CATALYTIC CONDENSATION OF ETHYL CYCLOPENT-ANONECARBOXYLATE WITH SCHIFF BASES

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Ethyl cyclopentanonecarboxylate reacts with Schiff bases to give amino keto esters, from which 5,6-benzoquinoline derivatives are synthesized in the presence of hydrochloric acid. Compounds of the enamine type are obtained in the presence of acetic acid.

Ethyl cyclopentanonecarboxylate (I) is the starting material in the synthesis of terpenes, azulenes, steroids, compounds of the cyclopentenylphenanthrene series, etc. The reaction of I with Schiff bases was described in [1], in which the products of the reaction of benzylideneaniline (II) and benzylidene- β -naphthyl-amine (III) with I in the presence of acetic acid were erroneously assigned the structure of benzoquinoline and quinoline derivatives.

In the present study it was established that the reaction of I with benzylideneaniline (II) and benzylidene- β -naphthylamine (III) and its derivatives leads, depending on the conditions, to different products and proceeds in one step. Thus, when warm alcohol solutions of II or III and I are mixed without the addition of a catalyst, cooling of the mixture gives a white crystalline precipitate, the IR spectrum of which contains absorption bands corresponding to the stretching vibrations of the N-H bonds (3395 cm⁻¹), ketone C = O (1750 cm^{-1}) , ester C = O (1730 cm⁻¹), and ester C-O-R (1230 cm⁻¹) [2]. These data make it possible to conclude that there is nucleophilic addition of I to the azomethine double bond with the generation of a compound of the amino keto ester type (IV and V, respectively) (see the scheme below). When IV are heated in strongly acidic media, they undergo cleavage to give the known benzylidene derivative of keto ester IX [3, 4]. The structure of the latter was also proved by alternative synthesis from I and benzaldehyde [4]. Consequently, the C_5 position is the active center of I in this reaction. The structure of the amino keto esters was confirmed by elementary analysis and the UV spectra. The UV spectrum of IV contains two bands λ_{\max} 262 nm, log ϵ 4.22 and λ_{\max} 306-312 nm, log ϵ 3.94). The UV spectrum of V (Fig. 1) consists of three bands (λ_{max} 255 nm, log ϵ 4.47; λ_{max} 270 nm, log ϵ 4.30; λ_{max} 320 nm, log ϵ 3.90). The character of the UV spectrum of IV is similar to that of the UV spectra of amino ketones of the cyclopentane series [5]. (See scheme on page 630.)

When hot alcohol solutions of III and I with the addition of one drop of concentrated HCl are mixed, one observes the formation of a bright-yellow crystalline precipitate, a solution of which has intense luminescence A_{max} 485 nm, in acetone). The same product can be obtained by heating an alcohol solution of amino keto ester V in the presence of a drop of concentrated HCl. One band at ~ 1695-1700 cm⁻¹ remains in the region of the absorption of the stretching vibrations of the C = O group in the IR spectrum of this compound; bands corresponding to the stretching vibrations of the C = O bonds of an ester at 1210 cm⁻¹ and of N-H bonds at 3400 cm⁻¹ are observed. The UV spectrum of a compound of this type is due to absorption of the condensed benzene rings. A considerable bathochromic shift of the long-wave band (Fig. 1). is characteristic for it. These data make it possible to assume that amino keto ester V has cyclized to dihydrobenzoquinoline derivative VI. The assumption is confirmed by the conversion of VI to a compound of the benzoquinoline series (VII) on heating to 100-130° in the presence of concentrated HCl and an oxidizing agent (nitrobenzene). The water-soluble potassium salt (X) and the acid (XI), which, as a result of decarboxylation, could be converted to the previously obtained [6] 2-phenyl-3,4-(1,2-cyclopentylene)-5,6-benzoquinoline (XII), were obtained for benzoquinoline VIIa. The UV spectrum of benzoquinoline derivative VIIa

