The Free Internet Journal for Organic Chemistry

Paper

Archive for Organic Chemistry

Arkivoc 2019, part vi, 141-148

Formation of indole trimers in Vilsmeier type reactions

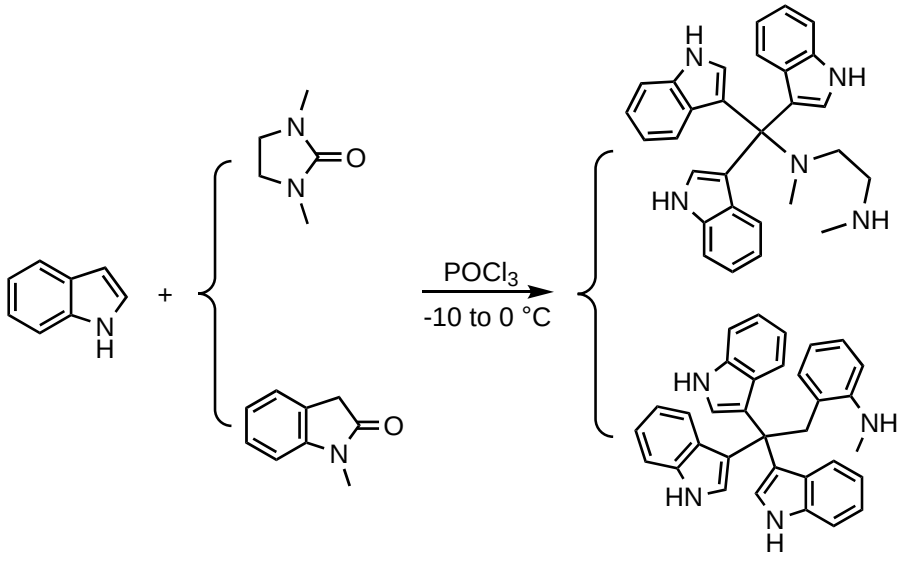
Masomeh Aghazadeh[a,b]

[a] *Department of Chemistry, Maku Branch, Islamic Azad University, Maku, 58619-93548, Iran*
[b] *Young Researchers and Elite Club, Maku Branch, Islamic Azad University, Maku, 58619-93548, Iran*
Email: aghazadehchemist@gmail.com

Received 07-02-2019 **Accepted** 09-27-2019 **Published on line** 10-10-2019

Abstract

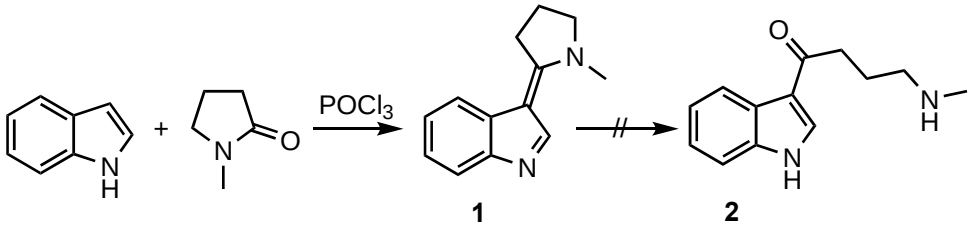
The reaction of indole with the complex formed from 1,3-dimethylimidazolidin-2-one or *N*-methyloxindole with phosphorus oxychloride (phosphoryl chloride), was studied. In similar reactions of five-membered tertiary amide rings, 3-(1-alkyl-pyrrolidin-2-ylidene)-3*H*-indoles or ring opening products were obtained but in these cases, new products N^1,N^2-dimethyl-N^1-[tri-(1*H*-indol-3-yl)methyl]ethane-1,2-diamine and *N*-methyl-2-(3,3,3-tri-(1*H*-indol-3-yl)propyl)aniline as trimers of indole were obtained.



Keywords: Indoles, Vilsmeier reactions, 1,3-dimethylimidazolidin-2-one, *N*-methyloxindole

Introduction

The reaction of indole with the Vilsmeier reagent, followed by base, is the classic and very efficient method for the 3-formylation of indoles.[1] 3-Acylindoles can be obtained from Vilsmeier reaction of indole and tertiary amides in combination with phosphorus oxychloride.[2] However, when 1-methylpyrrolidin-2-one is used as the cyclic amide component, 3-(1-methylpyrrolidin-2-ylidene)-3*H*-indole (**1**) is the product, without formation of an amino ketone product (**2**) (Scheme 1).[3,4] Compound **1** contains an intriguing combination of enamine and imine (as part of a 3*H*-indole) groups in conjugation.

