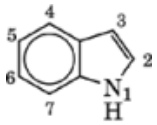
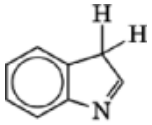
Kirk-Othmer Encyclopedia of Chemical Technology.

INDOLE

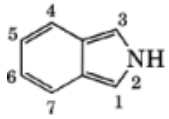
Indole is a heteroaromatic compound consisting of a fused benzene and pyrrole ring, specifically benzo[*b*]pyrrole. The systematic name, 1*H*-indole distinguishes it from the less stable tautomer 3*H*-indole [271-26-1] . 1*H*-Indole [120-72-9] is also more stable than the isomeric benzo[*c*] pyrrole, which is called isoindole, (2*H,* and 1*H*). A third isomer benzo[*a*]pyrrole is a stable compound called indolizidine [274-40-8].



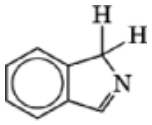
(1)



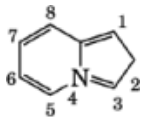
(2)



(3)

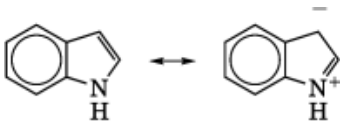


(4)



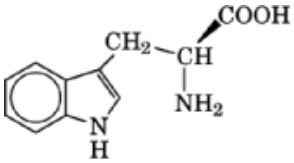
(5)

Indole is planar with 10 π-electrons in a completely conjugated system. The ring is classified as a π-excessive heteroaromatic compound because of the electron-donating character of the pyrrole-type nitrogen atom. The π-system is relatively electron-rich, particularly at C-3, as represented by resonance structure **(1b)**.



(1a) (1b)

The indole ring is incorporated into the structure of the amino acid tryptophan [6912-86-3] and occurs in proteins and in a wide variety of plant and animal metabolites. Much of the interest in the chemistry of indole is the result of efforts to understand the biological activity of indole derivatives in order to develop pharmaceutical applications.

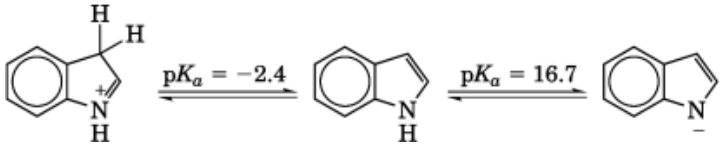


(6)

1. Properties

Indole is a colorless solid, mp 52–54°C, which is readily soluble in most organic solvents but sparingly soluble in water. Indole has a musty odor which is very persistent and its derivatives have some applications in the formulation of fragrances.

Indole is a neutral compound but can be protonated or deprotonated under strongly acidic or basic conditions, respectively. The pK_a of the conjugate acid is about -2.4; that of the neutral compound is about 16.7 (1).



Crystal structure data are available for an indole–trinitrobenzene complex (2) and for the lithium and sodium salts in the presence of polyamine ligands (3). The crystal structure of indole itself is evidently

Table 1. ^{1}H-nmr Chemical Shifts for Indole and ^{13}C-nmr Chemical Shifts[a] for Indole

Ring position	^{1}H	^{13}C
1	7.73	
2	7.00	124.2
3	6.51	102.4
3a		127.8
4	7.64	120.7
5	7.11	119.8
6	7.18	121.9
7	7.24	111.1
7a		135.7

[a] In $CDCl_3$.

disordered (4). Table 1 gives the ^{1}H and ^{13}C-nmr assignments in $CDCl_3$ (5). ^{13}C-nmr assignments have been tabulated for many other indole derivatives (6).

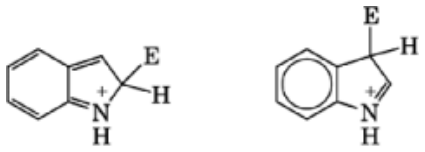
The industrial source of indole has been isolation from coal-tar distillate (7). Several patents for the manufacture of indole have been issued with aniline and ethylene glycol (8), aniline and ethylene oxide (9), 2-ethylaniline (10), and *N*-ethylaniline (11) as the starting materials.

2. Reactivity

Indole is a heterocyclic analogue of naphthalene. The basic reactivity patterns of indole can be understood as resulting from the fusion of an electron-rich pyrrole ring with a benzene ring.

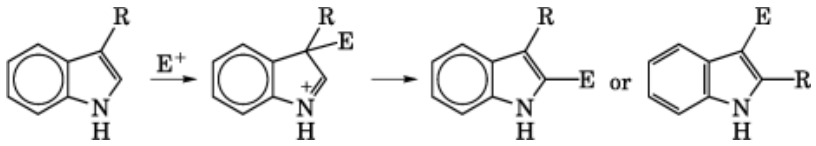
2.1. Electrophilic Aromatic Substitution

The π-excessive character of the pyrrole ring makes the indole ring susceptible to electrophilic attack. The reactivity is greater at the 3-position than at the 2-position. This reactivity pattern is suggested both by electron density distributions calculated by molecular orbital methods and by the relative energies of the intermediates for electrophilic substitution, as represented by the protonated structures **(7a)** and **(7b)**. Structure **(7b)** is more favorable than **(7a)** because it retains the benzenoid character of the carbocyclic ring (12).



