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Abstract

Full Text

Chemistry

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δ-LACTONES AND δ-LACTAMS

CHLOROMETHYLATION OF 2-PYRONES

(Presented by Academician A. N. Nesmeyanov, 15 VI 1962)

Earlier ([1],[2]) we showed that 2-pyrones enter into such typical electrophilic-substitution reactions as nitration and sulfochlorination. In the present work, for the first time* one more electrophilic-substitution reaction—chloromethylation—has been carried out for 2-pyrones. Attempts to carry out chloromethylation of 2-pyrones by the action of a mixture of paraform and concentrated hydrochloric acid, and also paraform and $ZnCl_2$ in a solution of dichloroethane saturated with hydrogen chloride, led to resinification of the reaction mixture. It turned out that 5,6-disubstituted 2-pyrones are chloromethylated comparatively readily under the action of a mixture of mono- and bis-chloromethyl ethers ([4]), as well as formalin saturated with hydrogen chloride. The reaction proceeds at 92–95° and gives the corresponding chloromethyl-2-pyrones (I-III) in yields of 35–41%:

$$\text{[structural scheme: 2-pyrone with } R, R'\text{]} \xrightarrow{\text{mixture } ClCH_2OCH_3 \text{ and } ClCH_2OCH_2Cl} \text{[structural scheme: chlorometh}$$

I $R = R' = CH_3$
II $R = CH_3,\ R' = C_3H_7$
III R and $R' = -(CH_2)_4-$

The presence of a chloromethyl group in the compounds I-III obtained was proved by the formation of crystalline thiuronium picrates (IV–VI):

$$\Big[\text{[structural formula: } R, R'\text{-substituted 2-pyrone-}CH_2{-}S{-}C(NH_2)_2{}^{+}\text{]}\Big]\ C_6H_2(NO_2)_3O^- \quad (IV–VI)$$

IV $R = R' = CH_3$
V $R = CH_3,\ R' = C_3H_7$
VI R and $R' = -(CH_2)_4-$

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Like the 2-pyrones themselves, the chloromethyl derivatives I-III readily gave the double adducts with maleic anhydride characteristic of compounds of the α-pyrone series (VII and VIII):

[structural formula of maleic-anhydride adducts] $(VII \text{ and } VIII)$

$$\begin{array}{ll} \text{VII} & R = R' = \mathrm{CH_3} \\ \text{VIII} & R = \mathrm{CH_3},\ R' = \mathrm{C_3H_7} \end{array}$$

It is interesting to note that the nitro-2-pyrones and acid chlorides of pyrone-2-sulfonic acids obtained by us earlier did not react with maleic anhydride ([1],[2]), whereas bromo-2-pyrones ([5]) readily entered into diene synthesis. Thus, the introduction of strong electron-acceptor substituents into the pyrone ring deactivates the diene system of 2-pyrone.

Under the action of anhydrous sodium acetate in glacial acetic acid, the chlorine atom of the chloromethyl compounds I-III is readily replaced by an acetoxy group, with formation of the corresponding acetoxymethyl-2-pyrones (IX-XI) (yields 33-79%), which also readily enter into reaction with maleic anhydride, forming double adducts (XII–XIV):

$$\text{IX–XI} \xrightarrow{\mathrm{CH_3COONa}} \text{acetates (IX–XI)} \xrightarrow[-\mathrm{CO_2}]{+2\,\text{maleic anhydride}} \text{adducts (XII–XIV)}$$

IX, XII $R = R' = \mathrm{CH_3}$; X, XIII $R = \mathrm{CH_3},\ R' = \mathrm{C_3H_7}$; XI, XIV R and $R' = -(\mathrm{CH_2})_4-$

