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CYCLOCONDENSATION OF 2-AMINOBENZIMIDAZOLE WITH DIMEDONE AND ITS ARYLIDENE DERIVATIVES

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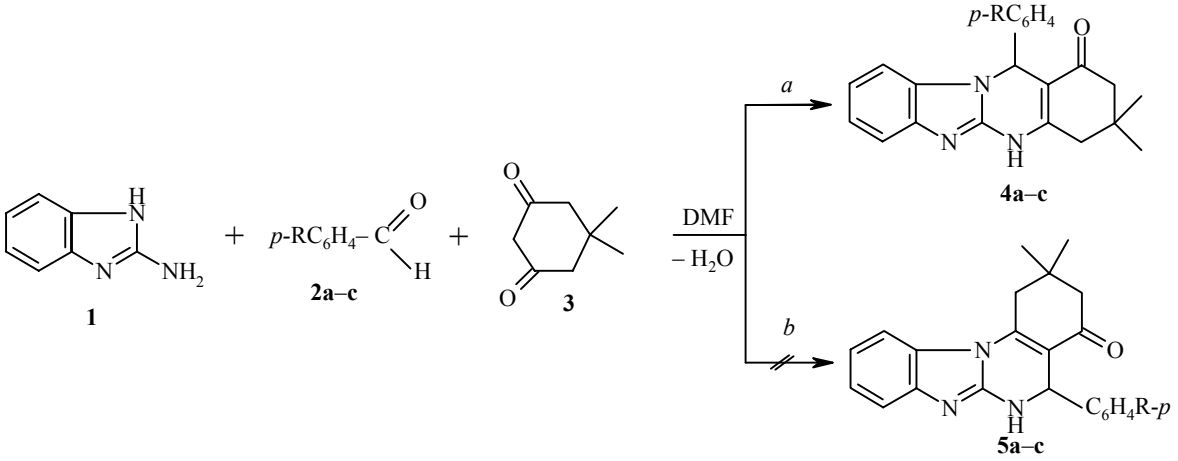
The reactions of 2-aminobenzimidazole with substituted benzaldehydes and dimedone, 2-arylidene derivatives of dimedone, 9-arylhexahydro-1H-xanthene-1,8(2H)-diones and also with dimedone and DMF have been studied. The direction of formation of the pyrimidine ring has been established and discussed. An X-ray structural investigation of 2,2-dimethyl-2,3-dihydrobenzimidazo[1,2-a]quinazolin-4(1H)-one has been carried out.

Keywords: 2-aminobenzimidazole, 2-arylidene derivatives of dimedone, dimedone, partially hydrogenated quinazoline systems, X-ray structural analysis, cyclocondensation.

Regiodirectivity in the cyclizations of α-amino azoles with carbonyl 1,3-biselectrophiles is the subject of a series of studies [1-4]. However, work in this area has not lost current interest because of the many reagents used in similar reactions. In this publication we report a study of the reaction of 2-aminobenzimidazole (**1**) in DMF solvent with the substituted benzaldehydes **2a-c** and dimedone **3**, with the products of the intermolecular condensation of the latter (2-arylidene-5,5-dimethylcyclohexane-1,3-dione (**6a**), and the 9-aryl-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-diones **7a-c**) as well as with dimedone **3**.



