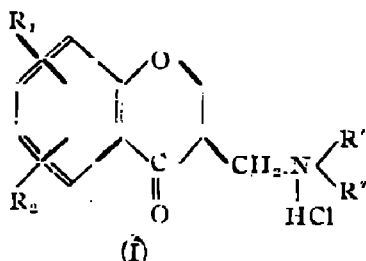


POSSIBLE ANTIAMOEBCIC AGENTS. PART IV. MANNICH BASES FROM  
SUBSTITUTED CHROMANONES

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Mannich bases from several substituted chromanones have been prepared with a view to testing their antiamoebic activity.

In continuation of the work carried out in this laboratory (Sen and Kulkarni, this *Journal*, 1957, 34, 467) we have now extended this work to the preparation of the Mannich bases from methoxy-, alkyl-chloro-, iodochloro- and iodo-chromanones, with a view to studying the effect of these groups and their position in the nucleus on the antiamoebic activity. Several amoebicides (Entero-vioform, Diodoquin etc.) contain iodine in their molecule; as such, iodine has been introduced in the nucleus of some of these compounds (I).



[R' & R = various substituents in the basic side chain.

R<sub>1</sub> & R<sub>2</sub> = ,, ,, in the chromanone nucleus].

The present work reports the synthesis of  $\beta$ -(2-iodo-4-chloro-, 2-iodo- and 4-iodo-phenoxy)-propionic acids, their conversion into chromanones and the preparation of 6-chloro-7-methylchromanone.

The required  $\beta$ -phenoxypropionic acids were obtained by applying the method of Gresham *et al.* (*J. Amer. Chem. Soc.*, 1949, 71, 661) from *o*-methoxy-, *p*-chloro-*m*-methyl-, *o*-iodo-*p*-chloro-, *o*-iodo- and *p*-iodo-phenols by condensing them with  $\beta$ -propiolactone in alkaline medium.

Only some of the  $\beta$ -phenoxypropionic acids could be cyclised by H<sub>2</sub>SO<sub>4</sub> (conc., 98%) as described by Hurd and Hayao (*ibid.*, 1954, 76, 5065). But in most of the cases, viz.,  $\beta$ -(2-iodo-, 4-iodo- and 2-methoxyphenoxy)-propionic acids, cyclisation could not be effected with H<sub>2</sub>SO<sub>4</sub> (conc.) satisfactorily, as treatment with it followed by dilution with crushed ice left a very small amount of a sticky black mass or in some cases no precipitate could be obtained. Cyclisation of these acids was effected with very good yields and purity by treating benzene solution of the  $\beta$ -phenoxypropionic acid with 5 parts of P<sub>2</sub>O<sub>5</sub>, as described by Robertson and Subramaniam (*J. Chem. Soc.*, 1936, 1832) and refluxing for 10 hours.

The Mannich base hydrochlorides of these chromanones were obtained by following the method of Harradence *et al.* (*J. Proc. Roy. Soc., N. S. Wales*, 1939, **27**, 273) as modified by Sen and Kulkarni (*loc. cit.*); equimolar quantities of chromanones, paraformaldehyde and amine hydrochloride were suspended in dry benzene and acidified either by the addition of a few drops of HCl (conc.) or where this method did not succeed, HCl gas was passed. The reaction mixture was refluxed for 6 to 8 hours.

#### EXPERIMENTAL

The following phenols were used, viz., *o*-methoxy-, *p*-chloro-*m*-methyl-; 2-iodo-4-chlorophenol was obtained by the method of Verma and Yashoda (*this Journal*, 1939, **16**, 477); 2-iodophenol was obtained according to Gilman (*Org. Syn.*, Vol. **1**, 1932, p. 319) and 4-iodophenol was obtained by following the method as described by Vogel (*"Practical Organic Chemistry"*, 1948, p. 651).  $\beta$ -Propiolactone was obtained from Eastman Kodak Ltd.

