CYCLOCONDENSATION OF α,β-UNSATURATED KETONES WITH 3-AMINO-1,2,4-TRIAZOLE

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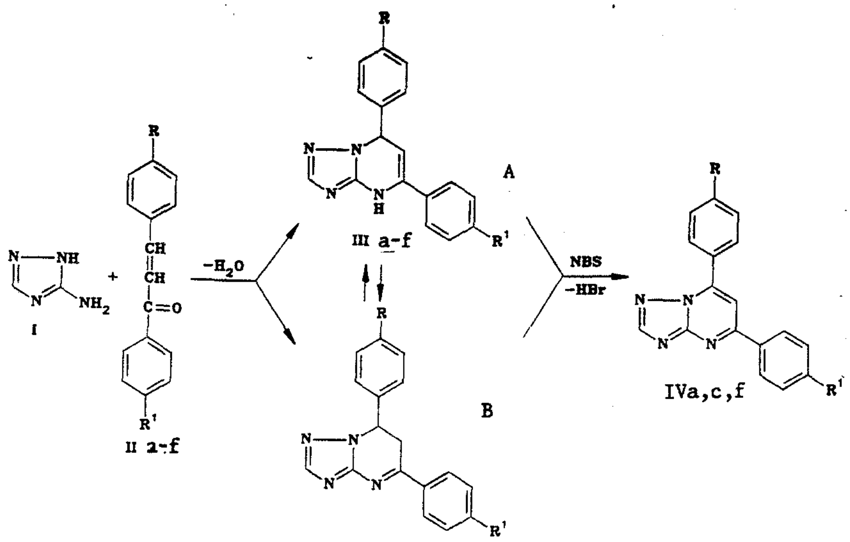
Dihydro-1,2,4-triazolo[1,5-a]pyrimidine derivatives were obtained by condensation of 3-amino-1,2,4-triazole with 1,3-diaryl-1-propen-3-ones. The structure of 5-phenyl-7-(4-methylphenyl)-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidine was established by x-ray diffraction analysis.

The condensation of heterocyclic amines with bielectrophilic compounds is a method for the synthesis of heterocyclic systems [1]. There are only individual reports of the use of aromatic unsaturated ketones as the electrophilic component [2-4].

The aim of the present research was to investigate the condensation of 3-amino-1,2,4-triazole (I) with 1,3-diaryl-1-propen-3-ones (chalcones) IIa-f. 5,7-Diaryldihydro-1,2,4-triazolo[1,5-a]pyrimidines IIIa-f (Table 1) are formed by refluxing solutions of the amine and ketone in dimethylformamide (DMF). Only the starting substances with admixed resin were recovered in the condensation of 4-nitro- and 4-dimethylamino-substituted chalcones.



II—IV a R=R'=H; b R=CH_3, R'=H; c R=H, R'=CH_3O; d R=H, R'=$(CH_3)_2N$; e R=R'=Cl; f R=H, R'=NO_2

Compounds IIIa-f are stable during storage but readily undergo aromatization to triazolo[1,5-a]pyrimidines IVa, c, f on treatment with N-bromosuccinimide (NBS). In contrast to the synthesis of azolopyrimidines by condensation of aminoazoles with β-dicarbonyl compounds, which is distinguished by low selectivity [1], in our case the formation of the pyrimidine heteroring occurs regioselectively; this was established by means of TLC and spectral methods.

The IR spectra of IIIa-f contain bands of medium intensity at 1590-1597 and 1655-1665 cm^{-1} (Table 1), which are due to stretching vibrations of C=N and C=C bonds of the two-ring system. A narrow band ($\Delta\nu_{1/2}$ = 40 cm^{-1}) with a frequency of 3443 cm^{-1}, which characterizes the vibrations of a free NH group, is observed in the spectrum of a solution of IIIa in CCl_4

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TABLE 1. Characteristics of IIIa-f and IVa, c, f