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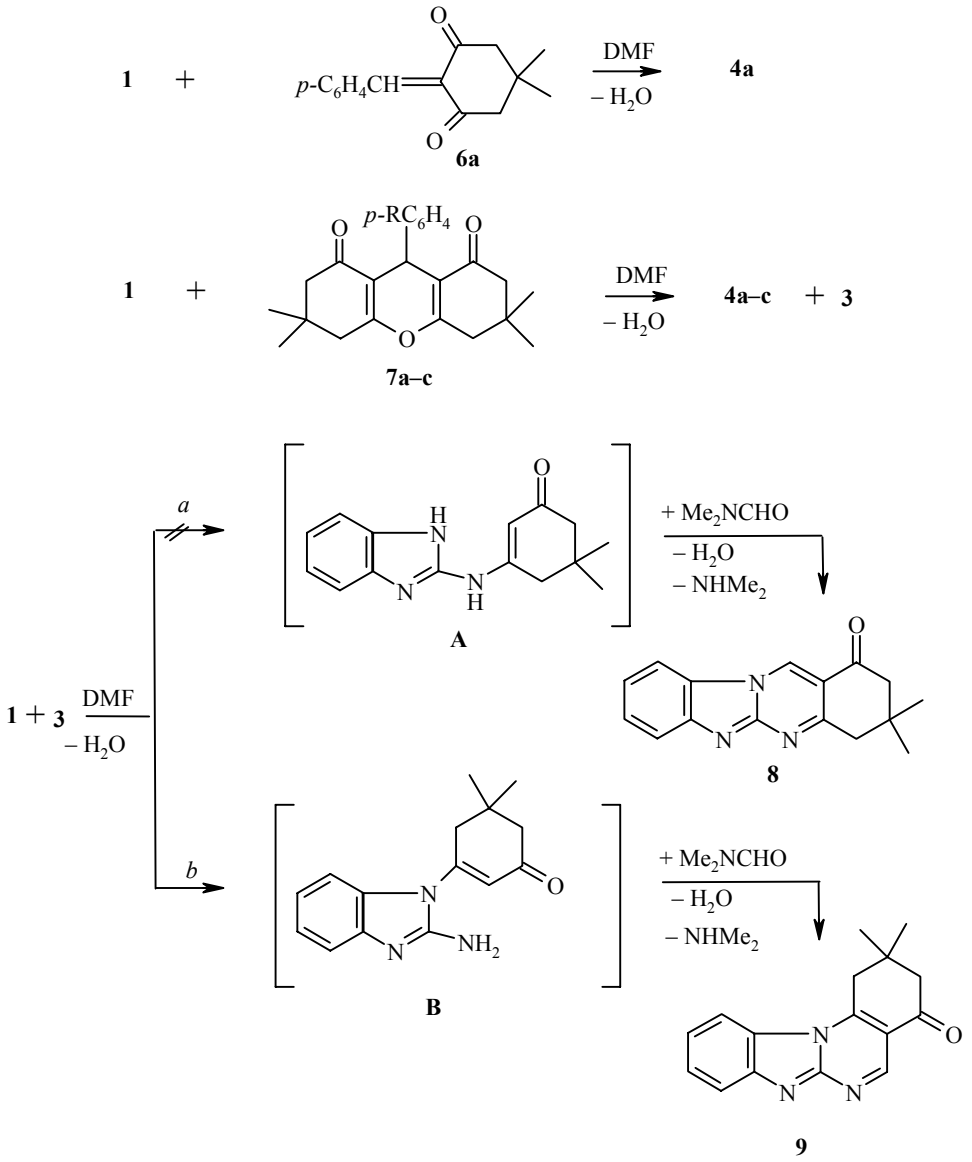

2, **4**, **5**, **7 a** R = H, **b** R = MeO, **c** R = NO_2

One of the alternative routes for formation of the pyrimidine ring (*a* or *b*) occurs depending on the nature of the carbonyl compounds taking part in the reaction with the amine **1**.

Hence a short reflux (3-5 min) of equimolar amounts of the amine **1**, aldehyde **2a-c**, and dimedone **3** in DMF gives the 12-aryl-3,3-dimethyl-3,4,5,12-tetrahydrobenzimidazo[1,2-*b*]quinazolin-1(2H)-ones **4a-c**. Similar results are obtained in the reactions of compound **1** with the arylidene derivative **6a** or the xanthenediones **7**.

On the other hand, the reaction of equimolar amounts of the aminobenzimidazole **1** with dimedone **3** in DMF occurs *via* the route *b* and gives compound **9** which has the benzimidazole and tetrahydroquinazoline fragments joined other than in the example of the products **4**.

The structure of the synthesized compounds **4a-c, 9** was proved by IR and mass spectrometry and by ^{1}H NMR (Tables 1 and 2). The structure of compound **9** was also confirmed by X-ray structural analysis.

The mass spectra of compounds **4a,b, 9** showed peaks for the molecular ions with *m/z* 343, 373, and 265 respectively. In the case of compound **9** (spectrum, see Experimental) this value shows that DMF molecule plays the part of one of the carbonyl functions in the formation of the reaction product.

