

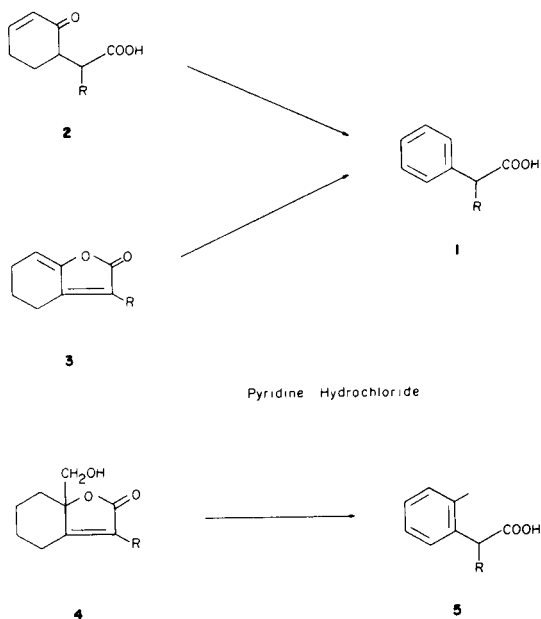
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2(4*H*)-5,6-Dihydrobenzofuranones **3** gave, when treated with pyridine hydrochloride at 200°, the corresponding arylacetic acids **1** in good yields, whereas the aza analogues, the tetrahydrooxindoles **6** gave indoles in poor yields. The oxidation products of **3** (**11** and **13**) and of **6** (**12**, **14** and **15**) gave, with the same reagent, benzofuranones and oxindoles, respectively, both in good yields.

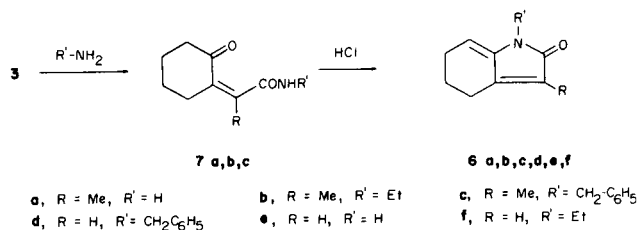
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In a previous paper we have described a new synthesis of arylacetic acids **1** starting from cyclohexenone-acetic acids **2** (2) by means of pyridine hydrochloride. Subse-

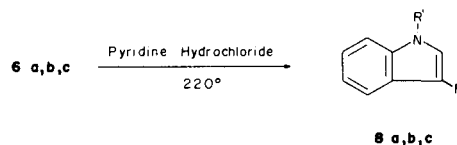


quently it was shown that not only the cyclohexenone-acetic acids **2** but also some of their synthetic equivalents, such as the lactones **2** or **4**, when treated with pyridine hydrochloride, gave in good yields, the corresponding aromatic acids, for example **1** or **5** (3,1), in this way increasing the practical applications of this reaction.