Compound	mp, °C	IR spectrum (KBr), ν, cm^{-1}		UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	Chemical shifts, δ, ppm (in d_6-DMSO)				N found, %	Empirical formula	N calc., %	Yield, %
		C=N	C=C		CH*, d	CH, d	ArH, m	NH, s				
IIIa	226—227	1593†	1665	287 (4,5)	5,21	6,24	7,31—7,75	10,09	20,6	$C_{17}H_{14}N_4$	20,6	68
IIIb	228	1594	1662	285 (4,6)	5,20	6,21	7,16—7,79	10,06	19,9	$C_{18}H_{16}N_4$	19,7	69
IIIc	207	1590	1665	282 (5,9)	5,12	6,22	6,94—7,74	10,01	18,5	$C_{18}H_{16}N_4O$	18,4	67
IIId	229	1612	—	278 (8,7)‡, 303 (8,0); 391 (16,6)	5,23**	5,96	6,78—8,00	—	21,8	$C_{19}H_{19}N_5$	21,7	65
IIIe	227—228	1597	1681	293 (5,1)	5,25	6,31	7,19—7,81	10,14	16,2	$C_{17}H_{12}N_4Cl_2$	16,3	70
IIIf	193—194	1598	1655	355 (4,6)	5,50	6,30	7,31—8,37	10,05	21,9	$C_{17}H_{13}N_5O_2$	21,9	78
IVa	158—159	1603	—	318 (15,0)	—	—	6,80—8,15	—	20,6	$C_{17}H_{12}N_4$	20,5	68
IVc	166	1602	—	337 (16,2)	—	—	6,75—8,45	—	18,7	$C_{18}H_{14}N_4O_2$	18,5	80
IVf	188	1611	—	266 (8,4), 315 (9,2)	—	—	7,28—8,60	—	22,4	$C_{17}H_{11}N_5O_2$	22,1	82

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*The spin-spin coupling constants (SSCC) for IIIa-f are 2.5-3 Hz.

†ν_{MH} (in CCl_4) 3343 cm^{-1}.

‡In connection with the unknown tautomeric composition of a solution of IIId in methanol it was difficult to determine ε. The $(D_{max}/c) \cdot 10^{-3}$ values are presented in parentheses.

**In CF_3COOH. PMR spectrum of IIId in d_6-DMSO: 9.86 (1H, s, NH), 6.48-8.09 (20H, m, ArH), 6.16 (1H, d, CH), 5.76 (1H, t, CH), 5.01 (1H, d, CH), 3.61 (2H, d, CH_2), 2.98 [6H, s, $(CH_3)_2N$], 2.89 [6H, s, $(CH_3)_2N$].

TABLE 2. Some Bond (ω) and Torsion (τ) Angles of the IIIb Molecule

Angle	ω°	Angle	τ°
$C_{(2)}N_{(1)}C_{(3)}$	126,6(3)	$C_{(2)}N_{(1)}C_{(3)}C_{(4)}$	−16,4(4)
$C_{(2)}N_{(1)}N_{(2)}$	109,6(3)	$N_{(2)}N_{(1)}C_{(3)}C_{(4)}$	166,2(4)
$C_{(3)}N_{(1)}N_{(2)}$	123,6(3)	$C_{(2)}N_{(1)}C_{(3)}C_{(12)}$	105,5(4)
$N_{(1)}C_{(3)}C_{(4)}$	105,7(3)	$N_{(2)}N_{(1)}C_{(3)}C_{(12)}$	−71,9(4)
$N_{(1)}C_{(3)}C_{(12)}$	111,5(3)	$N_{(1)}C_{(3)}C_{(4)}C_{(5)}$	16,6(3)
$C_{(4)}C_{(3)}C_{(12)}$	112,0(3)	$C_{(12)}C_{(3)}C_{(4)}C_{(5)}$	−105,0(4)
$C_{(3)}C_{(4)}C_{(5)}$	125,0(3)	$C_{(3)}C_{(4)}C_{(5)}N_{(4)}$	−5,0(3)
$C_{(4)}C_{(5)}N_{(4)}$	120,9(3)	$C_{(3)}C_{(4)}C_{(5)}C_{(6)}$	173,7(5)
$C_{(4)}C_{(5)}C_{(6)}$	124,9(3)	$C_{(4)}C_{(5)}N_{(4)}C_{(2)}$	−10,0(4)
$N_{(4)}C_{(5)}C_{(6)}$	114,2(3)	$C_{(5)}N_{(4)}C_{(2)}N_{(1)}$	10,6(3)
$C_{(2)}N_{(4)}C_{(5)}$	117,3(3)	$C_{(5)}N_{(4)}C_{(2)}N_{(3)}$	−167,3(5)
$N_{(1)}C_{(2)}N_{(4)}$	121,4(3)	$N_{(4)}C_{(2)}N_{(1)}C_{(3)}$	4,1(3)
$N_{(1)}C_{(2)}N_{(3)}$	111,2(3)	$N_{(4)}C_{(2)}N_{(1)}N_{(2)}$	−178,2(4)
$N_{(4)}C_{(2)}N_{(3)}$	127,5(3)	$N_{(4)}C_{(2)}N_{(3)}C_{(1)}$	177,7(5)
$C_{(1)}N_{(3)}C_{(2)}$	101,2(3)	$C_{(2)}N_{(3)}C_{(1)}N_{(2)}$	0,7(3)
$N_{(2)}C_{(1)}N_{(3)}$	116,6(3)	$N_{(3)}C_{(1)}N_{(2)}N_{(1)}$	−0,7(3)
$N_{(1)}N_{(2)}C_{(1)}$	101,3(3)	$C_{(1)}N_{(2)}N_{(1)}C_{(3)}$	178,2(5)
		$C_{(1)}N_{(2)}N_{(1)}C_{(2)}$	0,4(4)
		$N_{(2)}N_{(1)}C_{(2)}N_{(3)}$	−0,1(4)
		$N_{(1)}C_{(2)}N_{(3)}C_{(1)}$	0,0(4)

