[CONTRIBUTION FROM THE RESEARCH LABORATORIES, SCHOOL OF PHARMACY, UNIVERSITY OF MARYLAND]

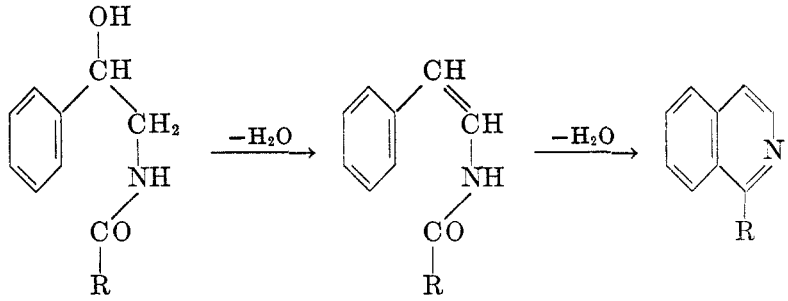
SYNTHESIS OF ISOQUINOLINE DERIVATIVES

WILSON M. WHALEY[1] AND WALTER H. HARTUNG[2]

Received February 28, 1949

The readiness with which amines of type $ArCH_2CHRNH_2$ and alkanolamines of type $ArCHOHCHRNH_2$ may be prepared (1) and converted to their N-acyl derivatives makes them available for the preparation of isoquinolines of potential pharmacological interest.

Cyclodehydration of N-acyl-β-phenethylamines to 3,4-dihydroisoquinolines by the reaction of Bischler and Napieralski (2) consists in heating the amides with a dehydrating agent such as phosphorus pentoxide. An improvement attributable to Pictet (3) utilizes the temperature-moderating influence of a refluxing, inert solvent and is almost invariably employed. Direct formation of isoquinolines from acyl derivatives of β-hydroxy-β-phenethylamines, often called the Pictet-Gams (4) reaction, represents a loss of two molecules of water in a stepwise manner, as demonstrated by isolation of an intermediate styrylamide in some cases (5).



As would be expected, the presence of an electron-donating group *para* to the point of ring-closure greatly facilitates the reaction and usually minimizes any inhibiting influence which may exist. The present study was designed to explore the effects of substitution in the ethylamine side chain as well as to provide compounds for pharmacological evaluation; consequently it was desired that the isoquinoline derivatives prepared should be unsubstituted in the homocyclic ring. The isoquinolines prepared had hydrocarbon residues in the 1-, 3-, and 4-positions. No previous attempt had been made to evaluate the influence of such substitution upon the formation of the isoquinoline ring. Several 3,4-dihydroisoquinolines were prepared for comparison.[3]

In Table II are listed the bases prepared and the maximum yield of each

[1] Present address: University of Illinois, Urbana, Ill.

[2] Present address: University of North Carolina, Chapel Hill, N. C.

[3] A study of the synthesis of 3,4-dihydroisoquinolines was made by Dey and Ramanathan (6); this paper was not abstracted and its contents were unknown before completion of the work reported here.

TABLE I

N-ACYL-β-PHENYLALKYLAMINES

NAME	YIELD, %	M.P., °C.	FORMULA	NITROGEN, %	
				Calc'd	Found[a]
1-Phenyl-2-butyrylaminopropanol	79	93–94	$C_{13}H_{19}NO_2$	6.33	6.56
1-Phenyl-2-phenylacetylaminopropanol	78	117–119	$C_{17}H_{19}NO_2$	5.20	5.27
1-Phenyl-2-benzoylamino-1-butanol	98	156–157	$C_{17}H_{19}NO_2$	5.20	5.39
2-Phenyl-3-benzoylamino-2-butanol	81	150–151	$C_{17}H_{19}NO_2$	5.20	5.40
1-Phenyl-2-benzoylamino-1-pentanol	95	150–151	$C_{18}H_{21}NO_2$	4.94	5.10
1-Phenyl-2-benzoylamino-1-hexanol	74	151–152	$C_{19}H_{23}NO_2$	4.71	4.93
1-Phenyl-2-benzoylamino-1-octanol	86	77–78	$C_{21}H_{27}NO_2$	4.30	4.37
1-(α-Naphthyl)-2-benzoylaminopropanol	83	172–173	$C_{20}H_{19}NO_2$	4.59	4.73

[a] Microanalyses by Oakwold Laboratories, Alexandria, Va.