(7a) **(7b)**

This basic reactivity pattern is not greatly affected by the presence of a 1- or 2- substituent, although electron-attracting substituents do diminish the reactivity. The pattern for substitution in 3-substituted indoles can be complicated by the fact that the electrophile may preferentially attack the 3-position, even when it is already substituted. When this is the case, migration of either the new or the original substituent to C-2 may occur.



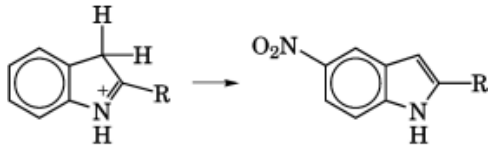
Many of the common electrophilic aromatic substitution reactions can be conducted on indole. Complications normally arise either because of excessive reactivity or the relative instability of the substitution product. This is the case with halogenation.

2.1.1. Halogenation

3-Chloroindole can be obtained by chlorination with either hypochlorite ion or with sulfuryl chloride. In the former case the reaction proceeds through a 1-chloroindole intermediate (13). 3-Chloroindole [16863-96-0] is quite unstable to acidic aqueous solution, in which it is hydrolyzed to oxindole. 3-Bromoindole [1484-27-1] has been obtained from indole using pyridinium tribromide as the source of electrophilic bromine. Indole reacts with iodine to give 3-iodoindole [26340-47-6]. Both the 3-bromo and 3-iodo compounds are susceptible to hydrolysis in acid but are relatively stable in base.

2.1.2. Nitration

Because nitration frequently generates nitrogen oxides which can participate in oxidative transformations, the nitration of indole itself is a complex reaction. In strongly acidic media, the nitration of 2-substituted indoles can proceed through the conjugate acid (**8**). Because the aromatic system is thereby transformed to an azastyrene, the 5-position is the primary site of reaction.

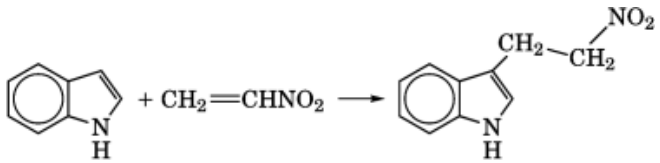


(**8**)

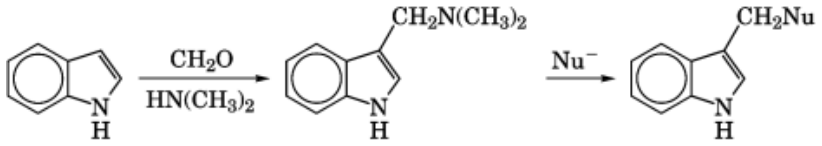
2.1.3. C-Alkylation

By choice of reaction conditions it is possible to favor alkylation of indole and substituted indoles at either the 1- or the 3-position. Reaction at the 3-position (*C*-alkylation) is favored by conditions which make the transition intermediate more like that in an electrophilic aromatic substitution. Tight metal coordination at nitrogen, as in the magnesium salt, promotes alkylation at C-3. Good yields are most likely to be obtained with highly reactive alkylating agents such as allylic and benzylic systems under conditions in which the alkylating agent assumes carbocationic character.

Unsaturated compounds activated by electron-attracting groups can also effect alkylation at the 3-position. An important example is the reaction with nitroethylene to form 3-(2-nitroethyl)indole [31731-23-4] (14).



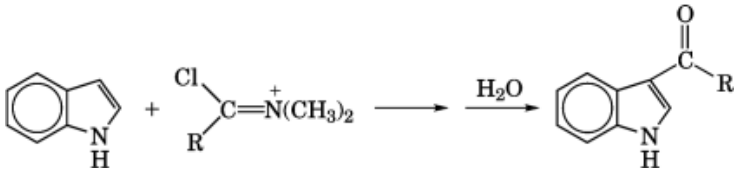
Another useful reagent for the 3-alkylation of indole is the *N,N*-dimethylformaldiminium ion, which forms the useful intermediate gramine [87-52-5] . The C-3 substituent can subsequently be modified by displacement of the dimethylamino group by a nucleophile. Alternatively, gramine can be converted to its quaternary salt prior to substitution. A variety of carbanions can function as the nucleophile.