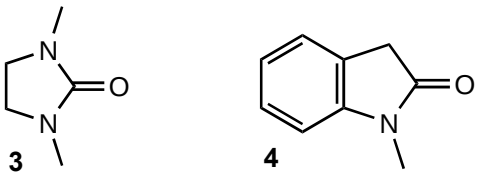


Scheme 1. The reaction of 1-methylpyrrolidin-2-one with indole under Vilsmeier conditions.

Usually the primary products, resulting from the Vilsmeier–Haack acylation, are hydrolyzed immediately without isolation of the intermediate iminium salts.[5] Iminium chemistry is the basis of an important formylation reaction of aromatic and heteroaromatic ring systems. Iminium salts and their neutral relatives, the imines, have found importance in the synthesis of heterocyclic ring systems.[6] They react as electrophiles with electron-rich systems such as indoles.[7] The iminium ion has a short lifetime in water and it is known to have an even shorter lifetime in the presence of a strong nucleophilic reagent.[8]

Indole derivatives are widely distributed in nature and are known as an important class of heterocyclic compounds and bioactive intermediates in pharmaceutical industry.[9] Various derivatives of indole have been synthesized to study their bioactivity. Thus di- and tri- indolylmethanes are well known, and the electrophilic substitution reaction of indoles with carbonyl compounds is an important method for their preparation. Bis(indolyl)methanes promote beneficial estrogen metabolism and induce apoptosis in human cancer cells.[10] Thus, there is great interest in the synthesis of these compounds.[11-15] Many simple indoles and bisindoles have been shown to have interesting biological activities.[16,17] It is reported that triindolylmethane cations could be used as the acceptors of hydride ions.[18] However, there is no report on the biological activity of triindoles, especially, triindolylmethanes.

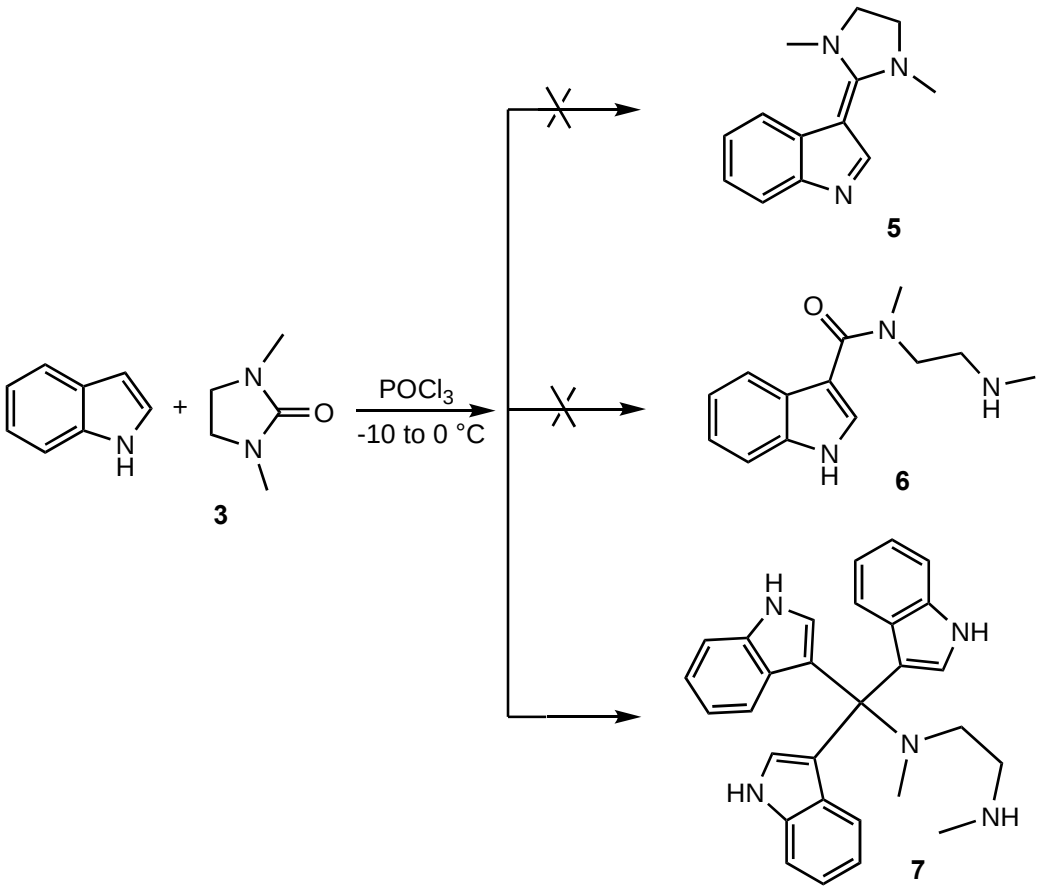
Our continuing interest involves using alternatives to 1-methyl-2-pyrrolidinone in Vilsmeier-type reactions with indole. The reactions of indole with the complex formed from different tertiary cyclic amides and phosphorus oxychloride were studied in our group.[19-24] In similar reactions of five-membered tertiary amide rings, 3-(1-alkyl-pyrrolidin-2-ylidene)-3*H*-indoles or ring opening products were obtained. The 3-(2-pyrrolidin-ylidene)-3*H*-indoles are stable compounds and they resist hydrolysis to the corresponding amino ketones.
Finally, we came to try 1,3-dimethylimidazolidin-2-one (**3**) and *N*-methyloxindole (**4**) as tertiary cyclic amides in reaction with indole and phosphorus oxychloride.



