06 ($C_{(11)}$, $^1J_{(11\text{-}11)}$ = 126.9, $^2J_{(11\text{-}10)}$ = 2.5 Hz); 31.62 (NCH_3, ^1J = 147.7 Hz); 35.87 (NCH_3, ^1J = 147.7 Hz); 60.52 ($C_{(10)}$, $^1J_{(10\text{-}10)}$ = 148.9, $^2J_{(10\text{-}11)}$ = 4.9 Hz; 114.44 ($C_{(3)}$); 132.68 ($C_{(5)}$, $^2J_{(5\text{-}4)}$ = 3.7; $^2J_{(5\text{-}6)}$ = 3.7 Hz); 133.53 ($C_{(4)}$, $^1J_{(4\text{-}4)}$ = 172.1, $^3J_{(4\text{-}6)}$ = 4.9 Hz); 140.79 ($C_{(3')}$, $^1J_{(3'\text{-}3')}$ = 219.7, $^3J_{3'\text{-}NCH_3)}$ = 3.7 Hz); 148.01 ($C_{(6)}$, $^1J_{(6\text{-}6)}$ = 185.5; $^3J_{(6\text{-}4)}$ = 3.7 Hz); 152.00 ($C_{(5')}$, $^3J_{(5'\text{-}3')}$ = 6.1, , $^3J_{(5'\text{-}NCH_3)}$ = 3.7 Hz); 161.09 ($C_{(2)}$, $^3J_{(2\text{-}4)}$ = 7.3; $^3J_{(2\text{-}6)}$ = 12.2 Hz); 165.03 ppm ($C_{(8)}$, $^3J_{(8\text{-}4)}$ = 6.1; $^3J_{(8\text{-}10)}$ = 3.1 Hz).

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CHEMICAL CONVERSIONS OF 5,7-DISUBSTITUTED DIHYDRO-1,2,4-TRIAZOLO[1,5-*a*]PYRIMIDINES

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Hydrolysis, oxidation, reduction, alkylation, and nitrosation of aromatic-substituted dihydro-1,2,4-triazolo-[1,5-a]pyrimidines have been studied.

We have studied the chemical properties of dihydrotriazolo[1,5-*a*]pyrimidines as exemplified by 5,7-diphenyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (Ia), previously described by us [1], and its 5-methyl analog (Ib), which was obtained by condensation of 3-amino-1,2,4-triazole (IIa) with benzalacetone (IIIb). The chemical conversions of (Ia, b) are shown in the scheme shown on page 1363.

We studied the behavior of dihydroazolopyrimidines in acid and alkaline media. When solutions of (Ia, b) in 1:1 HCl are heated for 1 h, the compounds are practically completely hydrolyzed to amine (II) and the respective unsaturated ketones (IIIa, b). Compounds (Ia, b) are insoluble in aqueous alkali. In alcoholic KOH they are ionized, as shown in the electron absorption spectra of their solutions by the bands with λ_{max} at 341 and 307 nm, respectively, which disappear upon neutralization. The ionization of (Ia, b), which are quite stable in neutral medium, facilitates their heteroaromatization by atmospheric oxygen. Holding an alcoholic alkali solution of (Ib) in air forms only 5-methyl-7-phenyl-1,2,4-triazolo[1,5-*a*]pyrimidine (IVb)

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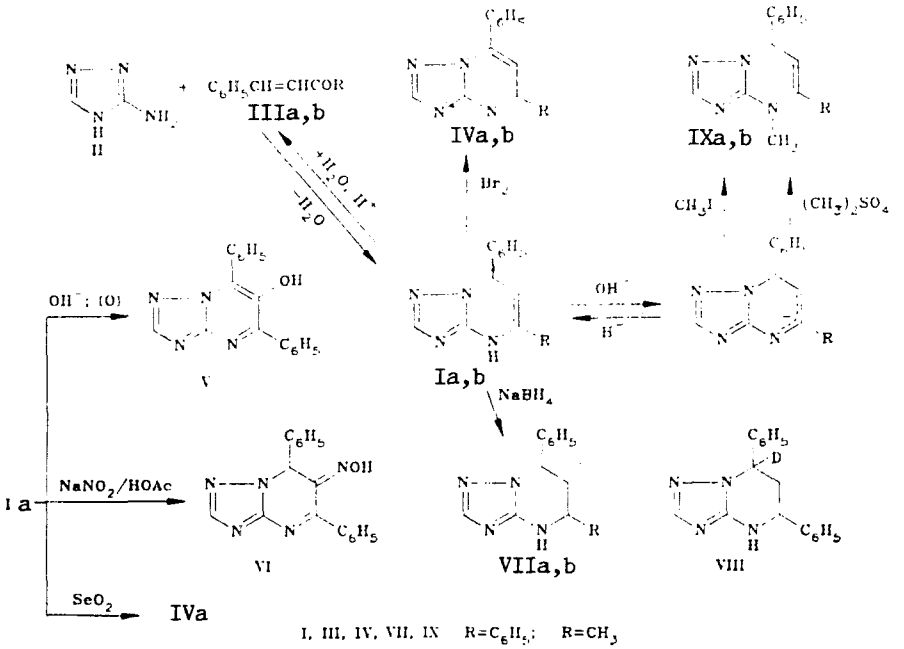

