The Chemistry of Heterocycles

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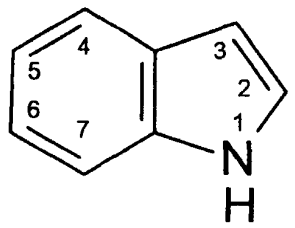
The Chemistry of Heterocycles, (Second Edition).

By Theophil Eicher and Siegfried Hauptmann, Wiley-VCH Veriag GmbH, 2003

5.13 Indole

[A] Benzo[*b*]pyrrole is known by the trivial name indole. The univalent radical is called indolyl. The UV and NMR data of indole are given in the table below:

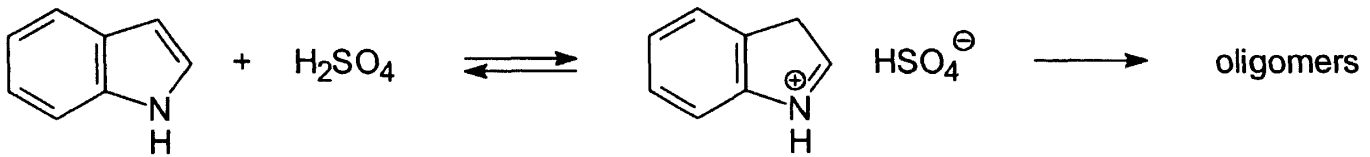


UV (ethanol) λ (nm) (ε)		^{1}H-NMR (acetone-d_6) δ (ppm)		^{13}C-NMR ($CDCl_3$) δ (ppm)	
216 (4.54)	276 (3.76)	H-1: 10.12	H-5: 7.00	C-2: 123.7	C-6: 119.0
266 (3.76)	278 (3.76)	H-2: 7.27	H-6: 7.08	C-3: 101.8	C-7: 110.4
270 (3.77)	287 (3.68)	H-3: 6.45	H-7: 7.40	C-4: 119.9	C-3a: 127.0
		H-4: 7.55		C-5: 121.1	C-7a: 134.8

[B] Indoles are less reactive than pyrroles. The following reactions are characteristic for the chemical behavior of indole.

Acid-base reactions

The basicity of indole, pK_a = -3.50, corresponds approximately to that of pyrrole. Protonation occurs mainly on C-3 with formation of the 3*H*-indolium ion which reacts further to give oligomers:



With a pK_a value of 16.97, indole possesses an NH-acidity similar to that of pyrrole. Indole reacts, therefore, with sodamide in liquid ammonia, with sodium hydride in organic solvents, with GRIGNARD reagents and with *n*-butyllithium to give 1-metalated indoles.

Electrophilic substitution reactions on carbon

In most electrophilic substitution reactions, indole reacts more slowly than pyrrole but faster than benzo[*b*]furan. In contrast to pyrrole substitution of the H-atom occurs preferably in the 3-position. There are two reasons for this:

• Attack of the electrophile on the 3-position leads to formation of a low energy iminium structure of the σ-complex. Attack on the 2-position, however, results in a high-energy orthoquinonoid iminium structure:

• With pyrrole, the coefficient of the HOMO is greatest in the 2- and 5-positions, whilst with indole this applies to the 3-position.

If the 3-position already carries a substituent, attack usually occurs first on the 2- and subsequently on the 6-position.

Indole is chlorinated with $SOCl_2$ or aqueous NaOCl to give 3-chloroindole, and 3-bromoindole is formed with *N*-bromosuccinimide.

Action of HNO_3 on indole causes oxidation of the pyrrole ring followed by polymerization. Indoles substituted in the 2-position react with HNO_3 in acetic acid to give 3,6-dinitro compounds.

Sulfonation of indole with pyridine-SO_3 complex leads to the formation of indole-3-sulfonic acid.

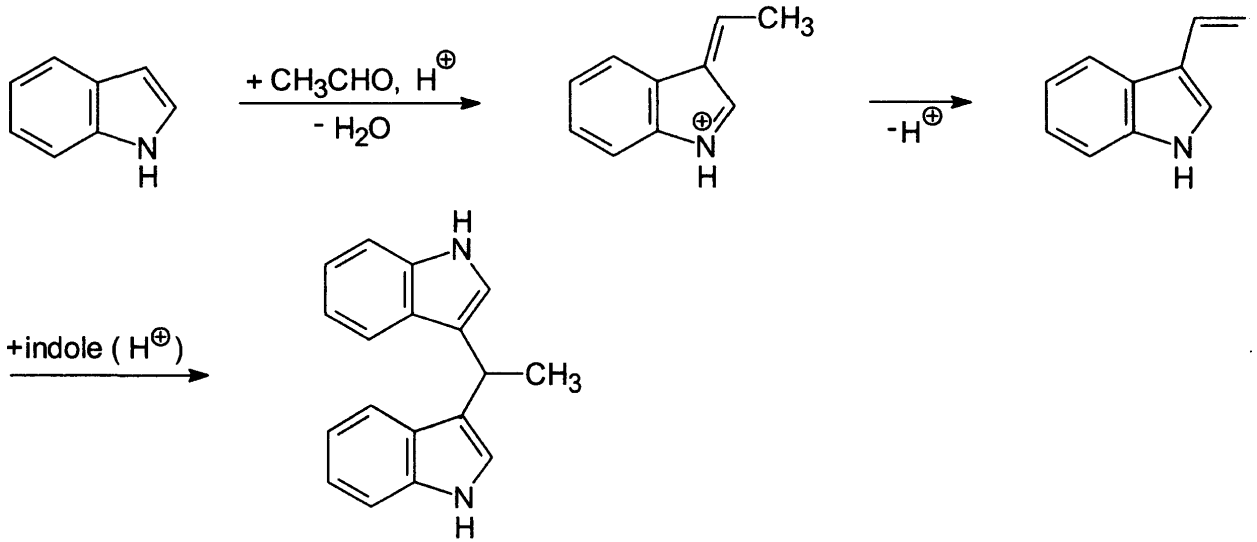
As is the case with pyrroles, *C*-alkylation of indoles results in mixtures of products. Formylation and acylation occur more readily. The VILSMEIER-HAACK reaction furnishes indole-3- carbaldehyde; heating with acetic anhydride produces 3-acetylindole.

In the HOUBEN-HOESCH acylation, substitution takes place in the 3-position.

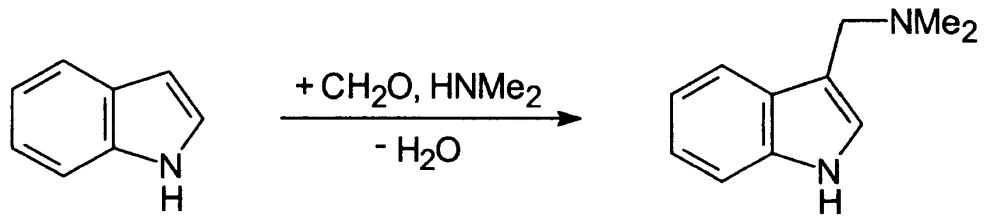
Although indoles are less reactive than pyrroles, they react with arenediazonium salts to give 3-(aryl-azo)indoles.