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%	Yield,	82	96	28	55	29	63	68	80	20	69	64	28	30	26
m	λ _{max3} (lg ε)	1	322—324 (3 90)	410-412 (3 70)	405 (3.61)	405-410	342; 360 (3.68: 3.79)	344; 362	346; 362 (3 73) (3 78)	-	1		370 (4.36)		1
IV spectri	λ_{max_3} (lg e)	306-312	270 270	278	275 (4.15)	276 276 (4.39)	280 (4.60)	280	285 (447)	330-338	(4.45) (4.45)	350	320 (4.32)	330 (4.64)	365—368 (4,60)
	2.max (1g g)	262-266	$(\frac{1}{4}, \frac{1}{4}, \frac{1}{2})$	248-250 (4 48)	248 (4.41)	248	260 260 (4 64)	260	265 265	265-270	275 (4.95)	235	240-245	235 235 (3.90)	290 (4,27)
-	z	4,1	3,6	3,8	3,4	3,5	3,8	3,4	3,5	3,8	3,5	3,5	6,8		4,8
1-	н	6,8	6,4	6,2	5,4	6,2	5,7	5,0	5,5	6,2	5,5	6,3	5,3	5,4	5,2
Ü	U	74,5	77,5	81,3	74,4	78,2	81,7	74,7	78,6	81,3	74,4	78,2	72,5	64,7	62,3
40	z	4,0	3,6	3,8	3,4	3,6	3,9	3,4	3,5	3,5	3,4	3,5	6,5	1	4,7
, put	н	6,8	6,4	6,0	5,7	6,1	5,6	5,3	5,7	6,3	5,8	6,2	5,3	5,8	5,3
FOI	υ	74,9	78,0	81,7	74,7	78,6	81,5	74,6	78,6	81,7	74,1	78,5	72,4	64,6	62,3
Coratica	Empirícal formula	$C_{21}H_{23}NO_3$	C25H25NO3	$C_{25}H_{23}NO_2$	C25H22CINO2 ³	C26H25NO3	$C_{25}H_{21}NO_2$	C25H20CINO2 ^b	C ₂₆ H ₂₃ NO ₃	C25H23NO2	C ₂₅ H ₂₂ CINO2 ^C	C ₂₆ H ₂₅ NO ₃	$C_{25}H_{22}N_{2}O_{4}$	C ₁₅ H ₁₅ O ₃ Cl d	C ₁₅ H ₁₅ NO ₅
	mp, °C	96—97	117-118	197-198	215-216	186—187	140-141	131-132	120-121	130—131e	146-147	123-124	117-118	123—124	171-172
	of con- centrated HCl, ml	1	ļ	0,06	0,06	0,06	0,06	0,05	0,05	ļ	l	-	Į	0,2	0,2
Terres	temp., C	60	60	09	60	60	140	120	100	Refluxing	Refluxing	Refluxing	Refluxing	100	60
I I I	Heating time, min	ŝ	3	5	5	5	06	06	06	20	30	30	15	60	က
	ш		Н	Н	<i>p</i> -CI	p-OCH ₃	Н	p-CI	p-OCH ₃	H	p-Cl	p-OCH ₃	p-NO2	p-C1	p-NO2
TADLE	Com- pound	IV	>	VIa	٩IV	VIc	VIIa	VIIb	VIIc	VIIIa	VIIIb	VIIIc	PIIIA	d XI	μXI

^a Found: Cl 8.7%, Calculated: Cl 8.8%, ^b Found: Cl 8.7%, Calculated: Cl 8.8%, ^c Found: Cl 8.9%, Calculated: Cl 8.8%, ^d Found: Cl 12.4%, Calculated: Cl 12.7%, ^eAccording to [1], mp 131°.



Fig. 1. UV spectra (in ethanol): 1) ethyl 5-[(phenyl) (β -naphthylamino)methyl]cyclopentan-1-one-2-carboxylate (V); 2) 2-phenyl-3,-4-(ethyl 2,3-cyclopentylene-1carboxylate)-1,2-dihydro-5,6benzoquinoline (VIa); 3) 2-phenyl-3,4-(ethyl 2,3-cyclopentylene-1carboxylate)-5,6-benzoquinoline (VIIa); 4) ethyl 2-(β -naphthylamino)-3-benzylidene (1,2-cyclopentenyl)carboxylate (VIIIa); 5) ethyl 5-benzylidenecyclopentan-1onecarboxylate (IXa).



