[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

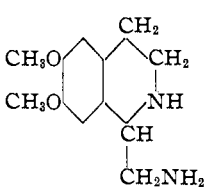
# Isoquinoline Derivatives. II. Synthesis of 1-Aminomethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline

BY H. J. HARWOOD[1] AND T. B. JOHNSON

In continuing a study of the effect of various groups on the pharmacological action of isoquinoline derivatives the preparation of a 1-aminomethylisoquinoline appeared to be of particular interest because of the combined isoquinoline and β-phenylethylamine groupings.

Child and Pyman[2] attempted to prepare such an aminomethylisoquinoline by the action of ammonia and of potassium phthalimide on 1-chloromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline but without success. These authors also dehydrated α-benzamido-N-(3,4-dimethoxyphenylethyl)-acetamide in the hope of obtaining 1-benzamidomethyl-6,7-dimethoxy-3,4-dihydroisoquinoline which could then be converted into the amino derivative. The desired compound was not obtained, however; a double ring-closure took place with the formation of 5,6-dihydro-8,9-dimethoxy-3-phenyl-imidaz-(4,3-α)-isoquinoline.

1-Aminomethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (I) has been prepared in this Laboratory. N-(3,4-Dimethoxyphenylethyl)-α-phthalimidoacetamide was dehydrated to give 1-phthalimidomethyl-6,7-dimethoxy-3,4-dihydroisoquinoline. The latter was reduced catalytically to the 1,2,3,4-tetrahydro derivative, which was then hydrolyzed to yield the desired aminoisoquinoline I.




I

The attempted ring closure of N-(β-phenylethyl)-α-phthalimidoacetamide to form 1-aminomethyl-3,4-dihydroisoquinoline yielded only an extremely small amount of product which was not investigated further.

A second and much simpler method of preparing I seemed possible through the ring closure of N-(3,4-dimethoxyphenylethyl)-α-triazoacetamide followed by catalytic reduction. Attempts to carry out this reaction were without success. The ring closure of α-amino-N-(3,4-dimethoxyphenylethyl)-acetamide hydrochloride was also unsuccessful.

TABLE I

| Compound | Yield, % | Analyses, % | Calcd. | Found |
|---|---|---|---|---|
| Phthalylglycine[a] (m. p. 191–192.5°) | 86 | ... | ... | ... |
| Phthalylglycyl chloride[b] | 77 | ... | ... | ... |
| N-(β-Phenylethyl)-α-phthalimidoacetamide[c] | 91 | N, | 9.09 | 8.63 8.76 |
| N-(3,4-Dimethoxyphenylethyl)-α-phthalimidoacetamide[d] | 72 | N, | 7.61 | 7.20 7.22 |

(1) E. R. Squibb and Sons Research Fellow in Organic Chemistry.

(2) Child and Pyman, *J. Chem. Soc.*, **36** (1931).

TABLE I (*Concluded*)

| Compound | Yield, % | Analysis, % Calcd. | Found | |
|---|---|---|---|---|
| 1-Phthalimidomethyl-6,7-dimethoxy-3,4-dihydroisoquinoline[e] | 87 | C, 68.53 | 68.62 | ... |
| | | H, 5.18 | 5.18 | ... |
| | | N, 8.00 | 7.93 | ... |
| 1-Phthalimidomethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride[f] | .. | C, 61.74 | 61.24 | ... |
| | | H, 5.45 | 5.61 | ... |
| | | Cl, 9.12 | 8.74 | ... |
| 1-Aminomethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline sulfate[g] | .. | C, 44.97 | 45.36 | ... |
| | | H, 6.30 | 6.51 | ... |
| | | S, 10.01 | 10.12 | ... |
| Triazoacetyl chloride[h] | 78 | ... | ... | ... |
| N-(3,4-Dimethoxyphenylethyl)-α-triazoacetamide[i] | 80 | C, 54.52 | 54.87 | ... |
| | | H, 6.11 | 6.14 | |
| α-Amino-N-(3,4-dimethoxyphenylethyl)-acetamide hydrochloride[j] | 87 | Cl, 12.91 | 12.70 | 12.60 |

[a] From glycine and phthalic anhydride according to the method of Drechsel.[3]

[b] From phthalylglycine and thionyl chloride; b. p. 172–174° (5 mm.). Gabriel[4] gives 84–85° as the melting point.

[c] From phthalylglycyl chloride, β-phenylethylamine and 10% sodium hydroxide solution. Crystallized from alcohol. An attempt to bring about ring closure in this amide using phosphorus oxychloride in boiling toluene was unsuccessful. Using phosphorus pentoxide in boiling xylene a very small amount of basic product was obtained which was not investigated further.

[d] From phthalylglycyl chloride, homoveratrylamine[5] and 6% sodium carbonate solution. Crystallized from alcohol.