The reaction with carbonyl compounds proceeds in an analogous way in the presence of acids. For this reason, indoles unsubstituted in the 3-position give a positive color test with EHRLICH's reagent.

Indole and acetaldehyde react via an azafulvenium salt to give 3-vinylindole, which on further reaction with indole forms 1,1-di(indol-3-yl)ethane:



Another electrophilic substitution which indole undergoes with ease is aminoalkylation (MANNICH reaction). Indole, formaldehyde and dimethylamine in acetic acid interact with formation of the natural product gramine [(3-dimethylaminomethyl)indole], which has been isolated from grasses (earlier gramineae; now poaceae):



Electrophilic substitutions on nitrogen

The salt-like alkali metal compounds of indole react with electrophiles such as haloalkanes, acyl halides, sulfonyl halides and trimethylchlorosilane to form the corresponding 1-substituted indoles.

1-Benzylindole isomerizes to 2-benzylindole when heated in polyphosphoric acid.

1-Phenyl-sulfonylindole is lithiated in the 2-position by *n*-butyllithium.

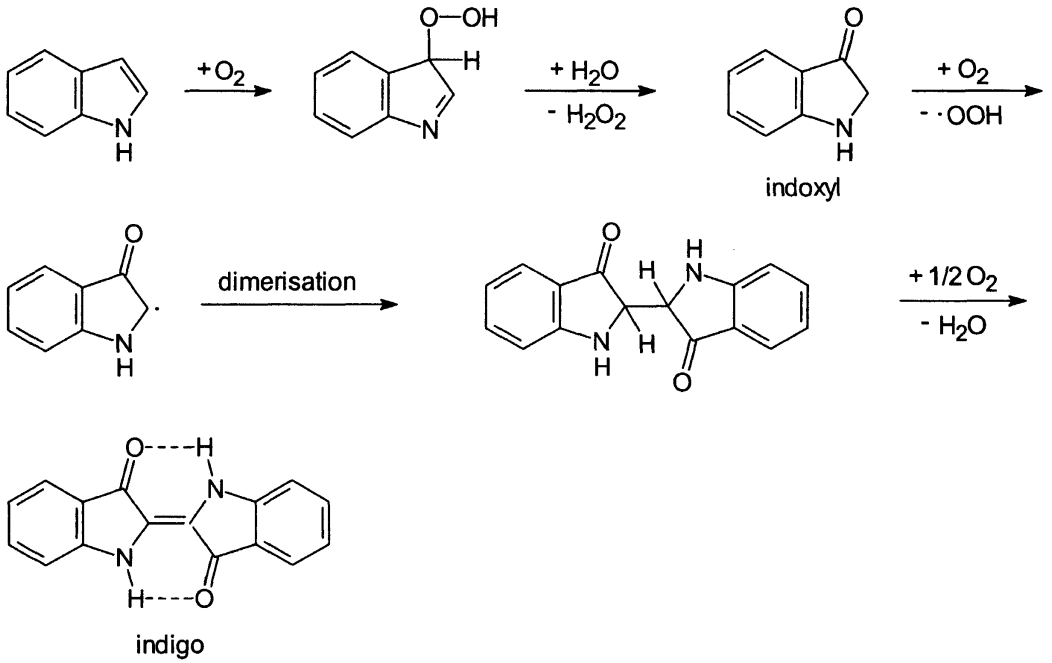
Subsequent alkylation with haloalkanes and cleavage of the phenylsulfonyl residue with sodium hydroxide yields 2-alkylindole.

The interaction of (indol-1-yl)magnesium halides and electrophilic reagents results mainly in 3-substituted indoles.

Addition reactions

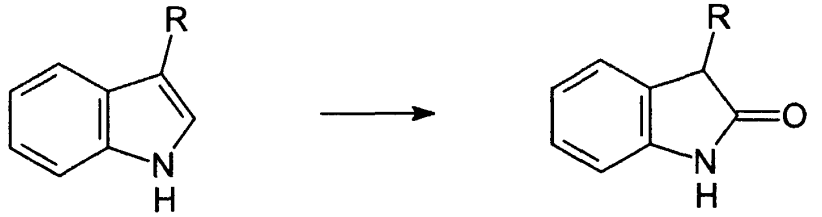
Catalytic hydrogenation of indoles under pressure and at elevated temperature leads to 2,3-dihydro-indoles (indolines). These compounds are also formed by the action of reducing agents (zinc and phosphoric acid or tin and hydrochloric acid) on indoles.

Indoles, like pyrroles, are easily oxidized. During autoxidation, the 3-position is attacked by oxygen leading to a hydroperoxide which gives rise to indol-3(2*H*)-one (indoxyl):



Indoxyl reacts further by radical coupling followed by oxidation to give indigo. Other oxidizing agents, as well as air, cause such reactions. On oxidation, indoles with substituents in the 3-position are converted into indol-2(3*H*)-ones (oxindoles):

Indoles show little inclination to undergo cycloadditions. The [2+1] cycloaddition with dichlorocarbene leads to mixtures of indole-3-carbaldehyde and 3-chloroquinoline.

