RESEARCH ON UNSATURATED LACTONES.

XXXIV.* REACTION OF 4-CARBALKOXY-5,6,6-TRIMETHYL-3,6-DIHYDRO-2-PYRONES WITH AMINES

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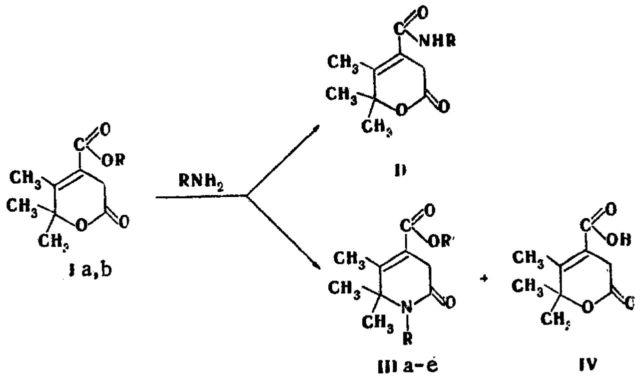
In the reaction of 4-carbalkoxy-5,6,6-trimethyl-3,6-dihydro-2-pyrones with amines nucleophilic attack is directed at the carbalkoxy group or the lactone ring to give amides of lactono acids or the corresponding substituted lactams, depending on the ratio of the components and the reaction conditions.

We have previously shown that 4-carbethoxy-5,6,6-trialkyl-3,6-dihydro-2-pyrones (I) react differently with aqueous solutions of amines and the anhydrous amines at room temperature [2]. When water is present, the lactone ring opens up and, depending on the reaction conditions, the ester group simultaneously undergoes hydrolysis [3].

In the present investigation we found that dihydropyrones I in absolute alcohol react with amines at different ratios of the starting components (lactone:amine 1:1 and 1:2) at room temperature or when the mixtures are heated (to 90-100°C) to give 4-carbamoyl-5,6,6-trimethyl-3,6-dihydro-2-pyrones (II) in high yields; i.e., nucleophilic attack occurs only at the carbethoxy group without involvement of the lactone ring. Under similar conditions, 4-carbobutoxy-5,6,6-trimethyl-3,6-dihydro-2-pyrone forms the same amides.

When the reaction is carried out in excess amine, and the mixtures are heated to 90-100°C, the yields of amides increase to 80-90%, but the corresponding lactams – substituted 3,6-dihydro-2-pyridones (III) – are formed in satisfactory yields when the reaction components are heated (refluxed at 135-145°C for 6-8 h) in a slightly polar solvent (xylene).

The presence of traces of water in the reaction medium also leads to simultaneous hydrolysis of the ester group to give 4-carboxy-5,6,6-trimethyl-3,6-dihydro-2-pyrone (IV) (in up to 25% yield).



I a R'=C_2H_5, b R'=C_4H_9; IIIa–d R'=C_2H_5; a R=C_4H_9; b R=C_5H_{11}; c R=$CH_2C_6H_5$; d R=C_6H_{13}; IIIe R'=C_4H_9, R=$CH_2C_6H_5$

The fact of nucleophilic attack at the lactone ring rather than at the carbethoxy group under the indicated conditions was proved by reaction of 4-carbobutoxy-5,6,6-trimethyl-3,6-dihydro-2-pyrone with amines. If the reaction proceeds in this case at the 4-carbalkoxy group, amides II described above should be obtained. However, the corresponding substituted lactams (IIIe) rather than the amides were obtained in this reaction.

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*See [1] for communication XXXIII.

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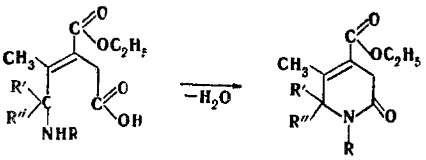
The literature contains data on the reactions of saturated and unsaturated six-membered lactones with primary amines; in this case primarily products of nucleophilic attack of the amine at the carbonyl group of the lactone ring are produced, and, depending on the reaction conditions, hydroxy amides or amino acids are obtained [4, 5]. For example, under the influence of amines, the ring system of α-pyrone opens up to give compounds of the aliphatic series, whereas under the influence of ammonia or an amine, 6-alkyl-3-carbethoxy-α-pyrones give α-carbethoxyaminoalka-2,4-dienoic acids [6].