TABLE 1. Characteristics of Compounds **4a-c** and **9**

Compound	Empirical formula	Found N, % / Calculated N, %	mp, °C	IR spectrum, (KBr), ν, cm^{-1}	Yield, %*
4a	$C_{22}H_{21}N_3O$	11.9 / 12.2	>300	3100-2500, 1640, 1612, 1592, 1568	65
4b	$C_{23}H_{23}N_3O_2$	11.1 / 11.3	>300	3100-2500, 1644, 1612, 1592, 1568	57
4c	$C_{22}H_{20}N_4O_3$	14.3 / 14.4	>300	3100-2500, 1644, 1612, 1592, 1568	53
9	$C_{16}H_{15}N_3O$	15.6 / 15.8	256-258	2972, 1692, 1592, 1512	60

* Using method A.

The IR spectra of compounds **4a-c** are similar and absorption bands are noted for a carbonyl group at 1640 and broad band in the range 3100-2600 cm^{-1}, this being the result of overlap of bands characteristic of associated NH, methyl, and methylene groups. The IR spectrum of compound **9** shows a typical carbonyl group absorption at 1648 cm^{-1}.

In the reactions of the amine **1** with benzaldehydes **2a-c** and dimedone **3** the two possible condensed systems **4** and **5** can be formed. The choice between these isomers can be made on the basis of an analysis of the ^{1}H NMR spectra of the obtained products (Table 2). They show signals for the aryl protons, the NH and CH groups, two CH_2 fragments (forming AB systems), and two CH_3 groups. The value for the NH group signal at 11.3-11.0 ppm is typical for dihydroazolopyrimidine systems which contain a C=C–N–H system. In the dihydro isomers with the separated amino group and ethylene fragment the proton discussed resonates at a much higher field (8-9 ppm) [4, 5]. Hence the synthesized compounds have structure **4**.

The reaction between the amine **1** and dimedone **3** with participation of DMF can also occur via routes a or b to give the structures **8** or **9** respectively.

The ^{1}H NMR spectrum of the product obtained by us has signals for all of the groups and fragments indicated in its potential structure. A marked shift was noted for the signals of the protons of one of the methylene groups to low field when compared with the compounds **4** (Table 2). This must result both from the electron acceptor influence of the pyrimidobenzimidazole fragment and also the strong deshielding effect through space which can be considered as indirect evidence supporting structure **9** for the obtained product.

An unambiguous answer regarding the structure of the compound discussed was obtained on the basis of the results of X-ray structural analysis (Figure 1, Tables 3 and 4). In the molecule of compound **9** the tricyclic pyrimido[1,2-*a*]benzimidazole fragment is planar within an accuracy of 0.03 Å. The cyclohexenone fragment

TABLE 2. ^{1}H NMR Spectra of Compounds **4a-c**

Compound	Chemical shift, δ, ppm (*J*, Hz)						
	NH (1H, br. s)	H_{arom} (m)	12-H (1H, s)	2,2- and 4,4-H_2 (H_AH_B)			CH_3 (3H, s)
				H_A (2H, d)	H_B (2H, d)	J_{AB}	
4a	11.10	7.41-6.92 (9H)	6.41	2.58, 2.53	2.06, 2.05	-14.1, -15.6	0.94, 1.06
4b*	11.01	7.42-6.73 (8H)	6.35	2.62, 2.53	2.06, 2.25	-16.5, -16.2	0.95, 1.06
4c	11.31	8.10-7.04 (8H)	6.60	2.66, 2.57	2.07, 2.28	-20.7, -15.9	0.92, 1.07

* The signal for the OCH_3 group is observed at 3.66 ppm (3H, s).

exists in a half chair conformation (folding parameters [6]: $S = 0.73$, $\theta = 37.34°$, $\psi = 29.36°$). The deviations of atoms $C_{(10)}$ and $C_{(9)}$ from the mean square plane of the remaining ring atoms are 0.33 and -0.40 Å respectively. The given asymmetry in the conformation of the half chair is likely due to the shortened intramolecular contacts $H_{(16A)}\cdots C_{(7)}$ 2.85, $H_{(16A)}\cdots C_{(11)}$ 2.67, $H_{(16A)}\cdots C_{(12)}$ 2.85, and $H_{(8A)}\cdots C_{(6)}$ 2.86 (sum of the van der Waal radii 2.87 Å [7]) and $H_{(8A)}\cdots H_{(5)}$ 2.17 Å (2.32 Å). It should be noted that the conformation of the tetrahydro ring as a half chair is not typical for such a compound (in similar systems a sofa type conformation occurs or one somewhat distorted towards a sofa half chair [8-13]). The $C_{(7)}$–$C_{(12)}$ bond in the molecule **9** (1.357(6) Å) is slightly lengthened when compared with the mean value of 1.326 Å [14] which typifies similar structures [8-13].

