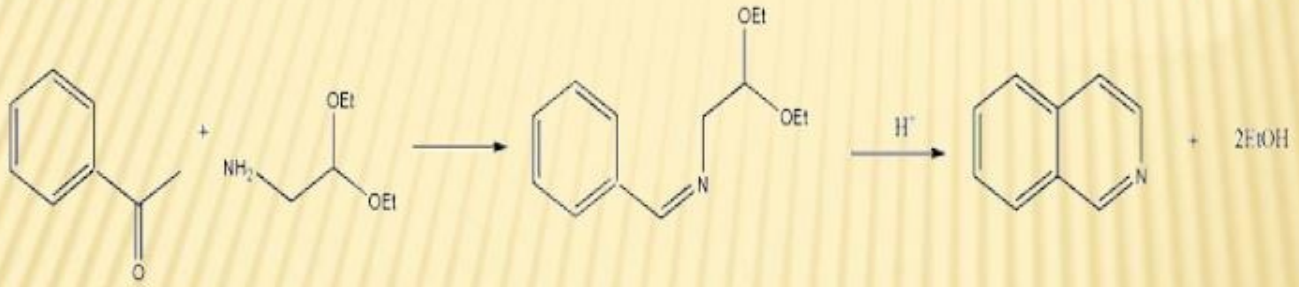
Isoquinolone

Production

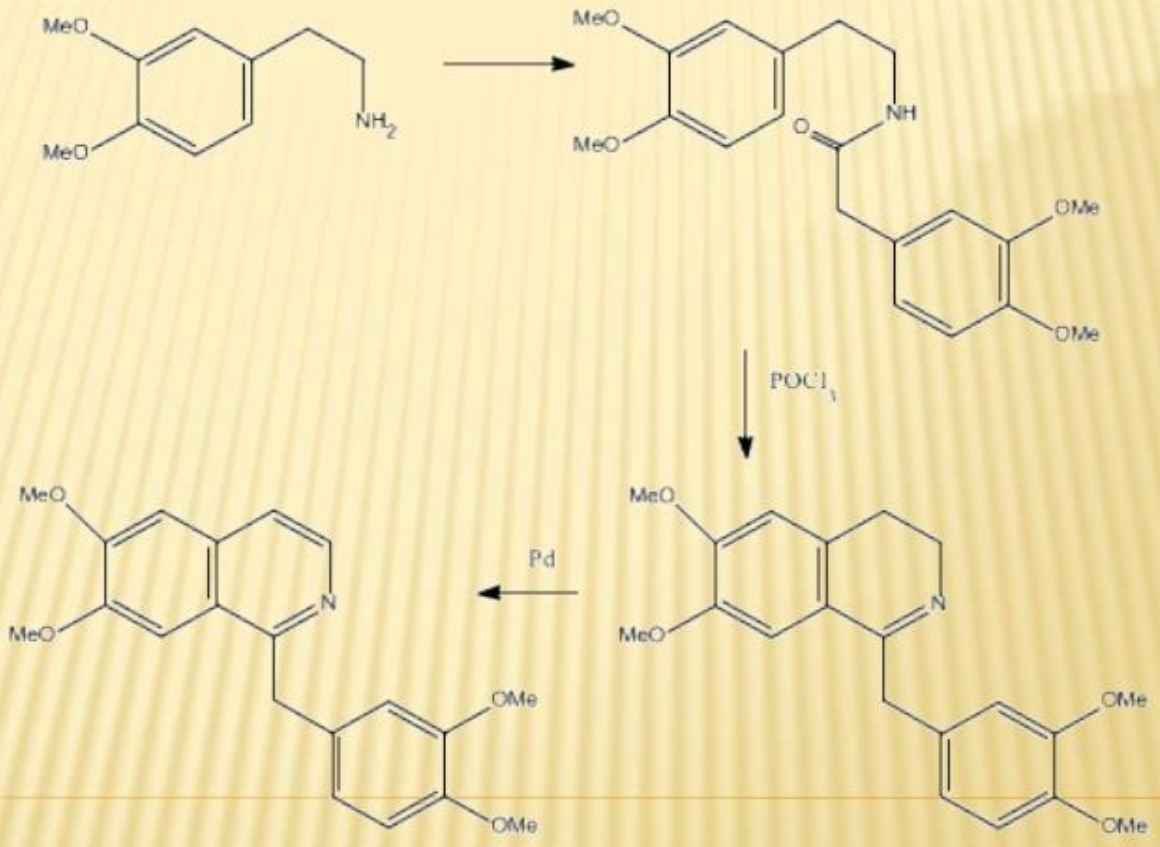
Isoquinolone was first isolated from coal tar in 1885 by Hoogewerf and van Dorp. They isolated it by fractional crystallization of the acid sulfate. Weissgerber developed a more rapid route in 1914 by selective extraction of coal tar, exploiting the fact that isoquinoline is more basic than quinoline. Isoquinoline can then be isolated from the mixture by fractional crystallization of the acid sulfate.