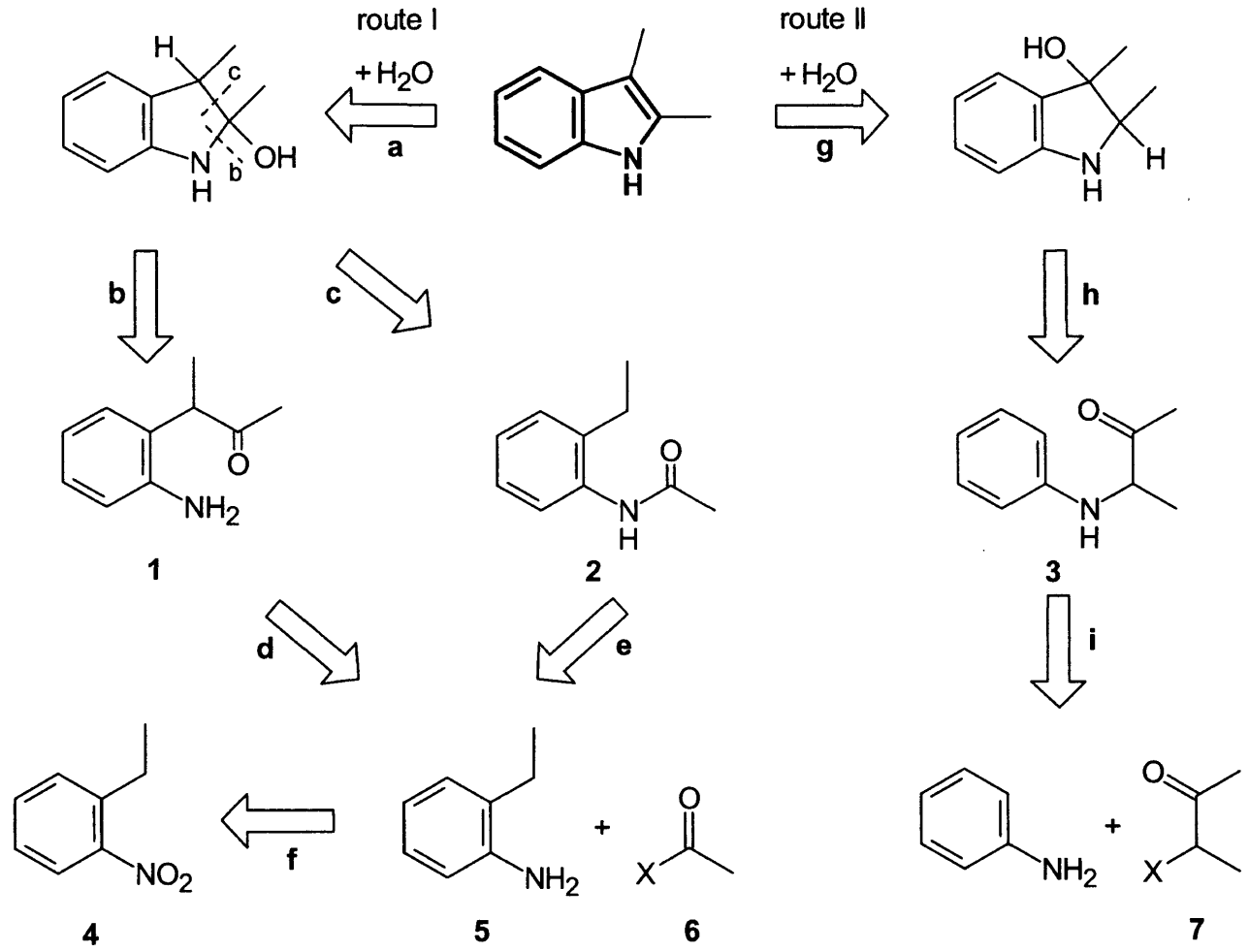


[C] For the retrosynthesis of indole, two routes (**I**/**II**) are proposed, as for pyrrole.

Route **I** suggests *o*-aminobenzyl ketone **1** or *o*-alkyl-*N*-acylaniline 2 as starting material on the basis of operations **a-c**. Their retroanalysis (**d**,**e**) in turn leads to 2-alkylaniline **5** and carboxylic acid derivative **6**.

Construction of the indole system should thus occur by *N*-or *C*-acylation of **5** (utilizing the *o*-nitrotoluene derivative **4**) followed by cyclodehydration of **1**/**2**.

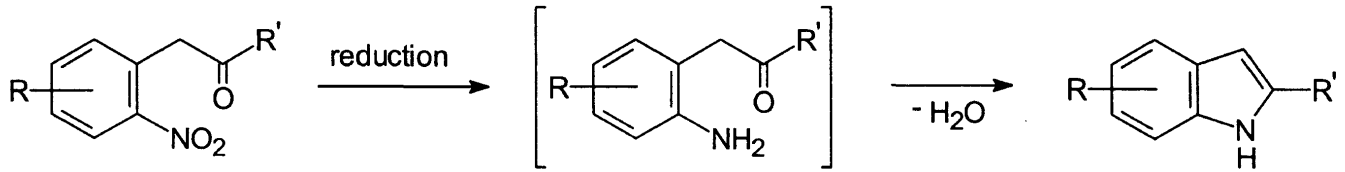
The alternative route **II**, based on retrosynthetic analysis **g**-**i**, leads to aniline via the α-(*N*-phenylamino)ketones **3** and to α-haloketones **7** as possible precursors for the indole synthesis.



Retrosynthetic analysis of indole

As predicted by retrosynthetic considerations, most indole syntheses start with aniline or 2-alkylanilines, upon which the heterocyclic part is constructed according to various methods.

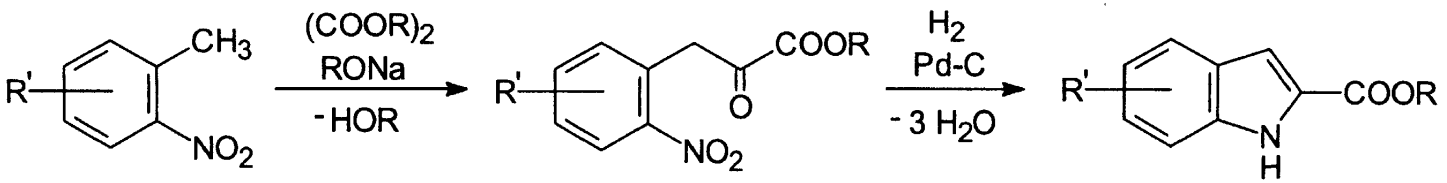
(1) The reductive cyclization of *o*-nitrobenzylcarbonyl compounds as shown for **8** serves above all for the preparation of 2-substituted indoles (Reissert synthesis).



8

In the classical version of this method, *o*-nitrophenylpyruvic acid **9**, obtained by a CLAISEN condensation of *o*-nitrotoluene with oxalic ester, is subjected to catalytic hydrogenation (H_2, Pd-C).

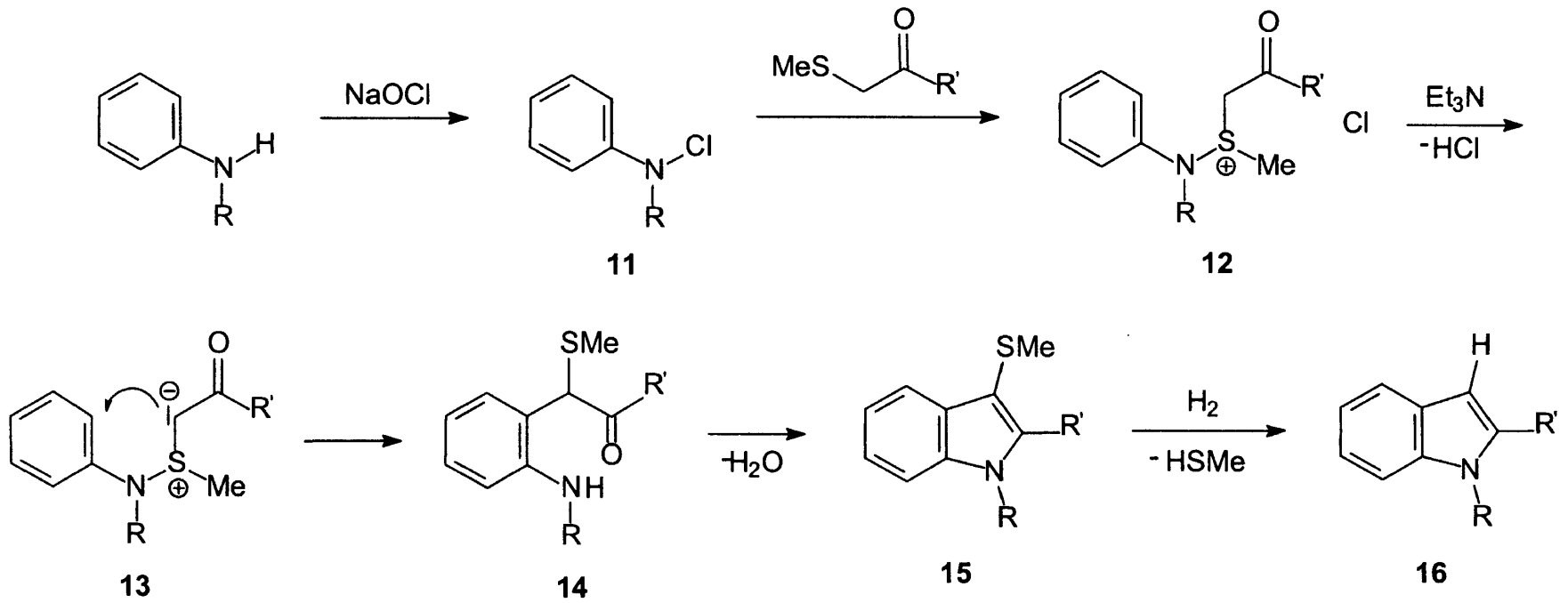
Reduction of the nitro group to an amino group is followed by a spontaneous cyclodehydration to give the indole-2-carboxylic ester **10**:



