

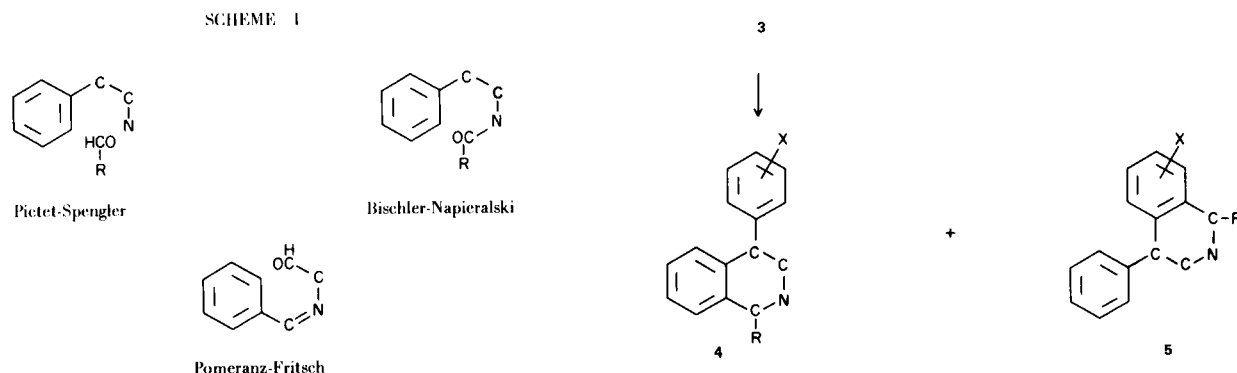
## A New Tetrahydroisoquinoline Synthesis

K. Freter, E. Dubois and A. Thomas

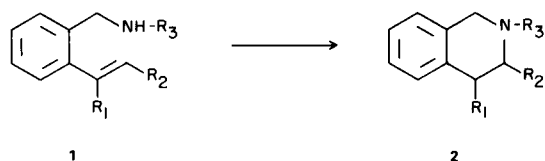
Pharma-Research Canada, Ltd.

Cyclization of 2-vinylbenzylamines affords 1,2,3,4-tetrahydroisoquinolines. The synthesis of the vinylbenzylamines from benzhydrols or isoindolones is described.

Most syntheses of tetra or dihydroisoquinolines require some activation for the ring closure through suitable substitution in the benzene ring. The Bischler-Napieralski (1) and the Pictet-Spengler (2) methods give best results, when the phenethylamines are substituted in the *para* position to the place of ring closure. The same seems to be true for the Bobbitt variation of the Pomeranz-Fritsch method (3). As a consequence, there are many hundreds of 6- and 7-substituted 1,2,3,4-tetrahydroisoquinolines known, most of them with 1-substitution. Very few tetrahydroisoquinolines, on the other hand, are available, which carry substituents in the 3- or 4-position without substitution in the benzene ring. A relatively new approach seems to be the exception, which results in the formation of 3,3-disubstituted-3,4-dihydroisoquinolines (4). Scheme 1 summarizes the classical methods of tetra- and dihydroisoquinoline syntheses.



We wish to report a general synthesis of 4-aryltetrahydroisoquinolines of the general formula 2 which consists of cyclization of 2-vinylbenzylamines 1 and which, contrary to the methods summarized in Scheme 1, requires no substitution in the aromatic ring (13).



Only very recently, a synthesis for substituted dihydroisocarbostyrils was published, which uses a similar principle of ring closure (14).

A number of examples of 2 have been prepared (Table I), with  $R_1$  = substituted aryl,  $R_2$  = H or alkyl and  $R_3$  = H or alkyl. The synthesis of these compounds, in our opinion, might have been difficult *via* the classical approaches of Scheme 1, especially in view of the fact that the ring closure of unsymmetrical 2,2-diarylethylamines (3) may lead to a mixture of 4 and 5.

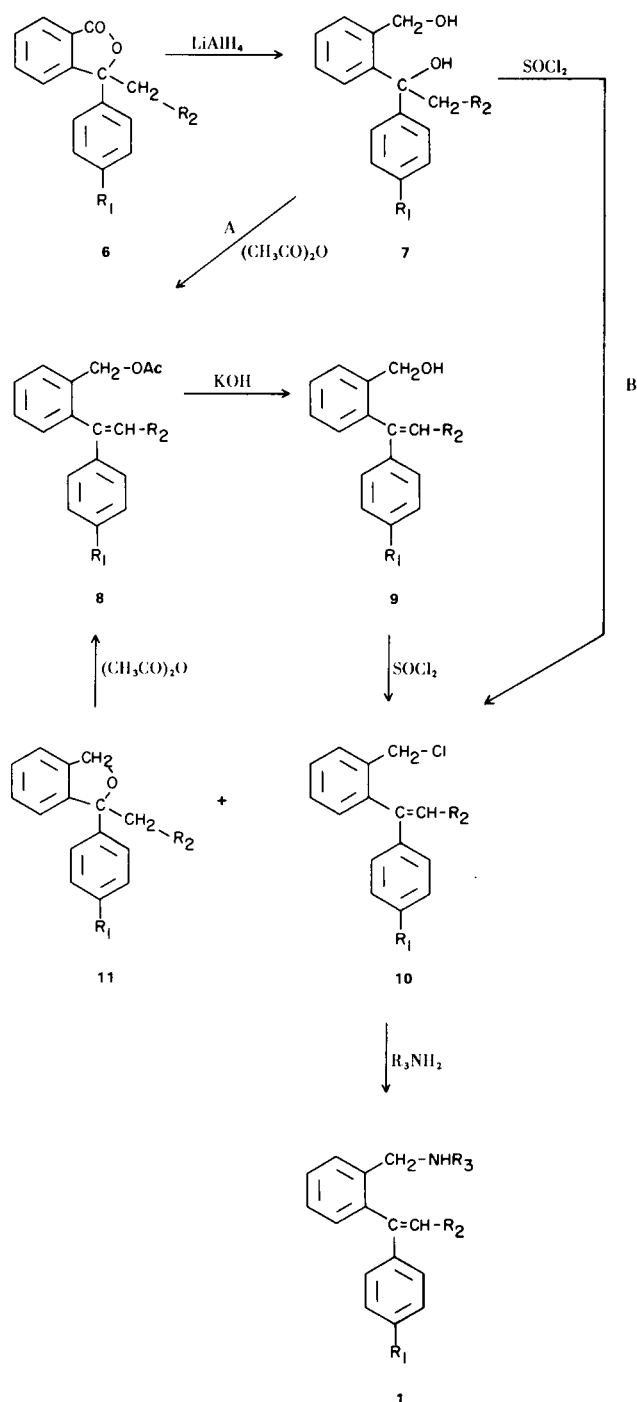
The intramolecular addition of the amino group to the ethylene double bond in 1 proceeds smoothly in refluxing alcohols under basic conditions, except when  $R_3$  = H; then the yield is low and purification is difficult.