The production of lactams in the reaction that we investigated can be explained by cyclization of the amino acids that are formed when the mixtures are refluxed in xylene.

In fact, these amino acids are converted to the corresponding dihydro-2-pyridones in good yields (up to 80%) when they are heated to 180°C for 2-3 h.

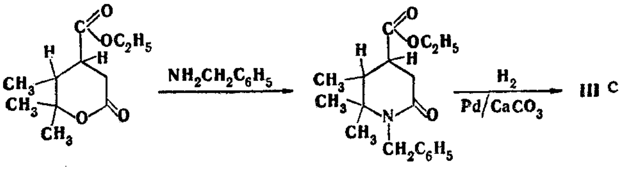


Va-b

V a $R'=R''=CH_3$; $R=CH_2C_6H_5$; b $R', R''=(CH_2)_5$; $R=CH_3$

It should be pointed out that we were also able to isolate a small amount of α-carboxymethyl-β,γ,γ-trimethyl-γ-N-alkylamino-2-butenoic acid amide in the reaction of dihydropyrones I with amines; i.e., when excess amine is present, the carbethoxy group may also undergo nucleophilic attack by the amine.

Absorption bands at 1720, 1680, and 1570 cm^{-1}, which are characteristic for an ester group, a lactam carbonyl group, and a C=C bond, respectively, are observed in the IR spectra of the 4-carbalkoxy-5,6,6-trimethyl-N-alkyl-3,6-dihydro-2-pyridones. We note that in the reaction of 4-carbethoxy-5,6,6-trimethyltetrahydro-2-pyrone with amines (excess amine, refluxing in xylene for 8 h) nucleophilic attack is also directed at the lactone ring with the formation of the corresponding 2-piperidone (VI).



VI

Hydrogenation of unsaturated IIIc led to the formation of 4-carbethoxy-5,6,6-trimethyl-N-benzyl-2-piperidone, which was identical to VI. Absorption bands at 1720 and 1690 cm^{-1}, which are characteristic for ester and lactam C=O groups, respectively, are observed in its IR spectrum.

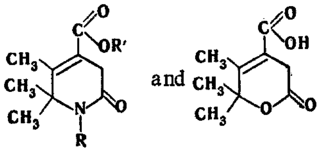
EXPERIMENTAL

The purity of the compounds obtained was monitored by thin-layer chromatography (TLC) on aluminum oxide [elution with ether–hexane (1:1)]. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer.

Amides of 4-Carboxy-5,6,6-trimethyl-3,6-dihydro-2-pyrones. A mixture of 1 g (0.0047 mole) of 4-carbalkoxy-5,6,6-trimethyl-3,6-dihydro-2-pyrone, 0.01-0.035 mole of the amine, and 15-20 ml of absolute dioxane was allowed to stand at room temperature for 24-72 h or was refluxed for 4 h, after which the solvent was removed by distillation, and the residue was recrystallized to give the product [2, 7].

Preparation of 4-Carbalkoxy-5,6,6-trimethyl-N-alkyl(aryl)-3,6-dihydro-2-pyridones (IIIa-d). A mixture of 0.005 mole of dihydropyrone I, 0.01 mole of the corresponding amine, and 10 ml of xylene was refluxed for 6-7 h, after which it was cooled and filtered, and the precipitated crystals of dihydropyrone IV [7] were removed by filtration. The xylene was removed from the mother liquor, and the residue was recrystallized to give the dihydropyridones IIIa-d (Table 1).

TABLE 1.