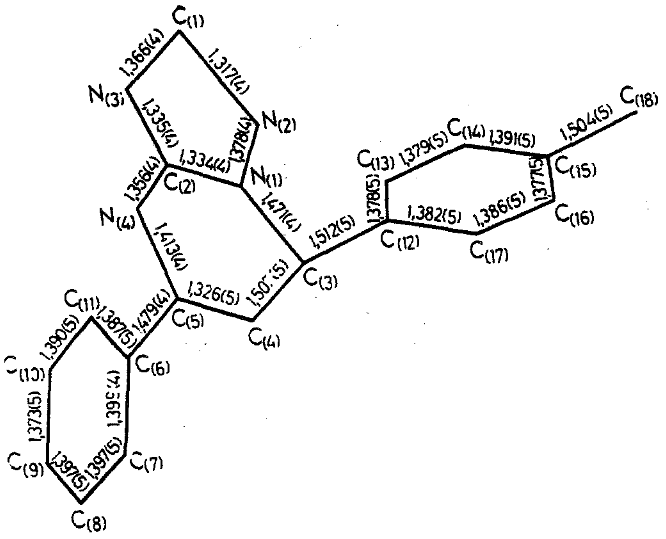

Fig. 1. Structure of the IIIb molecule (without the hydrogen atoms) with the bond lengths.

at a concentration of $2\cdot10^{-4}$ M (a study of the concentration IR spectral dependences was hindered in connection with the low solubilities of IIIa-f). The bands of stretching vibrations of NH groups cannot be unequivocally isolated in the IR spectra of KBr pellets, probably because of intermolecular hydrogen bonds.

The UV spectra of dihydro derivatives IIIa-f are generally similar; the long-wave absorption band in them lies at 282-335 nm [$\varepsilon \sim (4.5\text{-}5.9)\cdot10^3$]. Only the spectrum of IIId with $R^1 = (CH_3)_2N$, the long-wave band of which is intense and shifted bathochromically (λ_{max} 391 nm, Table 1), has an anomalous appearance.

The PMR spectra of IIIa-c, e, f confirm the individuality of the compounds and contain, in addition to a multiplet of aromatic protons, two doublets of CH protons and a singlet of the proton of an imino group (Table 1). The absence of signals that are typical for the protons of a CH_2—CH group constitutes evidence that 6,7-dihydro form B virtually is not realized (within the limits of the sensitivity of PMR spectroscopy). The situation is different in the case of IIId, the PMR spectrum of which (d_6-DMSO) contains, in addition to the signals noted above, signals of protons of the A_2X system of form B. According to the data on the integral intensities of the corresponding signals, the A/B ratio is ~1:1.

Tautomer B is distinguished by a more developed, as compared with A, chromophore system and is probably responsible for the specific characteristics of the UV spectra of IIId. A

TABLE 3. Coordinates of the Nonhydrogen Atoms ($\cdot 10^4$) and of the Hydrogen Atoms ($\cdot 10^3$) of the IIIb Molecule

