THREE COMPONENT CONDENSATION OF 3-AMINO-1,2,4-TRIAZOLE WITH CARBONYL COMPOUNDS. A NEW SYNTHESIS OF 1,2,4-TRIAZOLO[1,5-a]PYRIMIDINES

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Three component condensation of 3-amino-1,2,4-triazole with an aromatic aldehyde and ketone gives 1,2,4-triazolo[1,5-a]-pyrimidines. An x-ray structural investigation of 5-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-a]benzo[h]quinazoline was undertaken in order to determine the course of this reaction.

One of the most convenient methods for synthesis of dihydro-1,2,4-triazolo[1,5-a]pyrimidines is the reaction of amino-1,2,4-triazoles with unsaturated carbonyl compounds, the latter being crotonic condensation products [1, 2]. The current work was connected with the synthesis of 1,2,4-triazolo[1,5-a]pyrimidines and their dihydro derivatives by three component condensation of 3-amino-1,2,4-triazole (I) with the corresponding aromatic aldehyde and ketone.

Refluxing a solution of amine I, aldehyde IIa or IIb, and ketone IIIa or IIIc in DMF gave the aryl-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidines IVa-c. Treatment of I with benzaldehyde IIa and tetralone Va under the same conditions gave the isomeric tetrahydrotriazolobenzoquinazolines VIa and VIIa and a small amount (5%) of the dihydrotriazolobenzoquinazoline VIIIa. By contrast, reaction of I, IIa, and indanone Vb gave only VIb and VIIIb and none of VIIb, even when the condensation was performed in an inert atmosphere.

The increased tendency of dihydroazolopyrimidines annelated by a 5-membered carbocycle to aromatization has been noted previously [2].

The desired dehydrogenation of VIIa was carried out by standing a solution in alcoholic base in air. Comparator compounds IXa, b studied by us were prepared as reported before [2] (see scheme on top of following page).

TABLE 1. Physical Parameters for IVb, c, VIIa, and VIIIa, b*

Compound	Empirical formula	mp, °C	IR spectra, $\nu_{C=C}$, cm^{-1}	UV spectra, λ_{max}, nm (log ε)	Yield, %
IVb	$C_{17}H_{13}ClN_4$	221...223	1660	294 (5,5)	80
IVc	$C_{17}H_{13}ClN_4$	215...216	1642	291 (4,3)	78
VIIa	$C_{19}H_{16}N_4$	175...176	1648	308 (2,7)	24
VIIIa	$C_{19}H_{16}N_4$	234	—	328 (20,0)	60
VIIIb	$C_{19}H_{16}N_4$	167...168	—	336 (16,0)	29

*Compounds IVa, VIa, b were characterized in [1, 2]; their yields were 70, 60, and 80%, respectively.

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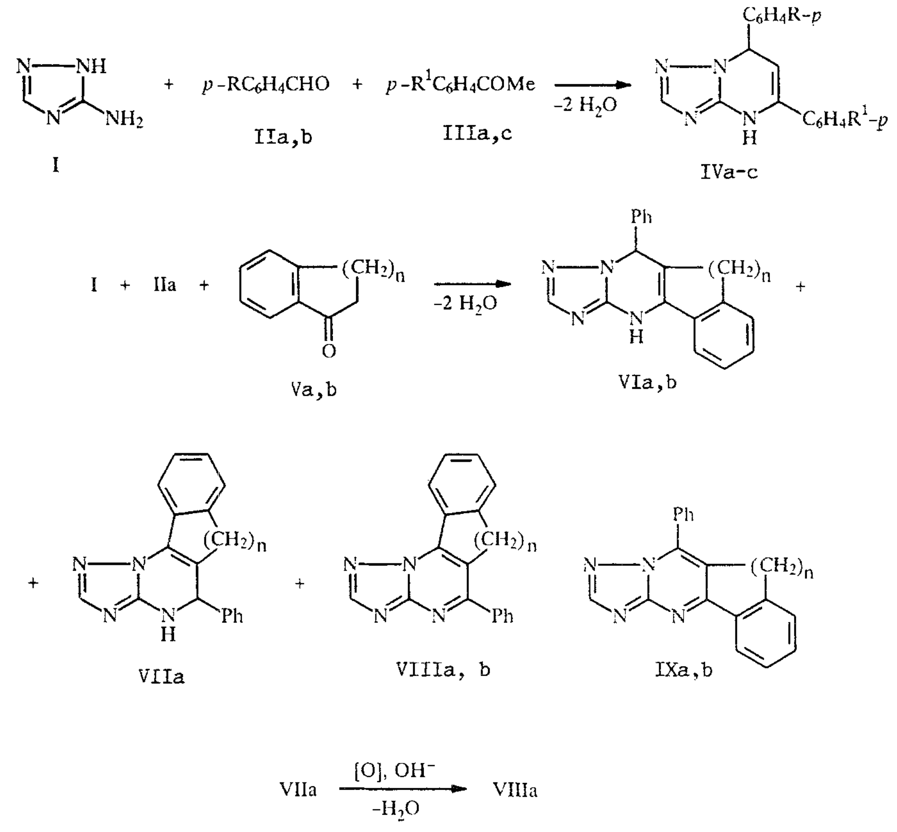