TABLE II

SUBSTITUTED ISOQUINOLINES

CPD. NO.	SUBSTITUENTS	YIELD, %	PICRATE M.P., °C.	HYDROCHLORIDE M.P., °C.	FORMULA	NITROGEN, %	
						Calc'd	Found[p]
1	1-Methyl-3,4-dihydro-	70	193[c]	196–198[j]	$C_{10}H_{12}ClN$	7.71	7.92
2	1-Phenyl-3,4-dihydro-	100	178[d]	245–248[k]	$C_{15}H_{14}ClN$	5.75	6.03
3	1-Benzyl-3,4-dihydro-	80[a]	176–178[e]	227–229	$C_{16}H_{16}ClN$	5.44	5.58
4	1-Phenyl-3-methyl-3,4-dihydro-	24	—[f]	205–210	$C_{16}H_{16}ClN$	5.44	5.61
5	1-Phenyl-4-methyl-3,4-dihydro-	92	152[g]	193	$C_{16}H_{16}ClN$	5.44	5.61
6	1-Phenyl-	91	174[h]	237–239[m]	$C_{15}H_{12}ClN$	5.80	5.59
7	1,3-Dimethyl-	37	—	168	$C_{11}H_{12}ClN$	7.23	7.06
8	1-Propyl-3-methyl-	35	—	165	$C_{13}H_{17}ClN$	—	—
9	1-Phenyl-3-methyl-	50[b]	188	229	$C_{16}H_{14}ClN$	5.48	5.26
10	1-Benzyl-3-methyl-	20	—	207(d)	$C_{17}H_{16}ClN$	5.19	5.32
11	1-Phenyl-3-ethyl-	26	—	210	$C_{17}H_{16}ClN$	5.19	5.13
12	1-Phenyl-4-ethyl-	10	165	113–115	$C_{17}H_{16}ClN$	5.19	5.48
13	1-Phenyl-3-propyl-	20	—	180–190	$C_{18}H_{18}ClN$	4.94	4.39[q]
14	1-Phenyl-3-butyl	1	—	*ca.* 130	$C_{19}H_{20}ClN$	—	—
15	1,3-Diphenyl-	20	185[i]	*ca.* 185[n]	$C_{21}H_{16}ClN$	4.41	4.32
16	1-Phenyl-3-methyl-5,6-benz-	12	—	235(d)	$C_{20}H_{16}ClN$	4.58	4.45

[a] The free base distilled at 130°/0.25 mm.; Ref. (12) gives b.p. 130–140°/35 mm.
[b] The free base melted at 123–125°.
[c] Ref. (3) gives m.p. 188–190°.
[d] Ref. (13) gives m.p. 175°.
[e] Ref. (12) gives m.p. 182°.
[f] Ref. (6) gives m.p. 150°.
[g] Ref. (6) gives m.p. 150°.
[h] Ref. (3) gives m.p. 164°.
[i] Ref. (14) gives m.p. 165°.
[j] Ref. (3) gives m.p. 160°.
[k] Ref. (3) gives m.p. 223°.
[m] Ref. (4) gives m.p. 236°.
[n] Ref. (14) gives m.p. 127°.
[p] Microanalyses by Oakwold Laboratories, Alexandria, Va.
[q] Not corroborative.

which could be obtained. It was found that in general isoquinolines may be prepared in as high yields as the corresponding 3,4-dihydroisoquinolines, though formation of the latter required less vigorous dehydrating conditions. In either series, compounds having aryl substituents in the 1-position were obtained in