9 **10**

o-Aminobenzyl carbonyl compounds, which are essential for the cyclizing step of the REISSERT synthesis, are also formed from aniline via anilinosulfonium salts **12** by a remarkable reaction sequence.

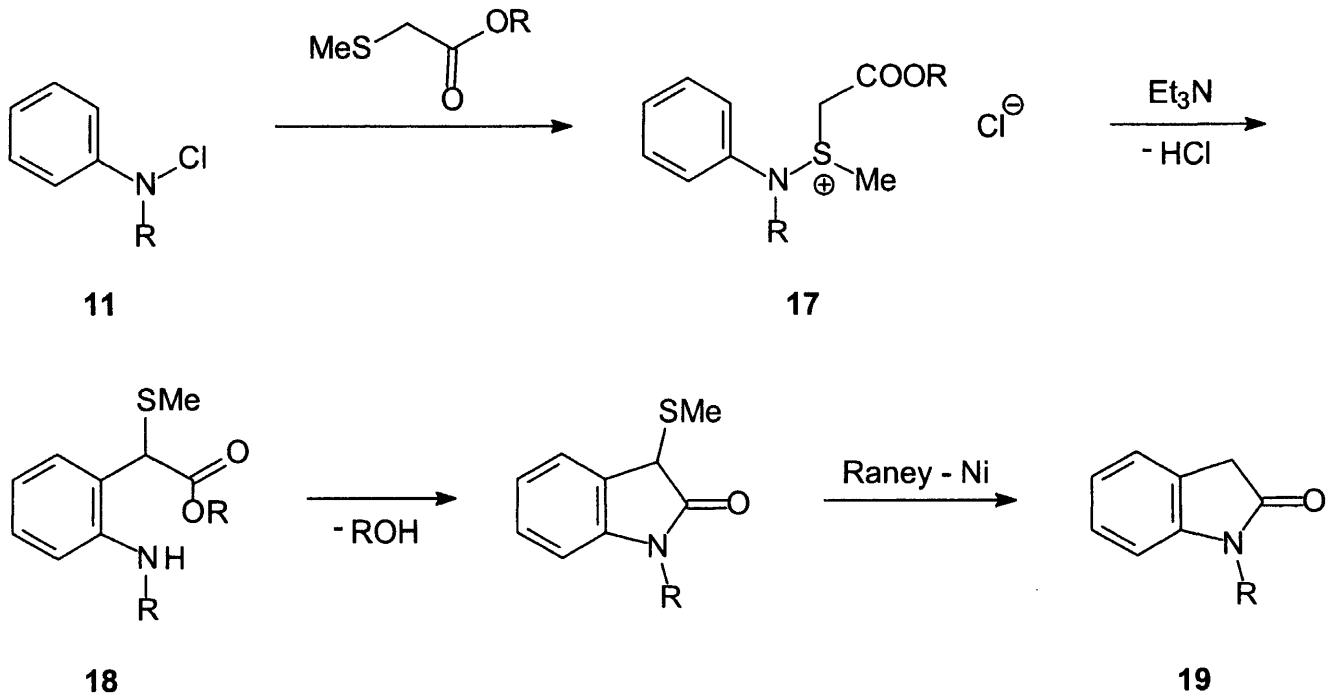
The latter are obtained from *N*-chloroanilines **11** and α-(methylsulfanyl)ketones; these react with bases to give 3-(methylsulfanyl)indoles **15**, which after a reductive cleavage of the SCH_3 group, furnish indoles **16** by hydrogenolysis (Gassmann synthesis):



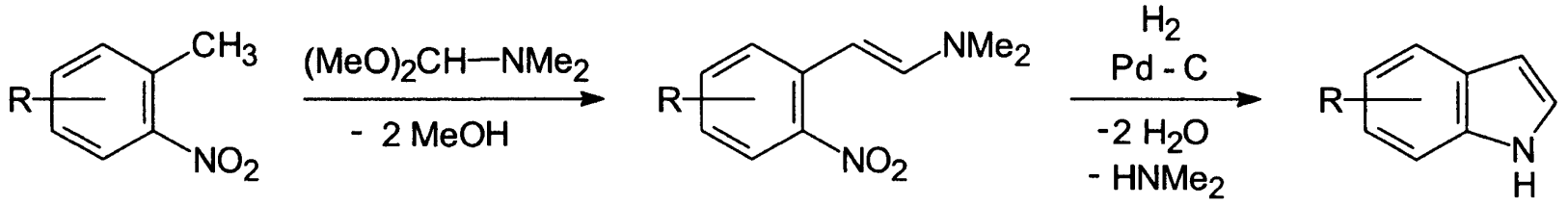
A SOMMELET-HAUSER rearrangement of the initially formed sulfonium ylide **13** is a key reaction step. This brings about the required *ortho*-linkage with the arene, which results in the formation of the *o*-aminobenzyl carbonyl compound **14**.

Anilinosulfonium compounds of type **17** can also be used to synthesize indol-2(3*H*)-ones **19** starting from *N*-chloroanilines and (methylsulfanyl)acetic ester.

The (*o*-aminophenyl)acetic esters **18** obtained via the *S*-ylide lead to indol-2(3*H*)-ones **19** after cyclization and reductive desulfurization.