*Substituted  $\beta$ -Phenoxypropionic Acids.*—The  $\beta$ -phenoxypropionic acids were obtained from the corresponding phenols by condensing with  $\beta$ -propiolactone (Gresham, *loc. cit.*).

$\beta$ -(3-Methyl-4-chlorophenoxy)-propionic acid has been reported by Hall *et al.* (*J. Chem. Soc.*, 1949, 2035), but we have prepared it by the condensation of the phenol with  $\beta$ -propiolactone.

The yields, m.p., neutralisation equivalents and the analytical data for these acids are recorded in Table I.

TABLE I

$\beta$ -Phenoxypropionic acids.	M.P.	% Yield.	Neut. equiv.		% Carbon.		% Hydrogen.	
			Found.	Calc.	Found <sup>a</sup>	Calc.	Found.	Calc.
3-Methyl-4-chloro-	141°	50	214.1	214.5	55.70	55.90	5.00	5.13
2-Iodo-4-chloro-	136°	48	327.0	326.5	32.90	33.70	2.35	2.45
2-Iodo-	123°	45.5	291.7	292.0	37.20	37.00	3.20	3.08
4-Iodo-	160-61°	43	292.3	292.0	36.90	37.00	2.80	3.08

#### Substituted Chromanones

7-Methyl-6-chloro- and 8-iodo-6-chloro-chromanones were obtained by cyclisation of the corresponding  $\beta$ -phenoxypropionic acids with H<sub>2</sub>SO<sub>4</sub> (conc., 98%). In the first case the acid was treated with 10 parts, whereas in the second case with 7.5 parts of H<sub>2</sub>SO<sub>4</sub> (conc.) and the solution kept for 36 hours with occasional shaking at the room temperature. The chromanones were then isolated in the usual way, as described by Hurd and Hayao (*loc. cit.*).

8- & 6-Iodo- and also 8-methoxy-chromanones were obtained by the cyclisation of the corresponding  $\beta$ -phenoxypropionic acids with P<sub>2</sub>O<sub>5</sub> in dry benzene according to the method described by Robertson and Subramaniam (*loc. cit.*).

8-Methoxychromanone has been reported by Wiley (*J. Amer. Chem. Soc.*, **1951**, **73**, 4205).

The chromanones were characterised through their 2:4-dinitrophenylhydrazones.

<sup>a</sup> The m.p., yields, m.p. of their 2:4-dinitrophenylhydrazones and the analytical data of these chromanones are recorded in Table III.