TABLE 1. Properties of Compounds (Ib), (IVb), and (V-IX)*[1]

Compound	Empirical formula	mp, °C*[2]	IR spectrum (in KBr), $\nu_{C=C}$, cm^{-1}	UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	Yield, %
Ib	$C_{12}H_{12}N_4$	212...215	1682	265 (4,30)	85
IVb	$C_{12}H_{10}N_4$	140...141	—	273 (3,72)	80
V	$C_{17}H_{12}N_4O$	222...224	—*[3]	250 (20,97), 323 (14,22)	31*[4]
VI	$C_{17}H_{13}N_5O$	213...214	—	336 (10,76)	91
VIIa	$C_{17}H_{16}N_4$	190...200	—	—	71
VIIb	$C_{12}H_{14}N_4$	150...151	—	—	50
VIII	$C_{17}H_{15}DN_4$	197...198	—	—	71
IXa	$C_{18}H_{16}N_4$	134...136	1650	280 (3,31)	93*[4]
IXb	$C_{13}H_{14}N_4$	116...118	1673	272 (2,70)	50*[4]

*[1](Ia) and (IVa) are described in [1].

*[2](Ib) was crystallized from 1:1 benzene–DMF; (VI) from AcOH; (VII) and (IXa) from 2-propanol.

*[3]ν_{OH} 3513 cm^{-1} (in 1,2-dichloroethane).

*[4]By procedure "A."

and a small amount of resin; but in the case of (Ia) both (V) and triazolo[1,5-*a*]pyrimidine (IVa) are separated (Table 1). Compound (V) was identified as 6-hydroxy-5,7-diphenyl-1,2,4-azolo[1,5-*a*]pyrimidine on the basis of: elemental analysis for C, H, and N, which showed that the molecule contains oxygen; in the mass spectrum, the peak of the molecular ion with m/z 288 (evidence that in the process of formation, the molecular weight of (V) increased by 14 units); in the PMR spectrum, the aromatic proton signals, the singlet of the triazole ring proton, and the broadened singlet of the OH proton (Table 2) (which was also confirmed by the IR spectrum (Table 1)).

Formation of oxy derivative (V) from the respective ambidentate anion (Ia) probably goes via oxidation at the carbanion reaction center followed by dehydrogenation.

It was previously determined [1] that (Ia) is easily heteroaromatized by N-bromosuccinimide. Compound (Ia) is dehydrogenated by either bromine or SeO_2. Compound (Ib) is also oxidized by Br_2 in good yield (Table 1), but is resinified by SeO_2. It is known [2] that dehydropyridine derivatives are easily oxidized by sodium nitrite in glacial acetic acid. But, under these conditions, (Ia) undergoes nitrosation, as follows from the nitrogen content of the resulting compound (VI). In this case the

TABLE 2. PMR Spectra of Compounds (Ib, IVb, V-IX)

