

Studies on the Syntheses of Heterocyclic Compounds. Part CCCXXIX. (1)  
Syntheses of 1-Spiroisquinoline Derivatives by Phenolic Cyclization

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Phenolic cyclization of 2-(3-hydroxyphenyl)-2-methylethylamine (XIIIa) and 2-(3-hydroxyphenyl)phenethylamine (XIIIb) with various carbonyl compounds afforded eight types of corresponding 1-spirocycloalkano- and 1-spiroheterocycloalkano-1,2,3,4-tetrahydroisquinoline derivatives (I-VIII) and 1,1-disubstituted-1,2,3,4-tetrahydroisquinoline derivative (IX). The acetyl derivatives of VI and IX and the benzoyl derivatives of III and V were also prepared. In addition, a synthetic method for obtaining the starting phenethylamines was examined.

We have reported that the treatment of 1-(3-hydroxyphenyl)-2-aminoethanol and 3-hydroxy-4-methoxyphenethylamine with several carbonyl compounds without acidic catalysts gave 1,2,3,4-tetrahydroisquinoline derivatives (3). The cyclization proceeded preferentially at the *para* position to the phenolic hydroxy group and this type of reaction was termed "Phenolic Cyclization." This reaction was also applicable to the syntheses of 1,1-dialkyl-, 1-spirocycloalkano- and 1-spiroheterocycloalkanoisquinoline derivatives (3).

We now report an extension of these studies. Phenolic cyclization of 2-(3-hydroxyphenyl)-2-methylethylamine (XIIIa) and 2-(3-hydroxyphenyl)phenethylamine (XIIIb) with various carbonyl compounds afforded a variety of the corresponding 1-spirocycloalkano- and 1-spiroheterocycloalkano-1,2,3,4-tetrahydroisquinolines (I-VIII) and 1,1-disubstituted-1,2,3,4-tetrahydroisquinolines (IX). Compounds XIIIa and XIIIb were synthesized *via* a previously reported method (4) (see Chart 2).

The reaction of the preceding amines (XIIIa) and (XIIIb) with cyclopentanone, cyclohexanone, 1-methyl-4-piperidone, 1-benzyl-4-piperidone and acetophenone under fusion or reflux for 10 hours using 2-propanol as solvent gave the expected tetrahydroisquinoline derivatives and the results are summarized in Table I. The acylation of cyclized compounds (III), (V), (VI), and (IX) were carried out to give diacyl derivatives (IIIa), (Va), (VIa) and (IXa) as shown in Table II.

Whereas the absorption maxima of all the cyclized products (I-IX) showed maxima at 280-284  $m\mu$  in the U.V. spectrum (Table III), the starting amines (XIIIa) and (XIIIb) showed absorption maxima at 276 and 278  $m\mu$ , respectively. This bathochromic shift was attributed to the hyperconjugation of the *p*-substituted methylene group. This assumption was supported by the evidence that 2,3-

CHART 1

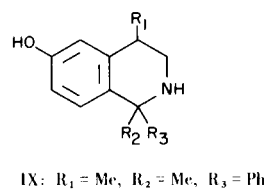
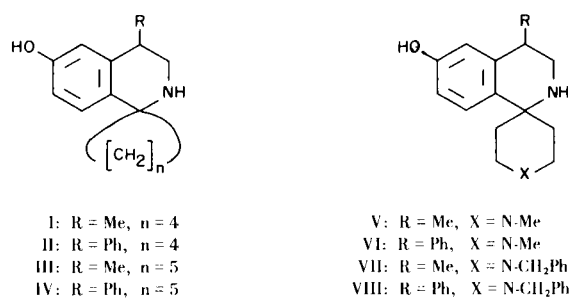