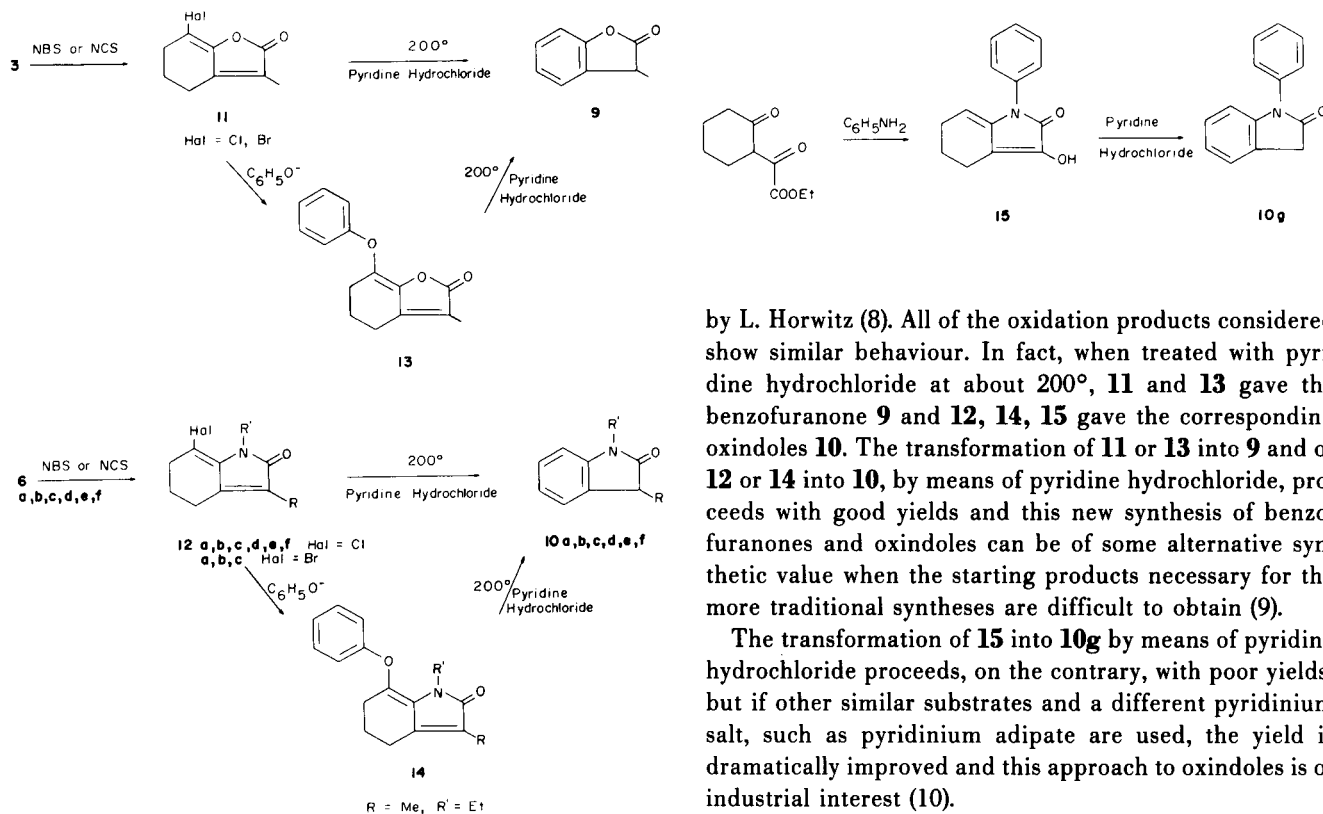
In order to investigate the scope and limitations of this new reaction we treated with pyridine hydrochloride some other compounds related to the lactones **3**. At first we chose some aza analogues of **3**, i.e. the 3-methyl-1,4,5,6-tetrahydro-2*H*-indol-2-ones **6a,b,c**, which were obtained by the action of ammonia or amines on the appropriate lactones **3**, through the intermediate amides **7**. This method resulted to be superior to the one described by Prasad for **6c** (4) which gave a hygroscopic product with a



lower mp. Also the compounds **6a,b,c** aromatize when treated with pyridine hydrochloride at a temperature above 200°, but while in **3** and **4** the cyclohexanic C-O bond is broken, the corresponding C-N bond in **6** is not broken and, consequently, the corresponding indoles **8a,b,c** can be obtained.