II—IV a R = H, R^1 = H; b R = Cl, R^1 = H; c R = H, R^1 = Cl; V—IX a n = 2, b n = 1

The IR spectra of IV, VII as KBr tablets showed $\nu_{C=C}$ bands at 1642-1660 cm^{-1} which were absent in the spectra of the heteroaromatics VIII (Table 1). The electronic spectra of the dihydrotriazolopyrimidines IV and the tetrahydrotriazolobenzoquinazoline VIIa showed absorption at 294-308 nm (Table 1), similar to the spectra of 5,7-diaryl dihydrotriazolo[1,5-a]pyrimidines described in [1, 2] and including compounds IVa, VIa, b.

The differences in the structures of isomers VI and VII, VIII, and IX were clearly revealed in their PMR spectra (Table 2). For VI (Table 2) and IX (see [2]) all of the aromatic protons resonate between 6.8 and 7.9 ppm. In the spectra of VIIa, VIIIa, b one proton signal appears to low field (8.4-9.1 ppm) of the aromatic protons due to the anisotropic effect of the triazole

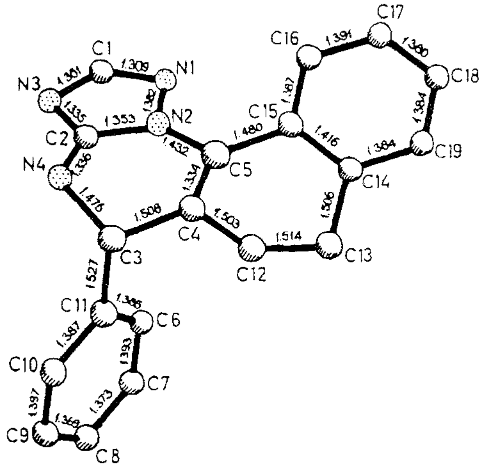

Fig. 1. Molecular structure and bond lengths for VIIb (excluding H atoms).

TABLE 2. PMR Spectra of IV, VI-VIII

Compound	δ, ppm (SSCC, Hz)					
	aromatic protons	CH* s	CHC_6H_5 s	=CH s	NH s	$(CH_2)_n$
IVb	7,0...7,7 m	7,67	6,30	5,20	9,9	—
IVc	7,0...7,8 m	7,65	6,25	5,26	10,0	—
VIa	6,8...7,4 m	7,79	6,01	—	10,6	1,8...2,7 m
VIb	6,8...7,6 m	7,75	6,29	—	10,4	3,13d (-22,7), 2,69d
VIIa	7,2...7,5 m 8,40 dd (7,5, 2,4)	7,70	5,25	—	8,1	1,9...2,8 m
VIIIa	7,3...7,8 m 9,11dd (7,3, 8,5)	8,76	—	—	—	2,8...3,0 m
VIIIb	7,5...8,2 m 8,58 dd (7,3, 2,3)	8,86	—	—	—	4,50 s

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*Triazole ring.