3 **4**

Results and Discussion

Our interest in this type of reaction promoted us to test the use of 1,3-dimethylimidazolidin-2-one (**3**) and *N*-methyloxindole (**4**). When 1,3-dimethylimidazolidin-2-one, instead of 1-methylpyrrolidin-2-one, was reacted with phosphorus oxychloride at –10 to 0 °C, an active complex was obtained that took a different path in its reaction with indole. The expected products (**5**) or (**6**) by analogy were not formed, but instead reaction proceeded to a trimer of indole with structure **7** (Scheme 2).

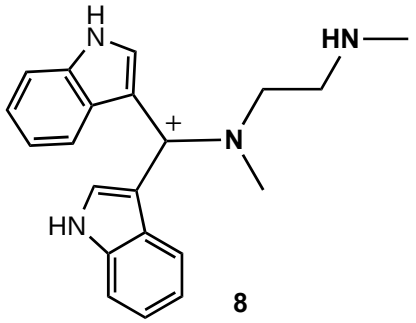


3 **5** **6** **7**

Scheme 2. The expected and found products of reaction of 1,3-dimethylimidazolidin-2-one (**3**) and indole under Vilsmeier conditions.

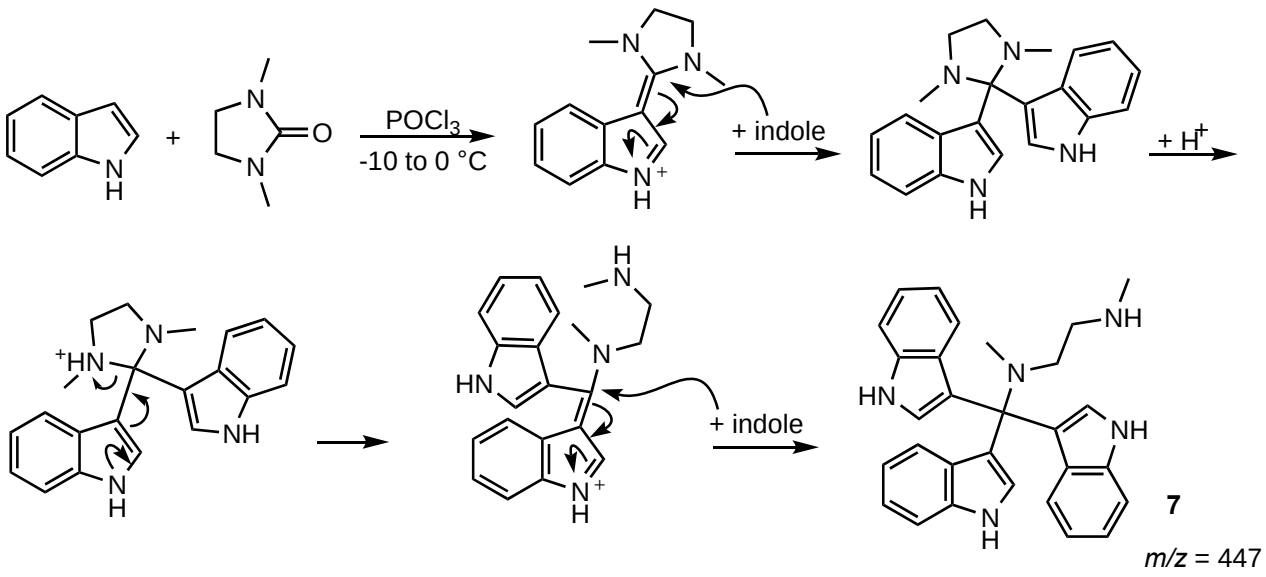
Identification and confirmation of the product structure (**7**) was carried out using various spectroscopic methods. In the ^{1}H-NMR spectrum, the –NH signals of indole rings and secondary amine, in a 3 to 1 ratio, were observed as single peaks at δ 10.77 ppm and δ 9.72 ppm respectively, which disappeared on addition a few drops of D_2O. The UV absorption spectrum of the compound was similar to that of indole. The base peak in its mass spectrum was observed at *m/z* 447. A peak at *m/z* 331.13 belongs to the stable fragment ion (**8**), which

