SYNTHESIS AND SOME PROPERTIES OF 4-AMINO-3-ACETYL-6-METHYL-2-PYRONES*

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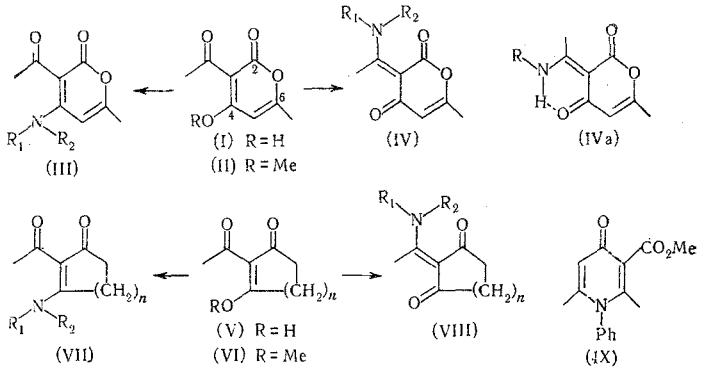
Dehydracetic acid (I) has long attracted the attention of investigators in view of the diversity of its properties. Its polyfunctional system enters in various form into the composition of many natural products [2], while the compound itself possesses a well-defined antibiotic action [3]. Its use as an effective agent for preventing the spoilage of food products is well-known [4]. The diversity in the properties of dehydracetic acid (I) is undoubtedly associated with the presence of several chemically active groupings in its molecule, and, in particular, the triacylmethane grouping. The behavior of the latter was studied previously in a series of carbocyclic β-triketones (V) [5, 6], and here their rich synthetic possibilities were demonstrated, for example, for building nitrogen-containing analogs of steroids [7]. Such possibilities can evidently be greatly expanded due to the use of acid (I) and some some of its derivatives for such purposes. The same as in the case of the isomeric enaminodiketones (VII) and (VIII) for the (V) triketones [5, 6], two series of amino derivatives (III) and (IV) can also correspond to acid (I), of which the former until recently [1] were in general unknown. The indicated γ-amino-α-pyrones (III) represent independent interest as polyfunctional compounds, and as subjects for studying individual tautomerism problems. In the present paper are discussed a method of preparation and some of the properties of these compounds.

It is known that acid (I) reacts with ammonia [8-11], aliphatic [8-15], aromatic [8, 10, 11, 15, 16] and aralkyl [8, 12, 17] primary amines to give, depending on the conditions of running the reactions, a number of nitrogen-containing products. In this connection the initial process, excluding salt formation [11, 13, 18], where the reaction at times stops [15, 16, 18], proceeds exclusively at the side acetyl group. Enaminodicarbonyl compounds (IV) are formed as a result, which, of several theoretically possible forms [11, 14, 17], apparently exist in the tautomeric form (IVa)



As it proved [19, 20], acid (I) reacts with secondary amines in a completely unexpected manner. Also, here the initial reaction products are salts. However, the latter are converted to the end products by

*See [1] for preliminary communication.

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TABLE 1. 4-Amino-3-acetyl-6-methyl-2-pyrones (IIIa-k)

III	Substituent		T, mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
	R_1	R_2		C	H	N		C	H	N	
a	H	H	168, then 198—200	57,60	5,46	8,70	$C_8H_9NO_3$	57,48	5,43	8,38	70
b	H	Me	170—171	59,73	5,93	7,97	$C_9H_{11}NO_3$	59,66	6,12	7,73	70
c	H	CH_2Ph	170—171	69,79	5,98	5,49	$C_{15}H_{15}NO_3$	70,02	5,88	5,44	60
d	H	Ph	145, then 155—156	68,72	5,33	5,98	$C_{14}H_{13}NO_3$	69,12	5,39	5,76	75
e	Me	Ph	89—90	70,17	5,92	5,53	$C_{15}H_{15}NO_3$	70,02	5,88	5,44	45
f	$-(CH_2)_2-$		133—134	62,09	5,64	7,36	$C_{10}H_{11}NO_3$	62,16	5,74	7,25	80
g	$-(CH_2)_3-$		149—150	63,59	6,43	6,97	$C_{11}H_{13}NO_3$	63,75	6,32	6,76	65
h	$-(CH_2)_4-$		141—142	65,12	6,85	6,28	$C_{12}H_{15}NO_3$	65,14	6,83	6,33	80
i	$-(CH_2)_5-$		131—132	65,92	7,23	6,11	$C_{13}H_{17}NO_3$	66,36	7,28	5,95	70
j	$-(CH_2)_2O(CH_2)_2-$		150—151	60,45	6,49	6,02	$C_{12}H_{15}NO_4$	60,75	6,37	5,90	50