(**9**)

2.1.4. Acylation

Acylation is the most reliable means of introducing a 3-substituent on the indole ring. Because 3-acyl substituents can be easily reduced to 3-alkyl groups, a two-step acylation–reduction sequence is often an attractive alternative to direct 3-alkylation. Several kinds of conditions have been employed for acylation. Very reactive acyl halides, such as oxalyl chloride, can effect substitution directly without any catalyst. Normal acid chlorides are usually allowed to react with the magnesium (15) or zinc (16) salts. The Vilsmeier-Haack conditions involving an amide and phosphorus oxychloride, in which a chloroiminium ion is the active electrophile, frequently give excellent yields of 3-acylindoles.



2.2. *N*-Alkylation

1-Substitution is favored when the indole ring is deprotonated and the reaction medium promotes the nucleophilicity of the resulting indole anion. Conditions which typically result in *N*-alkylation are generation of the sodium salt by sodium amide in liquid ammonia, use of sodium hydride or a similar strong base in *N,N*-dimethylformamide or dimethyl sulfoxide, or the use of phase-transfer conditions.

2.3. Arylation

Arylation is normally accomplished through some substituted intermediate, rather than directly on indole. The only direct means of arylation, via radical substitution, is not selective enough to be useful for synthetic purposes. Palladium-catalyzed cross-coupling reactions have become the preferred means for arylation of indoles, as well as other heteroaromatic rings (17). Cross-coupling requires one nucleophilic component, typically an aryltin or arylzinc reagent. Indoleboronic acids can also serve as the nucleophilic component (18). The second component is an aryl halide or aryl triflate which can undergo an oxidative addition reaction with the palladium catalyst. Arylation occurs by addition of the nucleophilic component to the palladium intermediate and regenerates the active palladium species. Reactions have been reported in which the indole is either the nucleophilic or the oxidative reactant, but the former is the more common case.

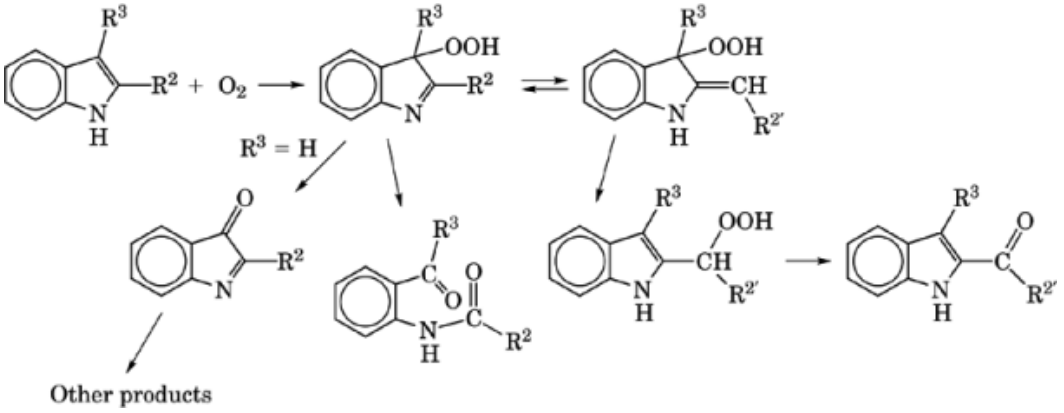
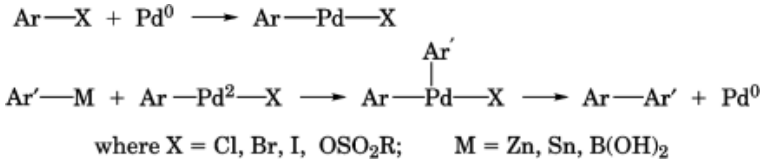
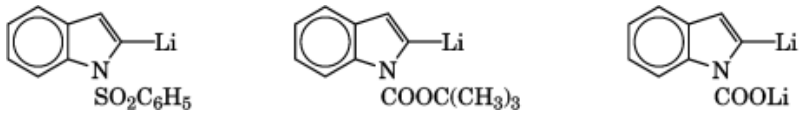


Fig. 1. Reactivity of 2,3-substituted indoles with oxygen.



2.4. Lithiation and Subsequent Transformations

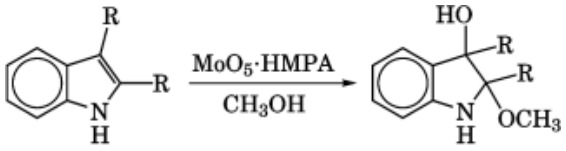
Lithiation is the most general means of introducing a 2-substituent on the indole ring. Three intermediates have been used most frequently in this context. These are 1-phenylsulfonylindole (19), 1-*t*-butoxycarbonylindole (20), and lithium indole-1-carboxylate (21).



Each of these intermediates can be lithiated in the 2-position in good yield. The reactivity toward lithiation is due to the inductive effect of the nitrogen atom and coordination by oxygen from the *N*-substituent. A wide variety of electrophiles can then carry out substitution at the 2-position. Lithiation at other positions on the ring can be achieved by halogen–metal exchange; 3-lithio and 5-lithioindoles have also been used as reactive intermediates.