Chloromethylpyrones-2 (I–III) also readily exchanged the chlorine atom for the diethylamino group; the resulting diethylaminomethylpyrones-2 (yields 48–55%) XV–XVII were characterized as crystalline picrates (XVIII–XX):

$$\text{I–III} \xrightarrow{(\mathrm{C_2H_5})_2\mathrm{NH}} \text{XV–XVII}$$

$$\text{XV } R = R' = \mathrm{CH_3}$$

$$\text{XVI } R = \mathrm{CH_3},\ R' = \mathrm{C_3H_7}$$

$$\text{XVII } R \text{ and } R' = -(\mathrm{CH_2})_4-$$

Attempts to obtain adducts of diethylaminomethylpyrones-2 with maleic anhydride under conditions analogous to those used for the reaction with chloromethylpyrones gave no positive results—rapid and complete resinification occurred.

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* See the preliminary communication on the chloromethylation of 5,6-cyclohexano-2-pyrone ([3]).

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Experimental Part

3-Chloromethylpyrones-2. Chloromethylation of 5,6-dimethylpyrone-2, 6-methyl-5-propylpyrone-2 (6), and 5,6-cyclohexanopyrone-2 (7) was carried out with a mixture of chloromethyl and bischloromethyl ethers with b.p. 60–110° at 760 mm (obtained (4) by saturation of 34% formalin with hydrogen chloride and subsequent distillation of the separated organic layer). A mixture of 10 g of pyrone-2, 10 ml of the chloromethyl ether mixture, and 10 ml of glacial acetic acid was heated for 6 h at 92–95° with stirring; the reaction mixture was poured into 50 ml of water, and the separated oil was extracted with ether. Ether was added to the aqueous layer and it was neutralized with solid soda; the ether layer was separated, and the aqueous layer was extracted several times with ether. The combined ether extracts were washed with 2 N sodium carbonate solution until alkaline and with water until neutral, dried, the ether was removed, and the resulting chloromethylpyrone was distilled in vacuo in a stream of nitrogen (except for chloromethylpyrone III, which resinifies on distillation).

3-Chloromethyl-6,5-dimethylpyrone-2 (I, 4.9 g, yield 35%) distilled at 139–145°/6 mm and crystallized on cooling: m.p. 65–65.5° (from petroleum ether).

Found, %:	C 55.88; 56.12; H 5.59; 5.48
$C_8H_9O_2Cl$. Calculated, %:	C 55.68; H 5.26

3-Chloromethyl-6-methyl-5-propylpyrone-2 (II, 4.7 g, yield 41%): b.p. 155–156°/5 mm, n_D^{20} 1.5308, d_4^{20} 1.1553, MR_D 53.76. $C_{10}H_{13}O_2ClF_2$. Calculated 51.65. EM_D 2.12*.

Found, %:	C 59.53; 59.54; H 6.76; 6.72
$C_{10}H_{13}O_2Cl$. Calculated, %:	C 59.84; H 6.53

3-Chloromethyl-5,6-cyclohexanopyrone-2 (III) was obtained as a thick oil (10.5 g), which completely resinified on distillation. To obtain this chloromethylpyrone, a different procedure was used. A strong stream of dry hydrogen chloride was passed for 7.5 h through a mixture of 15.5 g of 5,6-cyclohexanopyrone-2 (6), 15 ml of 34% formalin, and 15 ml of dichloroethane of hydrogen chloride while heating to 85-90°. The reaction mixture was poured into water, the dichloroethane layer was separated, the aqueous solution was neutralized with solid soda and extracted with dichloroethane. The combined dichloroethane solutions were washed with 2 N soda until alkaline and with water until neutral. After drying and distilling off the dichloroethane, a thick oil remains (12.2 g), which on distillation likewise resinifies completely, but gives the characteristic reactions of chloromethyl derivatives.

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* For compounds with an α-pyrone ring, exaltation of the molecular refraction is characteristic (6).

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Reactions of 3-chloromethylpyrones-2

Crystalline thiouronium picrates (IV–VI) were obtained in the usual way —by interaction of 3-chloromethylpyrones-2 with thiourea and picric acid in alcoholic solution (^{4}); they were purified by recrystallization from alcohol (see Table 1).