Atom	x	y	z	Atom	x	y	z
$N_{(1)}$	6350(2)	2638(5)	4107(2)	$C_{(16)}$	9043(3)	4362(7)	3539(2)
$N_{(2)}$	6826(2)	902(5)	4613(2)	$C_{(17)}$	8153(3)	3332(6)	3346(2)
$N_{(3)}$	5861(2)	2763(5)	5101(2)	$C_{(18)}$	10271(3)	7393(8)	4206(3)
$N_{(4)}$	5226(2)	5436(5)	4008(2)	$H_{(1)}$	670(2)	3(5)	566(2)
$C_{(1)}$	6496(2)	1070(6)	5183(2)	$H_{(3)}$	642(2)	195(4)	306(2)
$C_{(2)}$	5792(2)	3694(6)	4406(2)	$H_{(4)}$	561(2)	524(5)	236(2)
$C_{(3)}$	6487(3)	3236(6)	3369(2)	$H_{(N_4)}$	481(2)	600(5)	422(2)
$C_{(4)}$	5665(2)	4799(6)	2897(2)	$H_{(7)}$	385(2)	596(5)	162(2)
$C_{(5)}$	5119(2)	5852(6)	3202(2)	$H_{(8)}$	266(2)	873(5)	96(2)
$C_{(6)}$	4378(2)	7549(6)	2763(2)	$H_{(9)}$	251(3)	1189(6)	167(2)
$C_{(7)}$	3781(3)	7307(7)	1930(2)	$H_{(10)}$	350(2)	1234(6)	309(2)
$C_{(8)}$	3098(3)	8953(7)	1529(2)	$H_{(11)}$	465(2)	958(4)	373(2)
$C_{(9)}$	2999(3)	10774(7)	1947(2)	$H_{(13)}$	723(2)	699(5)	418(2)
$C_{(10)}$	3582(3)	11031(7)	2764(2)	$H_{(14)}$	874(2)	866(5)	449(2)
$C_{(11)}$	4269(3)	9411(6)	3170(2)	$H_{(16)}$	951(2)	374(6)	335(2)
$C_{(12)}$	7474(2)	4280(6)	3580(2)	$H_{(17)}$	796(2)	190(5)	303(2)
$C_{(13)}$	7701(3)	6262(6)	3999(2)	$H_{(18,1)}$	1078(3)	681(7)	468(3)
$C_{(14)}$	8595(3)	7250(6)	4194(2)	$H_{(18,2)}$	1055(3)	711(6)	381(3)
$C_{(15)}$	9292(2)	6317(6)	3971(2)	$H_{(18,3)}$	1030(3)	901(7)	422(3)

strong electron-donor group, which, by promoting the manifestation of conjugation effects, may stabilize tautomer B, is present in this compound. The dimethylamino group is evidently protonated in the case of measurement in trifluoroacetic acid, and the signals of tautomer B therefore vanish.

Spectral methods do not give a complete idea of the structures of IIIa-f and IVa, c, f. Thus the position (2 or 4) of the triazole heteroring at which cyclization takes place cannot be established unequivocally; in the case of compounds with $R \neq R^1$ they do not make it possible to establish the positions of the aromatic rings in the heteroring. The 3,5-, 3,7-, 4,5-, and 4,7-dihydro forms satisfy the PMR spectra of IIIa-f equally. The answer was obtained by means of x-ray diffraction analysis of IIIb ($R = CH_3$, $R^1 = H$), which demonstrated that the investigated compound has the 5-phenyl-7-(4-methylphenyl)-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidine structure (Fig. 1, Table 2). In addition, the data regarding the presence of one hydrogen atom each at the $N_{(4)}$ and $C_{(2)}$ atoms indicate unequivocally that the IIIb molecule exists in the crystal in 4,7-dihydro form A. The IIIb molecules in the crystal form centrosymmetric dimers due to $N_{(4)}$–$H_{(N_4)}$...$N_{(3)}$ hydrogen bonds. The parameters of the hydrogen bond are as follows: $N_{(4)}$–$H_{(N_4)}$ 0.92(3) Å, $H_{(N_4)}$...$N_{(3)}$ 2.03(3) Å, $N_{(3)}$...$N_{(4)}$ 2.935(4) Å, angle $N_{(4)}H_{(N_4)}N_{(3)}$ 169(3)°.

The structure suggests the formation of IIIb through cyclization of the 4-methylchalcone in the 2 position of the triazole heteroring and the amino group; the latter condenses with the carbonyl group of the ketone. This pathway can be explained by the fact that the $N_{(2)}$ atom is more nucleophilic than the $N_{(4)}$ atom of 1,2,4-triazoles with respect to alkylating agents [5].