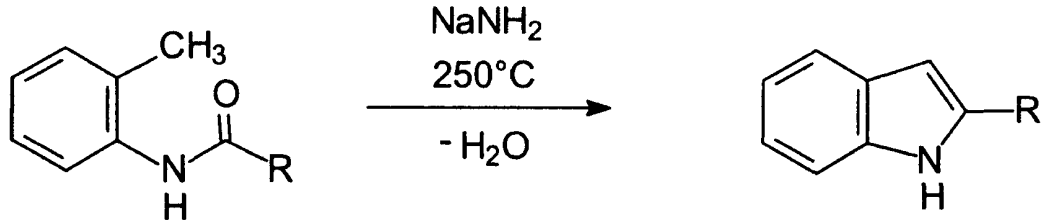
(2) 1-Dimethylamino-2-(o-nitrophenyl)ethenes **20**, obtained from *o*-nitrotoluene and *N*,*N*-dimethylformamide dimethyl acetal, yield indoles **21** on reductive cyclization of the corresponding *o*-aminophenyl derivatives:



20 **21**

This method (*Batcho-Leimgruber synthesis*) is particularly suitable for the synthesis of indoles substituted on the benzene ring but unsubstituted on the pyrrole moiety.

(3) *N*-Acyl-*o*-toluidines **22** can be cyclodehydrated by means of sodamide or *n*-butyllithium (*Madelung synthesis*). However, this method is essentially confined to the preparation of 2-alkylindoles because of the vigorous reaction conditions:

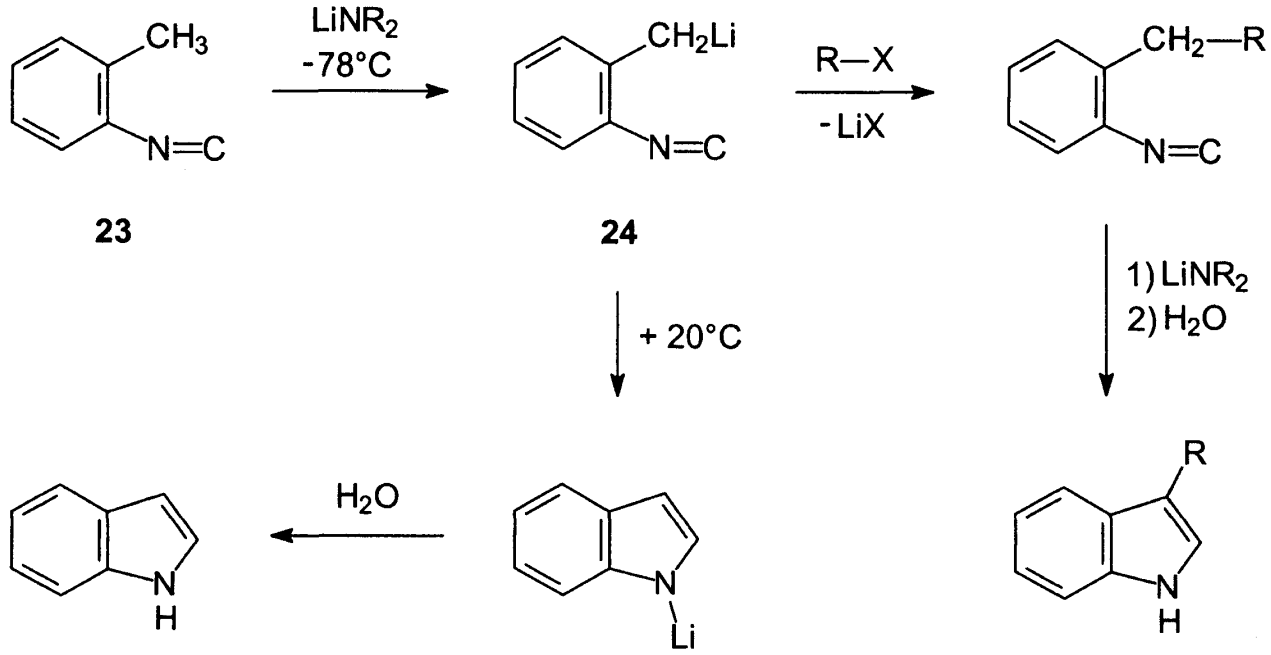


22

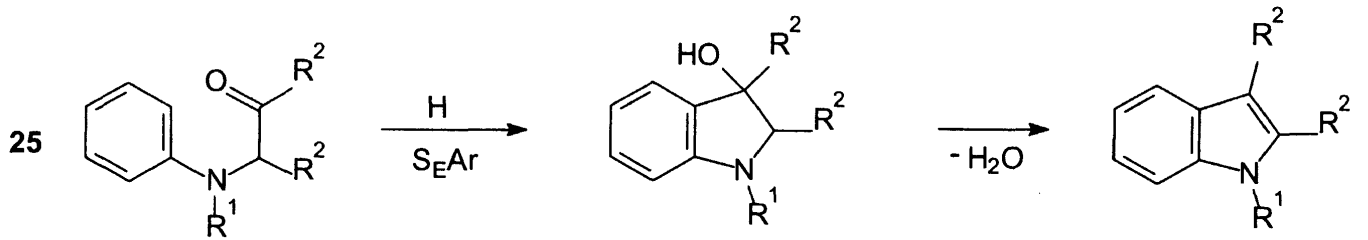
The cyclization necessitates deprotonation of the CH_3 group and its coupling with the acyl *C*-atom, but the mechanism has so far not been elucidated.

The indole formation from *o*-tolylisocyanide **23**, which is brought about by metallation with lithium dialkylamides, is related to the MADELUNG synthesis.