III, V-IX a R=H; b R=p-CI; C R=p-OCH₃₁ d R=p-NO₂

has the form characteristic for compounds of this type (Fig. 1). The band at 3400 cm⁻¹ in the IR spectrum of VIIa, which confirms the proposed structure, vanishes, and bands at 1728 and 1255 cm⁻¹, which correspond to the stretching vibrations of the ester C = O and C = O bonds, are observed. Intense characteristic bands at 1385 cm⁻¹, which correspond to the asymmetrical and symmetrical vibrations of the COO⁻ group [7], are present in the IR spectrum of X.

In the preparation of a benzoquinoline derivative from the Schiff base and I or from amino keto ester V in the presence of a

catalyst (HCl) and an oxidizing agent, a considerable amount of a product resulting from cleavage of the amino keto ester – benzylidene derivative of I (IXa) – was detected along with benzoquinoline. When a similar reaction was carried out with II, complete cleavage of amino keto ester IV was observed in acidic media.

Amino keto esters (Vb, c, d) could not be isolated in free form in the reaction of I with benzylidene- β -naphthylamine derivatives (R = p-Cl, p-OCH₃, p-NO₂). Dihydro derivatives of 5,6-benzoquinoline are formed under mild conditions in the reaction with p-chloro- and p-methoxybenzylidene- β -naphthylamine. The presence of a nitro group in the Schiff base promotes cleavage of the intermediate amino keto ester, while a methoxy group inhibits it [8]. In conformity with this, in the reaction with p-nitrobenzylidene- β -naphthyl-amine, we isolated only a cleavage product (IXd); on the other hand, we were unable to isolate a cleavage product (IXc) with p-methoxybenzylidene- β -naphthylamine, and only benzoquinoline derivatives VIc and VIIc were obtained.

The reaction of I with benzylidene- β -naphthylamine and its derivatives in the presence of acetic acid proceeds via a different scheme. It is known that carbonyl compounds readily react with amines in acetic acid to give compounds of the enamine type [9]. When a mixture of an alcohol solution of Va and I is refluxed in the presence of acetic acid, a yellow crystalline precipitate with a melting point similar to that of the compound obtained in [1] is formed. The IR spectrum of this compound contains intense bands at 1670 $\rm cm^{-1}$ (chelate C = O) and 1610 cm⁻¹ (conjugated C = C). A band due to the stretching vibrations of the N-H bond in compounds of this type [10, 11] is observed at ~ 3300 cm⁻¹. An intense long-wave maximum, which attests to inclusion of an ester group in the conjugation chain, is observed in the UV spectrum (Fig. 1). Arylidene derivative I in the enol form (IXa) is isolated in the hydrolysis of the product with mineral acid. The structure of IXa was proved by alternative synthesis and the IR spectrum, which contains intense bands at 1660 and 1615 $\rm cm^{-1}$, which are characteristic for the 5-benzylidene derivative in the enol form, and also by absorption in the UV region with a maximum at ~ 330 nm [3]. All of these data make it possible to assert that a compound of the enamine type (VIIIa) rather than a benzoquinoline derivative (as asserted in [1]) is formed in the reaction of IIIa and I in the presence of acetic acid. The reaction proceeds through a step involving the formation of amino keto ester V, which is cleaved in acetic acid to an amine and an unsaturated ketone, which react with one another to give the enamine. The reaction with benzylidene- β -naphthylamine derivatives proceeds similarly.

Thus reaction of I with benzylidene- β -naphthylamine and its derivatives leads, depending on the conditions, either to condensed 5,6-benzoquinoline derivatives VIIa-c or to enamines of the cyclopentane series (VIIIa-d, Table 1).

EXPERIMENTAL

The individuality and purity of the synthesized compounds were monitored by ascending thin-layer chromatography in a loose layer of activity-II aluminum oxide. The eluent was benzene, and the chromatogram was developed with iodine vapors. The UV spectra of 10^{-4} M alcohol solutions of the compounds were recorded with an SF-4A spectrophotometer. The IR spectra of KBr pellets were recorded with a UR-20 spectrophotometer at 3600-4000 cm⁻¹. The luminescence spectrum was measured by the method in [12].

Ethyl cyclopentanonecarboxylate (I) was synthesized by the method in [13]; the fraction with bp 86-87° (6 mm) and n_D^{20} 1.4526 was selected for the reaction.