The above mentioned indoles **8** were obtained in very poor yields and the reaction showed only a speculative but not a practical interest (5) (see Experimental). This can be ascribed to the easy decomposition of the indoles, once formed, in the reaction medium (6). Results having a preparative value were, on the other hand, obtained through the action of pyridine hydrochloride on some oxidation products of the lactones **3** and of their aza analogues **6**. Two kinds of monoxidation products were considered. The first ones corresponding to the general formulas **11**, **12**, **13** and **14**, were obtained by the action of *N*-bromo or *N*-chlorosuccinimide on **3** or **6** or by the subsequent substitution of the halogen atom with the phenoxy group (7). An example of the second type is compound **15** which can only formally be considered an oxidation product of **6** since it was obtained by a different approach starting from ethyl cyclohexanone-glyoxylate and aniline as described



by L. Horwitz (8). All of the oxidation products considered show similar behaviour. In fact, when treated with pyridine hydrochloride at about 200°, **11** and **13** gave the benzofuranone **9** and **12**, **14**, **15** gave the corresponding oxindoles **10**. The transformation of **11** or **13** into **9** and of **12** or **14** into **10**, by means of pyridine hydrochloride, proceeds with good yields and this new synthesis of benzofuranones and oxindoles can be of some alternative synthetic value when the starting products necessary for the more traditional syntheses are difficult to obtain (**9**).

The transformation of **15** into **10g** by means of pyridine hydrochloride proceeds, on the contrary, with poor yields, but if other similar substrates and a different pyridinium salt, such as pyridinium adipate are used, the yield is dramatically improved and this approach to oxindoles is of industrial interest (**10**).

Table 1

1,4,5,6-Tetrahydro-(2H)-indol-2-ones **6** and Amides **7**

Compound	Mp °C (bp) Solvent	Yield % (a)	Analysis	NMR (Deuteriochloroform, TMS)			
				CH <sub>3</sub>	=CH (7)	=CH (3)	CH <sub>2</sub> -N
<b>6a</b>	172-175 aqueous ethanol	33	C <sub>9</sub> H <sub>11</sub> NO Found C, 72.74 H, 7.71 N, 9.33 Calcd. C, 72.45 H, 7.43 N, 9.39	1.80 (s)	5.63 (t, J = 4 Hz)		
<b>6b</b>	(170/20 torr)	61	C <sub>11</sub> H <sub>15</sub> NO Found C, 74.28 H, 8.72 N, 7.67 Calcd. C, 74.54 H, 8.55 N, 7.60	1.80 (s)	5.55 (t, J = 4 Hz)		3.60 (q, J = 7 Hz)
<b>6c</b>	78-79 (b) ethyl acetate	35					
<b>6d</b>	95-97 hexane-ethyl acetate	35	C <sub>15</sub> H <sub>15</sub> NO Found C, 79.93 H, 6.75 N, 6.50 Calcd. C, 79.97 H, 6.71 N, 6.22		5.52 (t, J = 4 Hz)	5.72 (s)	4.72 (s)
<b>6f</b>	(105/0.3 torr)	32	C <sub>10</sub> H <sub>13</sub> NO Found C, 73.30 H, 8.00 N, 8.83 Calcd. C, 73.59 H, 8.03 N, 8.58		5.68 (t, J = 4 Hz)	5.70 (s)	3.70 (q, J = 7 Hz)
<b>7a</b>	152-154 hexane-ethyl acetate	83	C <sub>9</sub> H <sub>13</sub> NO <sub>2</sub> Found C, 64.67 H, 7.88 N, 8.13 Calcd. C, 64.65 H, 7.84 N, 8.38	1.80 (s)			
<b>7b</b>	114-115 hexane-ethyl acetate	77	C <sub>11</sub> H <sub>17</sub> NO <sub>2</sub> Found C, 67.79 H, 8.75 N, 6.90 Calcd. C, 67.66 H, 8.78 N, 7.17	1.67 (s)			3.35 (q, J = 7 Hz)
<b>7c</b>	152-153 ethyl acetate	50.6	C <sub>16</sub> H <sub>19</sub> NO <sub>2</sub> Found C, 74.96 H, 7.55 N, 5.40 Calcd. C, 74.68 H, 7.44 N, 5.44	1.80 (s)			4.55 (dd, J = 14 Hz) (geminal coupling)

(a) For compound **6** the yields are referred to the steps **3** — **7** — **6**. (b) Lit (4) mp 56°.