Compound	δ, ppm (SSCC, J, Hz)						
	2-H,S	5-H	6-H	7-H	CH_3		NH (OH), S
I b	7,83	—	4,61 d (2,0)	5,63 d	1,69 s	6,75 . . . 7,25	—
IV b	8,00	—	6,10 s	(J=2,0)	2,13 s	7,15 . . . 7,35	—
V	8,32	—	—	—	—	6,50 . . . 8,20	9,54
VI	8,05	—	—	—	—	6,90 . . . 7,55	—
VII a	8,35	5,12 d.d (J_{5A}=3,5; J_{5B}=10,5)	H_A:2,82 oct H_B:2,67 oct (J_{AB}=−14,0)	6,67 s 5,61 d.d (J_{7A}=4,5; J_{7B}=11,0)	—	7,20 . . . 7,50	7,85
VII	8,45	3,69 m	H_A:2,39 oct H_B:1,83 oct (J_{5A}=3,1; J_{5B}=9,7; J_{AB}=−14,1)	5,32 d.d (J_{7A}=4,8; J_{7B}=11,0)	1,23 d (J= =6,4)	7,15 . . . 7,50	7,60
VIII	8,30	5,10 d.d (J_{5A}=4,0; J_{5B}=10,5)	H_A:2,71 d.d H_B:2,59 d.d (J_{AB}=−14,0)	—	—	7,15 . . . 7,50	7,55
IX a	7,81	—	4,78 d (J=3,0)	5,89 d (J=3,0)	2,74 s	6,90 . . . 7,15	—
IX b	7,90	—	4,68 d (J=2,5)	5,60 d (J=2,5)	1,62 s 2,65 s	6,80 . . . 7,15	—

*Spectra of (V, VIIa, b, and VIII) were obtained in DMSO-D_6.

IR spectrum of (VI) (Table 1) lacks the C=C band, which denies the structure of the respective N-nitroso derivative. The PMR spectrum of the nitrosation product shows, besides the aromatic proton multiplet (6.88-7.45 ppm), two singlets (6.67 and 8.05 ppm, Table 2). These data permit us to assign (VI) an oxime structure, formed by nitrosation of (Ia) at the electron-rich $C_{(6)}$.

Reduction of dihydrotriazolopyrimidines (Ia, b) with sodium borohydride forms the tetrahydro derivatives (VIIa, b); in this case the C=C band in the IR spectrum and the long-wave absorption in the UV spectrum disappear (Table 1). Since (VIIa, b) have two chiral centers, the question arises concerning the stereoselectivity of their formation. The answer is given by the PMR spectra. The spectrum of each compound characterizes an individual isomer; this also appears in the case of the uncrystallized samples, which points unequivocally to the stereoselectivity of the reaction in question. In the PMR spectra of (VIIa, b) the signals of methyne and methylene protons are easily identified (Table 2). In the spectrum of (VIIb) the $H_{(5)}$ proton signal is additionally broadened by interaction with CH_3, and is substantially shifted to the strong field by comparison with the $H_{(7)}$ signal. Since in the (VIIa) spectrum the chemical shifts of the methyne protons are close together, the unequivocal assignment of these signals is based on the PMR spectrum of the 7-deutero substituted (VIII). When $H_{(7)}$ is replaced by deuterium the signals and δ 3.61 ppm disappear, and the multiplicity of the CH_2 proton signals decreases; however, the signals with δ 5.12 ppm are practically unchanged. In (VIIa, b) the two methyne protons have close-to-axial orientation; one of the vicinal SSCC of these protons lies between 9.7 and 11.0 Hz, which is typical of J_{aa} [3]. Thus, (VIIa, b) can be assigned a cis struc-ture, while in the predominant conformers the substituents at positions 5 and 7 of the bicycle have quasiequatorial orientation.

Attempts to acetylate (Ia, b) with acetic anhydride or acetyl chloride or to tosylate them with p-toluenesulfonyl chloride in pyridine or alcoholic alkali or by heating the reagents together without a solvent were unsuccessful. In all cases the original reagents were separated, sometimes contaminated with resin.

For the dihydropyridine derivatives it was determined that, depending on reaction conditions, they could be alkylated either at nitrogen or oxygen [4]. Compounds (Ia, b) were not alkylated in pyridine, DMF, or DMSO; but in alcoholic alkali the N-methyl derivatives (IXa, b) were obtained in good yield (Table 1) by reaction with methyl iodide or dimethyl sulfate. We obtained a similar result by treating (Ia) with a suspension of KOH in DMF; C-alkylation, noted for dihydropyridine derivatives [4], did not occur.

