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Pictet-Spengler Reactions of Tryptamine and Tryptophan with Cycloalkanones and Ketonic *Mannich* Bases

E. M. Afsah*, M. Hammouda, and **W. S. Hamama**

Chemistry Department, Faculty of Science, Mansoura University, Mansoura, Egypt

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A *Pictet-Spengler* reaction of Tryptamine (**1**) with cyclopentanone under physiological conditions gave 3-(cyclopentylideneaminoethyl)indole (**3**), which was cyclized to the 1-spirocyclic 1,2,3,4-tetrahydro-2-carboline (**4**). Treatment of (±)-tryptophan with cyclopentanone and cyclohexanone in acidic medium afforded the spirocyclic systems **5** and **6**, respectively. The *Pictet-Spengler* reaction was extended further using ketonic bis-*Mannich* bases, to give compounds **7** and **8**. The possibility of using other types of ketonic bases was investigated.

(Keywords: 1-Spirocyclic 1,2,3,4-tetrahydro-2-carbolines)

Die Pictet-Spengler-Reaktion von Tryptamin and Tryptophan mit Cycloalkanonen und Keto-Mannich-Basen

Die *Pictet-Spengler*-Reaktion von Tryptamin (**1**) mit Cyclopentanonen ergab unter physiologischen Bedingungen 3-(Cyclopentylidenaminoethyl)indole (**3**), die zu den spirocyclischen Tetrahydro-2-carbolinen **4** cyclisiert wurden. Die Behandlung von (±)-Tryptophan mit Cyclopentanon oder Cyclohexanon in saurem Milieu ergab die spirocyclischen Systeme **5** oder **6**. Die *Pictet-Spengler*-Reaktion wurde auch auf Keto-Bis-*Mannich*-Basen zur Synthese der Verbindungstypen **7** und **8** ausgeweitet. Die Möglichkeiten zur Nutzung anderer Keto-Basen wurde untersucht.

Introduction

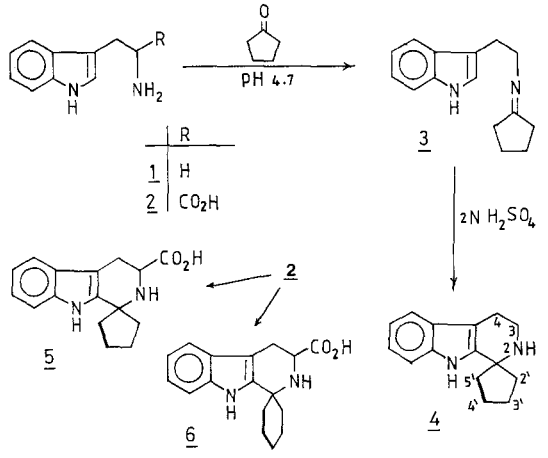
The synthesis of compounds containing the β-carboline nucleus is of interest because this ring system occurs in a number of physiologically active indole alkaloids and some hormones. The preparation of 1-substituted 1,2,3,4-tetrahydro-2-carbolines related to tetrahydroharman[1] and adrenoglomerulotropin[2] was accomplished by means of a *Pictet-Spengler* reaction[3] using tryptamine or (±)-tryptophan and various

aldehydes. The use of ketones instead of aldehydes in such reactions was reported by *Hester*[4], who obtained 1,1-dimethyl-1,2,3,4-tetrahydro-2-carbolines via condensation of tryptamines with acetone at *pH* 4.7.

These considerations prompted us to study the *Pictet-Spengler* reaction of tryptamine and (±)-tryptophan with cycloalkanones as a possible route to the 1-spirocyclic 1,2,3,4-tetrahydro-2-carboline ring system.

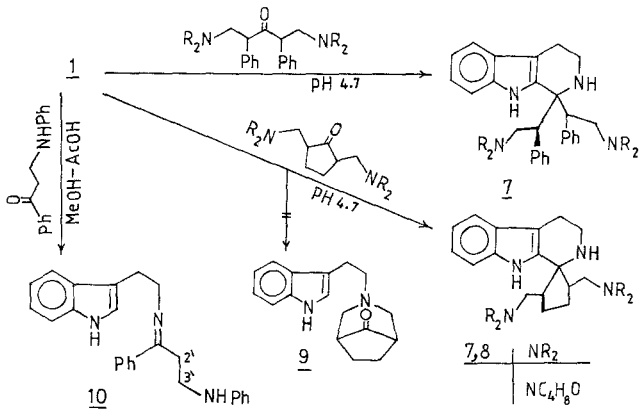
Results and Discussion

Reaction of tryptamine (**1**) with cyclopentanone at room temperature in a *pH* 4.7 acetate buffer gave 3-(cyclopentylideneaminoethyl)indole (**3**). The characteristic feature of its NMR spectrum is a signal at δ 6.7 for H 2 (Ref.[5]) which indicates that the α-position of the indole nucleus is unsubstituted. Cyclization of **3** with 2 *N* sulphuric acid gave **4**, which was demonstrated both by the absence of the signal due to the α-indolic proton in its NMR spectrum and by the presence of a singlet at 1.55 due to the (NH) proton at position 2 in the β-carboline system.