Table 2

Starting Product	Reaction Time	Indole	Yield %
<b>6a</b>	20 minutes	<b>8a</b> (a)	6
<b>6b</b>	25 minutes	<b>8b</b> (b)	12
<b>6c</b>	25 minutes	<b>8c</b> (c)	16

(a) E. Fisher, *Ber.*, **19**, 1566 (1886). (b) P. E. Verdake, J. Lieste and E. G. G. Werner, *Rec. Trav. Chim.*, **64**, 289 (1945). (c) K. H. Bauer and K. Bühler, *Arch. Pharm.*, 132 (1924).

## EXPERIMENTAL

The melting points were determined on a Büchi apparatus and are uncorrected. The nmr spectra were taken with a Perkin Elmer R 24 (60 MHz) spectrometer (with TMS as internal standard). Gas chromatographic analyses were performed on a Perkin Elmer F11 apparatus equipped with FID and OV 17 3% glass column (2 m × 2 mm φ).

1,4,5,6-Tetrahydro-2*H*-indol-2-ones **6** and Amides **7**.

In order to obtain *N*-unsubstituted and *N*-ethyltetrahydroindolones **6a,b,e,f**, the selected **3** (R = H or Me) was suspended in a concentrated aqueous solution (33%) of ammonia or ethylamine (20 ml) and stirred at room temperature overnight. The solid obtained (amide **7**) was filtered and suspended in concentrated hydrochloric acid (20 ml) and heated for 10 minutes on a steam bath. After cooling and diluting the mixture with water, **6** was filtered and recrystallized, if solid, or was taken up with ethyl ether and distilled, if an oil. To obtain the two *N*-benzyltetrahydroindolones **6c,d** a mixture of chosen **3** (R = H or Me) (0.02 moles) and

benzylamine (0.04 moles) was heated at 130° for 3 hours. After cooling the reaction mixture was taken up with ethyl ether and the solid amide **7** which separated was filtered and treated with concentrated hydrochloric acid as above. In some cases the intermediate amides were not recrystallized and characterized but used crude for the next step.

In Table 1 are listed the melting points, the analyses, the nmr and the yields of the new products **6** and **7**.

Action of Pyridine Hydrochloride on **6a,b,c**.

The chosen tetrahydroindolone **6a,b,c** was heated at 220° with five weights of pyridine hydrochloride under nitrogen for the time reported in Table 2. The cooled, but still molten mixture, was poured into water. The residue which was obtained after extraction with ethyl ether and removal of the solvent was analyzed *via* glc on an OV<sub>17</sub> column at suitable temperatures and the amounts of indole formed were estimated.

The following Table 2 reports the starting products, the reaction times and the gas chromatographic yields.

The crude mixture obtained from **6b** was analyzed in a glc/mass spectrometer and three peaks were detected: a major peak with mass spectrum, *m/e* (relative intensity): 159 (M<sup>+</sup>, 58), 144 (100), 130 (22), 115 (20), 91 (33), 77 (34), due to 1-ethyl-3-methylindole **8b**; a peak with a lower retention time and mass spectrum 175 (M<sup>+</sup>, 54), 160 (30), 147 (35), 132 (70), 117 (50), 91 (100), 77 (88) due to 1-ethyl-3-methyl-2-oxindole and a third peak with mass spectrum 173 (M<sup>+</sup>, 29), 158 (42), 144 (11), 115 (39), 104 (35), 91 (100), 77 (75), which could be attributed to 1-ethyl-2-oxo-dihydroquinoline. The gas chromatographic analyses showed the same pattern for the crude mixtures obtained by the action of pyridine hydrochloride on **6a** and **6c**.