EXPERIMENTAL

IR spectra were measured with a Specord IR-75 instrument in KBr tablets. UV spectra were measured with a Specord M-40 spectrophotometer in isopropyl alcohol [c = (2-3)·10^{-5} mole/liter]. PMR spectra of (IVb, V, VI, IXa, b) were obtained

with a Tesla BS-487-B (80 MHz), with HMDS internal standard; those of (VIIa, b) and (VIII) with a Bruker WP-200 (200 MHz), with TMS internal standard. Mass spectrum of (V) was recorded with a Varian MAT-212 instrument (70 eV ionizing voltage). Synthesized compounds were separated by preparative chromatography on a column of Al_2O_3 III (standard activity) (1 cm diameter, filled to a height of 10 cm). Compound individuality and reaction mixture composition were controlled by TCLC on Silufol UV-254 plates, with elution by chloroform and acetone.

Elemental content of N (IV-IX) and C and H (V) agreed with the calculated values.

Synthesis of 5,7-diphenyl-4,7-dihydro-1,2,4-triazolo-[1,5-*a*]pyrimidine (Ia) is described in [1].

5-Methyl-7-phenyl-4,7-dihydro-1,2,4-triazolo[1,5*a*]pyrimidine (Ia). A solution of 0.85 g (10 mmoles) of 3-amino-1,2,4-triazole and 1.45 g (10 mmoles) of benzalacetone in 0.5 ml of DMF was boiled for 1 h and stirred with 30 ml of benzene; 1.80 g of (Ib) was filtered off.

Hydrolysis of 5,7-Diphenyl-4,7-dihydro-1,2,4-triazolo-[1,5-*a*]pyrimidine (Ia). A solution of 0.82 g (3 mmoles) of (Ia) in 40 ml of 1:1 HCl was heated on a water bath for 1 h, neutralized with saturated Na_2CO_3 solution, and extracted with chloroform. The extract was dried and evaporated to dryness to give 0.54 g (90%) of benzalacetophenone (IIIa), mp 59°C [5] from ethanol. After extraction 3-amino-1,2,4-triazole (II) (R_f 0.56) and (Ia) (R_f 0.05) were identified in the aqueous layer by TLC with 1:1:1 acetone–hexane–methanol eluent.

Compound (Ib) was studied under analogous conditions; benzalacetone, mp 40°C [5] was obtained in 73% yield.

Oxidation of 5,7-Diphenyl-4,7-dihydro-1,2,4-triazolo-[1,5-*a*]pyrimidine (Ia). A. In 20 ml of 5% KOH in 2-propanol was dissolved 0.82 g (3 mmoles) of (Ia) and the solution was let stand for 24 h. The mixture was neutralized with acetic acid to pH 7-8 and poured into water, and the precipitate was filtered off and chromatographed on Al_2O_3, with $CHCl_3$ eluent. There were separated 0.45 g (56%) of (IVa), mp 159-160°C [3] (fraction with R_f 0.44), and 0.27 g of 6-hydroxy-5,7-diphenyl-1,2,4-triazolo[1,5-*a*]pyrimidine (V) (fraction with R_f 0.10). Mass spectrum of (V): 289 (20), 288 (100), 287 (11), 274 (11), 273 (49), 236 (12), 194 (21), 193 (21), 130 (13), 104 (12), 103 (29), 77 (13).

Under analogous conditions (Ib) gives 80% of (IVb).

B. To a solution of 2.6 g (9 mmoles) of (Ia) in 35 ml of acetic acid was added a solution of 1.5 g (9.4 mmoles) of bromine in 5 ml of acetic acid, and the mixture was stirred for 1 h. Then it was poured into water and 2.5 g (90%) of (IVa) was filtered off.

Compound (IVb) was obtained analogously.

C. To a solution of 0.82 g (3 mmoles) of (Ia) in 15 ml of acetic acid was added 0.4 g (3.6 mmoles) of SeO_2 and the mixture was stirred for 1 h at room temperature. The resulting solution was mixed with 50 ml of water, and the resinous precipitate was chromatographed on a column of Al_2O_3 with acetone eluent. The fraction with R_f 0.82 was collected; 0.25 g (30% of (IVa)).

6-Oximino-5,7-diphenyl-6,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (VI). To a solution of 0.82 g (3 mmoles) of (Ia) in 15 ml of AcOH was added 0.3 g (4.3 mmoles) of sodium nitrite in 0.05 g portions. The reaction mixture was poured into water, and 0.83 g of (VI) was filtered off.