2.5. Oxidation

As a π-excessive heterocycle, indole is susceptible to oxidation; a variety of oxidation intermediates and products have been observed. With oxygen as the oxidant, the key intermediate is normally a 3-hydroperoxy-3*H*-indole. These intermediates are observable for 2,3-disubstituted indoles but are unstable for less substituted derivatives. Figure 1 indicates typical reactivity patterns toward oxygen. Mixtures of products are frequently observed. Oxidation by peroxycarboxylic acids usually give similar products (22). Several chemical oxidants give good yields of specific oxidation products. Dimethyl sulfoxide in aqueous acid gives oxindoles (23). In methanol, $MoO_5 \cdot$HMPA (hexamethylphosphoramide) gives 3-hydroxy-2-methoxyindolines (24).

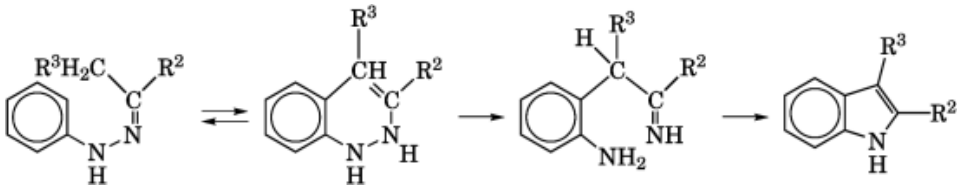


3. Syntheses

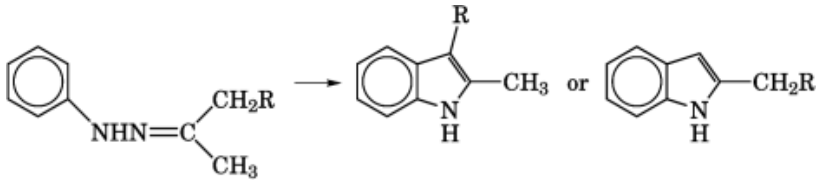
Although there are a wide variety of indole ring syntheses (25), most of the more useful examples fall within a small number of groups. Indole syntheses usually start with an aromatic compound, either monosubstituted or ortho-disubstituted. Those which begin with a monosubstituted starting material must at some point effect a substitution of the benzene ring.

3.1. The Fischer Indole Synthesis and Related Sigmatropic Syntheses

In the Fischer indole synthesis (26) an *N*-arylhydrazone is cyclized, usually under acidic conditions, to an indole. The key step is a [3,3]sigmatropic rearrangement of an enehydrazone tautomer of the hydrazone.

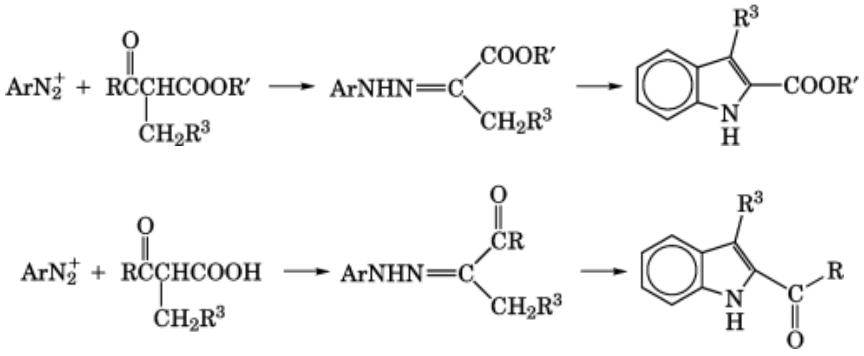


Thus to permit cyclization, there must be at least one hydrogen α to the C=N bond. If there is only one, the product will be a 3,3-disubstituted-3*H*-indole. However, if both substituents at the hydrazone carbon have one or more α-hydrogens, product mixtures can result. Generally, it is expected that the more branched substituent is more likely to be involved in cyclization, so typically phenylhydrazones derived from methyl alkyl ketones give 2-methylindoles. However, the selectivity is subject to the reaction conditions and with certain reagents the selectivity can be reversed to favor the 2-alkylindole.

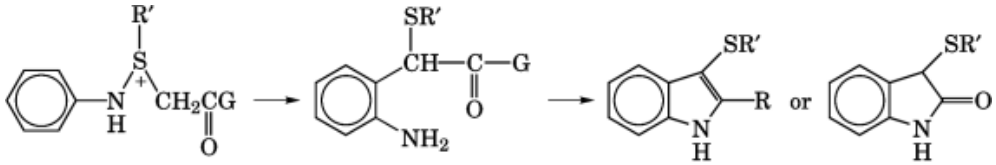


When the phenylhydrazone bears a meta-substituent, two isomeric indoles are possible; ortho-substituents also frequently introduce complications.

In addition to formation from a ketone, the hydrazones can be obtained from dicarbonyl compounds by a Japp-Klingemann reaction. This is especially useful for β-ketoesters and β-ketoacids, which undergo either deacylation or decarboxylation.