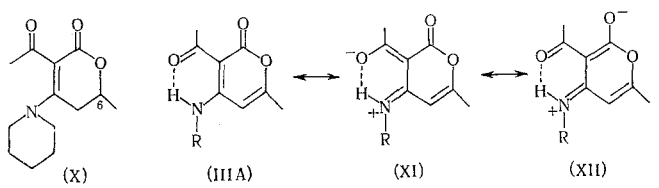
cleavage of the C_6-O bond in the (I) molecule. The formation of enaminodicarbonyl compounds (IV) is not observed here.

As a result, the discussed data testify to the fact that the C_4 center is not involved when acid (I) is reacted directly with ammonia and various primary and secondary amines, and consequently it is impossible to obtain the (III) pyrones by this method. However, it could be postulated that the latter are formed under the conditions of the substitutive addition of amines to the methyl ether (II) of acid (I). An analogous reaction proceeds easily with the methyl ethers (VI) of the (V) triketones [5, 6]. As was to be expected, the reaction of ammonia, and of primary and secondary aliphatic, aromatic, aralkyl and heterocyclic amines with ether (II) in an inert solvent gives pyrones (IIIa-k) (Table 1). With the exception of the tertiary amino derivatives (IIIe-k), all of the four structural isomers of the (IVa) series corresponding to the bases (IIIa-d) are described in the literature, which in all cases proved to be different compounds and which are absent in the reaction products of the corresponding amines with ether (II).

Mention is made in the literature of reacting the methyl ether of acid (I) with aniline, which leads to the formation of a compound with an empirical formula of $C_{15}H_{15}NO_3$, which was identified as being the lutidonecarboxylic ether (IX) [21]. However, compounds of the indicated structure were in general not detected in our case, the formation of which would testify to the preferential progress of processes involving the C_6 center in molecule (II). Moreover, the scheme of substitutive addition at C_4 is also predominant when ether (II) is reacted with reagents that attack the carbonyl group [22].

The structure of the obtained pyrones (III) was reliably corroborated by the results of their physicochemical study and some of their chemical transformations. For example, it was established that the primary and secondary bases (IIIa-d) are comparatively stable under catalytic hydrogenation conditions. The tertiary bases under the same conditions give a complex mixture of compounds, for which the pure compound could be isolated only in the case of piperidinopyrone (IIIj). According to the elemental analysis data and that of the vibrational spectra, this compound, being a dihydro derivative, contains the characteristic enaminodicarbonyl grouping. On this basis the discussed product was assigned the structure of the dihydropyrone (X). In harmony with this, in the NMR spectrum are present the signals of the methine proton at C_6 as an unresolved multiplet with a center at δ 4.36 ppm, and of the protons of the methyl group attached to it in the form of a doublet (δ 1.40 ppm). It should be mentioned here that the enaminodicarbonyl function, present in the (III) pyrones, proves to be stable under catalytic hydrogenation conditions, as is also observed in the carbocyclic series (VII) [5, 6].

The NMR spectra of the discussed pyrones (III) are in full agreement with their structure. In addition, the obtained data, which will be discussed in detail in the next communication, make it possible to conclude that the primary (IIIa) and secondary (IIIb-d) amino derivatives exist predominantly in the (IIIA) form, with a stable intramolecular hydrogen bond



(X) (IIIA) (XI) (XII)