When  $R_2$  in 2 was methyl, two stereoisomers were formed, which could be separated. Their coupling constants  $J_{3,4}$  showed little difference. With the data available, no unambiguous assignment could be made.

The dihydroxy compound 2l was prepared *via* ether cleavage from 2e. The preparation of the 2-(1-phenyl-

vinyl)benzylamines **1** can be achieved by different ways (Table II). The preferred route in most cases followed Scheme 2:

SCHEME 2

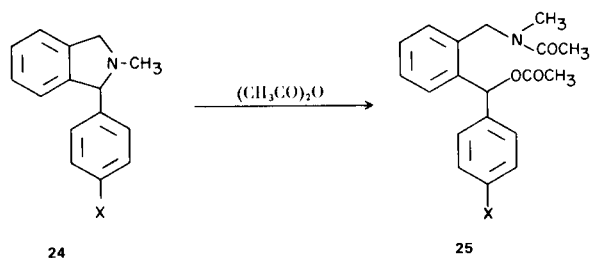


The 3,3-disubstituted phthalides **6** were obtained from the corresponding benzoylbenzoic acids with alkylmag-

nesium bromide; their reduction to the diols **7** with lithium aluminum hydride posed no problem. On treatment with acetic anhydride (Method A), the styrenes **8** were obtained which could be saponified to the benzyl alcohols **9**. With excess thionyl chloride, aside from the desired chloro compounds **10**, formation of the benzodihydrofurans **11** occurred. These by-products did not interfere with the next step, which was carried out by allowing the crude reaction mixture, containing **10** and **11**, to stand at room temperature in the ethanolic solution of the primary amine  $\text{NH}_2\text{-R}_3$  in excess.

The benzodihydrofuran formation was best suppressed when the excess thionyl chloride was dropped quickly into the boiling benzene solution of the alcohols **9**. At room temperature and with stoichiometric amounts, **11** was obtained almost exclusively,

The benzodihydrofuran could be used as starting material for the preparation of the styrene **8** ( $\text{R}_1 = o\text{-Cl}$ ): We found that ring cleavage occurred in high yield, when **11** ( $\text{R}_1 = o\text{-Cl}$ ) was refluxed in acetic anhydride. This is parallel to the properties of suitably substituted nitrogen heterocycles, where the C-N cleavage was first demonstrated on tetrahydrocarbolines (5,6) and later on tetrahydroisoquinolines and isoindolines (7), as for example, the conversion of **24** to **25**:

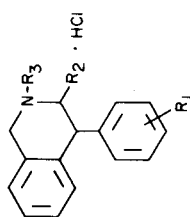


The same mixture of **10** and **11** was obtained and used for amine (**1**) synthesis, when the diols **7** were treated directly with thionyl chloride (Method B). Here the cyclic ether formation could not be suppressed very well, but the lower yield of the chloride was compensated by omission of the two steps **8** and **9**.

Scheme 3 illustrates the formation of a benzylamine **1** via the isoindolone (Method C). The ring opening of the phthalide **13** (prepared from **12** and methyl magnesium iodide) with methylamine solution is easily reversed by dissolving the amide **14** in acetic or trifluoroacetic acid at room temperature. With trifluoroacetic acid at  $0^\circ$ , however, the isoindolone **15** is formed in good yield. It can be isolated via its stable hydrogen chloride salt, a property which seems to be common for isoindolones (8).

Lithium aluminum hydride reduction of the open chain amide **14**, resulted in complete destruction of the molecule. On TLC some 20 basic fractions could be observed. As

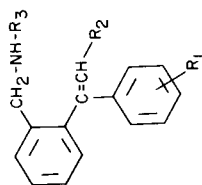
TABLE I



	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	M.p.	Time	Yield		C	H	Cl	N
<b>2a</b>	H	H	CH <sub>3</sub>	178-179° ethanol-ether	50 hours	75%	C <sub>16</sub> H <sub>17</sub> N · HCl 259.8	73.98 74.16	6.98 7.09	13.65 13.64	5.39 5.33
<b>2b</b>	<i>p</i> -Cl	H	CH <sub>3</sub>	94-95° (a) ether-pet. ether	18 hours	80%	C <sub>16</sub> H <sub>16</sub> CIN	74.59 74.39	6.25 6.19	13.73 13.76	5.43 5.84
<b>2c</b>	<i>o</i> -Cl	H	CH <sub>3</sub>	223-227° ethanol-ether	16 hours	45%	C <sub>16</sub> H <sub>16</sub> CIN · HCl 294.2	65.34 65.31	5.82 6.00	24.08 24.13	4.76 4.85
<b>2d</b>	<i>p</i> -SCH <sub>3</sub>	H	CH <sub>3</sub>	110-111° (a) ethyl acetate	30 hours	83%	C <sub>17</sub> H <sub>19</sub> NS 269.4	75.79 75.75	7.11 7.08	11.90 (b) 12.22	5.20 5.37
<b>2e</b>	3,4-OCH <sub>3</sub>	H	CH <sub>3</sub>	215-218° ethanol-ether	7 days (c)	50% (c)	C <sub>18</sub> H <sub>21</sub> NO <sub>2</sub> · HCl 319.8	67.58 67.54	6.94 6.83	11.09 10.93	4.38 4.28
<b>2f</b>	<i>p</i> -Cl	H	H	227-232° ethanol-ether	10 days	10%	C <sub>15</sub> H <sub>14</sub> CIN · HCl 280.2	64.29 64.33	5.40 5.60	25.31 25.36	5.00 4.91
<b>2g</b>	<i>p</i> -Cl	H	CH(CH <sub>3</sub> ) <sub>2</sub>	220-225° ethanol-ether	7 days	60%	C <sub>18</sub> H <sub>20</sub> CIN · HCl 322.3	67.08 67.02	6.57 6.64	22.00 22.30	4.35 4.48
<b>2h</b>	<i>p</i> -Cl	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	210-216° ethanol-ether	48 hours	50%	C <sub>22</sub> H <sub>20</sub> CIN · HCl 370.3	71.36 71.11	5.72 5.68	19.14 19.19	3.78 4.04
<b>2i</b>	<i>p</i> -Cl	CH <sub>3</sub> "β"	CH <sub>3</sub>	218-222° acetone- water-ether	8 days	50%	C <sub>17</sub> H <sub>18</sub> CIN · HCl 308.2	66.23 66.16	6.21 6.31	23.00 22.80	4.55 4.53
<b>2k</b>	<i>p</i> -Cl	CH <sub>3</sub> "α"	CH <sub>3</sub>	236° acetone- water-ether	8 days	20%		66.23 66.46	6.21 6.13	23.00 22.98	4.55 4.78
<b>2l</b>	3,4-OH	H	CH <sub>3</sub>	239-243° (d) methanol-ether	See exp. part		C <sub>16</sub> H <sub>17</sub> NO <sub>2</sub> · HBr 336.2	57.15 57.20	5.39 5.30	23.77 (b) 23.80	4.17 3.97

(a) Free Base. (b) Calculated and found for S or Br respectively. (c) Regardless, if the starting material is **1e** or **2l**. (d) Hydrobromide.