[e] By treatment of above amide with phosphorus oxychloride in boiling toluene for one and one-half hours. Toluene diluted with petroleum ether and precipitate dissolved in hot water and product precipitated with ammonium hydroxide. Crystallized from alcohol. If the above aqueous solution is allowed to cool without the addition of alkali, yellow crystals of a "phosphate" of undetermined constitution separate; sulfate obtained by diluting an alcoholic sulfuric acid solution with ether. Crystallized from absolute alcohol, m. p. 229–231°.

*Anal.* Calcd. for $C_{20}H_{18}N_2O_4 \cdot H_2SO_4 \cdot H_2O$: $H_2O$, 3.86. Found: loss at 60° and 3 mm., 3.93, 3.75. Calcd. for $C_{20}H_{18}N_2O_4 \cdot H_2SO_4$: S, 7.14. Found: S, 6.87 and 6.75.

[f] Prepared by the catalytic reduction of the dihydroisoquinoline. The reduction was carried out either on a dilute hydrochloric acid solution of the free base or on an aqueous solution of the "phosphate" at 3 atmospheres pressure using Adams platinum oxide catalyst. The isoquinoline hydrochloride was obtained by evaporation of the solution and was recrystallized from alcohol. Thirteen grams of dihydroisoquinoline "phosphate" yielded 10 g. of tetrahydroisoquinoline "phosphate," m. p. 244–245° (effervescence).

[g] Ten grams of the above phthalimido-tetrahydroisoquinoline "phosphate" was suspended in 30 cc. of alcohol and treated with 3 cc. of hydrazine hydrate. The mixture was warmed until all had dissolved, cooled and the gelatinous mass treated with an excess of dilute hydrochloric acid and warmed. The phthalic acid which separated was filtered and the filtrate evaporated to dryness. An attempt was made to convert this crude isoquinoline salt into the sulfate by treating an aqueous solution with about 50% sul-

(3) Drechsel, *J. prakt. Chem.*, [2] **27**, 418 (1883).

(4) Gabriel, *Ber.*, **40**, 2647 (1907).

(5) Prepared as previously described, Harwood and Johnson, THIS JOURNAL, **55**, 2555 (1933).

furic acid. The sulfate failed to precipitate. The solution was neutralized with sodium hydroxide, filtered from sodium sulfate and evaporated to a volume of about 100 cc. Upon making strongly alkaline with sodium hydroxide the aminoisoquinoline separated as a viscous oil. The aqueous layer was removed by means of a separatory funnel, the oil dissolved in a small volume of water and made just acid by the addition of 50% sulfuric acid. Upon diluting with alcohol a mass of white crystals formed. After recrystallization from dilute alcohol the 1-aminomethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline sulfate melted with effervescence at about 274–275°. The melting point varied considerably with the rate of heating. A yield of 3.4 g. of pure product was obtained.

*Anal.* Calcd. for $C_{12}H_{18}N_2O_2 \cdot H_2SO_4 \cdot 2H_2O$: $H_2O$, 10.12. Found: loss at 60° and 3 mm., 10.27, 10.38.

[h] Prepared according to the method of Bertho and Maier.[6]

[i] Six grams of homoveratrylamine was dissolved in 10 cc. of water, cooled in an ice-bath and with shaking treated alternately with small portions of *N* sodium hydroxide solution and triazoacetyl chloride. A total of 4.4 g. of acid chloride and 33 cc. of sodium hydroxide solution was used. The product separated as an oil which finally solidified and was crystallized from benzene. Attempts to bring about ring closure in this compound using phosphorus oxychloride in boiling toluene or benzene, phosphorus pentoxide in boiling xylene and phosphorus pentachloride in chloroform at room temperature were without success.

[j] Four grams of the above amide was dissolved in 50 cc. of alcohol and hydrogenated at 3 atmospheres pressure using Adams platinum oxide catalyst. After two hours the solution was filtered, treated with 1.25 cc. of concentrated hydrochloric acid and evaporated to dryness under reduced pressure. The residue was extracted with 30 cc. of hot absolute alcohol in several portions and the hot solution diluted with an equal volume of dry ether. A white crystalline precipitate separated which weighed 3.6 g. and was recrystallized from alcohol–ether. An attempt was made to bring about ring closure in this amide using phosphorus pentachloride in chloroform at room temperature. No definite product could be isolated.

## Summary

1. Starting with phthalylglycyl chloride and homoveratrylamine, N-(3,4-dimethoxyphenylethyl)-α-phthalimidoacetamide has been prepared in good yield.

2. By treatment with phosphorus oxychloride this amide undergoes a molecular condensation giving 1-phthalimidomethyl-6,7-dimethoxy-3,4-dihydroisoquinoline. The latter when reduced catalytically is converted smoothly into the corresponding 1,2,3,4-tetrahydroisoquinoline.

3. This 1,2,3,4-tetrahydroisoquinoline interacts smoothly with hydrazine hydrate to give 1-aminomethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline.

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(6) Bertho and Maier, *Ann.*, **498**, 50 (1932).