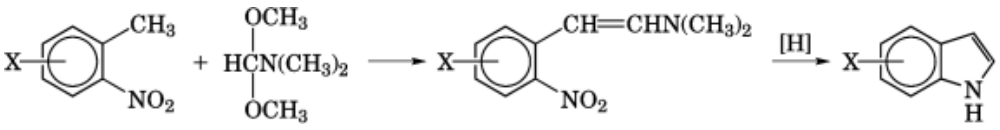


Another indole/oxindole synthesis achieves the critical ortho-substitution by Sommelet-Hauser rearrangement of an anilinosulfonium ion intermediate. Use of β-thioketones ($G = R$, an alkyl group) generates 2-substituted indoles, whereas β-thioesters ($G = OR$) lead to oxindoles. In each case, a 3-thio substituent must be removed by desulfurization.

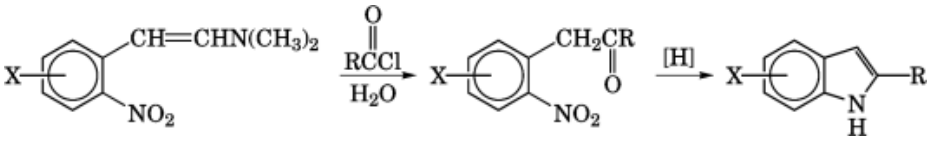


3.2. Reductive Cyclizations

The Batcho-Leimgruber protocol involves condensation of an *o*-nitrotoluene with a dimethylformamide acetal to form a β-(*o*-nitrophenyl)enamine (27). A reducing agent then affects the reductive cyclization to an indole.

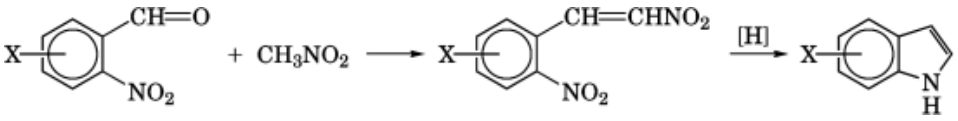


There have been a number of refinements to the procedure, both in the enamine formation and in the reduction. Furthermore, the procedure can be adapted to 2-substituted indoles by introducing an acyl substituent on the enamine intermediate.



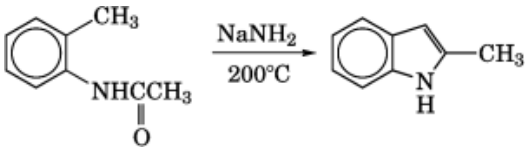
In general, any *o*-nitrobenzyl ketone or *o*-aminobenzyl ketone can be converted to a 2-substituted indole. There are a variety of specific examples of such syntheses, although there are not any truly general means of generating these kinds of starting materials.

o-Nitrobenzaldehydes condense with nitromethane to give *o*,β-dinitrostyrenes. A variety of reducing agents convert these to indoles.

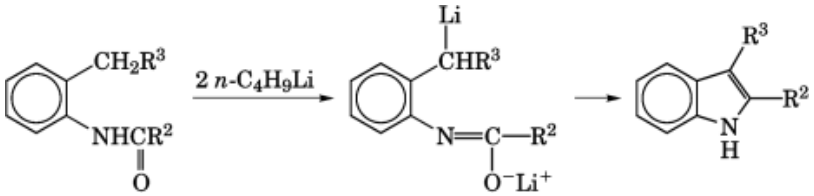


3.3. The Madelung Synthesis and Related Base-Catalyzed Condensations

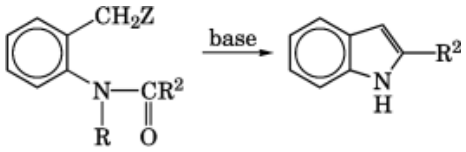
The Madelung cyclization involves an intramolecular condensation of an *o*-alkylanilide. A classic example of the Madelung synthesis is the high temperature condensation of *o*-methylacetanilide [120-66-1] to 2-methylindole [95-20-5] by sodium amide.



Cyclization can be achieved under much milder conditions by using *n*-butyllithium or lithium diisopropylamide to form a dilithio derivative of the anilide (28).



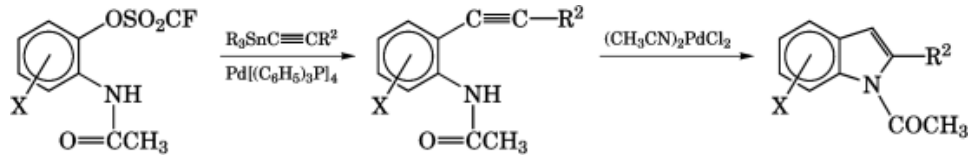
The same reactivity pattern is observed with *o*-methylanilides in which a carbanion-stabilizing substituent is attached to the methyl group. For Z = trimethylsilyl or triphenylphosphonio, elimination occurs with cyclization.