Although isoquinoline derivatives can be synthesized by several methods, relatively few direct methods deliver the unsubstituted isoquinoline. The Pomeranz-Fritsch reaction provides an efficient method for the preparation of isoquinoline:

The **Pomeranz-Fritsch reaction** uses a benzaldehyde and aminoacetoaldehyde diethyl acetal, which in an acid medium react to form isoquinoline. Alternatively, benzylamine and a glyoxal acetal can be used, to produce the same result



The following methods are useful for the preparation of various isoquinoline derivatives:
In the Bischler-Napieralski reaction an β-phenylethylamine is acylated and cyclodehydrated by a Lewis acid, such as phosphoryl chloride or phosphorus pentoxide. The resulting 1-substituted-3,4-dihydroisoquinoline can then be dehydrogenated using palladium. The following Bischler-Napieralski reaction produces papaverine.


MeO
MeO
NH2
MeO
MeO
O
NH
OMe
OMe
POCl3
MeO
MeO
N
OMe
OMe
Pd
MeO
MeO
N
OMe
OMe

The Pictet-Gams and Pictet-Spengler syntheses are both variations on the Bischler-Napieralski reaction. The differences are as follows:
The Pictet-Gams reaction avoids the final dehydrogenation step of the Bischler-Napieralski reaction by constructing a β-phenylethylamine with a hydroxy group in the side chain. This reaction results in a 1-alkyl-isoquinoline.
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The Pictet-Spengler reaction combines a β-phenylethylamine and an aldehyde in an acid medium, which cyclizes the imine in a reaction of the Mannich type. This produces the tetrahydroisoquinoline instead of the dihydroisoquinoline.

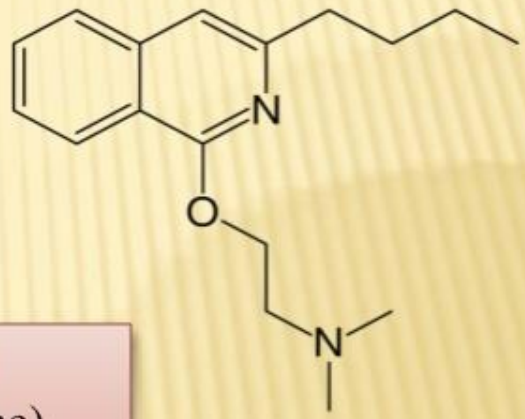
Intramolecular aza Wittig reactions also afford isoquinolines

Properties

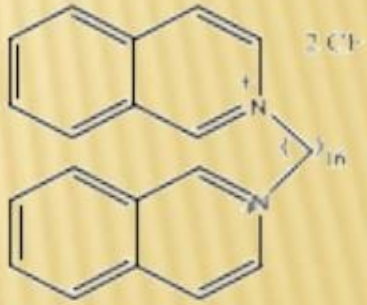
Isoquinoline is a colorless hygroscopic liquid at room temperature with a penetrating, unpleasant odor. Impure samples can appear brownish, as is typical for nitrogen heterocycles. It crystallizes platelets that have a low solubility in water but dissolve well in ethanol, acetone, diethyl ether, carbon disulfide, and other common organic solvents. It is also soluble in dilute acids as the protonated derivative. Being an analog of pyridine, isoquinoline is a weak base, with a pK_b of 8.6. It protonates to form salts upon treatment with strong acids, such as HCl. It forms adducts with Lewis acids, such as BF_3.

Applications of derivatives

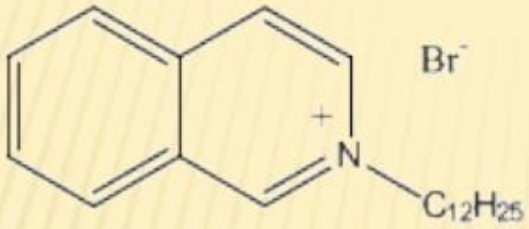
Isoquinolines find many applications, including (but not limited to):
anesthetics; dimethisoquin is one example (shown below).