## POSSIBLE ANTIAMOEBCIC AGENTS

Sl. No.	R <sub>1</sub> & R <sub>2</sub>	R' & R''	Acid medium.	M.P.	% Yield.	Mol. formula.	% Nitrogen.		M.P.	Mol. formula.	% Nitrogen.	
							Found.	Calc.			Found.	Calc.
1.	8-Methoxy-	Morpholinyl-	(B)	174°	56.80	C <sub>16</sub> H <sub>23</sub> ClNO <sub>4</sub>	4.28	4.46	155-56°	C <sub>21</sub> H <sub>29</sub> N <sub>4</sub> O <sub>11</sub>	11.10	11.07
2.	"	Piperidyl-	"	150°	25.00	C <sub>16</sub> H <sub>23</sub> ClNO <sub>3</sub>	4.30	4.49	...			
3.	"	Benzylyl-	"	209°	26.00	C <sub>18</sub> H <sub>25</sub> ClNO <sub>3</sub>	4.10	4.20	...			
4.	7-Methyl- 6-chloro-	Morpholinyl-	(A)	181°	53.00	C <sub>15</sub> H <sub>19</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub>	4.04	4.22	152-53°	C <sub>21</sub> H <sub>21</sub> ClN <sub>4</sub> O <sub>10</sub>	10.45	10.68
5.	"	Piperidyl-	"	194°	40.00	C <sub>16</sub> H <sub>21</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	4.30	4.24	154°	C <sub>22</sub> H <sub>23</sub> ClN <sub>4</sub> O <sub>9</sub>	10.50	10.71
6.	"	Dimethyl-	"	180°	29.00	C <sub>13</sub> H <sub>17</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	4.41	4.81	...			
7.	6-Iodo- <i>w</i>	Morpholinyl-	"	189°	60.00	C <sub>14</sub> H <sub>17</sub> ClINO <sub>3</sub>	3.21	3.42	162-63°	C <sub>20</sub> H <sub>19</sub> IN <sub>4</sub> O <sub>10</sub>	9.15	9.50
8.	"	Piperidyl-	"	201°	57.20	C <sub>19</sub> H <sub>19</sub> ClINO <sub>2</sub>	3.32	3-13	...			
9.	"	Dimethyl-	(B)	194°	33.00	C <sub>12</sub> H <sub>15</sub> ClINO <sub>2</sub>	3.93	3.81	...			
10.	"	Benzylyl-	"	201°	65.00	C <sub>17</sub> H <sub>17</sub> ClINO <sub>2</sub>	3.00	3.26	...			
11.	8-Iodo-	Morpholinyl-	"	191°	35.00	C <sub>14</sub> H <sub>17</sub> ClINO <sub>3</sub>	3.36	3.42	139-40°	C <sub>20</sub> H <sub>19</sub> N <sub>4</sub> O <sub>10</sub>	9.00	9.30
12.	8-Iodo- 6-chloro-	Piperidyl-	"	180°	30.00	C <sub>12</sub> H <sub>15</sub> Cl <sub>2</sub> INO <sub>2</sub>	3.20	3.17	...			
13.	"	Morpholinyl	"	Decomposes	30.00	C <sub>14</sub> H <sub>16</sub> Cl <sub>2</sub> INO <sub>3</sub>	3.15	3.15	...			
14.	"	Dimethyl	"	"	10.00	C <sub>12</sub> H <sub>14</sub> Cl <sub>2</sub> INO <sub>2</sub>	3.50	3.48	...			

TABLE II  
(Vide structure I)

TABLE III

Substituted chromanones.	M.P.	% Yield.	% Carbon.		% Hydrogen.		2:4-Dinitrophenyl-hydrazone.		
			Found.	Calc.	Found.	Calc.	M.P.	% Nitrogen Found. Calc.	
7-Methyl-6-chloro-	55°	37.0	60.90	61.10	4.60	4.58	229-30°	14.70	14.90
8-Iodo-6-chloro-	110-11°	14.5	35.15	35.00	2.00	1.94	255-56°	11.30	11.46
6-Iodo-	84-85°	95.7	39.60	39.41	2.45	2.55	265-86°	12.20	12.34
8-Iodo-	100-10°	65.8	39.45	39.41	2.60	2.55	249-50°	12.15	12.34

*Mannich Base Hydrochlorides from Substituted Chromanones (I)*

These were obtained according to the method of Sen and Kulkarni (*loc. cit.*) as described below.

A mixture of the chromanone (0.01 M) and paraformaldehyde (0.01 M) in dry benzene (25 c.c.) was taken in a flask and refluxed for about 30 minutes. To this was added the amine hydrochloride (0.01 M) and refluxed again for about 10 minutes. It was then acidified either with 5 to 10 drops of HCl (conc., A.R) (A) or by passing dry HCl gas (B) and refluxing the reaction mixture for 6 to 8 hours, during which the Mannich base hydrochloride separated as fine crystalline mass in most of the cases. After the completion of the reaction, the reaction mixture was cooled and the crystalline mass filtered at the pump, washed with dry benzene, then with ether and finally recrystallised from absolute ethyl alcohol.

The Mannich bases (I) were characterised by preparing their picrates. The melting points, analysis of the Mannich base hydrochlorides and their picrates are recorded in Table II.

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