Table 3

7-Halo-1,4,5,6-tetrahydro-2*H*-indol-2-ones and 7-Halo-5,6-dihydro-2(4*H*)-benzofuranones

Compound	Mp °C (bp) Solvent	Yield %		Analysis				NMR (Deuteriochloroform, TMS)		
				Found	C, %	H, %	N, %	CH <sub>3</sub>	=CH (3)	CH <sub>2</sub> -N
<b>12a</b> (Cl)	217-218 ethanol	61	C <sub>9</sub> H <sub>10</sub> ClNO	Found	C, 58.93	H, 5.55	N, 7.58	1.75 (s)		
				Calcd.	C, 58.87	H, 5.49	N, 7.63			
<b>12b</b> (Cl)	46-48 petroleum ether	71	C <sub>11</sub> H <sub>14</sub> ClNO	Found	C, 62.14	H, 6.60	N, 6.73	1.80 (s)		4.0 (q, J = 7 Hz)
				Calcd.	C, 62.42	H, 6.67	N, 6.62			
<b>12c</b> (Cl)	72-73 hexane-ethyl acetate	43	C <sub>16</sub> H <sub>16</sub> ClNO	Found	C, 69.93	H, 5.89	N, 5.32	1.90 (s)		5.2 (s)
				Calcd.	C, 70.20	H, 5.89	N, 5.12			
<b>12d</b> (Cl)	85-86 hexane	26	C <sub>15</sub> H <sub>14</sub> ClNO	Found	C, 69.24	H, 5.44	N, 5.48		5.85 (s)	5.2 (s)
				Calcd.	C, 69.37	H, 5.43	N, 5.39			
<b>12e</b> (Cl)	174 ethanol	46	C <sub>8</sub> H <sub>8</sub> ClNO	Found	C, 56.38	H, 4.78	N, 7.99		5.7 (s)	
				Calcd.	C, 56.63	H, 4.71	N, 8.22			
<b>12f</b> (Cl)	(150°/0.5 torr)	45	C <sub>10</sub> H <sub>12</sub> ClNO	Found	C, 60.50	H, 6.18	N, 7.12	5.75 (s)		3.97 (q, J = 7 Hz)
				Calcd.	C, 60.77	H, 6.12	N, 7.09			
<b>12a</b> (Br)	53-54 petroleum ether	64	C <sub>11</sub> H <sub>14</sub> BrNO	Found	C, 51.60	H, 5.60	N, 5.47	1.75 (s)		3.95 (q, J = 7 Hz)
				Calcd.	C, 51.58	H, 5.51	N, 5.47			
<b>12b</b> (Br)	204 ethanol	40	C <sub>9</sub> H <sub>10</sub> BrNO	Found	C, 47.43	H, 4.45	N, 6.12	1.72 (s)		
				Calcd.	C, 47.39	H, 4.42	N, 6.14			
<b>12c</b> (Br)	85-86 hexane-ethyl acetate	63	C <sub>16</sub> H <sub>16</sub> BrNO	Found	C, 60.39	H, 5.05	N, 4.48	1.90 (s)		5.2 (s)
				Calcd.	C, 60.39	H, 5.07	N, 4.40			
<b>11</b> (Br)	100-103 cyclohexane	38	C <sub>9</sub> H <sub>9</sub> BrO <sub>2</sub>	Found	C, 47.11	H, 3.94	Br, 34.70	2.05 (s)		
				Calcd.	C, 47.19	H, 3.95	Br, 34.88			
<b>11</b> (Cl)	107-109 hexane-ethyl acetate	30	C <sub>9</sub> H <sub>9</sub> ClO <sub>2</sub>	Found	C, 58.37	H, 4.70	Cl, 19.01	1.90 (s)		
				Calcd.	C, 58.55	H, 4.91	Cl, 19.21			