Double adducts of chloromethylpyrones I and II (0.5 g each) with maleic anhydride (0.5 g) were obtained by heating a solution of the components in 5 ml of xylene for three hours. The precipitated crystals* were purified by dissolution in ethyl acetate and subsequent precipitation with petroleum ether (see Table 1).

Table 1

Thiouronium picrates and double adducts with maleic anhydride of 3-chloromethylpyrones-2

Substance	Formula No.	R	R′	Yield, %	M.p., °C	Found, % C	Found, % H	Formula	Calculated, % C	Calculated, % H
Thiouronium picrates	IV	CH_3	CH_3	80	203–204 (with decomp.)	41.17; 41.05	3.59; 3.45	$C_{15}H_{15}O_9N_5S$	40.81	3.43
Thiouronium picrates	V	CH_3	C_3H_7	79	197–198 (with decomp.)	43.16; 43.11	4.30; 4.08	$C_{17}H_{19}O_9N_5S$	43.49	4.08
Thiouronium picrates	VI	—$(CH_2)_4$—	—$(CH_2)_4$—	60	193–194 (with decomp.)	44.32; 44.38	4.04; 4.02	$C_{17}H_{17}O_9N_5S$	43.68	3.67
Double adducts with maleic anhydride	VII	CH_3	CH_3	55	304–305	55.77; 55.39	4.40; 4.07	$C_{15}H_{13}O_6Cl$	55.47	4.03

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Substance	Formula No.	R	R′	Yield, %	M.p., °C	Found, % C	Found, % H	Formula	Calculated, % C	Calculated, % H
Double adducts with maleic anhydride	VIII	CH_3	C_3H_7	51	233–234	57.77; 57.58	4.85; 4.84	$C_{17}H_{17}O_6Cl$	57.88	4.86

Table 2

3-Acetoxymethylpyrones-2 and their adducts with maleic anhydride

Substance	Formula No.	R	R′	Yield, %	M.p., °C	Found, % C	Found, % H	Formula	Calculated, % C	Calculated, % H
3-Acetoxymethylpyrones-2	IX	CH_3	CH_3	79	69–70	61.20; 61.17	6.24; 6.29	$C_{10}H_{12}O_4$	61.20	6.17
3-Acetoxymethylpyrones-2	X	CH_3	C_3H_7	50	b.p. 164–165° (4 mm)*	63.97; 64.00	7.29; 7.20	$C_{12}H_{16}O_4$	64.28	7.19
3-Acetoxymethylpyrones-2	XI	—$(CH_2)_4$—	—$(CH_2)_4$—	33	76.5–77.5	65.29; 65.16	6.41; 6.21	$C_{12}H_{14}O_4$	64.86	6.35
Their adducts with maleic anhydride	XII	CH_3	CH_3	Quant.	280–281	58.68; 58.46	4.89; 4.70	$C_{17}H_{16}O_8$	58.61	4.63
Their adducts with maleic anhydride	XIII	CH_3	C_3H_7	83	193–194	60.34; 60.46	5.42; 5.40	$C_{19}H_{20}O_8$	60.64	5.36

Substance	Formula No.	R	R′	Yield, %	M.p., °C	Found, % C	Found, % H	Formula	Calculated, % C	Calculated, % H
Their adducts with maleic anhydride	XIV	— $(CH_2)_4$ —	— $(CH_2)_4$ —	20	286–287 (with decomp.)	60.71; 60.94	4.87; 4.99	$C_{19}H_{18}O_8$	60.96	4.89

* n_D^{20} 1.5050, d_4^{20} 1.1272, MR_D 59.00. $C_{12}H_{16}O_4F_2$. Calculated 57.79; EM_D 1.21.