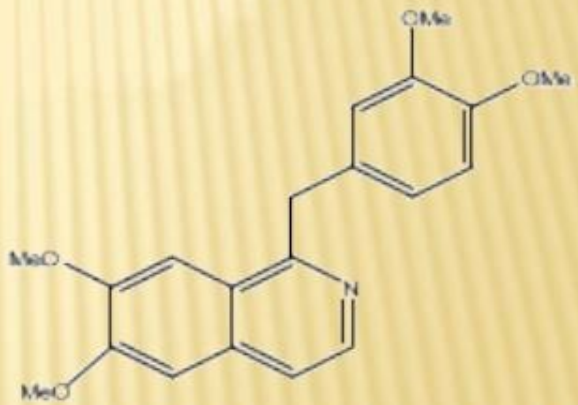
antihypertension agents, such as quinapril, quinapirilat, and *debrisoquine* (all derived from 1,2,3,4-tetrahydroisoquinoline).
antifungal agents, such as 2,2'Hexadecamethylenediisoquinolinium dichloride, which is also used as a topical antiseptic. This derivative, shown below, is prepared by N-alkylation of isoquinoline with the appropriate dihalide



disinfectants, like N-laurylisoquinolinium bromide (shown below), which is prepared by simple N-alkylation of isoquinoline



vasodilators, a well-known example, papaverine, shown below



Bisbenzylisoquinolinium compounds are compounds similar in structure to tubocurarine. They have two isoquinolinium structures, linked by a carbon chain, containing two ester linkages

Isoquinoline Benefits

Chemically, TDIQ (5,6,7,8-tetrahydro-1,3-dioxolo[4,5-g]isoquinoline) can be viewed as a conformationally restricted phenylalkylamine that is related in structure to amphetamine but does not stimulate (or depress) locomotor activity in rodents. In radioligand binding studies TDIQ displays selective affinity for alpha(2)-adrenergic receptor subsites (i.e., alpha(2A)-, alpha(2B)-, and alpha(2C)-adrenergic receptors), and behavioral data suggest that it might exert an agonist (or partial agonist) effect at alpha(2)-adrenergic receptors or interact at alpha(2)-adrenergic heteroreceptors. Drug discrimination studies in rats indicate that TDIQ: (1) serves as a discriminative stimulus, (2) may be useful in the treatment of symptoms associated with the abuse of cocaine, and (3) exhibits a low potential for abuse

. In addition, TDIQ exhibits a dose-dependent and wide dissociation between doses that produce an anxiolytic-like effect or an inhibition of "snack" consumption in mice and doses that produce minimal, if any, effects in tests that measure a potential for disruption of coordinated movement or motor activity
. Also, TDIQ displays negligible effects on the heart rate (HR) and blood pressure (BP) of mice. Taken together, the preclinical data suggest that TDIQ exhibits a favorable ratio of therapeutic-like effects (anxiolytic, therapeutic adjunct in the treatment of cocaine abuse

, and appetite suppression) to side effect-like activities (behavioral impairment, drug abuse, or adverse cardiovascular effect). As such, TDIQ could: (1) be a forerunner for a new type of chemical entity in the treatment of certain forms of anxiety and/or obesity and (2) serve as a structural template in the discovery and development of additional agents that might be selective for alpha(2)-adrenergic receptors

Other uses

Isoquinolines are used in the manufacture of dyes, paints, insecticides and antifungals. It is also used as a solvent for the extraction of resins an terpenes, and as a corrosion inhibitor

References

General references

- Gilchrist, T.L. (1997). *Heterocyclic Chemistry* (3rd ed.). Essex, UK: Addison Wesley Longman.
- Harris, J.; Pope, W.J. "*iso*Quinoline and the *iso*Quinoline-Reds" Journal of the Chemical Society (1922) volume 121, pp. 1029-1033.
- Katritsky, A.R.; Pozharskii, A.F. (2000). *Handbook of Heterocyclic Chemistry* (2nd ed.). Oxford, UK: Elsevier.
- Katritsky, A.R.; Rees, C.W.; Scriven, E.F. (Eds.). (1996). *Comprehensive* Heterocyclic Chemistry II: A Review of the Literature 1982-1995 (Vol. 5). Tarrytown, NY: Elsevier.
- Nagatsu, T. "Isoquinoline neurotoxins in the brain and Parkinson's disease" Neuroscience Research (1997) volume 29, pp. 99-111.
- O'Neil, Maryadele J. (Ed.). (2001). *The Merck Index* (13th ed.). Whitehouse Station, NJ: Merck.