TABLE II



	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Method	M.P.	Yield (d)		C	H	Cl	N	S
<b>1a</b>	H	H	CH <sub>3</sub>	A	136-138° (a)	44%	C <sub>16</sub> H <sub>17</sub> N · HCl	73.98	6.98	13.65	5.39	
							259.79	73.77	7.23	13.46	5.49	
<b>1b</b>	<i>p</i> -Cl	H	CH <sub>3</sub>	A	119-129° (b)	55%	C <sub>16</sub> H <sub>16</sub> ClN · HCl	65.35	5.82	24.07	4.76	
				B, C			294.2	65.08	6.15	24.25	4.74	
<b>1c</b>	<i>o</i> -Cl	H	CH <sub>3</sub>	B	129-133° (b)	40%	C <sub>16</sub> H <sub>16</sub> ClN · HCl	65.35	5.82	24.07	4.76	
							294.2	65.02	6.02	23.77	4.62	
<b>1d</b>	<i>p</i> -SCH <sub>3</sub>	H	CH <sub>3</sub>	A	121-122° (b)	29%	C <sub>17</sub> H <sub>19</sub> NS · HCl	66.75	6.59	11.59	4.58	10.49
							305.9	66.75	6.64	11.38	4.37	10.68
<b>1e</b>	3,4-diOCH <sub>3</sub>	H	CH <sub>3</sub>	D	147-148° (a)	20% (e)	C <sub>18</sub> H <sub>21</sub> NO <sub>2</sub> · HCl	67.58	6.94	11.09	4.38	
							319.8	67.88	6.86	11.20	4.30	
<b>1f</b>	<i>p</i> -Cl	H	H	A	210-212° (a)	11%	C <sub>15</sub> H <sub>14</sub> ClN · HCl	64.29	5.40	25.31	5.00	
							280.2	64.02	5.81	24.53	4.90	
<b>1g</b>	<i>p</i> -Cl	H	CH(CH <sub>3</sub> ) <sub>2</sub>	A	173-175° (a)	78%	C <sub>18</sub> H <sub>20</sub> ClN · HCl	67.08	6.57	22.00	4.35	
							322.3	67.17	6.80	22.10	4.23	
<b>1h</b>	<i>p</i> -Cl	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	A	191-195° (c)	55%	C <sub>22</sub> H <sub>20</sub> ClN · HCl	71.36	5.72	19.14	3.78	
							370.3	71.05	5.43	19.64	3.73	
<b>1i</b>	<i>p</i> -Cl	CH <sub>3</sub>	CH <sub>3</sub>	B	204-205° (a)	25%	C <sub>17</sub> H <sub>18</sub> ClN · HCl	66.25	6.22	23.00	4.58	
							308.2	66.41	6.48	23.03	4.43	

(a) Ethanol-ether. (b) Ethyl acetate. (c) Chloroform-ether. (d) Based on **7** as starting material. (e) Plus 40% **20** - see experimental part.