The defined structure for compounds **4a-c** shows that the direction of the process of pyrimidine ring formation takes the form of a reaction between a carbonyl atom of the dimedone **3** (or the dimedone fragment in compounds **6, 7**) and the amino group of the amino azole and not its endocyclic reaction center. This is in agreement with overall trends found for the reaction of amine **1** with α,β-unsaturated ketones [5] and points in favour of a first stage for the interaction of the 2-aminobenzimidazole with the aldehydes and dimedone as a condensation of two carbonyl components of the reaction.

A change in the direction of formation of the pyrimidine ring with the preparation of compound **9** must be connected to the change in the subsequent stage of the heterocyclization and, in fact, with initial reaction of the amine with dimedone and then with DMF. In addition, according to data in [15, 16], the formation of the two isomeric enamino ketones **A** and **B** might be expected in the first stage of the reaction. However, the subsequent reaction of intermediate **A** with DMF would lead to formation of the quinazoline system **8** and this is not observed. The scheme for the formation of the product **9** proposed by us includes the stage of condensation of the ketone at the endocyclic nitrogen atom in the amine **1** which leads to the intermediate **B**. With the participation of the DMF the latter cyclizes to the target product **9**. A similar mechanism has been proposed previously for the reaction of aminoazoles with DMF and benzocycloalkanones [16].

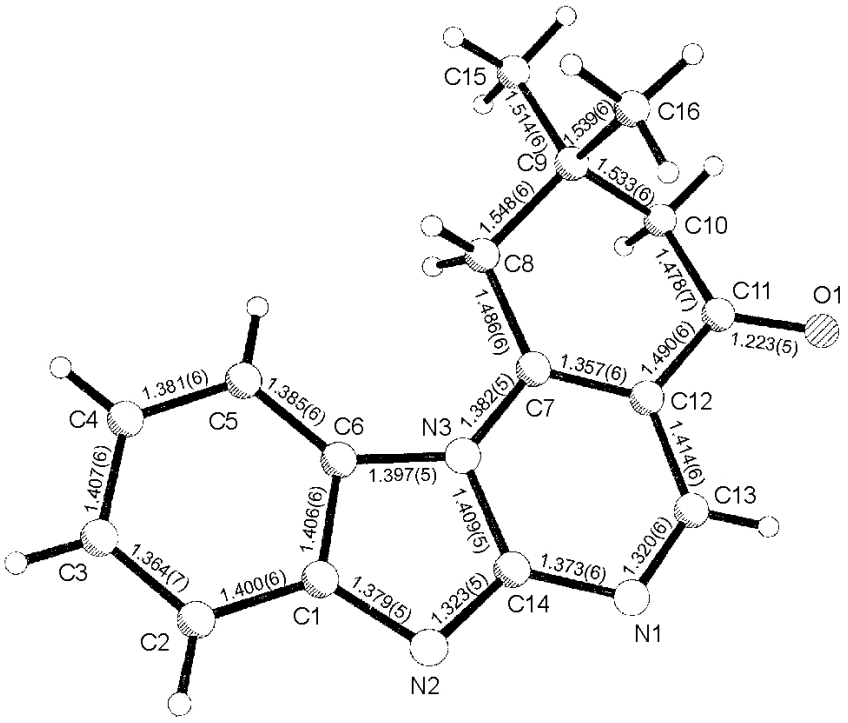

Fig. 1. Structure of the molecule of compound **9**.