3-Acetoxypyrones-2 (IX–XI). A mixture of 0.025 mole of 3-chloromethylpyrone-2, 0.05 mole of anhydrous sodium acetate in 10 ml of glacial acetic

The acids were boiled with stirring for 6 h. The acetic acid was distilled off in vacuo with heating; the residue was treated with water, the aqueous solution was neutralized with solid soda, and extracted with ether. After drying and distilling off the solvent, the crystalline residue was recrystallized from petroleum ether, while the liquid residue was distilled in vacuo (see Table 2). Adducts (XII–XIV) of 3-acetoxymethylpyrones-2 with maleic anhydride (see Table 2) were obtained and purified by the procedure described above for adducts of chloromethylpyrones-2.

Table 3

3-Diethylaminomethylpyrones-2 and their picrates

Substances	Formula no.	R	R′	Yield, %	M.p., °C	B.p., °C	Found, % C	Found, % H	Formula	Calculated, % C	Calculated, % H
3-Diethylaminomethylpyrones-2	XV	CH_3	CH_3	55	—	145–146* (5 mm)	68.51 68.62	9.03 9.02	$C_{12}H_{19}NO_2$	68.87	9.15
3-Diethylaminomethylpyrones-2	XVI	CH_3	C_3H_7	51	—	163–164** (6 mm)	70.74 70.78	9.83 9.89	$C_{14}H_{23}NO_2$	70.84	9.54

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* Chloromethylpyrone III (a non-distilling oil) contained an impurity of the initial pyrone-2, and its adduct with maleic anhydride could not be purified from the pyrone adduct.

Substances	Formula no.	R	R′	Yield, %	M.p., °C	B.p., °C	Found, % C	Found, % H	Formula	Calculated, % C	Calculated, % H
3-Diethylaminomethylpyrones-2	XVII	—$(CH_2)_4$—	—$(CH_2)_4$—	48	—	180—181*** (5 mm)	71.10 70.82	9.24 9.05	$C_{14}H_{21}NO_2$	71.44	8.99
Their picrates	XVIII	CH_3	CH_3	—	142—147	—	48.90 49.08	5.06 5.05	$C_{18}H_{22}N_4O_9$	49.32	5.06
Their picrates	XIX	CH_3	C_3H_7	—	99—100	—	51.38 51.58	5.80 5.74	$C_{20}H_{26}N_4O_9$	51.50	5.62
Their picrates	XX	—$(CH_2)_4$—	—$(CH_2)_4$—	—	137—138	—	51.77 51.57	5.33 5.37	$C_{20}H_{24}N_4O_9$	51.72	5.21

* n_D^{20} 1.5125; d_4^{20} 1.0202, MR_D 61.60. $C_{12}H_{19}O_2F_2$. Calculated 60.08; EM_D 1.42.

** n_D^{20} 1.5038, d_4^{20} 0.9868, MR_D 71.17. $C_{14}H_{23}O_2F_2$. Calculated 69.31; EM_D 1.86.

*** n_D^{20} 1.5322, d_4^{20} 1.0662, MR_D 68.42. $C_{14}H_{21}O_2F_2$. Calculated 67.21; EM_D 1.21.

3-Diethylaminomethylpyrones-2 (XV–XVII). To a mixture of 0.014 mole of chloromethylpyrone-2 and 0.014 mole of powdered anhydrous potassium carbonate, 0.04 mole of diethylamine was added with stirring. The reaction mixture was cautiously boiled for 3 h, then poured into water and extracted several times with ether. The ether solution was washed with water, and the ether was distilled off in vacuo. The residue was dissolved in 2 N hydrochloric acid solution and extracted with ether. The hydrochloric acid solution was alkalized with concentrated sodium hydroxide solution and extracted with ether. After drying the ether solution and evaporating the ether, the residue was distilled in vacuo in a stream of nitrogen (see Table 3). The resulting 3-diethylaminomethylpyrones-2 were characterized by picrates, recrystallized from alcohol (see Table 3).

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