results by loss of an indole unit and is stabilized by conjugation with two indole rings on one side and a nitrogen atom on the other.



8

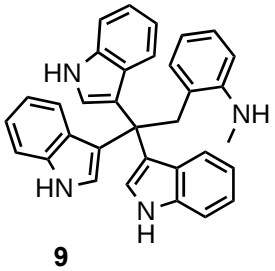
The mechanism by which we believe the reaction of 1,3-dimethylimidazolidin-2-one with phosphorus oxychloride and indole proceeds is shown in Scheme 3.



Scheme 3. The proposed mechanism for the synthesis of compound **7** from 1,3-dimethylimidazolidin-2-one (**3**) and phosphorus oxychloride and indole.

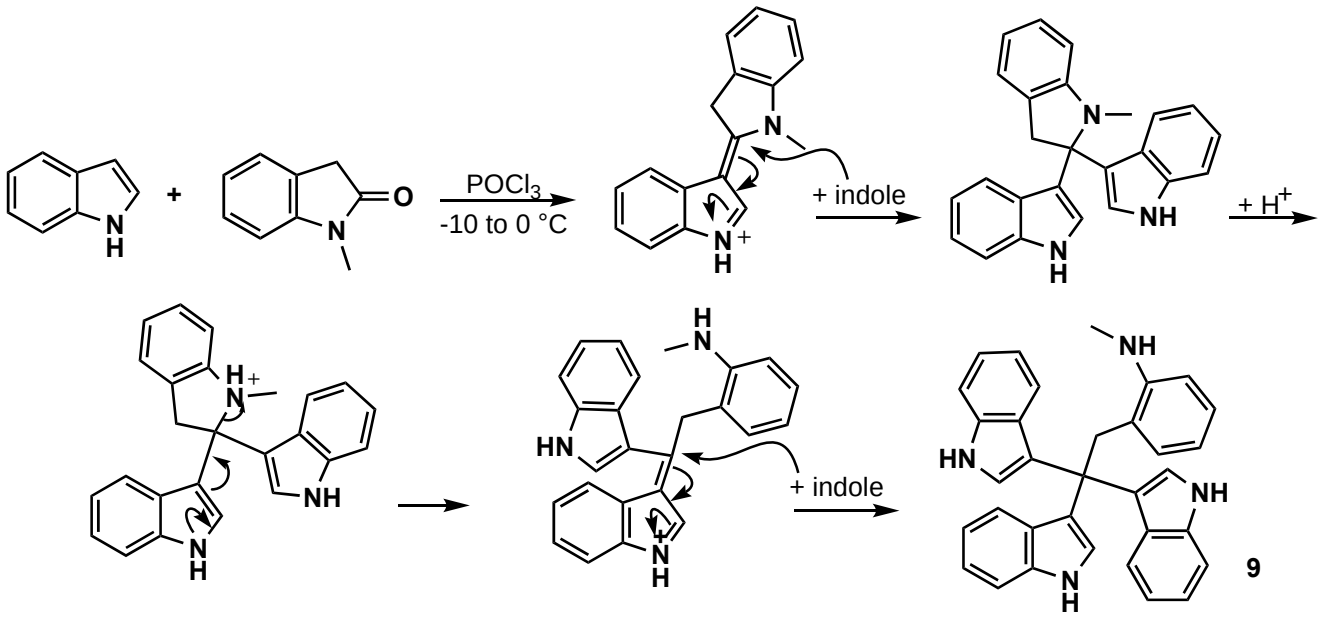
We also studied the reaction of *N*-methyloxindole (**4**) as a tertiary cyclic amide with phosphorus oxychloride and indole. Although it is commercially available, we prepared it from isatin.[25] In this method, isatin was first N-methylated using methyl iodide and then *N*-methyloxindole (**4**) was obtained in high yield by reduction with a Wolff-Kishner procedure.[26]

