SOME DERIVATIVES OF α-PYRONE-3-CARBOXYLIC ACID AND ITS HOMOLOGS

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 3, No. 4, pp. 589–591, 1967

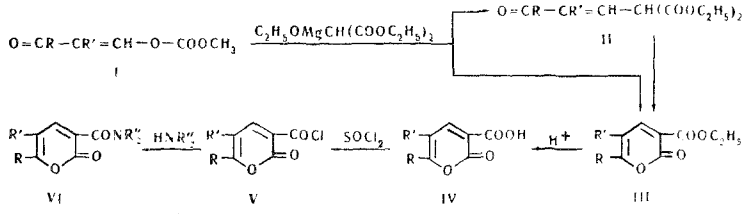
UDC 547.812

Saponification of the appropriate 3-carbethoxy-α-pyrones gives α-pyrone-3-carboxylic acid and its homologs, further converted via their acid chlorides to the substituted amides of the acids.

Until recently the only α-pyrone-3-carboxylic acids known were those with a substituent at position 6 in the pyrone ring, obtained by N. K. Kochetkov and coworkers from β-chlorovinylketones. [1, 2].

We recently showed [3, 4] that by reacting mixed carbonates of the enol forms of β-dialdehydes and β-ketoaldehydes O=CR—CR'=CH—O—$COOCH_3$ (I) with ethoxymagnesium malonic ester, it is possible to obtain hitherto inaccessible 3-carbethoxy-α-pyrone and its pyrone ring position 5 homologs. The reaction can be carried out either with separation of the intermediate β-acylvinylmalonic ester (O=CR—CR'=CH—CH$(COOC_2H_5)_2$ (II) or without it [4].

The synthesized esters of α-pyrone-3-carboxylic acid and its homologs III were further saponified to the corresponding acids IV, converted via acid chlorides V to substituted amides VI, of interest from the point of view of investigating their pharmacological and chemotherapeutical properties.



a) R = R'H; b) R = H; R' = CH_3; c) R = CH_3; R' = H;

d) R = C_6H_5; R' = H.

α-Pyrone-3-carboxylic acids are derivatives of lactones of unsaturated acids and unstable to alkali [5–8], so we saponified 3-carbethoxy-α-pyrone II with hot concentrated hydrochloric acid, the reaction conditions and time being so chosen that ester III was saponified to acid IV without the latter being decarboxylated. The unsubstituted α-pyrone-3-carboxylic acid (IVa) and its 5-methyl homolog (IVb) proved even less stable on heating than the previously known 6-substituted homologs (IVc, d) [2]. When IVa and b are heated in solution above 55°–60° C decarboxylation occurs, most readily with the unsubstituted α-pyrone-3-carboxylic acid IVa (for comparison we mention that 6-methyl-α-pyrone-3-carboxylic acid is decarboxylated at 70° C, while the corresponding 6-phenyl derivative withstands vacuum distillation [2]).

Treatment of acids IV with thionyl chloride gave high yields of the acid chlorides V, which were crystalline compounds, soluble in benzene and chloroform, less soluble in ether. The acid chlorides V were further used to prepare amides and piperazides VI, unobtainable directly from esters III, as then there is opening of the pyrone ring [9].

The amides (VI) were crystalline compounds, slightly soluble in water, soluble in the usual organic solvents, and unstable on prolonged keeping, some of them being hygroscopic. The most unstable were the amides containing not only amide nitrogen but also tertiary amine nitrogen; these gave very hygroscopic hydrochlorides.

EXPERIMENTAL

α-Pyrone-3-carboxylic acid. 5.39 g (0.032) 3-Carbethoxy-α-pyrone is heated for 2 hr at 40°–42° C with 15.9 ml concentrated HCl. The resultant dark homogeneous reaction products were extracted with methylene chloride. Removal of the solvent by distillation gave 2.15 g (48%) α-pyrone-3-carboxylic acid mp 127°–128° C (after washing with ether–petrol ether). Literature gives mp 127°–128° C [10].