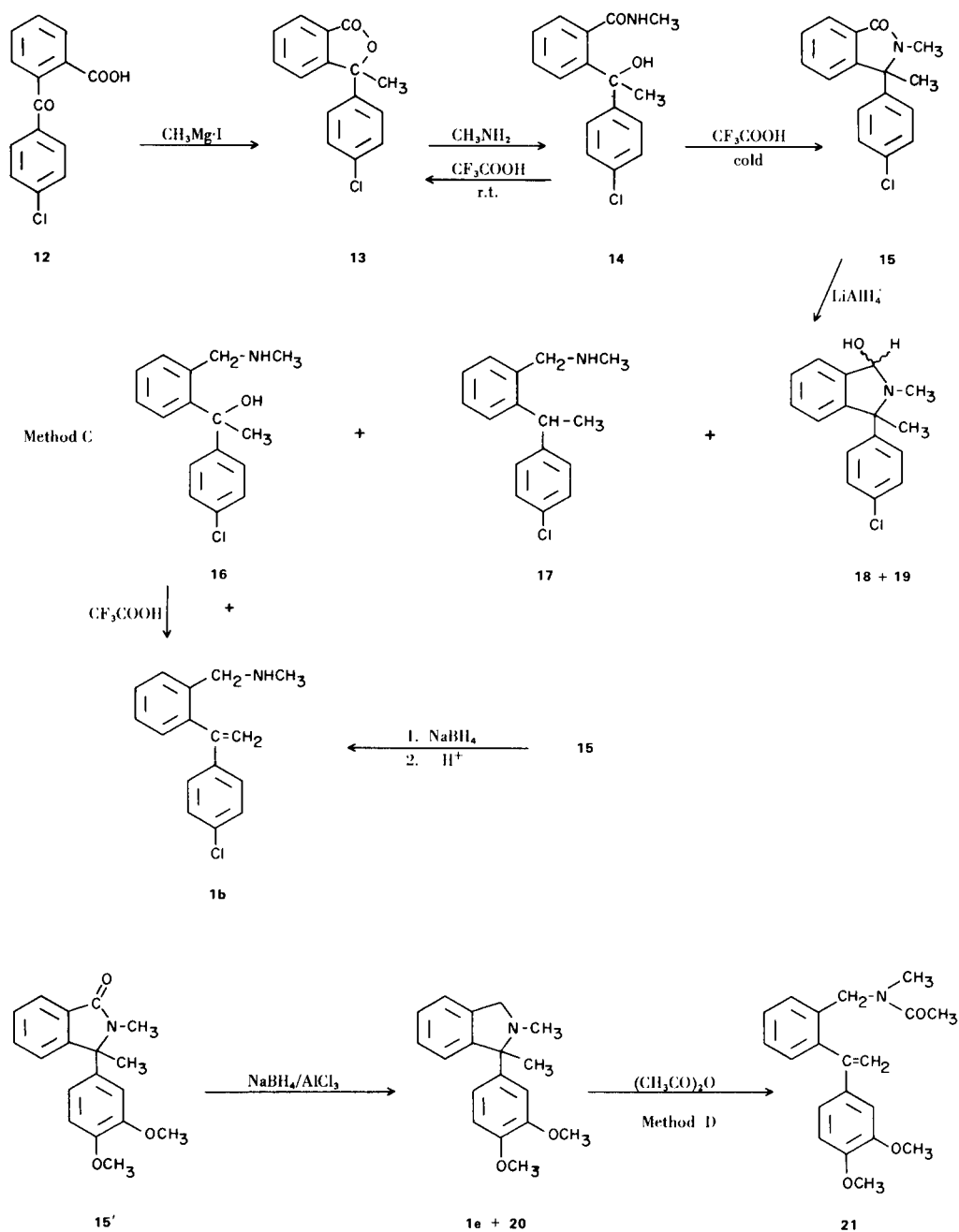
TABLE III

Name	Yield	M.p. °C	Crystallized from	Formula	C	H	Cl	S
2-Hydroxymethyl- $\alpha$ -methyl-benzhydrol	40%	111-112	ether-pet. ether	C <sub>15</sub> H <sub>16</sub> O <sub>2</sub>	78.92 79.22	7.06 7.02	--	--
2-Chloro-2'-hydroxymethyl- $\alpha$ -methyl-benzhydrol	87%	150-152	ethanol	C <sub>15</sub> H <sub>15</sub> ClO <sub>2</sub>	68.61 68.68	5.71 5.87	13.50 13.72	--
4-Chloro-2'-hydroxymethyl- $\alpha$ -methyl-benzhydrol	55%	121-122	ethanol	C <sub>15</sub> H <sub>15</sub> ClO <sub>2</sub>	68.61 68.82	5.71 5.56	13.50 13.27	--
4-Chloro-2'-hydroxymethyl- $\alpha$ -ethyl-benzhydrol	88%	106	ether-pet. ether	C <sub>16</sub> H <sub>17</sub> ClO <sub>2</sub>	69.45 69.45	6.19 6.00	12.82 13.02	--
4-Methylmercapto-2'-hydroxymethyl- $\alpha$ -methyl-benzhydrol	70%	112-114	chloroform-pet. ether	C <sub>16</sub> H <sub>18</sub> O <sub>2</sub> S	70.05 69.76	6.61 6.69	--	11.67 11.60
3,4-Dimethoxy-2'-hydroxymethyl- $\alpha$ -methyl-benzhydrol	75%	105-107	ether-pet. ether	C <sub>17</sub> H <sub>20</sub> O <sub>4</sub>	70.81 70.55	6.99 6.83	--	--
4-Chlorophenyl-2'-hydroxymethyl- $\alpha$ -isopropyl-benzhydrol	83%	103-105	ether-pet. ether	C <sub>17</sub> H <sub>19</sub> ClO <sub>2</sub>	70.22 69.45	6.59 6.87	12.19 12.53	--

TABLE IV

M.P.	Formula	C	H	Cl	S	NMR (in deuteriochloroform)
54°	C <sub>18</sub> H <sub>17</sub> ClO <sub>2</sub>	71.90 71.87	5.69 5.61	11.78 11.80	--	2.5-3.0, m (8H); 3.75, q (1H, J=7.0); 5.17, s (2H); 8.14, s (3H); 8.44, d (3H, J=7.0).
oil	C <sub>17</sub> H <sub>15</sub> ClO <sub>2</sub>	71.20 70.92	5.28 5.59	12.36 12.10	--	2.4-2.9, m (8H); 4.26, d (1H, J=1.0); 4.38, d (1H, J=1.0); 4.83, s (1H); 7.97, s (1H).
oil	C <sub>16</sub> H <sub>15</sub> ClO	74.30 74.71	5.84 5.89	13.70 13.78	--	2.4-3.3, m (8H); 3.82, q (1H, J=7.0); 5.72, s (2H); 8.00, s (1H); 8.50, d (2H, J=7.0).
89°	C <sub>16</sub> H <sub>16</sub> OS	74.98 74.87	6.29 6.30	--	12.49 12.52	2.5-3.0, m (8H); 4.28, d (1H, J=1.0); 4.87, d (1H, J=1.0); 5.62, s (2H); 7.59, s (3H); 8.32, s (1H).
88°	C <sub>17</sub> H <sub>18</sub> O <sub>3</sub>	75.53 75.26	6.71 6.38	--	--	2.5-3.4, m (7H); 4.40, d (1H, J=1.0); 4.96, d (1H, J=1.0); 5.63, s (2H); 6.24, s (3H); 6.28, s (3H); 8.05, s (1H).

SCHEME 3



“main” product only *N*-methylbenzylamine could be isolated in low yield. Under the same conditions, however, the lactam **15** gave reproducibly and in fair yield the open chain amine **16**, accompanied by at least 3 other basic products. One of these, **17**, could be identified as the completely reduced material. For the closely related **18** and **19**, which could be separated only after repeated

chromatography on silica, the analyses and spectral data leave no other interpretation but as *cis-trans*-isomers of the carbinolamines. The NMR spectra of both compounds (details see experimental part) show a broad exchangeable OH peak, and sharp singlets for the *C*-methyl, *N*-methyl and benzyl proton as the only features aside from the aromatic region. The IR spectra lack carbonyl absorptions

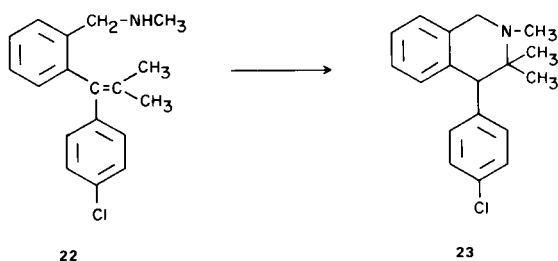
and show OH bands at  $3350\text{ cm}^{-1}$ . Analogous considerations as in a similar case of a 1,3-unsymmetrically substituted isoindoline (10) lead us to propose the following assignment: **18** has the  $\text{CH}_3\text{-C}$  and H in *cis* position, with the  $\text{N-CH}_3$  group in ecliptic position; **19** is *trans* in respect to  $\text{C-CH}_3$  and H with the  $\text{N-CH}_3$  in staggered position. The relative stability of these compounds is interesting; they form stable hydrochlorides, whereas open chain carbinolamines usually rapidly hydrolyze on addition of acid (9).

The amine **16** smoothly eliminated water with cold trifluoroacetic acid to give the styrene **1b**, identical to the compound obtained *via* Methods A or B.

Compound **1b** was obtained directly after reduction of **15** with sodium borohydride; presumably the double bond formation occurred on work-up with acid. The complete reduction of the lactam with sodium borohydride was unexpected; a number of cyclic imides investigated recently by Witkop (12) gave a variety of products, but no amines under these conditions.

An interesting transition from an isoindoline to an isoquinoline is illustrated as Method D. When the 1-(3,4-dimethoxyphenyl)-1,2-dimethylisoindolone (**15'**) was reduced with sodium borohydride-aluminum chloride, about equal amounts of the 2-[1-(3,4-dimethoxyphenyl)vinyl]-*N*-methylbenzylamine (**1e**) and of the isoindoline **20** were formed. The latter compound ring opened, as expected, with acetic anhydride under simultaneous formation of the double bond, to give **21**. This amide, under the strongly basic conditions of the isoquinoline ring closure, easily saponified and gave the tetrahydroisoquinoline **2e** in the same yield as from **1e**.

In addition to the tetrahydroisoquinolines shown in Table I, we obtained the 2,3,3,4-tetrasubstituted derivative **23** from **22**:



It appears, that this reaction will be useful for the preparation of 2-, 3- and 4-substituted tetrahydroisoquinolines, which might be difficult to obtain *via* conventional methods.