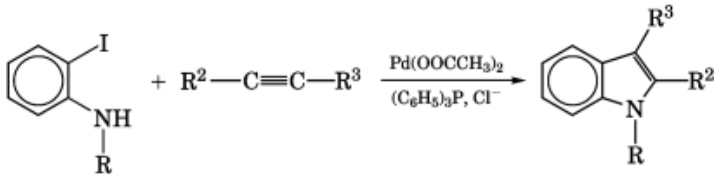
Z = H, $Si(CH_3)_3$, $\overset{+}{P}(C_6H_5)_3$, SO_2Ar

3.4. Transition-Metal Catalyzed Cyclizations

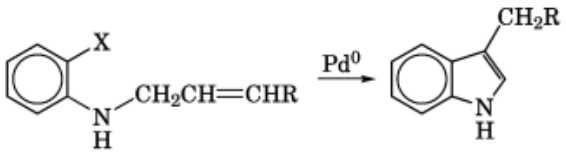
o-Halogenated anilines and anilides can serve as indole precursors in a group of reactions which are typically catalyzed by transition metals. Several catalysts have been developed which convert *o*-haloanilines or anilides to indoles by reaction with acetylenes. An early procedure involved coupling to a copper acetylide with *o*-iodoaniline. A more versatile procedure involves palladium catalysis of the reaction of an *o*-bromo- or *o*-trifluoromethylsulfonyloxyanilide with a trialkylstannylalkyne. The reaction is conducted in two stages, first with a Pd(0) and then a Pd(II) catalyst (29).



o-Iodoaniline or *o*-iodoanilides can be cyclized to 2,3-disubstituted indoles by reaction with disubstituted alkynes in the presence of a Pd(II) catalyst (30). With unsymmetrical alkynes the bulkier group occupies the 2-position.



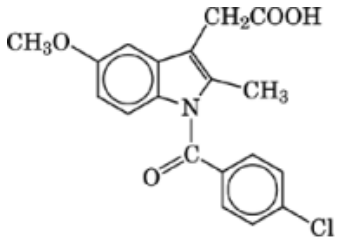
3-Substituted indoles can be prepared from *o*-bromo or *o*-iodoanilines by palladium-catalyzed cyclization of *N*-allyl derivatives (31).



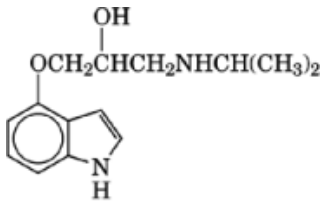
4. Biologically Active Indole Derivatives

4.1. Synthetic Derivatives of Indoles as Pharmaceuticals

Thousands of indole derivatives have been prepared and evaluated as potential pharmaceuticals (32). Of those which have been put into use perhaps the most important are the nonsteroidal antiinflammatory agent indomethacin [53-86-1] (33) and the β-adrenergic blocker pindolol [13823-86-9] (34).



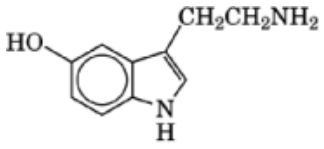
(10)



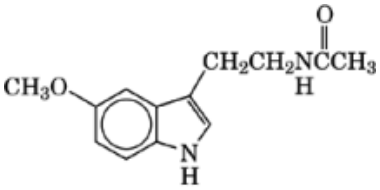
(11)

4.2. Naturally Occurring Compounds

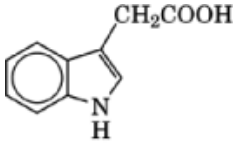
Many derivatives of indole are found in plants and animals where they are derived from the amino acid tryptophan. Several of these have important biological function or activity. Serotonin [50-67-9] functions as a neurotransmitter and vasoconstrictor (35). Melatonin [73-31-4] production is controlled daily by the circadian cycle and its physiological level influences, and seasonal rhythms in humans and other species (36). Indole-3-acetic acid [87-51-4] is a plant growth stimulant used in several horticultural applications (37).



(12)



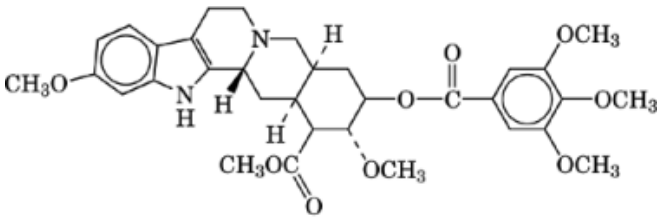
(13)



(14)

The largest single class of naturally occurring indoles are the plant alkaloids. These occur with a wide range of structural diversity and are typically derived from tryptophan and terpenoid structural units. Several of these compounds are pharmacologically significant. Reserpine [50-55-5] acts as a tranquilizer and hypotensive agent. Although not widely used at present, it was one of the first drugs to be introduced for the treatment of mental illness (38). The dimeric vinca alkaloids vincristine [57-22-7] and vinblastine [865-21-4] are used in the treatment of Hodgkin's disease, leukemia, and other forms of cancer (39). Derivatives of the ergot alkaloid

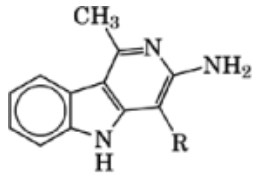
lysergic acid are used in the treatment of migraine (40) and the diethylamide is lysergic acid diethylamide (LSD) (see Alkaloids).



