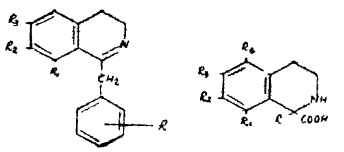
Studies in Heterocyclic Compounds
XII. Synthesis of Some New Isoquinolines

J. R. Merchant, R. R. Mhatre and J. R. Patell

The present communication describes the preparation of some isoquinolines by the application of the Bischler-Napieralski and Pictet-Spengler reactions.

In connection with a project for the synthesis of isoquinoline derivatives, we required a number of these compounds and the present paper describes the synthesis of some new isoquinolines by the application of the Bischler-Napieralski and Pictet-Spengler reactions[1a].

The dihydroisoquinolines of the general structure I, synthesised by the first reaction are described in Table I and can be obtained by the condensation of the appropriate β-phenethylamine derivatives with the acid chlorides of some phenylacetic acids in boiling benzene solution to yield the corresponding amides which were cyclised to the corresponding isoquinoline derivatives in the presence of phosphorus oxychloride. The phenylacetic acids reported here were prepared for the first time by the application of the Willgerodt reaction[1b] (See Table II). Attempts to obtain new phenylacetic acids by the application of the Willgerodt reaction on 2-methoxy-3,4-dimethyl- and 2-methoxy-3,6-dimethyl-acetophenones were unsuccessful.



I II

A quinolylisoquinoline derivative was prepared as follows. 8-Ethoxyquinoline[3] was nitrated to yield 8-ethoxy-5-nitroquinoline[3] which was reduced to 5-amino-8-ethoxyquinoline[3]. The latter on diazotisation and Sandmeyer reaction yielded 5-cyano-8-ethoxyquinoline[3]. Alkaline hydrolysis of the nitrile afforded 8-ethoxyquinoline-5-carboxylic acid[4].

The acid chloride of 8-ethoxyquinoline-5-carboxylic acid was condensed with 3-methyl-β-phenethylamine[5] to give 8-ethoxyquinoline-5-N-(3-methyl-β-phenethyl)carboxamide which was cyclised to 1-(8′-ethoxy-5′-quinolyl)-6-methyl-3,4-dihydroisoquinoline, using

1a. W. M. Whaley and T. R. Govindachari, *Organic Reactions*, 1951, **6**, 74, 151.
1b. C. Willgerodt, *Ber*, 1887, **20**, 2469: 1888, **21**, 535: M. Carmeda and M. A. Spielman, *Org. Reactions*, 1947, **3**, 83.
2. O. Fischer, *Ber.*, 1883, **16**, 717.
3. T. N. Ghosh, *J. Indian Chem. Soc.*, 1947, **24**, 310.
4. T. N. Ghosh and S. S. Chakravarti, *Indian J. Chem.*, 1963, **1**, 168.
5. F. Sommer, *Ber.*, 1900, **33**, 1078.

TABLE I

3,4-Dihydroisoquinolines prepared

β-phenethylamine	phenylacetic acid	Base (I) R	R_1	R_2	R_3	m.p.	Analysis Reqd. N%	Found N%	m.p. of Picrate	Analysis of Picrate Reqd. %	Found %
3,4-dimethoxy-	4-benzyloxy-	4′-$OCH_2C_6H_5$	H	OCH_3	OCH_3	—	—	—	180–81	C—60.4 H— 4.5	C—60.8 H— 4.9
-do-	4-methoxy-2-methyl-	4′-OCH_3, 2′-CH_3	H	OCH_3	OCH_3	108–09	4.3	4.2	208–09*	C—61.1 H— 5.3	C—61.5 H— 5.6
-do-	3,4-dimethyl-	3′-CH_3, 4′-CH_3	H	OCH_3	OCH_3	—	—	—	101–02	N—10.4	N—10.7
-do-	4-ethoxy-3-methyl-	4′-OC_2H_5, 3′-CH_3	H	OCH_3	OCH_3	—	—	—	151–52	N— 9.9	N—10.1
-do-	4-methoxy-3-methyl-	4′-OCH_3, 3′-CH_3	H	OCH_3	OCH_3	—	—	—	160–61	N—10.1	N—10.2
2,3-dimethoxy-[6]	phenylacetic acid	H	OCH_3	OCH_3	H	—	—	—	187	C—56.4 H— 4.3	C—56.6 H— 4.5

* Picrolonate.