TABLE III

CYCLODEHYDRATION DATA

CPD. NO.	AMIDE, (G.)	DEHYDRATING AGENT, (G.)	SOLVENT (ML.)	TIME, HRS.	YIELD, %
1	10	P_2O_5 (40)	Toluene (150)	0.5	11
1	5	P_2O_5 (10) + $POCl_3$ (10)	Xylene (75)	1	70
2	15	P_2O_5 (60)	Toluene (200)	3	83
2	3	Al_2O_3 (30)[a]	Decalin (100)	14	*ca.* 5[f]
2	3	P_2O_5 (10) + $POCl_3$ (10)	Xylene (25)	3	100
3	5	P_2O_5 (15)	Toluene (30)	1.5	24–60
3	5	$POCl_3$ (20)	Toluene (30)	1.5	0
3	5	P_2O_5 (20)	Xylene (100)	3.5	80
4	2	P_2O_5 (20)	Toluene (75)	3	12–19
4	5	P_2O_5 (25) + $POCl_3$ (50)	Xylene (150)	3	24
5	5	P_2O_5 (20)	Toluene (100)	3	92
6	2	P_2O_5 (20)	Toluene (75)	3	81
6	1	P_2O_5 (5) + $POCl_3$ (10)	Xylene (25)	3	91
7	2.7	P_2O_5 (15)	Toluene (50)	3	37
8	2	P_2O_5 (10) + $POCl_3$ (20)	Xylene (50)	3	35
9	2	P_2O_5 (20)	None[d]	1	8[f]
9	2	P_2O_5 (20)	Tetralin (75)[e]	1	35
9	2	P_2O_5 (20) + $POCl_3$ (20)	Xylene (50)	2.5	50
9	2	$POCl_3$ (40)	Xylene (50)	2.5	45[f]
10	2	P_2O_5 (4 × 5)[b]	Toluene (50)	2	10
10	2	P_2O_5 (20) + P_2O_5 (10)[c]	Tetralin (75)[e]	1	20
10	2	P_2O_5 (10) + $POCl_3$ (20)	Xylene (50)	3	16
11	2	P_2O_5 (10) + P_2O_5 (10)[b]	Toluene (50)	1.5	3.5
11	5	P_2O_5 (50) + $POCl_3$ (50)	Xylene (150)	3	26
12	5	P_2O_5 (50)	Xylene (150)	3	5–10
13	4	P_2O_5 (32)	Xylene (100)	3	3
13	2	P_2O_5 (20) + $POCl_3$ (20)	Xylene (50)	4	20
14	2.5	P_2O_5 (13) + $POCl_3$ (25)	Xylene (50)	3	1
15	2	P_2O_5 (16)	Xylene (75)	3	20
16	5	P_2O_5 (25) + $POCl_3$ (50)	Xylene (100)	3	12

[a] Activated by heating at 700°.
[b] Added at 30-min. intervals.
[c] Added after refluxing 15 minutes.
[d] At 250°.
[e] Practical grade tetralin reacted with P_2O_5. The material used was redistilled.
[f] Impure product.

higher yields than derivatives having 1-alkyl groups, in which cases there is evidence of considerable charring during dehydration. The use of phosphorus pentoxide in refluxing tetralin has been advocated for preparing 1-alkyl-3,4-dihydroisoquinolines (7).

Notably evident in Table II is the difficulty of cyclizing β-phenethylamines and β-hydroxy-β-phenethylamines having an alkyl group in the *alpha*-position, to the corresponding 3-alkyl derivatives. The adverse effect of an α-substituent is proportional to its size: 1-phenyl-3-butylisoquinoline was synthesized in only 1% yield and the 3-hexyl homolog could not be prepared. Isoquinolines with 3-phenyl substituents were more readily obtained than those with alkyl groups of comparable size.

1-Phenyl-4-methyl-3,4-dihydroisoquinoline was synthesized in excellent yield, indicating that a β-alkyl group does not hinder the cyclization of a β-phenethylamide. However, 1-phenyl-4-ethylisoquinoline could be prepared only in low yield and neither 1,4-diphenylisoquinoline nor 1-phenyl-3,4-dimethylisoquinoline could be prepared at all,[4] showing that a β-alkyl group definitely inhibits the cyclization of β-hydroxy-β-phenethylamides. It is known that the Pictet-Gams modification occasionally suffers from intervention of a side-reaction leading to an oxazoline (9), and such a transformation may have been responsible for the difficulties encountered. Attempts to prepare 1-phenyl-3-methyl-4-keto-3,4-dihydroisoquinoline were unsuccessful; previous attempts to synthesize such compounds resulted in the formation of oxazoles (10).

The conditions of cyclodehydration finally adopted for difficulty cyclized amides involve the use of both phosphorus pentoxide and phosphorus oxychloride in refluxing xylene. The choice is empirical, based upon numerous experiments as shown in Table III.

EXPERIMENTAL[5]

Amines. The β-phenethylamines used were available; the 1-phenyl-2-amino-1-alkanols were either available or were prepared according to an established procedure (1). Intermediates for the 4-alkylisoquinolines were obtained by the reaction of alkylmagnesium halides with the oximes of phenyl ketones under forcing conditions after the manner of Campbell and McKenna (11), but using dibutyl ether as solvent throughout the process.