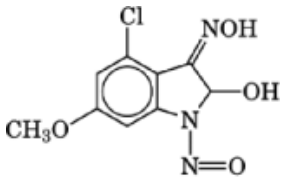
(15)

4.3. Toxic Indole Derivatives

There are several documented cases where indole derivatives, both natural and of synthetic origin, have been linked to pathological effects in humans. 3-Methylindole [83-34-1], which is produced by bacterial fermentation in cattle, can lead to pulmonary edema (41). The active metabolite is 3-methyleneindolenine, which forms adducts with proteins, primarily through sulfhydryl groups (42). The pyridoindoles Trp-P-1 ($R = CH_3$) and Trp-P-2 ($R = H$) are genotoxic substances which originate from pyrolysis of tryptophan and have been identified in foods cooked at excessively high temperatures (43). 4-Chloro-6-methoxyindole, which can be extracted from fava beans, yields a potent mutagen on interaction with nitrite ion. This mutagen has been associated with the etiology of stomach cancer in certain areas of Colombia (44). In the late 1980s a lethal pathological condition appeared which was associated with the consumption of L-tryptophan having a specific synthetic origin (45). The causative agent is believed to be a contaminant introduced by the specific manufacturing process. Several contaminants have been identified but the precise identity of the causative agent remains under investigation (46).



(16)



(17)

BIBLIOGRAPHY

"Indole" in *ECT* 1st ed., Vol. 7, pp. 839–847, by W. C. Sumpter, Western Kentucky State College, and F. M. Miller, University of Maryland; in *ECT* 2nd ed., Vol. 11, pp. 585–595, by W. C. Sumpter, Western Kentucky State College, and F. M. Miller, University of Maryland; in *ECT* 3rd ed., Vol. 13, pp. 213–222, by D. W. Bannister, Toms River Chemical Corp.