TABLE 3. Some Valence (ω) and Torsional (τ) Angles in VIIa

Angle	ω	Angle	τ
$N_{(2)}-N_{(1)}-C_{(1)}$	101,4 (1)	$N_{(2)}-N_{(1)}-C_{(1)}-N_{(3)}$	-1,4 (4)
$N_{(1)}-C_{(1)}-N_{(3)}$	117,0 (2)	$C_{(2)}-N_{(3)}-C_{(1)}-N_{(1)}$	0,6 (4)
$C_{(1)}-N_{(3)}-C_{(2)}$	101,8 (1)	$C_{(1)}-N_{(3)}-C_{(2)}-N_{(2)}$	0,5 (4)
$N_{(2)}-C_{(2)}-N_{(3)}$	110,3 (1)	$N_{(1)}-N_{(2)}-C_{(2)}-N_{(3)}$	-1,3 (5)
$N_{(1)}-N_{(2)}-C_{(2)}$	109,5 (1)	$C_{(2)}-N_{(2)}-N_{(1)}-C_{(1)}$	1,6 (5)
$N_{(2)}-C_{(2)}-N_{(4)}$	120,7 (1)	$C_{(3)}-N_{(4)}-C_{(2)}-N_{(2)}$	-27,4 (4)
$C_{(2)}-N_{(4)}-C_{(3)}$	117,6 (1)	$C_{(2)}-N_{(2)}-C_{(5)}-C_{(4)}$	12,7 (5)
$C_{(2)}-N_{(4)}-H_{(4N)}$	117,1 (14)	$N_{(4)}-C_{(3)}-C_{(11)}-C_{(6)}$	86,0 (4)
$C_{(3)}-N_{(4)}-H_{(4N)}$	115,4 (15)	$C_{(4)}-C_{(5)}-C_{(15)}-C_{(14)}$	15,4 (4)
$C_{(3)}-C_{(4)}-C_{(12)}$	115,0 (1)	$N_{(1)}-N_{(2)}-C_{(5)}-C_{(15)}$	15,2 (5)
$N_{(2)}-C_{(5)}-C_{(15)}$	121,4 (1)	$C_{(4)}-C_{(12)}-C_{(13)}-C_{(14)}$	43,8 (5)
$N_{(4)}-C_{(3)}-C_{(4)}$	109,8 (1)	$N_{(1)}-C_{(5)}-C_{(6)}-C_{(7)}$	-46,8 (4)
$C_{(3)}-C_{(4)}-C_{(5)}$	123,1 (1)	$C_{(2)}-N_{(4)}-C_{(3)}-C_{(4)}$	37,4 (5)

ring. In addition, the 4,5-dihydro structure of the triazolopyrimidine in VIIa is indicated by the higher field position of the NH signal (8.1 ppm) than in the 4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidines IVb, c, VIa, b (9.5-10.5 ppm, Table 2) in which the NH group has enamine character.

The structure of VIIa was proved unambiguously by x-ray structural investigation (Fig. 1, Table 3). The triazole ring in VIIa is planar (see torsional angles in Table 3). The dihydropyrimidine and cyclohexadiene rings have a chair conformation. The folding parameters for these rings were calculated as in [3] and were $S = 0.47$, $\vartheta = 53.4°$, $\psi = 29.3°$ and $S = 0.54$, $\vartheta = 55.0°$, and $\psi = 28.0°$, respectively. The C_3 phenyl substituent is pseudoaxial and rotated by 25.8° from the $N_2C_3C_{11}$ plane.

The length of the C_5-C_{15} bond [1.480(1) Å] points to conjugation between the π-electron systems of the C_{14}-C_{19} phenyl ring and the dihydrotriazolopyrimidine fragment. However, the conjugated system referred to is non-polar overall. The C_{14}-C_{19} benzene ring is tilted from the plane $C_1N_1N_2C_2N_3C_5N_4$ on the side opposite to the C_3 substituent and forming an angle of 24.5(4)° to it. This tilt is evidently determined by nonvalence interactions between atoms N_1 and H_{16}, the distance between which [2.34(1) Å] is significantly less than the sum of their van der Waal radii (1.50 and 1.16 Å, respectively [4]).

According to the C_2-N_4 bond length [1.338(4) Å] there is significant conjugation between the N_4 atom unsaturated electron pair and the triazole ring π-system. By contrast to 4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidines [1,5], however, the N_4 atom in VIIa is pyramidal and its tilt from the $C_2C_3H_{N4}$ plane is 0.19(1) Å.

TABLE 4. Coordinates for the Nonhydrogen Atoms ($\times 10^4$) and Hydrogen Atoms ($\times 10^3$) in VIIa