Treatment of *N*-methyloxindole with indole under Vilsmeier reaction conditions produced *N*-methyl-2-[3,3,3-tri-(1*H*-indol-3-yl)ethyl]aniline (**9**) in 48% yield.



9

In the ^{1}H-NMR spectrum of **9**, signals for the N-methyl, methylene and the NH of the indole rings were observed at δ 2.18, δ 3.71 and δ 4.47 ppm respectively. The main peak in the mass spectrum was observed at *m/z* 480. A suggested mechanism of this reaction is shown in Scheme 4.



Scheme 4. Proposed mechanism for the synthesis of compound **9** from the reaction of *N*-methyloxindole (**4**) with phosphorus oxychloride and indole.

Conclusions

In conclusion, we have reported a simple and convenient method for the synthesis of tri-(1*H*-indol-3-yl) derivatives by Vilsmeier-type reactions of indole with 1,3-dimethylimidazolidin-2-one and *N*-methyloxindole.

Experimental Section

General. Melting points were taken on a Philip Harris C4954718 apparatus. Infrared spectra were recorded on a Thermo Nicolet (Nexus 670) Fourier transform (FT) infrared spectrometer, using sodium chloride cells and measured in KBr pellets. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker 300 spectrometer using TMS as the internal reference. Mass spectra were recorded on Agilent 6890-N-Network-GC-system. Analytical thin-layer chromatography's (TLC) were carried out on Merck silica gel 60 F_{254} aluminum

sheets and detection was made with the help of a UV lamp (λ 254 nm). The ultraviolet spectra were recorded with a Perkin Elmer Lambda 25 UV device. Microanalyses were performed on a Leco Analyzer 932.

***N*^{1},*N*^{2}-Dimethyl-*N*^{1}-[tri-(1*H*-indol-3-yl)methyl]ethane-1,2-diamine** (**7**). To 1,3-dimethylimidazolidin-2-one (**3**) (4 mL, 0.04 mol) cooled in an ice bath was added $POCl_3$ (4.08 g, 0.026 mol) with stirring during 30 min. The temperature was maintained at –10-0 °C. The mixture was stirred an additional 10 min, and then a solution of indole (2.80 g, 0.024 mol) in 1,3-dimethylimidazolidine-2-one (4 mL, 0.04 mol) was added slowly during 2 h. The temperature rose to 45 °C. The mixture was heated at 80 °C for 3 h, and then mixed with water (100 mL). Some sediment began to form on dropwise addition of H_2O. The solid was filtered off and washed with water. Recrystallization from EtOH-H_2O afford the product **7** (5.6 g, 53%), mp 221-222 °C. ^{1}H-NMR (DMSO-d_6) δ (ppm) 2.39 (3H, s, CH_3-N), 3.32-3.45 (4H, m, CH_2CH_2), 3.62 (3H, s, CH_3-NH), 6.85-7.58 (15H, m, Ar), 9.72 (1H, bs, NH), 10.77 (3H, bs, three NH of indoles). ^{13}C-NMR (DMSO-d_6) δ (ppm) 19.00, 34.11, 34.90, 36.33, 48.91, 111.82, 118.23, 118.39, 119.48, 121.11, 122.87, 126.75, 126.95, 127.46, 127.9, 131.1, 134.6, 137.0, 137.8, 155.8. FT-IR (KBr, cm^{-1}) ν_{max} 3213, 2915, 1625, 1455, 1300, 745. UV (EtOH, nm) λ_{max} 223, 282, 291. MS (EI, 70 eV): *m/z* 202.00, 300.33, 331.13, 447. Anal. Calcd for $C_{29}H_{29}N_5$: C, 77.82; H, 6.53; N, 15.65. Found: C, 77.91; H, 6.27; N, 15.82%.