6. R. Hayworth, *J. Chem. Soc.*, 1927, 2283.

a mixture of polyphosphoric acid and phosphorus oxychloride. The quinolylisoquinoline derivative was characterised by the preparation of its dipicrate.

TABLE II

Phenylacetic acids prepared

Acetophenone (g.)	Phenylacetic acid (g.)	M.P.	Analysis			
			Reqd. %		Found %	
			C	H	C	H
4-methoxy-2-methyl- (8)	4-methoxy-2-methyl-[7] (2)	104–05°	66.7	6.7	66.6	6.5
3,4-dimethyl- (8)	3,4-dimethyl-[8] (5)	91–92°	73.2	7.3	73.2	7.4
4-ethoxy-3-methyl- (8)	4-ethoxy-3-methyl-[9] (4·5)	77–78°	68.1	7.2	67.9	7.5
4-methoxy-3-methyl- (8)	4-methoxy-3-methyl-[9] (5)	84°	66.7	6.7	66.7	6.7

The above acid chloride was also condensed with homoveratrylamine to give 8-ethoxyquinoline-5-N-(3,4-dimethoxy-β-phenethyl)carboxamide. All attempts at cyclisation of this amide with different reagents such as phosphorus oxychloride, polyphosphoric acid and phosphorus oxychloride in boiling toluene failed to give the required isoquinoline derivative.

In Table III are listed the isoquinolines of the general structure II, obtained by the application of the Pictet-Spengler reaction. The appropriate hydroxy β-phenethylamine (methoxy amine fails) was condensed with an α-keto acid at *p*H 6 in dioxan medium at room temperature.

EXPERIMENTAL

Preparation of phenylacetic acids : A mixture of the acetophenone (8 g.), morpholine (10–12 ml) and sulphur (3–4 g.) was refluxed in an oil bath with stirring for 8 hr. and then poured in ethanol (10 ml) and the whole heated under reflux for 18 hr. with potassium hydroxide (130 ml, 10% solution). The mixture was cooled and acidified to give the phenylacetic acid which was crystallised from water. (See Table II).

Preparation of 3,4-dihydroisoquinoline derivatives : A benzene solution of the acid chloride (from 1 g. of the phenylacetic acid) and β-phenethylamine (0·8–1·0 g.) was refluxed for half hr. The solvent was removed under reduced pressure and the resulting pasty mass was treated with sodium bicarbonate solution and with ether when a solid separated. It was crystallised from aqueous alcohol to give the required amide.

A mixture of the above amide (300 mg.), dry toluene (3 ml.) and phosphorus oxychloride (0·8 ml) was refluxed for 2 hr. The cooled reaction mixture was diluted with

7. E. Walton, Bertram and J. F. Hudson, Brit. Patent 600,114, Mar., 31 (1948); *C.A.*, 1948, **42**, 7795.
8. G. S. Skinner, T. F. Sanderson, *J. Org. Chem.*, 1959, **24**, 403.
9. A. A. Aroyan, T. R. Ovsepyan, *Izv. Akad. Nauk. Arm. SSSR. Khim. Nauki*, 1962, **15**, 263; *C.A.*, 1963, **58**, 6722.