Similarly, treatment of (±)-tryptophan (**2**) with cyclopentanone or cyclohexanone in dilute sulphuric acid gave **5** and **6**, respectively. Formation of the spirocyclic compounds **4**–**6** is in line with the reported *Pictet-Spengler* reaction of indan-1,2-dione with 3-hydroxy-4-methoxyphenylethylamine as the key step in the total synthesis of ochotensine[6,7] and syntheses of the related alkaloids fumariline, fumaritine and fumaricine with a 1-spirobenzylisoquinoline skeleton.

One of the specific objectives of this study was to investigate the possible synthesis of 1,1-di-basically substituted 1,2,3,4-tetrahydro-2-carbolines via a *Pictet-Spengler* reaction using ketonic *Mannich* bases. Therefore, in continuation of our studies[8,9] on bis-*Mannich* bases as synthetic intermediates we found that condensation of **1** with 1,5-bis(*N*-morpholino)-2,4-diphenylpentan-3-one[9] at room temperature in a *pH* 4.7 acetate buffer afforded 1,1-di[α-(N-morpholinomethyl)benzyl]-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indole (**7**).



Similar treatment of **1** with 2,5-bis(*N*-morpholinomethyl)cyclopentanone[10] gave compound **8**. **8** differed from **9** obtained previously by prolonged reflux of the same reactants in aqueous ethanol[8].

On the other hand, attempts to apply the *Pictet-Spengler* reaction using 4-diethylaminobutan-2-one and β-diethylaminopropiophenone were unsuccessful, yielding only an intractable mixture which could not be purified sufficiently for identification. In these instances a slow evolution of diethylamine occurred during the reaction time, indicating an amine exchange reaction between these ketonic bases and tryptamine, which severely limits the usefulness of such bases in a *Pictet-Spengler* reaction. This anomalous behaviour in these two cases is due to the ease with which such bases undergo deamination and amine exchange reactions when treated with primary amines even at room temperature[11,12], and the volatility of the eliminated diethylamine.

We also treated **1** with β-anilinopropiophenone[12] and obtained compound **10** which could not be cyclized to the corresponding β-carboline.

Our results provide a convenient synthesis of the alkaloids **7** and **8** and extend the scope of the *Pictet-Spengler* reaction.

Experimental

Melting points (°C) are uncorrected and were recorded with a Gallenkamp electrical melting point apparatus. NMR spectra were obtained in $CDCl_3$ solution with a Varian Model "EM-360" 60 MHz NMR Spectrometer. Elementary analyses (C, H, N) of **3–8** and **10** are in good agreement with the proposed structures.

3-(Cyclopentylideneaminoethyl)indole (**3**)

To a solution of tryptamine hydrochloride (1 g, 0.005 mol) in a *pH* 4.7 acetate buffer (50 ml) was added cyclopentanone (0.5 g, 0.006 mol). The resulting solution was allowed to stand in the dark at 25° for 7 days. The reaction mixture was basified with 40% ammonia hydroxide and the crystalline precipitate was filtered off and crystallized from 50% aqueous ethanol, to give **3** in 35% yield, m.p. 107°; NMR ($CDCl_3$): δ 1.6 (broad s, 4 H, 3′-H_2 and 4′-H_2), 1.9 and 2.2 (d, 4 H, 2′-H_2 and 5′-H_2), 2.9 (t, 2 H, indol-CH_2CH_2-N), 3.3 (t, 2 H, indol-CH_2CH_2-N), 6.7 (s, 1 H, 2-H of indole) and 7.8–6.9 (m, 5 H, indolic protons).

3′,4′-Dihydro-spiro[cyclopentane-1,1′(2′H)-pyrido[3,4-b]indole] (**4**)

A solution of **3** (0.5 g) in 2 *N* sulphuric acid (20 ml) was heated to 110° and maintained at this temperature for 20 minutes. The cooled solution was basified with 40% ammonia hydroxide, to give a crystalline solid which, on crystallization from aqueous ethanol, gave **4** in 50% yield, m.p. 89°; NMR ($CDCl_3$): δ 1.55 (s, 1 H, NH at position-2), 1.8 (broad s, 8 H, 2′-H_2, 3′-H_2. 4′-H_2 and 5′-H_2), 2.5 (t, 2 H, 3-H_2), 2.95 (t, 2 H, 4-H_2) and 7.5–6.85 (m, 5 H, indolic protons).