***N*-Methylisatin**.[25] A mixture of isatin (1.48 g, 10 mmol), K_2CO_3 (1.82 mg, 13 mmol), MeI (1.56 g, 11mmol) and DMF (50mL) was heated on an oil bath. After one hour the reaction mixture was poured into ice-H_2O and extracted with CH_2Cl_2. The organic layer was washed with H_2O, and then dried and concentrated in vacuum. Recrystallization from *n*-hexane/acetone afford the product as orange needle crystals (1.42 g, 88%), mp 125-126 °C (lit.[17] mp 130-133 °C). ^{1}H-NMR ($CDCl_3$) δ (ppm) 3.27 (3H, s, CH_3N), 6.89-7.63 (4H, m, Ar). ^{13}C-NMR ($CDCl_3$) δ 26.2, 109.9, 115.9, 123.8, 125.3, 130.2, 138.3, 183.3, 186.6. FT-IR (KBr, cm^{-1}) ν_{max} 1728, 1608, 1468, 757, 474.

***N*-Methyloxindole** (**4**).[26] *N*-Methylisatin (10 mmol) was dissolved in hydrazine hydrate (98%; 10 mL) and the mixture heated at reflux for 30 min. The reaction mixture was then poured in cold H_2O, extracted in EtOAc and the extract dried over Na_2SO_4. Evaporation of the solvent and subsequent recrystallization from hexane/EtOAc afforded the desired product (1.25 g, 85%), mp 86-87 °C (lit.[33] mp 85-88 °C). ^{1}H-NMR ($CDCl_3$) δ (ppm) 3.21 (3H, s, CH_3N), 3.52 (2H, s, CH_2), 6.80-7.31 (4H, m, Ar). ^{13}C-NMR ($CDCl_3$) δ 26.1, 35.7, 108.1, 122.3, 124.3, 124.5, 127.9, 145.2, 175.1. FT-IR (KBr, cm^{-1}) ν_{max} 1707, 1610, 1466, 747.

***N*-Methyl-2-[3,3,3-tri-(1*H*-indol-3-yl)ethyl]aniline (9)**. *N*-Methyloxindole (0.2 g, 1.4 mmol) was dissolved in a minimum quantity of 1,4-dioxane and cooled in an ice bath. Then $POCl_3$ (0.135 g, 0.88 mmol) was added with stirring during 30 min. The temperature was maintained at –10 to 0 °C. The mixture was stirred an additional 10 min, and then a solution of indole (0.098 g, 0.84 mmol) in the minimum or 1,4-dioxane was added slowly during 2 h. The temperature rose to 45 °C for 1 hour. The mixture was heated at 80 °C for 2.5 h, and then mixed with H_2O (10 mL). Some sediment began to form by dropwise addition of H_2O. The brown solid was filtered off and washed with H_2O. Recrystallization from EtOH-H_2O afforded the desired product (0.19 g, 48%), mp 159-160 °C. ^{1}H-NMR ($CDCl_3$) δ (ppm) 2.18 (3H, s, CH_3), 3.71 (2H, s, CH_2), 4.13 (1H, s, NH), 6.63-8.48 (22H, m, Ar). ^{13}C-NMR ($CDCl_3$) δ (ppm) 36.0, 53.3, 58.5, 109.2, 109.7, 118.9, 119.7, 121.7, 123.0, 124.0, 124.4, 125.5, 128.8, 139.2, 141.9, 142.1. FT-IR (KBr, cm^{-1}) ν_{max} 3382, 2924, 1609, 1465, 1323, 742. UV (EtOH, nm) λ_{max} 209, 219, 248, 293. MS (EI, 70 ev): *m/z* 480, 375, 246, 117. Anal. Calcd for $C_{33}H_{24}N_4$: C, 82.47; H, 5.87; N, 11.66 Found: C, 81.67; H, 5.28; N, 13.05.