TABLE 3. Several Valence (ω) and Torsional (τ) Angles in the molecule **9**

Angle	ω, deg.	Angle	τ, deg.
C(13)N(1)C(14)	115.3(4)	C(12)C(7)C(8)C(9)	-13.9(6)
C(14)N(2)C(1)	104.2(4)	C(7)C(8)C(9)C(10)	43.1(5)
C(6)N(3)C(14)	106.3(3)	C(8)C(9)C(10)C(11)	-58.1(5)
N(2)C(1)C(6)	112.7(4)	C(9)C(10)C(11)C(12)	43.7(5)
C(7)N(3)C(14)	120.7(4)	C(10)C(11)C(12)C(7)	-12.2(5)
C(5)C(4)C(6)	122.1(5)	C(11)C(12)C(7)C(8)	-3.1(6)
C(12)C(7)N(3)	116.8(4)	C(14)N(3)C(7)C(12)	2.8(5)
N(3)C(6)C(1)	104.0(4)	N(3)C(7)C(12)C(13)	-0.9(5)
C(12)C(7)C(8)	123.8(4)	C(7)C(12)C(13)N(1)	-0.9(6)
C(7)C(8)C(9)	114.1(4)	C(12)C(13)N(1)C(14)	0.7(6)
C(7)C(12)C(13)	120.2(4)	C(13)N(1)C(14)N(3)	1.2(5)
N(1)C(14)N(3)	122.3(4)	N(1)C(14)N(3)C(7)	-3.1(5)
C(7)C(12)C(11)	119.7(4)		
N(1)C(13)C(12)	124.6(4)		
N(2)C(14)N(3)	112.8(4)		

The absence of compound **9** in the reaction products of the aminobenzimidazole with aldehydes and dimedone must be associated with the significantly greater reactivity of benzaldehydes when compared with DMF.

TABLE 4. Coordinates ($\times 10^4$) and Equivalent Isotropic Thermal Parameters ($Å^2 \times 10^3$) for the Non-hydrogen Atoms in the Molecule **9**

Atom	*x*	*y*	*z*	$U_{(eq)}$
O(1)	3488(6)	6655(5)	3084(2)	78(1)
N(1)	2719(5)	7085(5)	4846(2)	49(1)
N(2)	2075(5)	5513(5)	5681(2)	49(1)
N(3)	2528(4)	4080(4)	4856(1)	39(1)
C(1)	1972(5)	3836(6)	5778(2)	43(1)
C(2)	1674(6)	3037(7)	6300(2)	54(1)
C(3)	1669(6)	1353(7)	6311(2)	54(1)
C(4)	1963(6)	437 6)	5809(2)	50(1)
C(5)	2263(6)	1188(6)	5288(2)	47(1)
C(6)	2241(5)	2898(6)	5279(2)	42(1)
C(7)	2829(5)	3971(5)	4273(2)	39(1)
C(8)	2816(6)	2324(5)	3987(2)	43(1)
C(9)	2657(6)	2391(5)	3307(2)	43(1)
C(10)	4003(7)	3756(6)	3138(2)	49(1)
C(11)	3521(6)	5382(6)	3373(2)	41(1)
C(12)	3106(6)	5412(5)	3993(2)	49(1)
C(13)	3052(6)	6932(6)	4295(2)	43(1)
C(14)	2433(5)	5630(6)	5130(2)	60(1)
C(15)	3219(7)	730(6)	3077(2)	56(1)
C(16)	548(6)	2776(6)	3050(2)	78(1)

EXPERIMENTAL

X-ray Structural Analysis of Compound 9. Crystals of 2,2-dimethyl-2,3-dihydrobenzimidazo[1,2-*a*]-quinazolin-4(1H)-one **9** are monoclinic, $C_{16}H_{15}N_3O$, at 20°C: a = 6.972(3), b = 8.097(2), c = 22.905(12) Å; β = 97.85(4)°; V = 1280.9(9) Å^3; M_r = 265.31; Z = 4, space group $P2(1)/c$; d_{calc} = 1.376 g/cm^3; μ(Mo$K\alpha$) = 0.089 mm^{-1}; $F(000)$ = 560. The unit cell parameters and intensities of 2409 reflections (2214 independent with R_{int} = 0.07) were measured on a Siemens P3/PC automatic, four circle diffractometer (Mo$K\alpha$ graphite monochromator, 2θ/θ scanning, $2\theta_{max}$ = 50°).