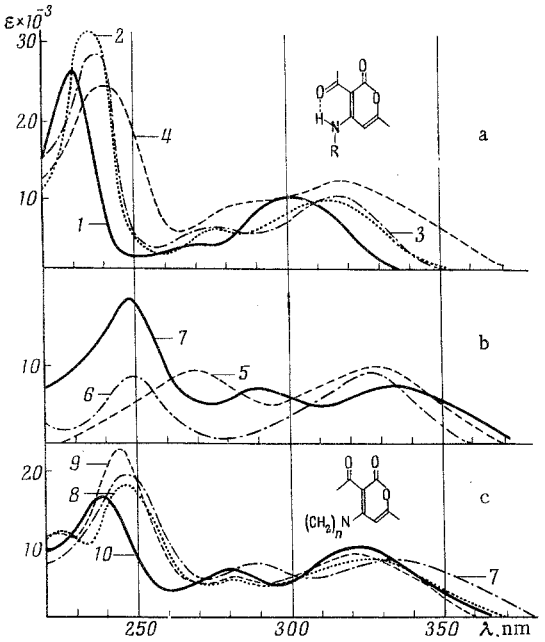
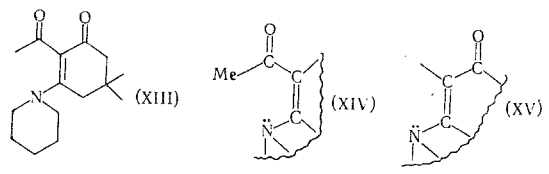


Fig. 1. Ultraviolet spectra. a: 1) (IIIA; R = H); 2) (IIIA; R = Me); 3) (IIIA; R = CH_2Ph); 4) (IIIA; R = Ph). b: 5) (XIII); 6) (X); 7) (IIIj). c: 7) (IIIj); 8) (IIIh); 9) (IIIg); 10) (IIIf).

The parameters of the vibrational spectra given in Table 2 can serve as confirmation. Several absorption bands in the range 1500-1710 cm^{-1} are observed in the IR spectra of (IIIa-d). Besides this, imine (IIIa) is characterized by an additional band at 3340 cm^{-1} in the region of the stretching vibrations of the NH group, not taking part in the intramolecular hydrogen bond. The absence of such vibrations in the spectra of pyrones (IIIb-d), together with the marked decrease in the carbonyl frequencies that was observed in all cases, indicates the formation of an intramolecular hydrogen bond, which is evidently stabilized by the high contribution made by the resonance structures (XI) and (XII). In this connection, the same as in the series of the simpler β-aminovinyl ketones [23], the broad vibration bands of NH can be shifted toward the stretching vibrations of CH in the vicinity of 3000 cm^{-1}.

The tertiary pyrones (IIIe-k), with the exception of the aziridine derivative (IIIf), absorb in the range 1470-1695 cm^{-1}. A decrease in the frequencies in this case can be explained by the marked interaction between the C=C and C=O groups, which leads to a substantial contribution made by dipolar structures of the (XI) and (XII) type.

In Table 2 and Fig. 1 are given the UV spectra of the discussed compounds (III). The absorption curves contain at least three intense bands in the 230-340 nm region, which are very sensitive to change in the structure of the amino function. Thus, an increase in the degree of substitution of the latter is accompanied by a bathochromic shift of the absorption bands (see Fig. 1a, c) in the order: $\lambda_{NH_2} < \lambda_{NHR} < \lambda_{NR_1R_2}$. In the case of the tertiary amino derivatives (IIIf-j) an increase in the size of the nitrogen-containing ring leads to the same effect (see Fig. 1c). An analogous spectral relationship, for the most part in agreement with an increase in the p-character of the orbitals of the unshared pair of the nitrogen atom, is observed for the enaminodiketones (VII) [5, 6]. Besides this, anilide (IIId) can serve as an example that corroborates the ability of the nitrogen bridge to transmit the effect of the groups that are conjugated with it [24]: in its spectrum is present additional bathochromic shift relative to the bands of imidine (IIIa)



