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# Chemistry

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**Abstract**

**Full Text**

**Chemistry**

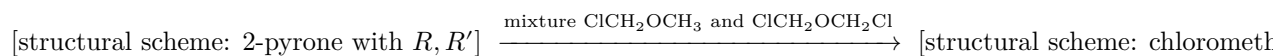
**N. P. SHUSHERINA, N. D. DMITRIEVA, R. Ya. LEVINA**

**$\delta$ -LACTONES AND  $\delta$ -LACTAMS**

**CHLOROMETHYLATION OF 2-PYRONES**

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

Earlier (<sup>1,2</sup>) 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<sub>2</sub> 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 (<sup>4</sup>), 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%:



- I  $R = R' = \text{CH}_3$   
 II  $R = \text{CH}_3, R' = \text{C}_3\text{H}_7$   
 III  $R \text{ and } R' = -(\text{CH}_2)_4-$

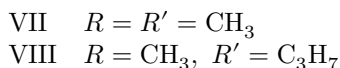
The presence of a chloromethyl group in the compounds I-III obtained was proved by the formation of crystalline thiuronium picrates (IV-VI):



- IV  $R = R' = \text{CH}_3$   
 V  $R = \text{CH}_3, R' = \text{C}_3\text{H}_7$   
 VI  $R \text{ and } R' = -(\text{CH}_2)_4-$

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

[structural formula of maleic-anhydride adducts] (VII and VIII)



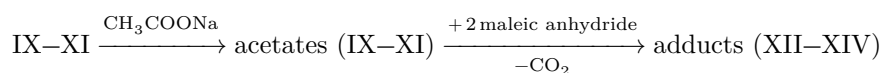
It is interesting to note that the nitro-2-pyrones and acid chlorides of pyrone-2-sulfonic acids obtained by us earlier did not react with maleic anhydride (<sup>1,2</sup>), whereas bromo-2-pyrones (<sup>5</sup>) readily entered into diene synthesis. Thus, the introduction of strong electron-acceptor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

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 male-

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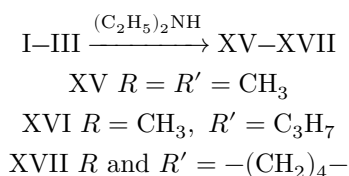
\* See the preliminary communication on the chloromethylation of 5,6-cyclohexano-2-pyrene (<sup>3</sup>).

maleic anhydride, forming double adducts (XII-XIV):



IX, XII  $R = R' = \text{CH}_3$ ; X, XIII  $R = \text{CH}_3, R' = \text{C}_3\text{H}_7$ ; XI, XIV  $R$  and  $R' = -(\text{CH}_2)_4-$

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):



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.

## Experimental Part

**3-Chloromethylpyrones-2.** Chloromethylation of 5,6-dimethylpyrone-2, 6-methyl-5-propylpyrone-2 (<sup>6</sup>), and 5,6-cyclohexanopyrone-2 (<sup>7</sup>) was carried out with a mixture of chloromethyl and bischloromethyl ethers with b.p. 60–110° at 760 mm (obtained (<sup>4</sup>) 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 <sub>8</sub> H <sub>9</sub> O <sub>2</sub> Cl. 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<sub>10</sub>H<sub>13</sub>O<sub>2</sub>ClF<sub>2</sub>. Calculated 51.65.  $EM_D$  2.12\*.

Found, %:	C 59.53; 59.54; H 6.76; 6.72
C <sub>10</sub> H <sub>13</sub> O <sub>2</sub> Cl. 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 (<sup>6</sup>), 15 ml of 34% formalin, and 15 ml of dichloroethane

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\* For compounds with an  $\alpha$ -pyrone ring, exaltation of the molecular refraction is characteristic (<sup>6</sup>).

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.

## Reactions of 3-chloromethylpyrones-2

**Crystalline thiuronium picrates (IV-VI)** were obtained in the usual way –by interaction of 3-chloromethylpyrones-2 with thiourea and picric acid in alcoholic solution (<sup>4</sup>); 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**

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

Substance No.	Formula		Yield, %	M.p., °C	Found, % C	Found, % H	Calculated,	
	R	R'					Formula	% C
Thiuronium picrates IV	CH <sub>3</sub>	CH <sub>3</sub>	80	203-204	41.17; 41.05	3.59; 3.45	C <sub>15</sub> H <sub>15</sub> N <sub>3</sub> S	40.81; 3.43
Thiuronium picrates V	CH <sub>3</sub>	C <sub>3</sub> H <sub>7</sub>	79	197-198	43.16; 43.11	4.30; 4.08	C <sub>17</sub> H <sub>19</sub> N <sub>3</sub> S	43.49; 4.08
Thiuronium picrates VI	— (CH <sub>2</sub> ) <sub>4</sub>	— (CH <sub>2</sub> ) <sub>4</sub>	60	193-194	44.32; 44.38	4.04; 4.02	C <sub>17</sub> H <sub>17</sub> N <sub>3</sub> S	43.68; 3.67
Double adducts with maleic anhydride VII	CH <sub>3</sub>	CH <sub>3</sub>	55	304-305	55.77; 55.39	4.40; 4.07	C <sub>15</sub> H <sub>13</sub> O <sub>4</sub> N <sub>3</sub> S	55.41; 4.03