5-Methyl-α-pyrone-3 carboxylic acid was obtained similarly. Yield 35%, mp 123.5–125° C (after washing with ether–petrol ether).

Found: C 54.84; 54.85; H 3.89; 3.98%, calculated for $C_7H_6O_4$: C 54.55; H 3.29%.

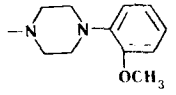
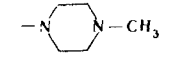
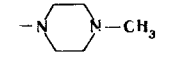
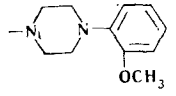
α-Pyrone-3-carbonyl chloride. 1.4 g (0.01 mole) α-Pyrone-3-carboxylic acid was heated with 7.2 ml thionyl chloride for 4 hr at 45°. The solvent was vacuum distilled off, and the residue recrystallized from mixed benzene–petrol ether. Yield 1.45 g (91.4%) yellowish crystals, 102°–103° (ex benzene–petrol ether). Found: Cl 22.05; 22.19%, calculated for $C_6H_3ClO_3$: Cl 22.36%.

5-Methyl-α-pyrone-3-carbonyl chloride was prepared similarly from 0.55 g (0.0036 mole) acid, yield 0.59 g (95.8%), mp 82°–83° C (ex benzene–petrol ether). Found: Cl 20.39; 20.47%, calculated for $C_7H_5ClO_3$: Cl 20.55%.

6-Phenyl-α-pyrone-3-carbonyl chloride was prepared as described in [2], by heating (2 hr, 60°–65° C) 1.08 g (0.005 mole) acid with 3.6 ml $SOCl_2$. Yield 1.1 g (94%), mp 160.5°–161.5° C (ex benzene). Found: Cl 14.79; 14.95%, calculated for $C_{12}H_7ClO_3$: Cl 15.11%.

α-Pyrone-3-carboxamide (typical run). A solution of 0.085 g (0.005 mole) ammonia in 15 ml dry ether was added with cooling (for reaction temperature see table) to a suspension of 0.396 g (0.0025 mole) α-pyrone-3-carbonyl chloride in 10 ml dry ether,

Amides of α-Pyrone-3-Carboxylic Acids (VI)

R	R'	$-NR_2''$	Reaction temperature	Mp. °C (decomp)	Formula	Found, %			Calculated, %			Yield, %
						C	H	N	C	H	N	
H	H	$-NH_2$	−50	131—132	$C_6H_5NO_3$	52.24 51.91	3.42 3.42	10.18 10.23	51.81	3.63	10.07	66.2
H	H		−50	88—90	$C_{17}H_{18}N_2O_4$	64.66 64.51	5.76 5.62	9.18 9.23	64.86	5.75	8.92	82.8
H	CH_3		−50	108—110	$C_{12}H_{16}N_2O_3$	60.56 60.28	7.15 7.12	11.91 11.95	60.99	6.83	11.86	85.0
CH_3	H		−5	59—61	$C_{12}H_{16}N_2O_3$	61.17 61.25	7.01 6.82	11.64 11.74	60.99	6.83	11.86	63.5
CH_3	H		−5	136—137	$C_{18}H_{20}N_2O_3$	65.81 66.04	6.14 6.11	8.28 8.41	65.86	6.14	8.53	85.3
C_6H_5	H	$-N(C_2H_5)_2$	−5	77.5—78.5	$C_{16}H_{17}NO_3$	70.68 70.65	6.28 6.39	5.25 5.23	70.81	6.32	5.17	73.8
C_6H_5	H	$-NH \cdot CH(CH_2)_3N(C_2H_5)_2$ (CH₃ on CH)	−5	42—44	$C_{21}H_{28}N_2O_3$	70.08 69.92	8.03 8.04	7.86 8.03	70.76	7.92	7.86	92.0

and the whole then stirred for 3 hr at the same temperature. The precipitate of ammonium chloride was filtered off and washed with dry benzene, and the filtrate vacuum evaporated at room temperature to give 0.23 yellowish crystals (see table).

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25 September 1965

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