Atom	x	y	z	Atom	x	y	z
$N_{(1)}$	10696 (2)	14824 (2)	3833 (1)	$C_{(17)}$	9742 (3)	15105 (2)	2130 (1)
$N_{(2)}$	12550 (2)	14421 (2)	3763 (1)	$C_{(18)}$	10409 (2)	14260 (2)	1712 (1)
$N_{(3)}$	12585 (2)	15158 (2)	4613 (1)	$C_{(19)}$	12021 (2)	13345 (2)	1807 (1)
$N_{(4)}$	15496 (2)	14315 (2)	4268 (1)	$H_{(1)}$	974 (3)	1566 (3)	451 (1)
$C_{(1)}$	10840 (3)	15260 (2)	4339 (1)	$H_{(3)}$	1752 (3)	1345 (3)	385 (1)
$C_{(2)}$	13634 (2)	14613 (2)	4234 (1)	$H_{(4N)}$	1614 (3)	1433 (3)	461 (1)
$C_{(3)}$	16174 (2)	13143 (2)	3890 (1)	$H_{(6)}$	1334 (3)	1091 (3)	384 (1)
$C_{(4)}$	15066 (2)	13296 (2)	3348 (1)	$H_{(7)}$	1336 (3)	841 (3)	426 (1)
$C_{(5)}$	13313 (2)	13882 (2)	3283 (1)	$H_{(8)}$	1607 (3)	738 (3)	472 (1)
$C_{(6)}$	14515 (3)	10538 (2)	4047 (1)	$H_{(9)}$	1895 (3)	891 (3)	480 (1)
$C_{(7)}$	14498 (3)	9035 (2)	4268 (1)	$H_{(10)}$	1894 (3)	1155 (3)	441 (1)
$C_{(8)}$	16084 (3)	8458 (2)	4560 (1)	$H_{(121)}$	1693 (3)	1189 (3)	299 (1)
$C_{(9)}$	17696 (3)	9356 (3)	4623 (1)	$H_{(122)}$	1687 (3)	1364 (3)	275 (1)
$C_{(10)}$	17724 (3)	10866 (3)	4403 (1)	$H_{(131)}$	1530 (3)	1201 (3)	209 (1)
$C_{(11)}$	16126 (2)	11471 (2)	4113 (1)	$H_{(132)}$	1415 (3)	1107 (3)	252 (1)
$C_{(12)}$	16058 (2)	12743 (2)	2873 (1)	$H_{(16)}$	1021 (3)	1566 (3)	295 (1)
$C_{(13)}$	14654 (2)	12168 (2)	2421 (1)	$H_{(17)}$	858 (3)	1576 (3)	207 (1)
$C_{(14)}$	12956 (2)	13226 (2)	2317 (1)	$H_{(18)}$	977 (3)	1429 (3)	134 (1)
$C_{(15)}$	12251 (2)	14065 (2)	2748 (1)	$H_{(19)}$	1252 (3)	1279 (3)	151 (1)
$C_{(16)}$	10665 (2)	15013 (2)	2645 (1)				

EXPERIMENTAL

X-Ray Investigation. Crystals of VIIa ($C_{19}H_{16}N_4$) are monoclinic; at $-120°C$, $a = 7.0828(1)$, $b = 8.482(2)$, $c = 24.948(3)$ Å, $\beta = 95.16(3)°$, $Z = 4$, $d_{calc} = 1.337$ g/cm^3, space group $P2_1/c$. Unit cell parameters and intensities of 3981 independent reflections were measured on an automated Syntex four circle $P2_1$ diffractometer with graphite monochromator ($\lambda_{MoK\alpha}$, $\theta/2\theta$ scanning, $2° < 2\theta < 46°$).

The structure was solved by a direct method using the complex SHELXTL PLUS program. All of the hydrogen atoms were revealed by difference synthesis. Refinement in the anisotropic approximation (isotropic for hydrogen atoms) was carried out to $R = 0.041$ ($R_W = 0.058$). Atomic coordinates are given in Table 4.

IR spectra were taken on a Specord IR-75 instrument for KBr tablets. Electronic spectra were obtained on a Specord M-40 spectrophotometer for alcohol solutions at a concentration of $2\text{-}4 \cdot 10^{-5}$ M. PMR spectra were taken on a Gemini-200 instrument using DMSO-D_6 solvent and TMS internal standard. TLC analysis was carried out on Silufol UV-254 plates with chloroform and acetone eluents.

The elemental analysis for nitrogen agreed with that calculated for the synthesized materials.

Reaction of 3-Amino-1,2,4-triazole (I) with Benzaldehyde (IIa) and Tetralone (Va). A solution of amine I (0.84 g, 1 mmole), aldehyde IIa (1.06 g, 1 mmole), ketone Va (1.46 g, 1 mmole) in DMF (1 ml) was refluxed for 3 h, mixed with acetone (50 ml), and the product VIa (1.8 g, 60%) with mp 286°C [2] was filtered off. The filtrate was evaporated to 5 ml, cooled to 20°C, and filtered to give VIIa (0.5 g, 17%) with mp 175-176°C (from ethanol). The filtrate was chromatographed on an Al_2O_3 column (1 cm diameter, filling height 20 cm, acetone eluent) to give VIIIa (0.15 g, 5%) with mp 234°C from the fraction with R_f 0.67 and a further amount of VIIa (0.2 g, 7%) from the fraction with R_f 0.53.

Under similar conditions, condensation of amine I with aldehydes IIa, b and ketones IIIa, c and Vb gave IVa-c, VIb, and VIIIb.

5-Phenyl-6,7-dihydro-1,2,4-triazolo[1,5-a]benzo[h]quinazoline (VIIIa). A solution of VIIa (0.2 g, 0.4 mmole) in 5% KOH (50 ml) in ethanol was allowed to stand in air for 5 h at 40-50°C. Water (100 ml) was added and VIIIa (0.12 g, 60%) was filtered off.

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