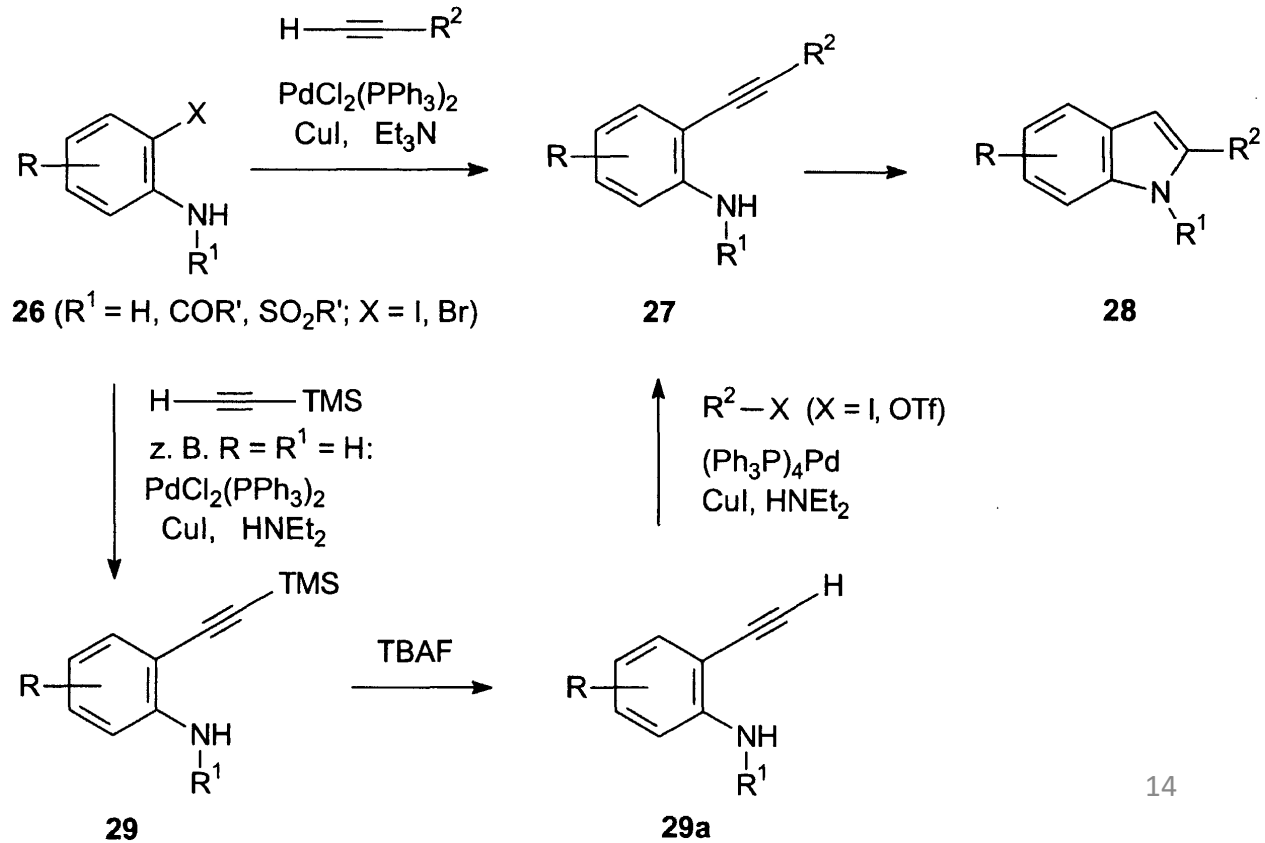
The lithium compound **24** can undergo cyclization to form indole (via *N*-lithioindole) or, after alkylation and renewed metallation, to produce 2- substituted indoles:



(4) α-Arylamino ketones **25** are easily accessible from arylamines and α-halo ketones. They undergo an intramolecular S_EAr reaction under acid catalysis, which is followed by H_2O elimination to produce indoles (*Bischler synthesis*). The preparative value of this simple indole synthesis is limited to systems with the same C-2/C-3 substituents.



(5) (*o*-Alkynyl)arylamines and their *N*-acyl or *N*-sulfonyl derivatives **27** are cyclized to the corresponding indoles **28** by treatment with (a) TBAF, (b) Pd (and Cu) complexes:

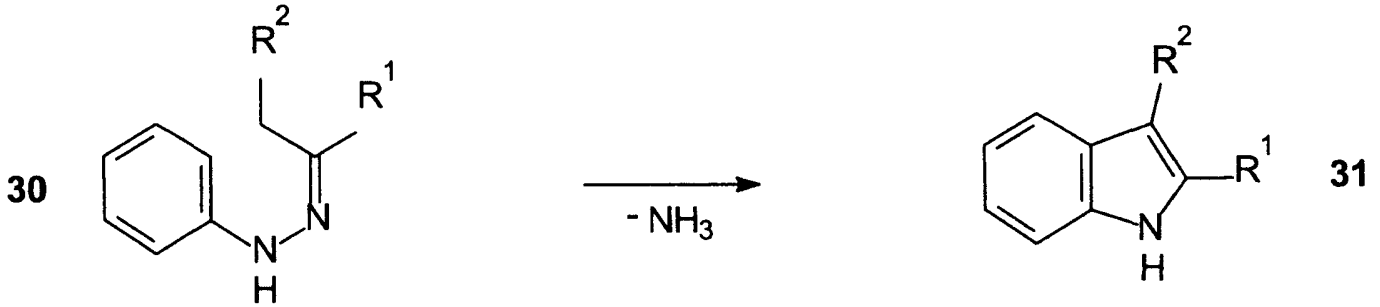


In (b), the organopalladium intermediate can be trapped either by protonation to give 2-substituted indoles **28** or by alkylation with R^3-X leading to introduction of an additional substituted R^3 in the 3-position of the indoles 28.

The (*o*-aminoaryl)acetylenes **27** are easily accessible by Pd-mediated SONOGASHIRA cross coupling reactions of (*o*-halogeno)aniline derivatives *26* (X preferably I) with terminal acetylenes. Alternatively, **27** is prepared by SONOGASHIRA coupling of **26** with TMS-acetylene (to give **29**), desilylation of **29** and base-induced alkylation at the free acetylene terminus (**29** → **29a** → **27**).

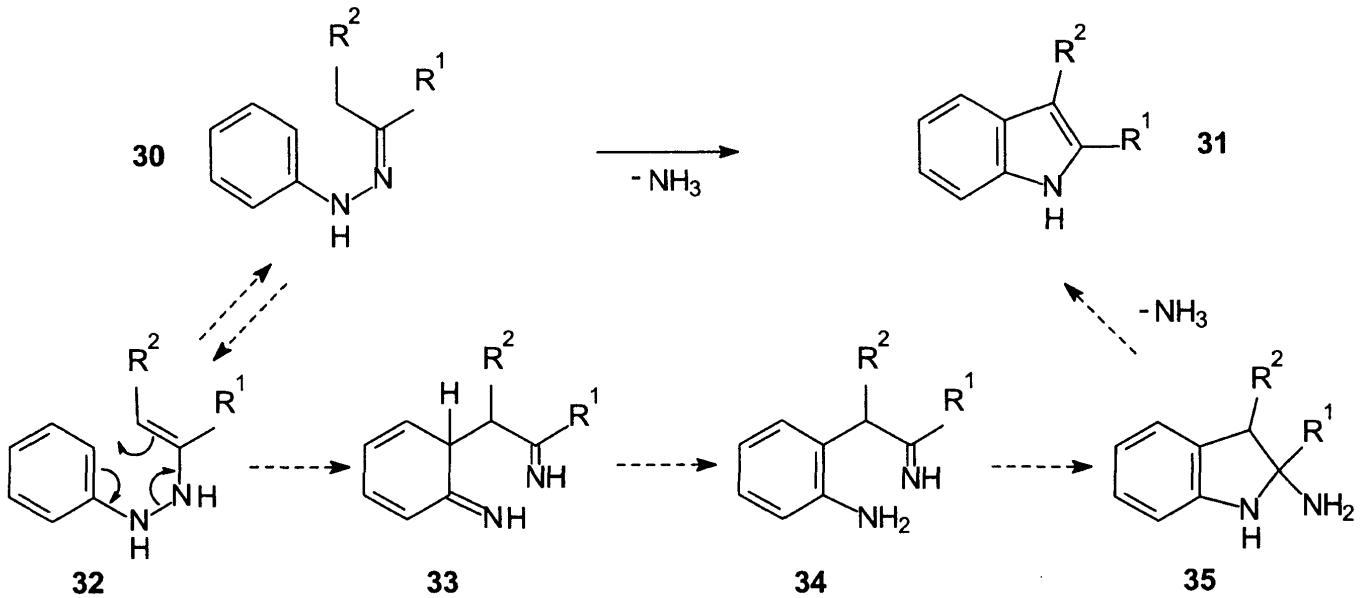
The potentiality of this method for indole synthesis is demonstrated by solid-phase versions utilizing polymer-bound (*o*-halogeno)anilines and their transformation according to the sequence **26** → **27** → **28**.