Amides. The amides were prepared by treating each amine in alcohol-free ether with one equivalent each of 20% sodium hydroxide and the appropriate acid chloride, or by treating the amine hydrochloride in alcohol-free ether with two equivalents of 20% sodium hydroxide and one equivalent of acid chloride. The amides which were new compounds are described in Table I.

Isoquinoline derivatives. The substituted isoquinolines characterized in Table II were prepared by techniques outlined in Table III, which illustrates the effects upon yield of various conditions of reaction. Numerous experiments of little utility have been omitted from the table, including attempts to effect cyclization by means of concentrated sulfuric acid, boron trifluoride, phosphorus pentachloride, aluminum chloride, and heating *in vacuo*. As generally useful methods for cyclizing amides unactivated by alkoxyl groups, the following conditions are recommended:

3,4-Dihydroisoquinolines—the amide is refluxed with two parts each of phosphorus pentoxide and phosphorus oxychloride in fifteen parts of dry xylene for one hour under anhydrous conditions.

Isoquinolines—the amide is refluxed with five parts of phosphorus pentoxide and ten

[4] The synthesis of 1,4-diphenylisoquinoline in 80% yield has been reported (8), but could not be confirmed.

[5] Melting points were determined with a calibrated apparatus.

parts of phosphorus oxychloride in twenty-five parts of dry xylene for three hours under anhydrous conditions.

At the end of the refluxing time the flask is cooled with ice-water while its contents are cautiously treated with ice to hydrolyze excess dehydrating agents. The layers are separated, the aqueous layer washed with benzene and then made strongly alkaline with 20% sodium hydroxide (a large volume of water is necessary to keep the inorganic salts in solution). The desired base is extracted with benzene, the extract dried over magnesium sulfate and treated with hydrogen chloride. An oily hydrochloride usually separates and may be crystallized from a mixture of isopropanol and ligroin after evaporation of the benzene, though crystallization is often induced with difficulty.

All of the *hydrochlorides* are colorless and moderately soluble in distilled water.

SUMMARY

A study is reported of the Pictet-Gams and the Bischler-Napieralski reactions as applied to the synthesis of isoquinolines and 3,4-dihydroisoquinolines alkylated in positions 3 and 4, but unsubstituted in the benzenoid ring.

Production of isoquinolines from N-acyl-β-hydroxy-β-phenethylamines required more drastic conditions but did not afford lower yields than the production of corresponding 3,4-dihydroisoquinolines. Synthesis of isoquinolines or 3,4-dihydroisoquinolines having alkyl groups in the 3-position was possible only in low yield, the yield decreasing with increase in size of the alkyl group. 3,4-Dihydroisoquinolines alkylated in the 4-position were prepared with greater facility than similar isoquinolines. In the 1- or 3-position a phenyl radical was less hindering than an alkyl group of comparable size.

Numerous preparative techniques were explored in seeking the most reliable methods.

BALTIMORE, MD.

REFERENCES

(1) HARTUNG AND MUNCH, *J. Am. Chem. Soc.*, **51**, 2262 (1929); **53**, 1875, 4149 (1931).
(2) BISCHLER AND NAPIERALSKI, *Ber.*, **26**, 1903 (1893).
(3) PICTET AND KAY, *Ber.*, **42**, 1973 (1909).
(4) PICTET AND GAMS, *Ber.*, **42**, 2943 (1909); **43**, 2384 (1910).
(5) KRABBE, *Ber.*, **69**, 1569 (1936).
(6) DEY AND RAMANATHAN, *Proc. Natl. Inst. Sci. India*, **9**, 193 (1943).
(7) SPÄTH, BERGER, AND KUNTARA, *Ber.*, **63**, 134 (1930).
(8) KRABBE, Ger. pat. 652,041 (1936); [FRDL., **24**, 378].
(9) KRABBE, EISENLOHR, AND SCHÖNE, *Ber.*, **73**, 656 (1940).
(10) YOUNG AND ROBINSON, *J. Chem. Soc.*, 275 (1933); DEY AND RAJAGOPALAN, *Current Sci. (India)*, **13**, 204 (1944).
(11) CAMPBELL AND MCKENNA, *J. Org. Chem.*, **4**, 198 (1939).
(12) DECKER, KROPP, HOYER, AND BECKER, *Ann.*, **395**, 299 (1913).
(13) DECKER AND KROPP, *Ber.*, **42**, 2075 (1909).
(14) KRABBE, SCHMIDT, AND EISENLOHR, *Ber.*, **74**, 1905 (1941).