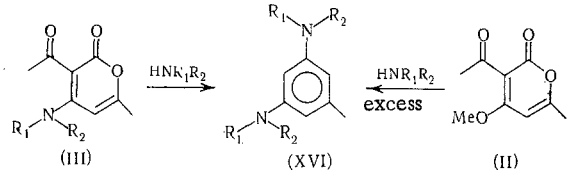
A comparison of the absorption curves shown in Fig. 1b of piperidinopyrone (IIIj), its dihydro derivative (X), and the carbocyclic analog (XIII) [5], makes possible a preliminary assignment of the observed absorption bands in the UV spectra of the studied compounds. The longwave band proved to be the least sensitive to a change in the structure of the molecule: the insertion of an oxygen atom and a double bond into the starting carbocyclic skeleton are hardly without effect on its position and intensity. For this reason the

TABLE 2. Infrared and Ultraviolet Spectra of 4-Amino-3-acetyl-6-methyl-2-pyrones (IIIa-k)

III	γ, cm^{-1}					λ_{max}, nm (ε)		
a	1512s,	1610s,	1650m,	1685s,	3340s,	231 (26 000),	268 (3700),	302 (9700)
b	1508m,	1587s,	1602s,	1673s,	1709s,	237 (31 000),	278 (5900),	318 (9400)
c	1500m,	1560s,	1600m,	1660s,	1712s,	237 (28 800),	278 (6600),	317 (9200)
d	1493m,	1563s,	1590s,	1655s,	1702s,	240 (23 400),	281 (8200),	319 (11 600)
e	1470s,	1515s,	1650s,	1663s,	1695s,	253 (13 600),	281 (9000),	326 (8600)
f	1475s,	1495s,	1645m,	1670s,	1705s,	237 (16 000),	278 (6700),	323 (9000)
g	1475m,	1530s,	1650m,	1678s,	1693s,	245 (23 000),	282 (5800),	323 (8400)
h	1470s,	1520s,	1642m,	1660s,	1694s,	246 (17 800),	283 (5700),	325 (7700)
j	1475m,	1523s,	1640m,	1660s,	1685s,	247 (19 700),	288 (7700),	333 (7500)
k	1477s,	1510s,	1640m,	1660s,	1695s,	247 (18 900),	290 (7300),	339 (8400)

given band must be assigned to the cisoid chromophore (XIV) that is present in each of the compared molecules. Correspondingly, the short-wave band should be associated to a greater degree with the transoid chromophore (XV). Actually, a weakening of the acceptor ability of the cyclic C=O group, for example, in the dihydropyrone (X), is exerted primarily on this band, causing its hypsochromic shift. The insertion of an endocyclic double bond into the dihydropyrone (X) molecule leads to the appearance in the spectrum of the (III) pyrone of a third band in the 270-290 nm region, which is characteristic for an α-pyrone that contains an electron-donor substituent in the γ-position [25].

Besides the above discussed catalytic hydrogenation of the (III) pyrones, we also studied the behavior of these compounds under the influence of various amines. It proved that active amines attack the C_6 center in the (III) molecule with the formation of intermediate compounds that are easily converted in the case of secondary cyclic amines to symmetrical aminotoluidines (XV). The latter are also formed when methyl ether (II) is reacted with an excess of the same amines



The indicated reaction, apparently having biogenetic importance [1], will be discussed by us separately.

EXPERIMENTAL

The melting points were determined on a Kofler block. The IR spectra (in KBr) were obtained on a UR-10 instrument, while the UV spectra (in alcohol) were obtained on a recording Unicam SP-700 spectrophotometer. The melting points and elemental analysis data for the obtained compounds are given in Table 1.

Synthesis of 4-Amino-3-acetyl-6-methyl-2-pyrones (IIIa-k). A solution of 0.8 g of the methyl ether (II) [26] in 125 ml of an 0.06 M solution of NH_3 in toluene was heated in a sealed ampul at 60°C for 5 h, after which it was evaporated and the residue was recrystallized from a THF–hexane mixture. We obtained 0.5 g of 4-amino-3-acetyl-6-methyl-2-pyrone (IIIa) as colorless prisms.

A solution of 1.0 g of ether (II) in 180 ml of an 0.05 M solution of $MeNH_2$ in toluene was allowed to stand at 0 to 5° for 2 days, after which it was evaporated and the residue was recrystallized from a THF–ether mixture. We obtained 0.7 g of 3-acetyl-4-N-methylamino-6-methyl-2-pyrone (IIIb) as colorless needles.