3′,4′-Dihydro-spiro[cyclopentane-1,1′(2′H)-pyrido[3,4-b]indole]-3′-carboxylic acid (**5**) *and 3′,4′-Dihydro-spiro[cyclohexane-1,1′(2′H)-pyrido[3,4-b]indole]-3′-carboxylic acid* (**6**)

A mixture of (±)-tryptophan (1 g, 0.005 mol) and cyclopentanone (0.5 g, 0.006 mol) or cyclohexanone (0.6 g, 0.006 mol) in water (25 ml) containing 1 *N* sulphuric acid (5 ml) and ethanol (5 ml) was heated under reflux for 72 h, then cooled and filtered. The filtrate was concentrated and basified with dilute NaOH solution to *pH* 7.5–8, to give a crystalline product, which was crystallized from methanol-DMF to afford **5** and **6**, respectively, in 20–30% yield, m.p. 208° (decomp.) for **5** and 192° (decomp.) for **6**.

1,1-Di[α-(N-morpholinomethyl)benzyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b] indole (**7**) *and 2,5-Bis-(4-morpholinomethyl)-3′,4′-dihydrospiro[cyclopentane-1,1′(2′H)-pyrido[3,4-b]indole]* (**8**)

To a solution of tryptamine hydrochloride (1 g, 0.005 mol) in a *pH* 4.7 acetate buffer (50 ml) was added 1,5-bis(*N*-morpholino)-2,4-diphenylpentan-3-one (2 g, 0.005 mol) followed by 2 *N* sulphuric acid (3 ml), to dissolve the bis-base. The reaction mixture was allowed to stand in the dark at 25° for 12 days, then basified with 40% ammonia hydroxide and the crystalline precipitate was filtered off and crystallized from 50% aqueous ethanol, to give **7** in 45% yield, m.p. 145°.

8 was obtained similarly, except that the bis-base, 2,5-bis(*N*-morpholinomethyl)cyclopentanone dihydrochloride, was used instead; yield of **8** 15% and m.p. 280° (decomp.).

Compound **7**: NMR ($CDCl_3$): δ 1.6 (broad s, 1 H, NH at position-2), 2.4–2.0 (m, 12 H, 2 CH_2—N—CH_2 of morpholines and 2 CH_2-N of side-chains), 2.8 (t, 2 H, 3-H_2), 3.2 (t, 2 H, 4-H_2), 3.5 (t, 8 H, 2 CH_2—O—CH_2 of morpholines) 3.8 (m, 2 H, 2 Ph-C**H** of side-chains) and 7.6–6.9 (m, 15 H, 10 aromatic and 5 indolic protons).

3-[(3'-Anilino-1'-phenyl-1'-propylideneamino)ethyl]indole (**10**)

To a solution of tryptamine (0.5 g, 0.003 mol) and β-anilinopropiophenone (0.7 g, 0.003 mol) in methanol (25 ml) was added a few drops of acetic acid, and the reaction mixture was heated under reflux for 3 h, then left to stand at room temperature for 3 days. The crystalline precipitate was filtered off and recrystallized from methanol, to give **10** in 55% yield, m.p. 108°; NMR ($CDCl_3$): δ 2.2 (broad s, 4 H, indol-CH_2CH_2), 3.7–3.0 (complex m, 5 H, 2'-H_2, 3'-H_2 and N**H**Ph) and 7.5–6.5 (m, 16 H, 10 aromatic and 6 indolic protons).

References

[1] *Hahn G., Ludewig H.*, Chem. Ber. **67**, 2031 (1934).
[2] *Meek B., Szinai S. S., Wallis D.*, Chem. and Ind. (London), (1964) 622; cf. The Merk Index of Chemicals and Drugs, 9th ed., p. 160. Rahway, N.J.: Merk and Co. Inc. 1976.
[3] *Whaley W. M., Govindachari T. R.*, Org. React. **6**, 151 (1951).
[4] *Hester J. B.*, J. Org. Chem. **29**, 2864 (1964).
[5] *Cohen L. A., Daly J. W., Kny H., Witkop B.*, J. Amer. Chem. Soc. **82**, 2184 (1960).
[6] *McLeon S., Lin M., Whelen J.*, Tetr. Lett. **1968**, 2425.
[7] *Irie H., Kishimoto T., Uyeo S.*, J. Chem. Soc. **C 1968**, 3051.
[8] *Afsah E. M., Metwally M. A., Khalifa M. M.*, Monatsh. Chem. **115**, 303 (1984).
[9] *Afsah E. M., Hammouda M., Abou-Elzahab M. M.*, ibid., **115**, 581 (1984).
[10] *Blicke F. F., McCarty F. J.*, J. Org. Chem. **24**, 1069 (1959).
[11] *Craig J. C., Johns S. R., Moyle M.*, J. Org. Chem. **28**, 2779 (1963).
[12] *Craig J. C., Moyle M., Johnson L. F.*, ibid. **29**, 410 (1964).