#### EXPERIMENTAL

All melting points are uncorrected. Elemental microanalyses were obtained from Dr. C. Daesslé, Montreal, P. Q., Nuclear magnetic resonance spectra were recorded on a Varian Associates

Model HA-60 spectrometer. We are very indebted to Dr. H. Pook of C. H. Boehringer Sohn, Ingelheim, Germany, for providing the spectra and assistance in interpretation. The 100 MHz (Jeolco 4H-100) NMR spectra for the compounds **2k** and **2l** were obtained through the courtesy of Dr. M. St. Jacques (Université de Montréal) and Dr. F. K. Hess (Pharma-Research), whom we wish to thank for helpful discussions.

Preparation of Substituted 2-Hydroxymethyl- $\alpha$ -alkylbenzhydrols (**7**) from Phthalides (**6**).

Thirty g. of an appropriate phthalide (**6**) were dissolved in 100 ml. of dry tetrahydrofuran. This solution was added in an atmosphere of nitrogen, under cooling and stirring, dropwise, to the suspension of 6 g. of lithium aluminum hydride in 20 ml. of tetrahydrofuran. After all starting material had been introduced, the mixture was allowed to stand at room temperature for 10 more minutes; it was then diluted with 200 ml. of anhydrous ether and the excess lithium aluminum hydride was decomposed by dropwise addition of water. The inorganic precipitate was filtered by suction and washed thoroughly with warm ethyl acetate. The combined filtrates were dried over magnesium sulfate and evaporated to dryness. The residues were crystallized; the yields and properties are shown in Table III.

Preparation of Substituted 2-(1-Phenylvinyl)benzylamines (**1**). Method A.

Fifteen g. of the appropriate diol **7** were dissolved in 130 ml. of acetic anhydride and heated in an oil bath of  $120^\circ$  for 20 minutes. Then one drop of concentrated sulfuric acid was added and the mixture stirred for 2 more minutes, cooled to room temperature and evaporated to half of its original volume. The residue was poured on a mixture of 100 g. of ice and 100 ml. of concentrated ammonia and extracted with 3 portions of 100 ml. of ether. The combined ether extracts were washed with water and sodium carbonate solution and dried over magnesium sulfate. The solution was evaporated to dryness and the residue (approximately 18 g.) was used without further purification for the next step.

The above *O*-acetyl compound (**8**) was dissolved in 60 ml. of ethanolic potassium hydroxide (10%) and left for 30 minutes at room temperature. The solution was then concentrated *in vacuo*, diluted with 100 ml. of water and extracted with three 50 ml. portions of ether. The combined ether extracts were washed with sodium carbonate, dried over magnesium sulfate and evaporated to dryness. A pale oil remained (approximately 16 g.) which was used without purification for the next step.

In a few cases, an attempt was made to isolate and purify the intermediates **8** and **9**. Table IV shows the elemental analyses and NMR data for these compounds.

Ten ml. of thionyl chloride were dropped, under stirring, into the boiling solution of the above hydroxy compound, (**9**), dissolved in 150 ml. of dry benzene. When all the thionyl chloride was introduced, refluxing was continued for an additional 20 minutes. The solution was allowed to cool to room temperature and was evaporated to dryness. The residue, consisting essentially of the substituted benzyl chloride (**10**), was used for the following step without further purification.

The crude benzyl chloride (**10**) was dissolved in 200 ml. of a saturated ethanolic solution of the appropriate amine and allowed to stand at room temperature for 20 hours (8 days in the case of ammonia). The solution was then evaporated to dryness and the residue treated with concentrated sodium carbonate solution and extracted with three 200 ml. portions of ethyl acetate. The combined ethyl acetate extracts were washed with sodium carbonate,

dried over magnesium sulfate and evaporated to dryness. The residue either directly crystallized as hydrochloride or after purification on silica (benzene-methanol 90:10). For yields, melting points, and elemental analyses see Table II.

As an example of the NMR signals of this group of compounds, the spectrum of 2-(1-phenylvinyl)-*N*-methylbenzylamine (7a) is given: NMR (hydrochloride in deuteriochloroform)  $\tau$  0.3 (broad s, 2H, exchangeable with deuterium oxide), 2.1-2.9 (m, 9H), 4.15 (s, 1H), 4.73 (s, 1H), 6.15 (t, 2H, s after exchange), 7.72 (t, 3H, s after exchange).

#### Method B.

Five g. of the appropriate diol (7) were added to a boiling mixture of 20 ml. of benzene and 15 ml. of thionyl chloride; the mixture was then refluxed for 4 hours and evaporated to dryness *in vacuo*. The residue was dissolved in 40 ml. of a saturated alcoholic solution of methylamine and allowed to stand overnight at room temperature. The solution was evaporated to dryness. The residue was triturated with concentrated sodium carbonate and the base was extracted with ethyl acetate. The dried ethyl acetate solution was taken to dryness *in vacuo* and the residue dissolved in ether. From this solution the desired compound was precipitated as hydrochloride by addition of ethereal hydrochloric acid. The salt was recrystallized. See Table II.

#### Method C.

#### 2-(4-Chloro- $\alpha$ -methyl- $\alpha$ -hydroxybenzyl)-*N*-methylbenzamide (14).

3-(4-Chlorophenyl)-3-methylphthalide (60 g.) was dissolved in 500 ml. of a saturated solution of methylamine in ethanol. After standing for 24 hours at  $-10^\circ$  the product crystallized and was collected. The yield was 58 g. (90%) of a product, melting at 155-157 $^\circ$ .

*Anal.* Calcd. for  $C_{16}H_{16}ClNO_2$ : C, 66.32; H, 5.57; N, 4.83; Cl, 12.24. Found: C, 66.34; H, 5.41; N, 4.84; Cl, 12.41.

#### 1-(4-Chlorophenyl)-1,2-dimethylisoindolone (15).

2-(4-Chloro- $\alpha$ -methyl- $\alpha$ -hydroxybenzyl)-*N*-methylbenzamide, (14), (24 g.), was dissolved under ice cooling in 80 ml. of cold anhydrous trifluoroacetic acid. The solution was allowed to warm to 20 $^\circ$  (approximately 30 minutes) and was then evaporated to dryness without heating. The oily residue was triturated with concentrated sodium carbonate solution and the lactam was extracted with ether. The ether solution was dried over magnesium sulfate, filtered and concentrated *in vacuo*. Ethereal hydrochloric acid was added until no more lactam-hydrochloric acid-adduct precipitated. A yield of 20.5 g. (89%) was obtained. The melting point after recrystallization from ethanol-ether was 178-182 $^\circ$ .

*Anal.* Calcd. for  $C_{16}H_{14}ClNO$  · HCl: C, 62.35; H, 4.90; N, 4.55; Cl, 23.01. Found: C, 62.52; H, 5.08; N, 4.56; Cl, 23.11.

#### Lithium Aluminum Hydride Reduction of 15.

Thirty g. of the above isoindolone (15), freshly prepared from the hydrochloric acid adduct by treatment with sodium carbonate solution and extraction with ether, were dissolved in 250 ml. of dry tetrahydrofuran. This solution was added dropwise to a stirred suspension of 7 g. of lithium aluminum hydride in 100 ml. tetrahydrofuran under nitrogen. After all lactam had been introduced, the mixture was refluxed for 24 hours, then cooled and decomposed by dropwise addition of water. The inorganic precipitate was filtered and the filtrate evaporated to dryness.