A solution of 0.9 g of ether (II) and 0.5 g of benzylamine in 190 ml of benzene was allowed to stand at room temperature for 3.5 h, after which it was evaporated in vacuo and the residue was recrystallized from a THF–hexane mixture. We obtained 0.8 g of 3-acetyl-4-N-benzylamino-6-methyl-2-pyrone (IIIc) as colorless needles.

A solution of 0.8 g of ether (II) and 1.4 g of aniline in 100 ml of toluene was heated at reflux for 7 h, after which it was evaporated in vacuo and the residue was treated with ether and then recrystallized from

a THF–hexane mixture. We obtained 0.8 g of 3-acetyl-4-N-phenylamino-6-methyl-2-pyrone (IIId) as colorless prisms, which changed at 144-145° to needles with mp 155-156°.

In a similar manner, from 1.15 g of ether (II) and 0.65 g of freshly distilled N-methylaniline, after heating for 30 h, we obtained 0.7 g of 3-acetyl-4-(N-methyl-N-phenyl)amino-6-methyl-2-pyrone (IIIe) as pale yellow rhombic prisms (from ether–hexane).

In a similar manner, using a threefold molar excess of ethylenimine and heating for 1.5 h, we obtained 3-acetyl-6-methyl-4-N-ethylenimino-2-pyrone (IIIf) as colorless plates (from THF–hexane).

In exactly the same manner, from 0.55 g of ether (II) and 70 mg of azetidine we obtained 0.41 g of 3-acetyl-6-methyl-4-N-trimethyleneamino-2-pyrone (IIIg) as fine needles (from THF–hexane).

A solution of 1.0 g of ether (II) and 0.39 g of freshly distilled pyrrolidine in 200 ml of toluene was allowed to stand at 0 to 5° for 3 h, after which it was evaporated in vacuo and the residue was recrystallized from a THF–hexane mixture. We obtained 1.0 g of 3-acetyl-6-methyl-4-(N-pyrrolidyl)-2-pyrone (IIIh) as colorless prisms.

In a similar manner, from 0.5 g of ether (II) and 230 mg of piperidine, after allowing to stand for 3 days, was obtained a product that when refluxed in toluene until the color disappeared, followed by recrystallization from a THF–hexane mixture, gave 0.5 g of 3-acetyl-6-methyl-4-(N-piperidyl)-2-pyrone (IIIj) as colorless plates.

In exactly the same manner, from 0.9 g of ether (II) and 430 mg of morpholine after 3 h was obtained 0.6 g of 3-acetyl-6-methyl-4-(N-morpholyl)-2-pyrone (IIIk) as colorless prisms.

Hydrogenation of Piperidinopyrone (IIIj). A solution of 0.8 g of (IIIj) in 80 ml of alcohol was hydrogenated under conventional conditions in the presence of 150 mg of 30% $Pd/SrCO_3$. The catalyst was separated after the absorption of 150 ml of H_2, the filtrate was evaporated in vacuo, and the oily residue, which, on the basis of the TLC data, represented a complex mixture of products, was filtered through a bed of silicic acid in a nitrogen atmosphere. From the fraction, obtained by elution with a 1:1 mixture of acetone–hexane, was isolated 120 mg (15%) of 3-acetyl-6-methyl-4-(N-piperidyl)-5,6-dihydro-2-pyrone (X) as prisms with mp 132-134° (decompn.) (from THF–hexane). Found: C 65.48; H 8.11; N 5.80%. $C_{13}H_{19}NO_3$. Calculated: C 65.80; H 8.07; N 5.90%. Infrared spectrum (ν, cm^{-1}): 1435 s, 1465 m, 1540 s, 1630 s, 1677 s. Ultraviolet spectrum (λ_{max}, nm): 249 (ε 8800); 328 (ε 9100).

CONCLUSIONS

1. 4-Amino-3-acetyl-6-methyl-2-pyrones were obtained in 50-80% yields when the methyl ether of dehydracetic acid was reacted with ammonia, and primary amines.

2. The absorption spectra of the compounds, formed from ammonia and primary amines, indicate that these compounds contain the enaminodicarbonyl fragment with a stable intramolecular hydrogen bond.

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