(6) *N*-Arylhydrazones, derived from enolizable aldehydes or ketones **30**, are converted into indoles **31** under LEWIS ($ZnCl_2$, BF_3) or BRÖNSTED acid (H_2SO_4, polyphosphoric acid, CH_3COOH, HCl in ethanol) catalysis with loss of ammonia (Fischer synthesis, E. FISCHER 1883):



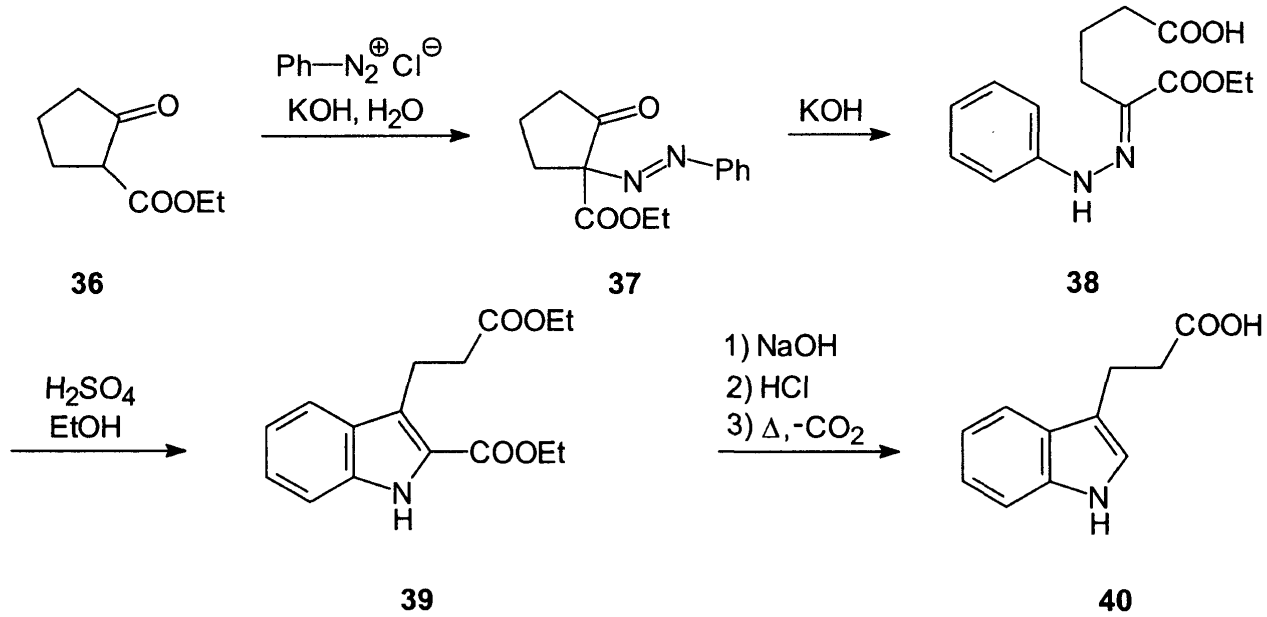
The mechanism of this indole synthesis, which has wide application and is of great general importance, has been the subject of intensive studies. It was shown that the hydrazone **30** first tautomerizes to an enehydrazine **32** which, by a [3,3] sigmatropic rearrangement, establishes a C-C bond in the *ortho*-position of the arene (diaza-COPE rearrangement).

The resulting bisimine **33** is converted into 2-amino-2,3-dihydroindole **35** via the intermediate **34**, and finally cyclizes to give indole **31** with elimination of NH_3. Experiments with ^{15}N isotopes prove that the nitrogen attached to the arene of **30** is retained in the indole.



The phenylhydrazones required for the FISCHER synthesis are prepared from carbonyl compounds and phenylhydrazine. Alternatively, they can be obtained by a JAPP-KLINGEMANN reaction from CH-acidic compounds (β-diketones, β-keto esters, etc.) or from enamines by interaction with aryldiazonium salts.

More complex indoles are thus accessible by a simple route. This is demonstrated by the synthesis of 3-(indol-3-yl)propionic acid **40**, the starting material of WOODWARD'S lysergic acid synthesis.

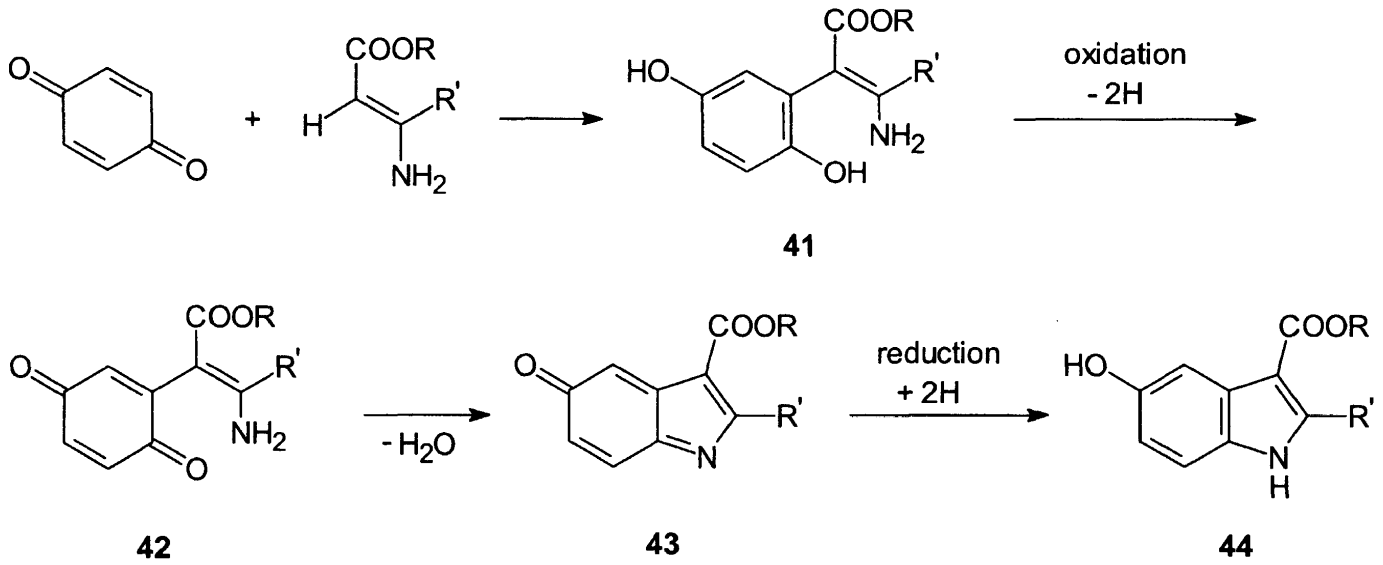


The 2-oxocyclopentane-1-carboxylic ester **36** is coupled with benzenediazonium chloride in a basic medium with simultaneous acid cleavage of the product **37**.