The oily residue (20 g.) consisted of a complex mixture of reaction products.

TLC (Silica Gel G, Merck, AG, Darmstadt, eluant benzene-

ethanol 80:20) showed as major products on spraying with Iodoplateate (11) spots with  $R_F$ -values of 0.15, 0.25, 0.50. The corresponding compounds were separated on silica (Kieselgel 80-100 mesh, Gebr. Hermann, Köln, Germany, 600 g., diameter 10 cm, eluant benzene-ethanol 80:20). The fraction with  $R_F$  0.5, on repeated chromatography, separated in two compounds  $R_F$  0.49 and 0.51. All four bases were crystallized and identified as hydrochlorides. The relative yields varied with different batches. The  $R_F$ -values, naturally, could not be reproduced with the indicated accuracy; the second decimal point is given only to describe the relative polarity in the chromatography system used.

#### 4-Chloro-2'-(methylaminomethyl)- $\alpha$ -methylbenzhydrol Hydrochloride (16).

$R_F$  0.15, yield: 3-6 g., m.p. 223-224 $^\circ$  from ethanol-ether; NMR (base in deuteriochloroform),  $\tau$  2.1-3.0 (m, 8H), 4.69 (s, 2H), 6.84 (s, 2H), 7.73 (s, 3H), 8.20 (s, 3H).

*Anal.* Calcd. for  $C_{16}H_{18}ClNO$  · HCl: C, 61.56; H, 6.13; N, 4.49; Cl, 22.70. Found: C, 61.68; H, 6.32; N, 4.37; Cl, 22.32.

#### 2-(4-Chloro- $\alpha$ -methylbenzyl)-*N*-methylbenzylamine Hydrochloride (17).

$R_F$  0.25, yield, 5-7 g., m.p. 268-269 $^\circ$  from ethanol; NMR (hydrochloride in  $d_6$ DMSO)  $\tau$  0.3 (s, 2H), 2.1-2.8 (m, 8H), 5.31 (q, 1H,  $J=7$  cps), 5.86 (d, 2H,  $J=3$  cps), 7.40 (s, 3H), 8.43 (d, 3H,  $J=7$  cps).

*Anal.* Calcd. for  $C_{16}H_{18}ClN$  · HCl: C, 64.86; H, 6.47; Cl, 23.94; N, 4.71. Found: C, 64.64; H, 6.98; Cl, 23.52; N, 4.71.

#### *cis*-1-(4-Chlorophenyl)-1,2-dimethyl-3-hydroxyisoindoline Hydrochloride (18).

$R_F$  0.49, yield, 1 g., m.p. 295 $^\circ$  from ethanol; NMR (base in deuteriochloroform),  $\tau$  2.7-3.2 (m, 8H), 6.37 (s, 1H), 6.63 (broad s, 1H), 7.84 (s, 3H), 8.47 (s, 3H).

*Anal.* Calcd. for  $C_{16}H_{16}ClNO$  · HCl: C, 61.93; H, 5.52; Cl, 22.87; N, 4.52. Found: C, 61.36; H, 6.11; Cl, 22.65; N, 4.69.

#### *trans*-1-(4-Chlorophenyl)-1,2-dimethyl-3-hydroxyisoindoline Hydrochloride (19).

$R_F$  0.51, yield, 1 g., m.p. 236-239 $^\circ$  from ethanol-ether; NMR (base in deuteriochloroform),  $\tau$  2.5-3.3 (m, 8H), 6.33 (s, 1H), 7.21 (broad s, 1H), 7.86 (s, 3H), 8.79 (s, 3H).

*Anal.* Calcd. for  $C_{16}H_{16}ClNO$  · HCl: C, 61.93; H, 5.52; Cl, 22.87; N, 4.52. Found: C, 61.58; H, 5.95; Cl, 22.64; N, 4.54.

#### 2-(1-*p*-Chlorophenylvinyl)-*N*-methylbenzylamine (1b) from 16.

One g. of 4-chloro-2'-(methylaminomethyl)- $\alpha$ -methylbenzhydrol (16), as the free base, was dissolved in 20 ml. of anhydrous trifluoroacetic acid and allowed to stand for 15 minutes. The solution was then evaporated to dryness, treated with ice, sodium carbonate solution, dried over magnesium sulfate and evaporated to dryness. The residue was crystallized as hydrochloride and recrystallized from ethanol-ether, yield: 0.9 g. (85%)

This compound was identical in all respects to the same compound prepared *via* Method A or B, see Table II.

#### 2-(1-*p*-Chlorophenylvinyl)-*N*-methylbenzylamine (1b) from 15.

Five g. of 1-(4-chlorophenyl)-1,2-dimethylisoindolone (15) were dissolved in a mixture of 50 ml. of ethanol and 20 ml. of water and stirred on a water bath of 60 $^\circ$ . To this mixture 10 g. of sodium borohydride were added in several portions during 2 days. The suspension was then treated with excess 2*N* hydrochloric acid for 10 minutes on a steam bath. Thereafter the mixture was made alkaline by addition of sodium hydroxide and extracted with three



portions of ethyl acetate. The combined ethyl acetate extracts were washed with water, dried over magnesium sulfate and evaporated to dryness. The residue was chromatographed on silica gel using a mixture of benzene ethanol (80:20) as eluant. The main fraction was crystallized as hydrochloride from ethanol-ether. The compound was identical in all respects with the material obtained via Method A, B or C, see Table II; yield, 1.9 g. (40%).

Preparation of 4-(3,4-Dimethoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline.

Method D.

3,4-Dimethoxy- $\alpha$ -methyl-2'-(*N*-methylcarbamide)benzhydrol.

A suspension of 50 g. of 3,4-dimethoxybenzoylbenzoic acid in 500 ml. of anhydrous tetrahydrofuran was prepared. To this, the Grignard reagent, prepared from 10.5 g. of magnesium and 45 g. of methyl iodide in 100 ml. of ether, was added. When the addition was completed, the mixture was heated to reflux for 2 hours. The mixture was then cooled in ice and decomposed by addition of 400 ml. of 1*N* hydrochloric acid and extracted with three 200 ml. portions of ether. The combined ether extracts were dried over magnesium sulfate and evaporated to dryness. The crude material was partly purified on a silica column using benzene-methanol (90:10) as eluant. The main product consisted of 44 g. crude 1-methyl-1-(3,4-dimethoxyphenyl)phthalide was used without further purification for the following step.

Thirty g. of the above oil were dissolved in 150 ml. of a saturated methylamine solution in ethanol, and stirred under cooling in an ice bath for 2 hours. The mixture was then allowed to stand overnight at  $-5^{\circ}$ . The crystalline material was filtered by suction and recrystallized from ethanol, giving a yield of 27 g. (82%) with a melting point of  $155-160^{\circ}$ .

*Anal.* Calcd. for  $C_{18}H_{21}O_4N$ : C, 68.55; H, 6.71; N, 4.44. Found: C, 68.75; H, 6.69; N, 4.55.