Ethyl 5-[(Phenyl)(anilino)methyl]cyclopentan-1-one-2-carboxylate (IV) and 5-[(Phenyl)(β -naphthylamino)methyl]cyclopentan-1-one-2-carboxylate (V), 2-Aryl-3,4-(ethyl 2,3-cyclopentylene-1-carboxylate)-1,2-dihydro-5,6-benzoquinolines (VIa-c, Table 1), 2-Aryl-3,4-(ethyl 2,3-cyclopentylene-1-carboxylate)-5,6benzoquinolines (VIa-c, Table 1), and Ethyl 5-Arylidenecyclopentan-1-onecarboxylate (IXa,b,d, Table 1). A. Several drops of concentrated HCl and an equimolecular amount of I were added to a solution of 0.01 mole of the appropriate Schiff base in alcohol, and the mixture was heated (see Table 1); IV and V were obtained without acid; VIIa-c and IXa,b,d were synthesized in an ampul (with the addition of 0.01 mole of nitrobenzene in the case of VIIa-c). The reaction mixture was cooled, and the precipitated crystals were removed by filtration, treated with NH₄OH, and crystallized from alcohol or toluene. Compounds VIIa,b are formed as a mixture with IXa,b in a yield of 10-15% (based on the amounts of starting materials used). The precipitated IXa,b were separated and crystallized from alcohol; the mother liquor was evaporated to give VIIa,b which were worked up by the previously described method.

B. Compound VIa was also obtained from V: 1 g of V, 15 ml of ethanol, and two drops of concentrated HCl were heated on a boiling-water bath for 2-3 min. The mixture was cooled, and the precipitate was worked up in the usual manner to give a product in 58% yield.

<u>C</u>. Compounds VIIa-c were obtained from VIa-c (general method): 1 g of VI was dissolved in 10 ml of ethanol, five drops of nitrobenzene and concentrated HCl were added, and the mixture was heated in an ampul. The conditions used to carry out the reactions and the yields are presented in Table 1. The precipitate that formed on cooling was worked up in the usual manner.

Ethyl $2-(\beta$ -Naphthylamino)-3-arylidene (1,2-cyclopentenyl)carboxylates (VIIIa-d, Table 1). A mixture of 0.01 mole of the appropriate Schiff base, 1 ml of I, 7 ml of glacial acetic acid, and 7 ml of absolute ethanol was refluxed for 20-30 min, after which it was cooled, and the precipitate was crystallized from alcohol or toluene. The yields and conditions used to carry out the reactions are presented in Table 1. Under the same conditions, VIIIa was obtained from V in 52% yield.

2-Phenyl-3,4- (potassium 2,3-cyclopentylene-1-carboxylate)-5,6-benzoquinoline (X). A mixture of 1 g of VIIa, 0.2 g of KOH, and 25 ml of ethanol was refluxed on a water bath for 10 h. The ethanol was removed by distillation, and the salt was extracted with isopropyl alcohol. The alcohol was removed by distillation, and the residue was treated with methylene chloride to give 0.9 g (87%) of a product with mp 281-282° (isopropyl alcohol). Found: C 73.3; H 4.3; N 3.6%. $C_{23}H_{16}KNO_2$. Calculated: C 73.2; H 4.2; N 3.7%. The COO⁻ group absorption appeared at 1580 and 1385 cm⁻¹ in the IR spectrum.

 $\frac{2-\text{Phenyl-3,4-}(\text{carboxy-2,3-cyclopentylene})-5,6-\text{benzoquinoline Hydrochloride (XI).} A 0.5-\text{g sample}}{\text{of X was dissolved in water, and the solution was acidified to pH 6 with hydrochloric acid.} The precipitate (0.45 g) was removed by filtration and washed with water to give a product with mp 198-201°. Found: C 73.3; H 5.2; Cl 9.6%. C₂₃H₁₇NO₂·HCl. Calculated: C 73.6; H 4.8; Cl 9.5%. In the IR spectrum, <math>\nu_{C=O}$ appeared at 1728 cm⁻¹.

2-Phenyl-3,4-(1,2-cyclopentylene)-5,6-benzoquinoline (XII). A 0.5-g sample of XI was fused with 0.5 g of solid KOH, and the resulting XII was extracted from the melt with benzene and crystallized from alcohol. The product did not depress the melting point of the product obtained from cyclopentanone and IIIa by the method in [6].

The presence of an $-OC_2H_5$ group was confirmed for all of the compounds by qualitative reaction with mercury nitrate [14].

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