As in other 1,2,4-triazoles (for example, see [6]), the triazole ring in the IIIb molecule is actually planar (see the torsion angles in Table 2). The conformational parameters of the dihydropyrimidine ring calculated in accordance with the data in [7] are as follows: $S = 0.25$, $\theta = 108°$, and $\varphi_2 = 92°$, according to [7], this indicates that this ring exists in the form of a nonuniformly compressed tub. In fact, the $N_{(1)}$, $C_{(2)}$, $C_{(4)}$, and $C_{(5)}$ atoms are located in the same plane (the P_1 plane) with an accuracy of no less than 3σ. The $C_{(3)}$ and $N_{(4)}$ atoms deviate from the P_1 plant on the same side by 0.207(4) and 0.111(3) Å, respectively. The p-methylphenyl substituent attached to the $C_{(3)}$ atom of the two-ring system occupies a pseudoaxial position, while the $H_{(3)}$ atom occupies a pseudoequatorial position [the $C_{(3)}$–$H_{(3)}$ and $C_{(3)}$–$C_{(12)}$ bonds form angles of 44.9(4)° and –65.6(4)°, respectively, with the P_1 plane].

Attention is directed to the nonequivalence of the lengths of the $C_{(2)}$–$N_{(4)}$ [1.356(4) Å] and $C_{(2)}$–$N_{(3)}$ [1.335(4) Å] bonds in the IIIb molecule; the lengths of these bonds in 3-amino-2H-1,2,4-triazole are virtually equal (1.342 and 1.340 Å, respectively [6]). The lengthening of the $C_{(2)}$–$N_{(4)}$ bond and shortening of the $C_{(2)}$–$N_{(3)}$ bond in the IIIb molecule are probably associated with weakening of the p,π conjugation in the iminotriazole fragment of this molecule when it is included in the dihydropyrimidine ring.

EXPERIMENTAL

X-Ray Diffraction Analysis. The crystals of 5-phenyl-7-(4-methylphenyl)-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidine $C_{18}H_{16}N_4$ were monoclinic and had the following parameters at 20°C: $a = 15.075(2)$, $b = 6.0335(5)$, $c = 17.995(2)$ Å, $\beta = 114.515(7)°$, $Z = 4$, $d_{calc} = 1.286$ g/cm³, and space group $P2_1/n$. The cell parameters and the intensities of 1229 independent reflections with $|F| \geq 2\sigma$ were measured with a Hilger–Watts automatic four-circle diffractometer ($\lambda_{Cu\ K\alpha}$).

The structure was decoded by the direct method by means of the MULTAN program. All of the hydrogen atoms were revealed by differential synthesis. Refinement within the anisotropic (isotropic for the hydrogen atoms) approximation was carried out up to $R = 0.044$ ($R_W = 0.033$). The coordinates of the atoms are presented in Table 3.

The IR spectra of KBr pellets of IIIa-f and IVa, c, f (and of a solution of IIIa in CCl_4 with a concentration of $2 \cdot 10^{-4}$ M) were recorded with a Specord IR-75 spectrometer. The UV spectra of solutions in methanol with a concentration of $(2\text{-}3) \cdot 10^{-5}$ M were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of solutions in d_6-DMSO and CF_3COOH were recorded with a Tesla BS-2487-B spectrometer (80 MHz, hexamethyldisiloxane as the internal standard). The individuality of IIIa-f and IVa, c, f was monitored by TLC on Silufol UV-254 plates with chloroform and methanol as the eluents.

5,7-Diphenyl-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidine (IIIa). A solution of 0.4 g (4.7 mmole) of 3-amino-1,2,4-triazole and 0.83 g (4 mmole) of the chalcone in 1 ml of DMF was refluxed for 1 h, after which it was diluted with 30 ml of benzene. The mixture was cooled, and the precipitated crystals were removed by filtration to give 0.75 g (68%) of IIIa with mp 226°C [from benzene–dimethylformamide (3:1)].

Compounds IIIb-f were similarly obtained.

5,7-Diphenyl-1,2,4-triazolo[1,5-a]pyrimidine (IVa). A 0.45-g (2.5 mmole) sample of N-bromosuccinimide was added with stirring to a suspension of 0.55 g (2 mmole) of IIIa in 30 ml of warm (50-60°C) methanol, and the reaction mixture was refluxed for 2 h. The filtrate was concentrated to one third of the original volume, and the residue was cooled and filtered to give 0.37 g (68%) of crystals of IVa with mp 151-152°C (from methanol).

Compounds IVc, f (from IIIc, f, respectively) were similarly obtained.

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