1,2-Dimethyl-2-(3,4-dimethoxyphenyl)isoindolone (15').

Trifluoroacetic acid (150 ml.) was cooled to  $-16^{\circ}$ ; then 27 g. of the above benzamide were introduced under stirring in small portions until all crystals were dissolved. The temperature was allowed to rise to  $20^{\circ}$  and the mixture was evaporated to dryness *in vacuo*. The residue was treated with sodium carbonate and extracted with ether. The ether extracts were dried over magnesium sulfate and evaporated to dryness. The remaining oil (26 g., 90%), was suitable for the following step.

A sample was analyzed as the hydrochloride, prepared from the ethereal solution of the base with ethereal hydrochloric acid and recrystallized from ethanol-ether, m.p.  $150-154^{\circ}$ .

*Anal.* Calcd. for  $C_{18}H_{19}NO_3 \cdot HCl$ : C, 64.76; H, 6.04; N, 4.20; Cl, 10.62. Found: C, 64.41; H, 6.00; N, 3.98; Cl, 10.64.

Sodium Borohydride-Aluminum Chloride Reduction of 15'.

A suspension of 3 g. of aluminum chloride in anhydrous diglyme was introduced in small portions under stirring and cooling, in an atmosphere of nitrogen, into the suspension of 16 g. of the isoindolone 15' and 3.5 g. of sodium borohydride in 150 ml. of diglyme. When the introduction was complete, the mixture was heated to  $100^{\circ}$  for 2 hours. The reaction mixture was cooled in an ice bath and decomposed with stirring by dropwise addition of 20 ml. of water followed by 120 ml. of 6*N* hydrochloric acid. The mixture was then stirred at room temperature for 2 hours and made alkaline with 30% aqueous sodium hydroxide. The reaction mixture was then extracted with 300 ml. portions of ethyl acetate, the combined extracts were washed with water and dried over magnesium sulfate and evaporated to dryness. On TLC on silica

(benzene-methanol, 90:10) two basic major components were detected, which were separated on a silica column using the same solvent mixture as eluant.

1,2-Dimethyl-1-(3,4-dimethoxyphenyl)isoindoline (20).

The basic fraction, corresponding to  $R_f$  0.6, was crystallized as hydrochloride and recrystallized from ethanol-ether, yield 7.0 g. (40%), m.p.  $185-190^{\circ}$ ; NMR (base in deuteriochloroform),  $\tau$  2.7-3.4 (m, 7H), 6.02 (q, 2H,  $J=5$  cps), 6.21 (s, 3H), 6.29 (s, 3H), 7.75 (s, 3H), 8.47 (s, 3H).

*Anal.* Calcd. for  $C_{18}H_{21}NO_2 \cdot HCl$ : C, 67.58; H, 6.94; N, 4.38; Cl, 11.09. Found: C, 67.72; H, 6.82; N, 4.61; Cl, 11.42.

2-[1-(3,4-Dimethoxyphenyl)vinyl]-*N*-methylbenzylamine (1e).

The second basic fraction, corresponding to TLC  $R_f$  0.2, was crystallized as hydrochloride from ethanol-ether, yield 3.5 g. (20%); m.p.  $147-148^{\circ}$ ; NMR (base in deuteriochloroform),  $\tau$  2.25 (s, 1H), 2.5-3.5 (m, 7H), 4.25 (s, 1H), 4.85 (s, 1H), 6.11 (s, 2H), 6.19 (s, 3H), 6.21 (s, 3H), 7.67 (s, 3H).

*Anal.* Calcd. for  $C_{18}H_{21}NO_2 \cdot HCl$ : C, 67.58; H, 6.94; N, 4.38; Cl, 11.09. Found: C, 67.88; H, 6.86; N, 4.30; Cl, 11.20.

2-[1-(3,4-Dimethoxyphenyl)vinyl]-*N*-methyl-*N*-acetylbenzylamine (21).

Two g. of 1,2-dimethyl-1-(3,4-dimethoxyphenyl)isoindoline hydrochloride (20) were heated to reflux for 10 minutes in 15 ml. of acetic anhydride. The mixture was then poured on 50 g. of ice and 50 ml. of concentrated ammonia and extracted with ether. The combined ether extracts were dried and evaporated to dryness. The residue was crystallized from ethanol-ether-petroleum ether, yielding 2 g. of product (98%) with a melting point of  $95-96^{\circ}$ .

*Anal.* Calcd. for  $C_{20}H_{23}NO_3$ : C, 73.82; H, 7.12; N, 4.30. Found: C, 73.74; H, 6.97; N, 4.28.

Ring Closure to Isoquinolines (2a-h).

The appropriate styrene (1a-i) as the free base, (3 g.), was dissolved in 30 ml. of 1-propanol, containing 2 g. of potassium hydroxide. The mixture was refluxed for the time indicated in Table I. After cooling, the mixture was diluted with twice the volume of water and extracted with three 50 ml. portions of ethyl ether. The combined ether extracts were washed with water, dried over magnesium sulfate and evaporated to dryness *in vacuo*. The oily residue was transferred to the hydrochloride by addition of ethereal hydrochloric acid and recrystallized as indicated in Table I. As example for the NMR signals of this group of compounds, the spectrum of 2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (2a) is given: NMR (base in deuteriochloroform),  $\tau$  2.7-3.5 (m, 9H), 5.81 (t, 1H,  $J=7$  cps), 6.42 (s, 2H), 6.88-7.55 (m, 2H), 7.65 (s, 3H).

" $\alpha$ "- and " $\beta$ "-4-(4-Chlorophenyl)-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (2i, 2k).

A mixture of 5 g. of the benzylamine derivative (1i), 50 ml. of ethylene glycol, 50 ml. of 1-propanol, 50 ml. of water and 30 g. of potassium hydroxide was heated to reflux for 8 days. It was diluted with 500 ml. of water and extracted 4 times with 100 ml. portions of ether. The combined ether extracts were washed with water, dried over magnesium sulfate and evaporated to dryness. The oily residue (4.8 g.) was then separated on silica gel using a mixture of chloroform-methanol (99:1) as eluant. Two fractions of basic material were obtained. Fraction A, the isomer " $\alpha$ " (2k), at first eluted from the column consisted of 0.9 g. (20%) of a light oil, which was converted to the hydrochloride, recrystallized from ethyl acetate and then from an acetone-water-ether mixture, m.p.  $236^{\circ}$ .

*Anal.* Calcd. for  $C_{17}H_{18}ClN \cdot HCl$ : C, 66.23; H, 6.21; Cl, 23.00; N, 4.55. Found: C, 66.46; H, 6.13; Cl, 22.98; N, 4.78.

The base, prepared from the hydrochloride and crystallized from ethanol, had m.p. 87°; NMR, 100 MHz (base in deuteriochloroform),  $\tau$  2.3-3.1 (m, 8H), 5.97 (d, 1H,  $J=4.4$  cps), 6.22 (q, 2H,  $J=16$  cps), 7.16 (o, 1H,  $J_{3,4}=4.4$  cps,  $J_3CH_3=6.8$  cps), 7.62 (s, 3H), 9.16 (d, 3H,  $J=6.8$  cps).