Substance No.	Formula No.	R	R'	Yield, %	M.p., °C	Found, % C	Found, % H	Calculated, % C	Calculated, % H
Double VIII adducts with maleic anhydride	VIII	CH <sub>3</sub>	C <sub>3</sub> H <sub>7</sub>	51	233-234	57.77; 57.58	4.85; 4.84	C <sub>17</sub> H <sub>17</sub> O <sub>4</sub>	57.88; 4.86

**Table 2**

**3-Acetoxymethylpyrones-2 and their adducts with maleic anhydride**

Substance No.	Formula No.	R	R'	Yield, %	M.p., °C	Found, % C	Found, % H	Calculated, % C	Calculated, % H
3-Acetoxymethylpyrones-2	IX	CH <sub>3</sub>	CH <sub>3</sub>	79	69-70	61.20; 61.17	6.24; 6.29	C <sub>10</sub> H <sub>12</sub> O <sub>4</sub>	61.20; 6.17
3-Acetoxymethylpyrones-2	X	CH <sub>3</sub>	C <sub>3</sub> H <sub>7</sub>	50	b.p. 164-165° (4 mm)*	63.97; 64.00	7.29; 7.20	C <sub>12</sub> H <sub>16</sub> O <sub>4</sub>	64.28; 7.19
3-Acetoxymethylpyrones-2	XI	—	—	33	76.5-77.5	65.29; 65.16	6.41; 6.21	C <sub>12</sub> H <sub>14</sub> O <sub>4</sub>	64.86; 6.35
Their adducts with maleic anhydride	XII	CH <sub>3</sub>	CH <sub>3</sub>	Quant.	280-281	58.68; 58.46	4.89; 4.70	C <sub>17</sub> H <sub>16</sub> O <sub>8</sub>	58.61; 4.63
Their adducts with maleic anhydride	XIII	CH <sub>3</sub>	C <sub>3</sub> H <sub>7</sub>	83	193-194	60.34; 60.46	5.42; 5.40	C <sub>19</sub> H <sub>20</sub> O <sub>8</sub>	60.64; 5.36

Substance	Formula No.	R	R'	Yield, %	M.p., °C	Found, % C	Found, % H	Calculated, % C	Calculated, % H
Their adducts with maleic anhydride	XIV	—	—	20	286–287	60.71; 60.94	4.87; 4.99	C <sub>19</sub> H <sub>18</sub> O <sub>8</sub>	60.96 4.89
		(CH <sub>2</sub> ) <sub>4</sub>	(CH <sub>2</sub> ) <sub>4</sub>		(with de-comp.)				

\*  $n_D^{20}$  1.5050,  $d_4^{20}$  1.1272,  $MR_D$  59.00. C<sub>12</sub>H<sub>16</sub>O<sub>4</sub>F<sub>2</sub>. Calculated 57.79;  $EM_D$  1.21.

**3-Acetoxyprones-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

\* 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.

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**

Substance	Formula No.	R	R'	Yield, %	M.p., °C	B.p., °C	Found, % C	Found, % H	Calculated, % C	Calculated, % H
3-Diethylaminomethylpyrones-2	XV	CH <sub>3</sub>	CH <sub>3</sub>	55	—	145	68.516896	8.339.02	C <sub>12</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub>	68.87 9.15
						146* (5 mm)				
3-Diethylaminomethylpyrones-2	XVI	CH <sub>3</sub>	C <sub>3</sub> H <sub>7</sub>	51	—	163	70.747097	8.339.89	C <sub>14</sub> H <sub>23</sub> N <sub>2</sub> O <sub>2</sub>	71.84 9.54
						164** (6 mm)				

Substance	Formula	R	R'	Yield, %	M.p., °C	B.p., °C	Found, % C	Found, % H	Calculated, % C	Calculated, % H
3-Diethylaminomethylpyrones-2	XVII	—	—	48	—	180	71.1070	8.249.05	C <sub>14</sub> H <sub>21</sub> N <sub>2</sub> O <sub>2</sub>	8.99
						181*** (5 mm)				
Their pi-crates	XVIII	CH <sub>3</sub>	CH <sub>3</sub>	—	142	—	48.9049	5.065.05	C <sub>18</sub> H <sub>24</sub> N <sub>2</sub> O <sub>9</sub>	5.06
Their pi-crates	XIX	CH <sub>3</sub>	C <sub>3</sub> H <sub>7</sub>	—	99	—	51.3851	5.805.74	C <sub>20</sub> H <sub>28</sub> N <sub>2</sub> O <sub>9</sub>	5.62
Their pi-crates	XX	—	(CH <sub>2</sub> ) <sub>4</sub> (CH <sub>2</sub> ) <sub>4</sub>	—	137	—	51.7751	5.335.37	C <sub>20</sub> H <sub>24</sub> N <sub>2</sub> O <sub>9</sub>	5.21

\*  $n_D^{20}$  1.5125;  $d_4^{20}$  1.0202,  $MR_D$  61.60. C<sub>12</sub>H<sub>19</sub>O<sub>2</sub>F<sub>2</sub>. Calculated 60.08;  $EM_D$  1.42.

\*\*  $n_D^{20}$  1.5038,  $d_4^{20}$  0.9868,  $MR_D$  71.17. C<sub>14</sub>H<sub>23</sub>O<sub>2</sub>F<sub>2</sub>. Calculated 69.31;  $EM_D$  1.86.

\*\*\*  $n_D^{20}$  1.5322,  $d_4^{20}$  1.0662,  $MR_D$  68.42. C<sub>14</sub>H<sub>21</sub>O<sub>2</sub>F<sub>2</sub>. 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 alkalinized 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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*Note: Figure translations are in progress. See original paper for figures.*

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