TABLE III

1,2,3,4-*Tetrahydroisoquinolines prepared*

Amine hydrobromide	α-Keto Acid	*p*H	Time in hrs.	Base (II) R	R_1	R_2	R_3	R_4	Yield %	m.p.	Analysis Reqd. %	Analysis Found %
3,4-dihydroxy-β-phenethylamine[10]	Butyric	6	72	CH_2CH_3	H	OH	OH	H	25.3	243*	C—60.7 H— 6.3	C—60.9 H— 6.5
-do-	Caproic	6	192	$(CH_2)_3CH_3$	H	OH	OH	H	33.9	241*	N— 5.2	N— 5.6
-do-	Caprylic	6	48	$(CH_2)_5CH_3$	H	OH	OH	H	30.7	239*	C—65.5, H— 7.8	C—65.8, H— 7.5
-do-	Pelargonic	6	48	$(CH_2)_6CH_3$	H	OH	OH	H	59.2	225*	N— 4.5	N— 4.7
-do-	Capric	6	16	$(CH_2)_7CH_3$	H	OH	OH	H	62.3	226*	N— 4.3	N— 4.4
2,3-dihydroxy-β-phenethylamine[a]	Caproic	6	72	$(CH_2)_3CH_3$	OH	OH	H	H	33.9	255*	N— 5.2	N— 5.6
-do-	Caprylic	6	72	$(CH_2)_5CH_3$	OH	OH	H	H	37.5	230*	N— 4.7	N— 5.0
-do-	Pelargonic	6	16	$(CH_2)_6CH_3$	OH	OH	H	H	42.3	245*	N— 4.5	N— 4.8
-do-	Capric	6	16	$(CH_2)_7CH_3$	OH	OH	H	H	53.0	241*	N— 4.3	N— 4.5
3,4,5-trihydroxy-β-phenethylamine[a]	Butyric	6	100	CH_2CH_3	H	OH	OH	OH	11.8	264*	N— 5.5	N— 5.2
-do-	Caprylic	6	72	$(CH_2)_5CH_3$	H	OH	OH	OH	25.8	240*	N— 4.5	N— 4.6
3-hydroxy-β-phenethylamine[a]	Caproic	6	192	$(CH_2)_3CH_3$	H	OH	H	H	32.1	255*	N— 5.6	N— 5.7
-do-	Caprylic	6	48	$(CH_2)_5CH_3$	H	OH	H	H	43.3	249*	N— 5.1	N— 5.3
-do-	Pelargonic	6	72	$(CH_2)_6CH_3$	H	OH	H	H	61.8	250*	N— 4.8	N— 4.5

* decomposition.

[a] Prepared from 2,3-dimethoxy-β-phenethylamine[7], 3,4.5-trimethoxy-β-phenethylamine[11] and 3-methoxy-β-phenethylamine[12] by demethylation with hydrobromic acid in acetic acid.

10. G. Berger and A. J. Wins, *J. Chem. Soc.*, 1910, 2257.
11. E. Spath, *Monatsh*, 1919, **40**. 129; *C.A.*, 1919, **14**, 1114.
12. A. M. Marchant and A. R. Pinder, *J. Chem. Soc.*, 1956, 327; J. M. Gulland and C. J. Virden, *J. Chem. Soc.*, 1929, 1795.

petrol ether (40–60°) (30 ml) and the supernatant liquid was decanted. The resulting oil was dissolved in a small amount of alcohol, the solution made alkaline and poured on crushed ice and the solid which separated was dissolved in alcohol and added to a hot alcoholic solution of picric acid to give the picrate on cooling. (See Table I).

Preparation of 8-*ethoxyquinoline*-5-N-(3-*methyl*-*β*-*phenethyl*)*carboxamide* : A benzene solution of 3-methyl-*β*-phenethylamine (250 mg.) and the acid chloride of 8-ethoxyquinoline-5-carboxylic acid (250 mg.) was refluxed for half hr. and the benzene distilled under reduced pressure. The residual mass on treatment with sodium bicarbonate solution and with ether gave the amide (150 mg.) which was crystallised from alcohol in needles m p. 144° (Found : N, 8·4; Calcd. for $C_{21}H_{22}O_2N_2$: N, 8·4%).

Preparation of 1-(8′-*ethoxy*-5′-*quinolyl*)-6-*methyl*-3,4-*dihydroisoquinoline* : A mixture of phosphorus pentoxide (710 mg.) and phosphoric acid (0·45 ml) was heated at 95–100° for 2 hr. and cooled. To it was added the above amide (100 mg.) and phosphorus oxychloride (0·14 ml) and heated at 130–35° for 8 hr. The reaction mixture was diluted with ice water and the solution treated with alkali and extracted with ether. Removal of the solvent gave an oil (60 mg.). The picrate of the oil was crystallised from aqueous acetic acid in needles, m.p. 187°. (Found : N, 14·2; Calcd. for $C_{33}H_{26}O_{15}N_8$: N, 14·5%).

General Method[13] *for the condensation of α-keto acids with different β-phenethylamine hydrobromides* : To a solution of 1 millimole of the amine hydrobromide in a minimum amount of water was added a solution of 1·2 millimole of the *α*-keto acid in dioxan. The *p*H was adjusted to 6 by addition of dilute ammonia. A crystalline solid usually separated in 48–96 hr. Where no solid separated, the solution was concentrated under reduced pressure. The product was crystallised with difficulty from aqueous acetic acid.

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Institute of Science,
Madame Cama Road,
Bombay-32.

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