Cited Publications

1. M. Balon and co-workers, *Tetrahedron* **45**, 7501 (1989).
2. A. W. Hanson, *Acta Cryst.* **17**, 359 (1964).
3. K. Gregory and co-workers, *Organometallics* **9**, 1485 (1990).
4. P. Roychowdhury and B. S. Basak, *Acta Crystallogr., Sect. B* **B31**, 1559 (1975).
5. P. Joseph-Nathan, R. E. del Rio, and M. S. Morales-Rios, *Heterocycles* **27**, 377 (1988).
6. M. S. Morales-Rios, J. Espineira, and P. Joseph-Nathan, *Magn. Reson. Chem.* **25**, 377 (1987).
7. R. Liu and Y. Zhang, *Xiandai Huagong* **9**, 18 (1989); T. Y. Gogoleva and S. N. Olshanskaya, *Koks Khim.*, 41 (1990).
8. Jpn. Kokai Tokkyo Koho 62 22, 758 (Jan. 30, 1987), T. Ueno and co-workers (to Mitsui Toatsu Chemicals, Inc.).
9. Jpn. Kokai Tokkyo Koho 59 172,467 (Sept. 29, 1984), (to Mitsui Toatsu Chemicals, Inc.).
10. Jpn. Kokai Tokkyo Koho 01 199,943 (Aug. 11, 1989), M. Tsuzaki and M. Sato (to Idemitsu Kosan Co., Inc.); Brit. Pat. Appl. 2,232,152 (Dec. 5, 1990), E. Gerecs an co-workers (to Reanal Finomvegyszergyar).
11. Jpn. Kokai Tokkyo Koho 63 196,562 (Aug. 15, 1988), H. Sato and M. Tsuzuki (to Idemitsu Kosan Co., Inc.).
12. J. Catalan and co-workers, *J. Am. Chem. Soc.* **110**, 4105 (1988); J. Catalan and M. Yanez, *J. Am. Chem. Soc.* **106**, 421 (1984).
13. M. R. Brennan and co-workers, *Heterocycles* **24**, 2879 (1986); P. G. Gassman, G. A. Campbell, and G. Mehta, *Tetrahedron* **28**, 2749 (1972); M. De Rosa, L. Carbognani, and A. Febres, *J. Org. Chem.* **46**, 2054 (1981).
14. M. E. Flaugh and co-workers, *J. Med. Chem.* **22**, 63 (1979); D. Ranganathan and co-workers, *J. Org. Chem.* **45** 1185 (1980).
15. R. A. Heacock and S. Kasparek, *Adv. Heterocycl. Chem.* **10**, 61 (1969).
16. J. Bergman and L. Venemalm, *Tetrahedron* **46**, 6061 (1990).
17. L. S. Hegedus, *Angew. Chem., Int. Ed. Engl.* **27**, 1113 (1988); T. Sakamoto, Y. Kondo, and H. Yamanaka, *Heterocycles* **27**, 2225 (1988).
18. M. A. Siddiqui and V. Sniekus, *Tetrahedron Lett.* **31**, 1523 (1990).
19. R. J. Sundberg and H. F. Russell, *J. Org. Chem.* **38**, 3324 (1973); M. G. Saulnier and G. W. Gribble, *J. Org. Chem.* **47**, 757 (1982).
20. I. Hasan and co-workers, *J. Org. Chem.* **46**, 157 (1981).
21. A. R. Katritzky and K. Akutagama, *Tetrahedron Lett.* **26**, 5935 (1985).
22. E. Braudeau, S. David, and J.-C. Fischer, *Tetrahedron* **30**, 1445 (1974).
23. K. Szabo-Pusztay and L. Szabo, *Synthesis* 276 (1979).
24. C.-S. Chien and co-workers, *Chem. Pharm. Bull.* **34**, 1493 (1986).
25. U. Pindur and R. Adam, *J. Heterocyclic Chem.* **25**, 1 (1988); M. A. Yurovskaya, *Chemistry of Heterocyclic Compounds (Engl. Transl.)* **23**, 919 (1987).
26. B. Robinson, *The Fischer Indole Synthesis*, John Wiley & Sons, Inc., New York, 1982.
27. R. O. Clark and D. B. Repke, *Heterocycles* **22**, 195 (1984).
28. W. J. Houlihan, V. A. Parrino, and V. Uke, *J. Org. Chem.* **46**, 4511 (1981).
29. D. E. Rudisill and J. K. Stille, *J. Org. Chem.* **54**, 5856 (1989).
30. R. C. Larock and E. K. Yum, *J. Am. Chem. Soc.* **113**, 6689 (1991).
31. R. Odle and co-workers, *J. Org. Chem.* **45**, 2709 (1980).
32. K. C. Joshi and P. Chand, *Die Pharmazie* **37**, 1 (1982); J. K. Sugden and T. O. Yoloye, *Pharm. Acta Helv.* **53**, 65 (1978).
33. T. Y. Shen and C. A. Winter, *Adv. Drug Res.* **12**, 89 (1977).
34. W. H. Frishman, *N. Engl. J. Med.* **308**, 940 (1983).
35. N. N. Osborne, ed., *Biology of Setonergic Transmission*, John Wiley & Sons, Inc., Chichester, U.K., 1982; P. M. Van Loutte, R. A. Cohen, and J. M. Van Neuten, *J. Cardiovasc. Pharmacol.* **6**, (Suppl. 2), 421 (1984).

36. S. M. Armstrong, *Experientia* **45**, 932 (1989); T. J. Bartmess and D. B. Goldman, *Experientia* **45**, 939 (1989).
37. E. A. Schneider and F. Wrightman, *Phytohom. Related Compd; Compr. Treatise* **1**, 29 (1978).
38. E. Schlittler, *The Alkaloids* **8**, 231 (1965).
39. A. Brossi and M. Suffness, *The Alkaloids* **37**, 1 (1990).
40. I. Ninomiya and T. Kiguki, *The Alkaloids* **38**, 1 (1990).
41. J. R. Carlson and co-workers, *J. Toxicol., Toxin Rev.* **5**, 217 (1986).
42. W. Ruangyuttikarn, G. L. Skiles, and G. S. Yost, *Chem. Res. Toxicol.* **5**, 713 (1992).
43. Y. Hashimoto, K. Shudo, and T. Okamoto, *Acc. Chem. Res.* **17**, 403 (1984).
44. D. Yang and co-workers, *Carcinogenesis* **5**, 1219 (1984).
45. E. A. Belongia and co-workers, *N. Engl. J. Med.* **323**, 357 (1990).
46. M. J. Smith and co-workers, *Tetrahedron Lett.* **32**, 991 (1991); Y. Goda and co-workers, *Chem. Pharm. Bull.* **40**, 2236 (1992).

General References

47. C. W. Bird and G. W. H. Cheeseman, eds., *Comprehensive Heterocyclic Chemistry*, Vol. **4**, Pergamon Press, Oxford, 1984, Chapts. 3.04, 3.05, and 3.06.
48. W. J. Houlihan, ed., *The Chemistry of Heterocyclic Compounds*, Vol. **25**, Parts 1, 2, and 3, Wiley-Interscience, New York, 1972.
49. R. J. Sundberg, *The Chemistry of Indoles*, Academic Press, Inc., New York, 1970.

RICHARD J. SUNDBERG
University of Virginia

Related Articles

Pharmaceuticals; Alkaloids