5,7-Diphenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine (VIIa). To a suspension of 2.7 g (10 mmoles) of (Ia) in 20 ml of methanol was added 3.75 g (0.1 mole) of $NaBH_4$. After gas evolution stopped, the reaction mixture was boiled for 15 min and poured into water, and 1.93 g of (VIIa) was filtered (recrystallized from 2-propanol).

Compound (VIIb) was obtained analogously.

5,7-Diphenyl-4-deutero-4,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine (VIII). A solution of 0.4 g (1.9 mmoles) of β-deuterochalcone and 0.17 g (2 mmoles) of 3-amino-1,2,4-triazole in 0.5 ml of DMF was boiled for 1.5 h, then mixed with benzene. The precipitate was filtered off, suspended in 10 ml methanol, and treated with 0.5 g (13 mmoles) of $NaBH_4$. The mixture was boiled for 15 min and poured into water; 0.25 g of (VII) was filtered off, mp 191-192°C (from 2-propanol).

4-Methyl-5,7-diphenyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (IXa). A. To a solution of 3% KOH in 2-propanol was added 0.82 g (3 mmoles) of (Ia) and 0.85 g (6 mmoles) of CH_3I. The reaction mixture was held for 1 h, then poured into water, and the precipitate was filtered off; 0.80 g of (IXa) was obtained (crystallized from 2-propanol).

Compound (IXb) was obtained analogously.

B. Following procedure A, but using 0.77 g (6 mmoles) of dimethyl sulfate instead of CH_3I, 0.6 g (70%) of (IXa) was obtained.

Compound (IXb) was obtained analogously in 50% yield.

C. To a suspension of 0.9 g of KOH in 10 ml of DMF were added 0.82 g (3 mmoles) of (Ia) and 0.85 g (6 mmoles) of CH_3I. The mixture was stirred for 2 h at room temperature, mixed with 50 ml of H_2O, and neutralized with acetic acid. The

resulting solution was extracted with chloroform, the extract was evaporated, and the residue was chromatographed on a column of Al_2O_3 (elution with acetone). The fraction with R_f 0.75 was collected; 0.75 g (86%) of (IXa).

D. Following procedure C, but using 0.77 g (6 mmoles) of dimethyl sulfate instead of CH_3I, 0.63 g (73%) of (IXa) was obtained.

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SELECTIVE $N_{(2)}$ ALKYLATION OF TETRAZOLE AND 5-SUBSTITUTED TETRAZOLES BY ALCOHOLS

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Alkylation of tetrazole and its 5-substituted derivatives by 5-tert-butyl, isopropyl, and cyclohexyl alcohols in concentrated H_2SO_4 results in high yields of the corresponding 2-alkyltetrazoles alone, irrespective of electronic properties and size of the substituent at the 5-position of the tetrazole ring. The tert-butylation of tetrazole in phosphoric acid results in the formation of a mixture of isomeric 1- and 2-substituted derivatives, the concentration of the 1-isomer increasing with decrease in the concentration of the acid in the mixture.

Alkylation is one of the main methods of the synthesis of N-substituted tetrazoles. Up to the present time the alkylation of salts of tetrazoles by alkyl halides and alkyl sulfates, which generally results in a mixture of isomeric 1- and 2-substituted tetrazoles has been most extensively studied [1]. Practically all the described cases of selective alkylation of tetrazoles at the $N_{(2)}$ atom involve steric hindrances to the approach to the reaction center at $N_{(1)}$ and/or the presence of a strong electron-acceptor group at the 5-position of the tetrazole ring [1, 2]. The reactions of tetrazoles with other alkylating agents and in other media (neutral, acidic) have been studied to a considerably lesser extent.

In [3-5] was described the alkylation of a series of tetrazoles with α-ferrocenyl alcohols in acetic and trifluoroacetic acids, also leading to the formation of a mixture of isomeric 1- and 2-substituted derivatives in the absence of a bulky aryl substituent, or a strong electron-acceptor (NO_2) at the 5-position of the tetrazole ring. Using the α-ferrocenylalkylation of tetrazole as an example, it was shown that on transition from acetic to trifluoroacetic acid, i.e., when the acidity of the medium is increased, the proportion of the 1-isomer in the mixture substantially increases [4].

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