CHART 2

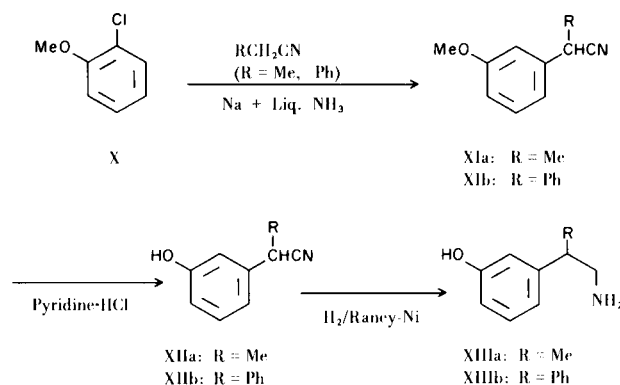
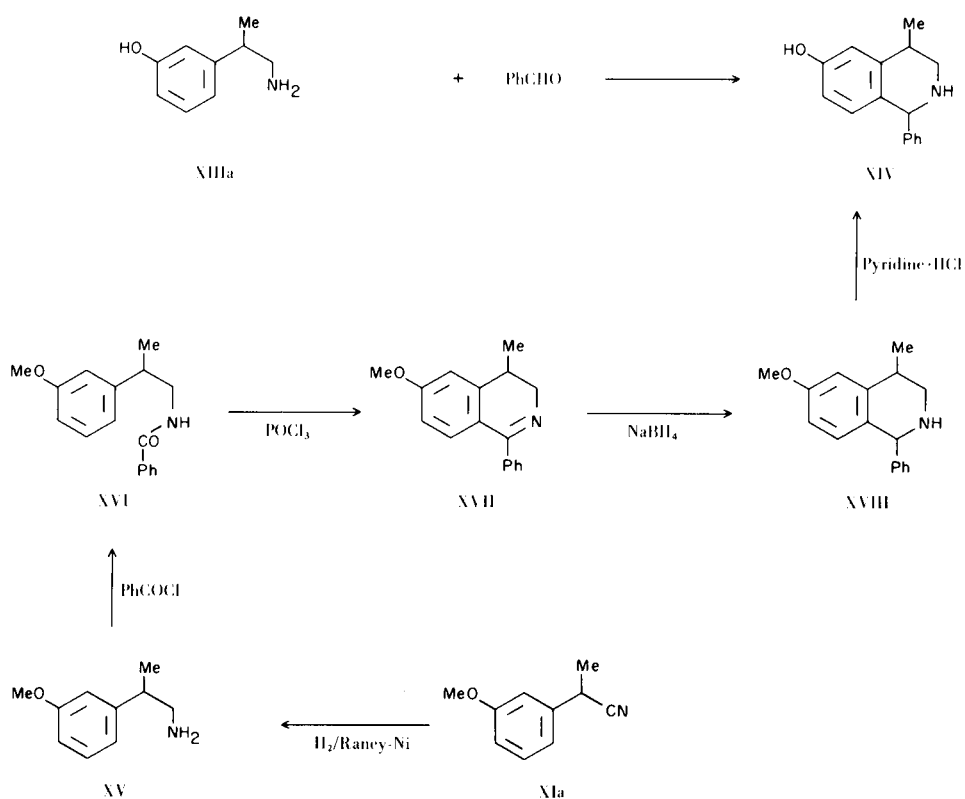


CHART 3



dimethoxyphenol showed an absorption maxima at 275  $\mu$  and 3,4-dimethylphenol also showed an absorption maximum at 281  $\mu$ . Further confirmation was made by the alternative synthesis of tetrahydroisoquinoline (XIV) according to the previous report as shown in Chart 3 (4).

#### EXPERIMENTAL

##### 1-(3-Hydroxyphenyl)-1-phenylacetone (XIIb).

A mixture of 50 g. of pyridine hydrochloride and 23.6 g. of 1-(3-methoxyphenyl)-1-phenylacetone (3) was heated in an oil bath at 220° for 1 hour. The reaction mixture was treated with water and extracted with ether. The ethereal extract was again extracted with 10% sodium hydroxide solution, the resultant alkaline solution was acidified with 10% hydrochloric acid and the resulting precipitate was further extracted with ether. The extract was washed with saturated sodium chloride solution, dried on sodium sulfate, and evaporated to give 19.2 g. of a brown syrup,  $\nu$  max (liquid)  $\text{cm}^{-1}$ , 3000-3500 (OH), 2250 ( $\text{C}\equiv\text{N}$ ); nmr (ppm in deuteriochloroform), 5.3 (1H, singlet  $> \text{CH}-\text{CN}$ ).

##### 2-(3-Hydroxyphenyl)phenethylamine (XIIIb).

A solution of 15.8 g. of XIIIb in 500 ml. of ethanol was saturated with ammonia at room temperature. This mixture was hydrogenated in the presence of 7.5 g. of Raney Nickel W-6. After absorption of the calculated amount of hydrogen, the reaction mixture was filtered and the filtrate was concentrated to give a

solid which was recrystallized from 2-propanol to give 8.3 g. of colorless prisms, m.p. 178-180°;  $\nu$  max (potassium bromide)  $\text{cm}^{-1}$ , 3300, 3350 ( $\text{NH}_2$ ).

Anal. Calcd. for  $\text{C}_{14}\text{H}_{15}\text{NO}$ : C, 78.84; H, 7.09; N, 6.57. Found: C, 78.86; H, 7.23; N, 6.32.

Phenolic Cyclization between 2-(3-Hydroxyphenyl)-2-methylethylamine (XIIIa) or 2-(3-Hydroxyphenyl)phenethylamine (XIIIb) and Carbonyl Compounds.

A mixture of XIIIa or XIIIb with carbonyl compounds were fused or refluxed in 2-propanol for 10 hours under the conditions shown in Table I. The reaction mixture was evaporated and the residue was recrystallized with the appropriate solvent to give the tetrahydroisoquinoline derivatives (I-IX).

##### Acetylation of the Tetrahydroisoquinoline Derivatives (VI and IX).

Tetrahydroisoquinoline derivatives VI and IX were acetylated with an excess of acetic anhydride as usual to give the diacetyl derivatives (VIa and IXa).

##### Benzoylation of the Tetrahydroisoquinoline Derivatives (III and V).

To a mixture of III or V, chloroform and 10% sodium hydroxide was added an excess of benzoyl chloride under stirring. The reaction mixture was treated as usual to give the dibenzoyl derivatives (IIIa) and (Va).