References

1. James, P. N.; Snyder, H. R., *Org. Synth.* **1963**, *IV*, 539.
2. Anthony, W. C. *J. Org. Chem.* **1960**, *25*, 2049. https://doi.org/10.1021/jo01081a615
3. Youngdale, G. A.; Anger, D. G.; Anthony, W. C.; Da Vanzo, J. P.; Greig, M. E.; Heinzelman, R. V.; Keasling, H. H; Szmuszkovicz, J. *J. Med. Chem.* **1964**, *7*, 415. https://doi.org/10.1021/jm00334a006
4. Harris, M.; Joule, J. A. *J. Chem. Res*. **1978**, *25*.
5. Jutz, C., In *Advances in Organic Chemistry*, Bohme, H.; Viehe, H. G., Eds.; Wiley: New York, 1976; Vol 9(1), pp 225–342.
6. Overman, L. E.; Ricca, D. J., In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p1007. https://doi.org/10.1016/B978-0-08-052349-1.00055-X
7. Risch, N.; Arend, M., In *Houben–Weyl*, 1995; Vol. E21b, p 1881.
8. Eldin, S.; Jencks W. P. *J. Am. Chem. Soc*. **1995**, *117*, 4851. https://doi.org/10.1021/ja00122a015
9. Sundberg, R. J. *The Chemistry of Indoles*, Academic Press: New York, USA, 1996.
10. Zeligs, M. A. *J. Med. Food* **1998**, *1*, 67. https://doi.org/10.1089/jmf.1998.1.67
11. Chakrabarty, M.; Ghosh, N.; Basak, R.; Harigaya, Y. *Tetrahedron Lett*. **2002**, *43*, 4075. https://doi.org/10.1016/S0040-4039(02)00682-2
12. Bandgar, B. P.; Shaikh, K. A. *Tetrahedron Lett*. **2003**, *44*, 1959. https://doi.org/10.1016/S0040-4039(03)00032-7
13. Reddy, A. V.; Ravinder, K.; Reddy, V. L. N.; Venkateshwer Goud, T.; Ravikanth, V.; Venkateswarlu, Y. *Synth. Commun.* **2003**, *33*, 3687. https://doi.org/10.1081/SCC-120025177
14. Ramesh, C.; Ravindranath, N.; Biswanath, D. *J. Chem. Res. (S),* **2003**, 72. https://doi.org/10.3184/030823403103174452
15. Li, J.; Zhou, M.; Li, B.; Zhang, G. *Synth. Commun*. **2004**, *34*, 275. https://doi.org/10.1081/SCC-120027263
16. Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2002**, *19*, 148. https://doi.org/10.1039/b007740m
17. Riby, J. E.; Chang, G. H. F.; Firestone, G. L.; Bjeldanes, L. F. *Biochem. Pharmacol*. **2000**, *60*, 167. https://doi.org/10.1016/S0006-2952(00)00307-5
18. Preobrazhenskaya, M. N.; Korolev, A. M.; Rozhkov, I. I.; Yudina, L. N.; Lazhko, E. I.; Aiello, E.; Almerico, A. M.; Mingoia, F. *IL Farmaco*, **1999**, *54*, 265. https://doi.org/10.1016/S0014-827X(99)00026-9
19. Helliwell, M.; Aghazadeh, M.; Baradarani, M. M.; Joule, J. A. *Acta Cryst*. **2009**, *E65*, o3114. https://doi.org/10.1107/S1600536809047606
20. Aghazadeh, M.; Baradarani, M. M.; Helliwell, M. *Med. J. Chem*. **2011**, *3*, 98.
21. Aghazadeh, M.; Badali, M.; Baradarani, M. M. *Chimica Oggi-Chemistry Today* **2016**, *34*, 34.
22. Aghazadeh, M.; Raftery, J.; Baradarani, M. M.; Joule, J. A. *Arkivoc* **2012**, (*vii)*, 158. https://doi.org/10.3998/ark.5550190.0013.710

23. Helliwell, M.; Aghazadeh, M.; Baradarani, M. M.; Joule, J. A. *Acta Cryst*. **2010**, *E66*, o1532.
24. Aghazadeh, M. *Progress in Chemical and Biochemical Research* **2019**, *2*, 34. https://doi.org/10.33945/SAMI/PCBR.2019.2.3439
25. Shmidt, M. S.; Reverdito, A. M.; Kremenchuzky, L.; Perillo, I. A.; Blanco, M. M. *Molecules* **2008**, *13*, 831. https://doi.org/10.3390/molecules13040831
26. Cresthi, C.; Saladino, R. *Synth. Commun*. **1994**, *24*, 2835. https://doi.org/10.1080/00397919408010603