Table 4  
3-Methylbenzofuran-2-one **9** and Oxindoles **10**

Starting Halo or Phenoxy Derivative	Temperature °C/Reaction Time	Products	Yield %	mp °C (bp) Solvent	Literature	NMR (Deuteriochloroform)		
						-CH <sub>2</sub> -CO	CH <sub>2</sub> -N-	-CH <sub>3</sub> -CH(CH <sub>3</sub> )-CO-
<b>12a</b> (Cl)	200/1 hour	<b>10a</b>	82	118-120	121-123 (a)			1.47 (d, 3.45 (q, J = 7 Hz) J = 7 Hz)
<b>12a</b> (Br)			78	isopropyl ether ethyl acetate				
<b>12b</b> (Cl)	200/3 hours	<b>10b</b>	90	(152)	not reported (b)			3.72 (q, 1.45 (d, 3.35 (q, J = 7 Hz) J = 7 Hz) J = 7 Hz)
<b>14</b>	200/2 hours		30	20 torr				
<b>12c</b> (Cl)	200/1.5 hours	<b>10c</b>	92	116-118	117-118 (c)			4.9 (s) 1.55 (d, 3.45 (q, J = 7 Hz) J = 7 Hz)
<b>12c</b> (Br)			47	ethanol				
<b>12d</b> (Cl)	200/10 minutes	<b>10d</b>	93	73-75	65-67 (d)	3.6 (s)	4.9 (s)	
				ethanol				
<b>12e</b> (Cl)	200/20 minutes	<b>10e</b>	40	124-126	127-129 (e)	3.5 (s)		
				ethyl acetate				
<b>12f</b> (Cl)	200/20 minutes	<b>10f</b>	70	94-96	97-98 (f)	3.45 (s)	3.75 (q, J = 7 Hz)	
<b>11</b> (Hal = Cl)	200/2 hours	<b>9</b>	33	(88-90)	(88-90) (g)			1.45 (d, 3.55 (q, J = 8 Hz) J = 8 Hz)
<b>13</b>	200/3 hours		32	2 torr	2 torr			

(a) A. S. Endler and E. I. Becker, *J. Am. Chem. Soc.*, **77**, 6608 (1955). (b) G. Stefanovich and S. Mialovic, *Glasnick Khem. Durshtva, Beograd*, **22**, 459 (1959); *Chem. Abstr.* **56**, 3442h (1962). (c) A. C. Rodriguez and P. R. Leeming, *J. Med. Chem.*, **15**, 762 (1972). (d) G. Palazzo and V. Rosnati, *Gazz. Chim. Ital.*, **83**, 24 (1953). (e) F. J. Di Carlo, *J. Am. Chem. Soc.*, **66**, 1420 (1944). (f) M. S. Kisteneva, *Zh. Obshch. Khim.*, **26**, 1169 (1956). (g) T. Kariyone and S. Imai, *J. Pharm. Soc. Japan*, **55**, 679 (1938).

#### 7-Halo-1,4,5,6-tetrahydro-2H-indol-2-ones **12** and 7-Halo-5,6-dihydro-2(4H)-benzofuranones **11**.

A solution of the selected **6a,b,c,d,e\*,f** (6e was used crude) or **3** (0.05 mole) and *N*-chlorosuccinimide (0.05 mole) in a mixture of water-dioxane 1:1 (120 ml) was heated at 50° for 40 minutes. After removal of the solvent, the residue was dissolved in concentrated hydrochloric acid (35 ml) and the solution heated at 50° for 15 minutes. After cooling, the solid which separated was filtered and recrystallized to give **12a,b,c,d,e,f** or **11** (Hal = Cl). Using the same procedure **12a,b,c** (Hal = Br) were respectively obtained from **3** or **6a,b,c** by the action of *N*-bromosuccinimide.

In Table 3 are listed the mp, analyses, nmr spectra and yields of the new products.

#### 3-Methyl-7-phenoxy-5,6-dihydro-2(4H)-benzofuranone **13**.

Compound **11** (Hal = Br) (18.5 g, 0.1 mole) and copper powder (few mg) were added, at a temperature of 100° to a molten mixture of phenol (11.5 g, 0.2 mole) and potassium hydroxide (5.7 g, 0.1 mole). The mixture was heated at 140-150° with stirring for 1 hour, then cooled, poured into water and extracted with ether. The ethereal solution was washed with 2*N* sodium hydroxide and evaporated to give a residue which was crystallized twice from hexane-ethyl acetate. Compound **13** was obtained in 30% yield, mp 91-93°; <sup>1</sup>H nmr (deuteriochloroform): δ 1.9 (s, 3H, =C-CH<sub>3</sub>).