TABLE I  
 The Reaction of Carbonyl Compounds with 2-(3-Hydroxyphenyl)-2-methylethylamine (XIIIa) or  
 2-(3-Hydroxyphenyl)phenethylamine (XIIIb).

Compound Number	Carbonyl compound	Starting materials Carbonyl compound (g)	Amine (g)	Solvent	Temp. (°C)	Time hours	Yield g. (%)	M.p.	Recrystallization solvent	Appearance
I	cyclopentanone	0.7	(XIIIa) 0.7	isoPrOH	Reflux	10	0.76 (73)	177-179°	C <sub>6</sub> H <sub>6</sub> -cyclohexane	colorless prisms
II	cyclopentanone	0.5	(XIIIb) 0.5	---	180°	2	0.40 (61)	138° (decom.)	C <sub>6</sub> H <sub>6</sub>	colorless prisms
III	cyclohexanone	0.5	(XIIIa) 0.5	isoPrOH	Reflux	10	0.73 (72)	144-146°	C <sub>6</sub> H <sub>6</sub> -cyclohexane	colorless prisms
IV	cyclohexanone	0.5	(XIIIb) 0.5	---	180°	1.5	0.36 (52)	174-177°	C <sub>6</sub> H <sub>6</sub>	colorless prisms
V	1-methyl-4-piperidone	0.5	(XIIIa) 0.5	isoPrOH	Reflux	10	0.80 (94)	190-193°	C <sub>6</sub> H <sub>6</sub>	colorless needles
VI	1-methyl-4-piperidone	0.5	(XIIIb) 0.5	---	180°	1	0.45 (62)	253-256°	MeOH	colorless needles
VII	1-benzyl-4-piperidone	0.7	(XIIIa) 1.0	isoPrOH	Reflux	10	1.51 (95)	137-140°	C <sub>6</sub> H <sub>6</sub> -cyclohexane	colorless needles
VIII	1-benzyl-4-piperidone	0.5	(XIIIb) 0.5	---	180°	1	0.96 (89)	270° (as HCl salt)	MeOH	colorless prisms
IX	acetophenone	0.5	(XIIIa) 0.5	isoPrOH	Reflux	10	0.38 (43)	223-226°	EtOH	colorless prisms

TABLE II

The Character of Acyl Derivatives of Tetrahydroisoquinoline.

Compound Number	Derivative	M.p.	Recrystallization solvent	Appearance
IIIa	dibenzoyl deriv. of III	173-175°	benzene-cyclohexane	colorless needles
Va	dibenzoyl deriv. of V	129-131°	cyclohexane	colorless prisms
VIa	diacetyl deriv. of VI	147-149°	cyclohexane	colorless needles
IXa	diacetyl deriv. of IX	164-166°	benzene-cyclohexane	colorless prisms

TABLE III

Microanalyses and UV Spectra of Tetrahydroisoquinoline Derivatives

Compound Number	Formula	Calcd.			Found			UV $\lambda$ max (ethanol)
		C	H	N	C	H	N	
I	C <sub>14</sub> H <sub>19</sub> NO	77.38	8.81	6.45	77.53	8.90	6.35	282
II	C <sub>19</sub> H <sub>24</sub> NO	81.68	7.58	5.01	81.50	7.55	5.02	284
III	C <sub>15</sub> H <sub>21</sub> NO	77.88	9.15	6.05	78.15	9.02	5.90	280
IV	C <sub>20</sub> H <sub>23</sub> NO	81.87	7.90	4.77	82.18	8.00	4.98	283
V	C <sub>15</sub> H <sub>22</sub> N <sub>2</sub> O	73.13	9.00	11.37	73.11	9.07	11.79	280
VI	C <sub>20</sub> H <sub>24</sub> N <sub>2</sub> O	77.88	7.84	9.08	78.31	7.87	9.14	283
VII	C <sub>21</sub> H <sub>26</sub> N <sub>2</sub> O	78.22	8.13	8.69	78.58	8.44	8.66	280
VIII	C <sub>26</sub> H <sub>28</sub> N <sub>2</sub> O·½H <sub>2</sub> O	66.96	6.69	6.01	65.68	6.78	5.87	
IX	C <sub>17</sub> H <sub>19</sub> NO	80.57	7.56	5.53	80.31	7.69	5.43	282
IIIa	C <sub>29</sub> H <sub>29</sub> NO <sub>3</sub>	79.24	6.65	3.19	79.38	6.94	3.47	
Va	C <sub>19</sub> H <sub>26</sub> N <sub>2</sub> O <sub>2</sub>	69.06	7.93	8.48	68.91	7.97	8.38	
VIa	C <sub>24</sub> H <sub>28</sub> N <sub>2</sub> O <sub>3</sub>	73.44	7.19	7.14	73.23	7.03	7.06	
IXa	C <sub>21</sub> H <sub>23</sub> NO <sub>3</sub>	74.75	6.87	4.15	74.61	6.86	4.06	

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