III IV

Compound No.	R	R¹	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %	
				C	H	N		C	H	N	III	IV
IIIa	C_4H_9	C_2H_5	83—84	66,9	9,0	4,8	$C_{15}H_{25}NO_3$	67,4	9,3	5,2	48	12
IIIb	$CH_2C_4H_9$	C_2H_5	74—75	68,0	9,5	5,0	$C_{16}H_{27}NO_3$	68,3	9,6	5,0	69	5
IIIc	$CH_2C_6H_5$	C_2H_5	102—103	72,0	7,2	4,6	$C_{18}H_{23}NO_3$	71,8	7,6	4,6	43	23
IIId	C_6H_{13}*	C_2H_5	92—93	67,9	10,3	12,8	$C_{17}H_{29}NO_3$	68,4	10,8	13,3	40	10
IIIe	$CH_2C_4H_9$	C_4H_9	106—108	72,3	8,5	4,3	$C_{20}H_{27}NO_3$	72,9	8,2	4,3	66	5

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*In this case α-carboxymethyl-β,γ,γ-trimethyl-γ-N-hexylamino-2-butenoic acid amide, with mp 173-174°C (from benzene), was also isolated in 4% yield. Found: C 68.7; H 11.0; N 12.8%. $C_{21}H_{40}N_2O_3$. Calculated: C 68.4; H 10.8; N 13.3%.

Ethyl α-Carboxymethyl-β,γ,γ-trimethyl-γ-N-benzylamino-2-butenoate (Va). A mixture of 2 g (0.009 mole) of dihydropyrone I, 1.1 g (0.01 mole) of benzylamine, three drops of water, and 10 ml of benzene was allowed to stand at room temperature for 10-15 h, after which the solvent was removed, and the residue was recrystallized to give 2.4 g (85.5%) of Va with mp 122-124°C (from xylene) (mp 122°C, from xylene [2]).

4-Carbethoxy-5,6,6-trimethyl-N-benzyl-3,6-dihydro-2-pyridone (IIIc). A 0.5-g (0.015 mole) sample of Va was heated at 150°C for 2 h, after which the residue was recrystallized to give 0.35 g (77.7%) of IIIc with mp 102-103°C (from hexane). No melting-point depression was observed for a mixture of this product with an authentic sample.

4-Carbethoxy-5-methyl-6,6-pentamethylene-N-methyl-3,6-dihydro-2-pyridone. Similarly, 0.11 g (50%) of 4-carbethoxy-5-methyl-6,6-pentamethylene-N-methyl-3,6-dihydro-2-pyridone, with mp 135-136°C [from xylene—petroleum ether—(1:1)], was obtained from 0.2 g (0.007 mole) of Vb. Found: C 69.8; H 6.3; N 5.9%. $C_{15}H_{17}NO_3$. Calculated: C 69.4; H 6.5; N 5.4%.

4-Carbethoxy-5,6,6-trimethyl-N-benzyl-2-piperidone (VI). A mixture of 1 g (0.0046 mole) of 4-carbethoxy-5,6,6-trimethyltetrahydro-2-pyrone, 1 g (0.01 mole) of benzylamine, and 10 ml of xylene was refluxed for 8 h, after which the xylene was removed, and the residue was recrystallized to give 0.7 g (54%) of VI with mp 90-91°C (from benzene). Found: C 70.8; H 7.8; N 4.4%. $C_{18}H_{25}NO_3$. Calculated: C 71.3; H 8.2; N 4.6%.

Hydrogenation of 4-Carbethoxy-5,6,6-trimethyl-N-benzyl-3,6-dihydro-2-pyridone. A 0.3-g (0.001 mole) sample of IIc was dissolved in 20 ml of absolute alcohol, 0.1 g of Pd/$CaCO_3$ catalyst was added, and hydrogen was passed through the mixture with shaking for 5 h. The catalyst was then removed by filtration, the solvent was removed from the filtrate by distillation, and the residue was recrystallized from benzene to give 0.2 g (83%) of VI with mp 90-91°C.

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