Fraction B, the " $\beta$ " isomer (2i), eluted as second fraction, consisted of 2.2 g. (50%) of a light oil, which was converted to the hydrochloride and recrystallized twice from acetone-water-ether, m.p. 218-222°.

*Anal.* Calcd. for  $C_{17}H_{18}ClN \cdot HCl$ : C, 66.23; H, 6.21; Cl, 23.00; N, 4.55. Found: C, 66.16; H, 6.31; Cl, 22.80; N, 4.53.

The hydrochloride was converted to the base, which now could be recrystallized from ethanol-water, with m.p. 76°; NMR, 100 MHz (base in deuteriochloroform),  $\tau$  2.6-3.3 (m, 8H), 6.17 (s, 2.5H), 6.24 (s, 0.5H), 7.29 (five broader peaks,  $J$  approximately 7 cps 1H), 7.58 (s, 3H), 8.96 (d, 3H,  $J=6.5$  cps).

The second signal of the  $H_4$  doublet is superimposed on the  $CH_2$ -singlet at  $\tau=6.17$ . From a spectrum at slow sweep rate, however, it becomes obvious, that the coupling constant  $J_{3,4}$  must be in the range 6.0-8.0 cps. This is in agreement with the coupling constant obtained from the  $H_3$  quintet.

#### 4-(3,4-Dihydroxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (20).

A solution of 2.5 g. of (2e) in 30 ml. of acetic acid, which was saturated with hydrogen bromide at room temperature, was prepared. It was allowed to stand at room temperature for three days, after which the solvent was removed *in vacuo*. The residue was crystallized from methanol-ether, yield, 1.5 g. (50%); properties see Table I.

#### 2-Methyl-2-(2-chlorophenyl)dihydrobenzofuran (11, $R_1=o-Cl$ , $R_2=H$ ).

The solution of 15 g. of 2-chloro-2'-hydroxymethyl- $\alpha$ -methylbenzhydrol (7) in 100 ml. of chloroform was treated with 30 ml. of thionyl chloride for one hour at room temperature. The mixture was then evaporated to dryness and the oily residue was purified on a silica gel column using benzene as eluant. The main fraction was crystallized from petroleum ether, yielding 8.6 g. (66%) with m.p. 56°; NMR (in deuteriochloroform),  $\tau$  2.1-3.0 (m, 8H), 4.78 (s, 2H), 8.01 (s, 3H).

*Anal.* Calcd. for  $C_{15}H_{13}ClO$ : C, 73.64; H, 5.35; Cl, 14.47. Found: C, 74.13; H, 5.32; Cl, 14.59.

#### 2-Chloro- $\alpha$ -(2-acetoxymethylphenyl)styrene (8, $R_1=o-Cl$ , $R_2=H$ ).

The above benzofuran (11), (4.5 g.), was dissolved in 30 ml. of acetic anhydride and one drop of concentrated sulfuric acid was added. The mixture was heated for 10 minutes to 90-100°. The excess acetic anhydride was evaporated *in vacuo* and the residue treated with sodium carbonate and extracted with ether. The ether extracts were washed with water, dried and evaporated to dryness. The oily residue was used as such for the next step (saponification with potassium hydroxide), as described in Method A, yield, 3.8 g. (72%).

A sample was purified by column chromatography (silica, using benzene as eluant) and submitted for analysis as oil; NMR (deuteriochloroform),  $\tau$  2.4-2.9 (m, 8H), 4.26 (d, 1H,  $J=1.5$  cps), 4.38 (d, 1H,  $J=1.5$  cps), 4.83 (s, 2H), 7.97 (s, 3H).

*Anal.* Calcd. for  $C_{17}H_{15}ClO_2$ : C, 71.20; H, 5.28; Cl, 12.36. Found: C, 70.92; H, 5.59; Cl, 12.10.

#### 2-[1-(4-Chlorophenyl)-2,2-dimethylvinyl]benzyl Alcohol.

The solution of 14.5 g. 4-chlorophenyl-2'-hydroxymethyl- $\alpha$ -isopropylbenzhydrol in 145 ml. of acetic anhydride was heated to reflux for 15 minutes. The mixture was poured on ice-ammonia and extracted with ether. The ether extracts were washed with water, dried and evaporated to dryness. The oily residue (16 g.) was dissolved in 100 ml. of ethanol containing 4 g. of potassium hydroxide and heated on a steam bath for 10 minutes. The solution was then concentrated *in vacuo*, diluted with water and extracted with ether; the ether extracts were dried, evaporated and the residue crystallized from ether-petroleum ether, 11.3 g. (83%), m.p. 86-87°.

*Anal.* Calcd. for  $C_{17}H_{17}ClO$ : C, 74.85; H, 6.28; Cl, 13.00. Found: C, 74.96; H, 6.00; Cl, 13.28.

#### 2-[1-(4-Chlorophenyl)-2,2-dimethylvinyl]-*N*-methylbenzylamine (22).

Fifty ml. of thionyl chloride were added rapidly to the boiling and stirred solution of 10.3 g. of the above benzyl alcohol in 200 ml. of dry benzene. Refluxing was continued for 20 minutes. The mixture was then evaporated *in vacuo*. The oily residue was dissolved in 100 ml. of a saturated solution of methylamine in ethanol and the mixture was allowed to stand at 20° for 16 hours. It was then evaporated to dryness *in vacuo*. The residue was dissolved in 50 ml. of 1*N* hydrochloric acid and washed with ether. After addition of ammonia the base was extracted with ether (3 x 100 ml.), the combined ether extracts were washed, dried and evaporated to dryness. The residue was crystallized as hydrochloride from ethanol-ether, yield, 7.0 g. (57%), m.p. 210-212°.

*Anal.* Calcd. for  $C_{18}H_{20}ClN \cdot HCl$ : C, 67.10; H, 6.57; N, 4.35; Cl, 22.00. Found: C, 67.54; H, 6.73; N, 4.18; Cl, 21.86.

#### 4-(4-Chlorophenyl)-2,3,3-trimethyl-1,2,3,4-tetrahydroisoquinoline (23).

A mixture of the above benzylamine (22) (3.4 g.), 35 ml. of 1-propanol, 35 ml. of ethylene glycol and 15 g. of potassium hydroxide was heated to 160° for 72 hours in a sealed steel cylinder. After cooling, 300 ml. of water were added and the mixture extracted with two 200 ml. portions of ethyl ether. The combined ether extracts were washed thoroughly with water, dried and evaporated to dryness. The crystalline residue was recrystallized from ethanol, yield, 2.5 g. (73%), m.p. 112°.

*Anal.* Calcd. for  $C_{18}H_{20}ClN$ : C, 75.62; H, 7.06; N, 4.90; Cl, 12.41. Found: C, 75.62; H, 7.03; N, 4.91; Cl, 12.37.

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Received September 11, 1969

Pointe Claire, P. Q., Canada