The structure was solved by a direct method using the SHELX97 program package [17]. The positions of the hydrogen atoms were revealed in electron density difference synthesis and refined using the "rider" model with $U_{iso} = nU_{eq}$ for the non-hydrogen atom bound to the given hydrogen (n = 1.5 for a methyl group and n = 1.2 for the remaining hydrogen atoms). The structure was refined for F^2 in full matrix least squares analysis in the anisotropic approximation for non hydrogen atoms to wR_2 = 0.250 for 2214 reflections (R_1 = 0.082 for 1181 reflections with $F > 4\sigma(F)$, S = 0.979). The coordinates and equivalent isotropic thermal parameters for the non-hydrogen atoms in the molecule **9** are given in Table. 4.

IR spectra were recorded on a Specord M-82 spectrometer for KBr tablets and NMR spectra on a Varian 300 (300 MHz) spectrometer for solutions in DMSO-d_6 with TMS internal standard. Mass spectra were obtained on a Finnigan M-95 spectrometer with direct introduction of the sample into the ion source. The ionization chamber temperature was 180°C, ionizing intensity 70 eV, and emission current 100 μA. Monitoring of the purity of the compounds was carried out by TLC on Silufol UV-254 plates with acetone–chloroform (1:1) as eluent.

3,3-Dimethyl-12-phenyl-3,4,5,12-tetrahydrobenzimidazo[2,1-*b*]quinazolin-1(2H)-one (4a). A. A mixture of 5,5-dimethylcyclohexane-1,3-dione **3** (0.14 g, 1 mmol), benzaldehyde **2a** (0.11 g, 1 mmol), and 2-aminobenzimidazole **1** (0.133 g, 1 mmol) in DMF (1 ml) was refluxed for 5 min until the formation of a crystalline precipitate. The reaction mixture was cooled, 2-propanol (5 ml) was added, and compound **4a** (0.22 g) was filtered off and recrystallized from a mixture of DMF and 2-propanol (1:2).

Compounds 4b,c were prepared similarly using the aldehydes **2b,c**.

B. A mixture of compound **6a** (0.272 g, 1 mmol) and 2-aminobenzimidazole **1** (0.133 g, 1 mmol) in DMF (1 ml) was refluxed for 3 min. The reaction mixture was cooled, 2-propanol (5 ml) was added, and the precipitated product **4a** was filtered off to give a yield of 0.21 g (62%). The product was purified by recrystallization from a mixture of DMF and 2-propanol (1:2). The **4a** obtained agreed in spectroscopic parameters and melting point with the sample synthesized using method A.

C. A mixture of 3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydroxanthene-1,8(2H)-dione **7a** (0.35 g, 1 mmol) and amine **1** (0.133 g, 1 mmol) in DMF (1 ml) was refluxed for 3-5 min to the appearance of a precipitate. After cooling, the reaction mixture was treated with 2-propanol (5 ml) and the precipitated product was filtered off to give compound **4a** (0.172 g, 51%). The filtrate was extracted with chloroform and the extract was dried over sodium sulfate, filtered, and the filtrate evaporated. With the use of methanol, the oily residue yielded dimedone **3** (0.13 g) with mp 150-151°C (mp 150°C [18]).

Compounds 4b,c were prepared similarly from compounds **7b,c** respectively.

2,2-Dimethyl-2,3-dihydrobenzimidazo[1,2-*a*]quinazolin-4(1H)-one (9). A mixture of dimedone **3** (0.14 g, 1 mmol) and amine **1** (0.133 g, 1 mmol) in DMF (1 ml) was refluxed for 25 min. 2-Propanol (5 ml) was added to the cooled product which was then filtered to give compound **9** (0.16 g, 60%) and this was recrystallized from 2-propanol. ^{1}H NMR spectrum, δ, ppm: 8.44-7.51 (4H, m, 8-H to 11-H); 9.08 (1H, s, 5-H); 2.61, 3.70 (2H, s, CH_2); 1.21 (6H, s, CH_3). Mass spectrum, *m/z* (*I*, %): 265 (88), 250 (15), 209 (100), 181 (30), 154 (40), 133 (25), 103 (28), 77 (18), 51 (32).

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