*Anal.* Calcd. for C<sub>13</sub>H<sub>14</sub>O<sub>3</sub>: C, 74.36; H, 5.83. Found: C, 74.29; H, 5.98.

#### *N*-Ethyl-3-methyl-7-phenoxy-1,3,4,6-tetrahydro-2H-indol-2-one **14**.

As already described for **13**, from **12a** (Hal = Br) was obtained **14**, mp 84-86° (isopropyl ether) in 5% yield; <sup>1</sup>H nmr (deuteriochloroform): δ 2.05 (s, 3H, =C-CH<sub>3</sub>), 3.95 (q, 2H, J = 7 Hz, N-CH<sub>2</sub>-CH<sub>3</sub>).

*Anal.* Calcd. for C<sub>17</sub>H<sub>19</sub>NO<sub>2</sub>: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.64; H, 7.11; N, 5.20.

#### 3-Methylbenzofuranone **9** and Oxindoles **10**.

A mixture of chosen **11**, **12**, **13** or **14** (about 5 mmoles) and five weights of pyridine hydrochloride was heated at 200° for the time period in Table 4 until the tlc analysis showed the disappearance of the starting product. The cooled but still molten reaction mixture was then poured into water and, after cooling, the precipitate obtained, was collected by suction and recrystallized.

The results obtained are summarized in the following Table 4.

#### *N*-Phenylloxindole **10g** (11).

Compound **15** and a 5-fold excess of pyridine hydrochloride were melted together and the crude reaction mixture obtained was worked up as described above. Several trials were performed by varying the temperature from 190° to 230° and varying the heating time. Comparatively better results were obtained by heating **15** and pyridine hydrochloride at 230° for 1 hour in order to obtain **10g**, mp 120° from ethanol, lit 121° (11) in 12.4% yield.

#### REFERENCES AND NOTES

- Note VI. L. Baiocchi and M. Giannangeli, *Tetrahedron Letters*, 4499 (1979).
- G. Palazzo and L. Baiocchi, *ibid.*, 4739 (1968).
- L. Baiocchi, M. Bonamomi, M. Giannangeli and G. Picconi, *Synthesis*, 434, (1979).
- M. Prasad and C. G. Wermuth, *Bull. Soc. Chim. France*, 1386 (1967).
- A similar reaction was recently described by E. Bisagni, C. Ducrocq and N. Chi Hung in an article which appeared in *Tetrahedron*, **36**, 1327 (1980) where some carbazole derivatives were obtained from oxyclohexylindoles in good yields.

(6) Some oxidation byproducts which were detected in the aromatization mixture of **6b** are described in the Experimental.

(7) In the case of **6d**, by the action of *N*-chlorosuccinimide, we found, besides **12d**, also a 3-chloro derivative. In a following paper we will more particularly report on the action of *N*-haloimides on **3** and **6** and on the intermediate bromohydrins or chlorohydrins which we isolated in several cases.

(8) L. Horwitz, *J. Am. Chem. Soc.*, **75**, 4060 (1953).

(9) For the synthesis of oxindoles see R. C. Elderfield, "Heterocyclic Compounds", Vol **3**, John Wiley and Sons, New York, 1952, p 128. For the synthesis of 2(3*H*)-benzofuranones see A. Clossé, W. Haefliger and D. Hauser, German Offen. 2,503,223 (Sandoz Patent); *Chem. Abstr.*, **84**, 17121x (1976).

(10) L. Baiocchi, U. S. Patent, 4,256,639 (Aziende Chimiche Riunite Angelini Francesco).

(11) R. Stollè, *Ber.*, **47**, 2120 (1914).