The resulting phenylhydrazone of the α-oxo adipic ester **38** is cyclized by H_2SO_4 in ethanol to give the indole derivative **39.** Saponification and selective decarboxylation yield the indole **4**0.

(7) Only a few indole syntheses make use of building blocks in which the *N*-atom is not directly bonded to an arene. The *Nenitzescu synthesis* is of this type.

In this synthesis, 1,4-quinones are condensed with 3-aminoacrylic esters to give 5-hydroxyindole-3-carboxylic esters **44**. The mechanism of this synthesis has not been completely clarified. It includes a MICHAEL addition (→ 41) and a cyclodehydration (42 → 43) as well as a redox transformation (41 → 42 and 43 → 44):

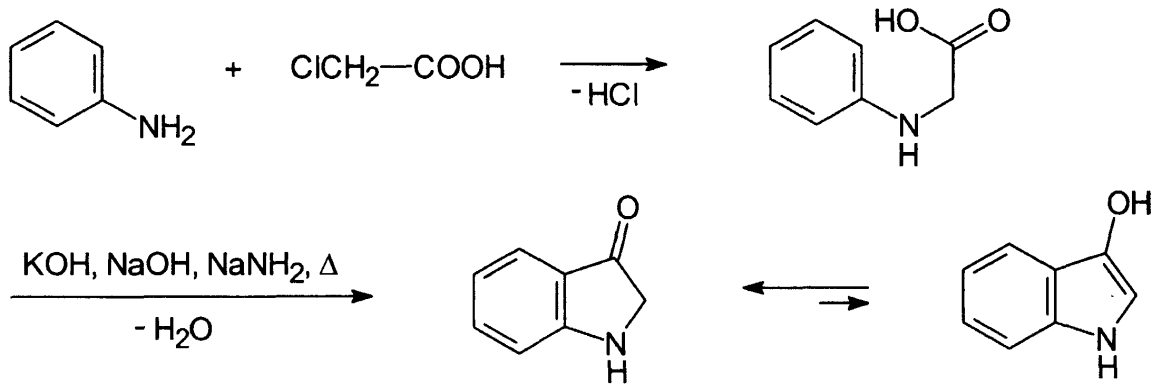


[D] Indole is a colorless solid forming leaflet crystals, moderately soluble in water, of mp 52 °C and bp 253 °C. It occurs in coal tar and jasmine oil.

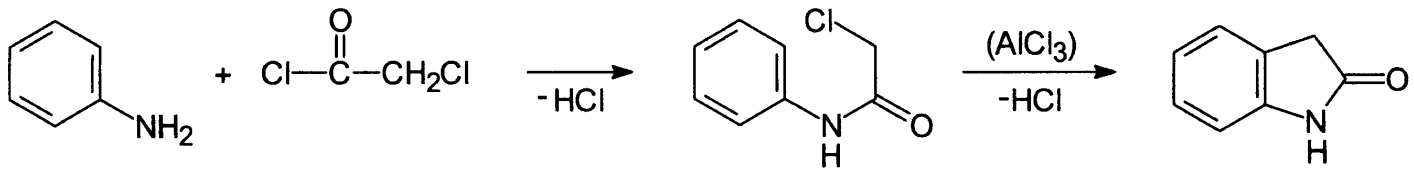
Indole has an unpleasant faecal-like odor, but in high dilution has a pleasantly flowery aroma. It was found recently that indole is one of the compounds responsible for the smell of flowering rape fields.

Indole-3(2*H*)-one (indoxyl), bright yellow crystals, mp 85 °C, is manufactured by a process developed by HEUMANN and PFLEGER (1890, 1898). Aniline and chloroacetic acid yield (phenylamino)acetic acid. On melting with KOH/NaOH/$NaNH_2$, its potassium salt cyclizes to indoxyl.

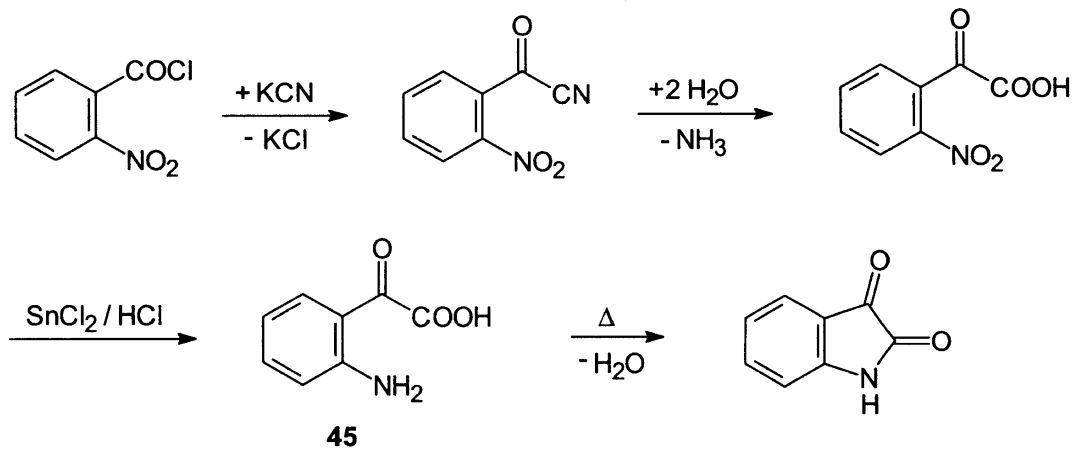
This reaction is the basis of the manufacture of indigo dye, which is produced by aerial oxidation of indoxyl. Indoxyl is present predominantly in its keto form.



Indole-2(3*H*)-one (oxindole), colorless needle-like crystals, mp 127 °C, is made from aniline and chloroacetyl chloride as follows:



Indole-2,3-dione (isatin), red crystals, mp 204 °C, is formed by the oxidation of indigo with nitric acid. It can be synthesized from *o*-nitrobenzoyl chloride via isatinic acid **45**:



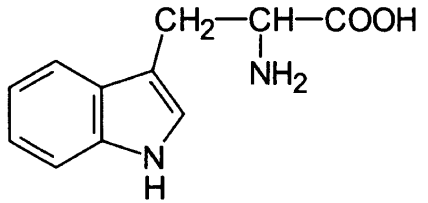
45

A considerable number of natural products are derived from indole. Of greatest importance is the essential amino acid tryptophan **46**, a constituent of many proteins.

Enzymatic conversion of tryptophan in living organisms produces additional natural products, e.g. serotonin (5-hydroxytryptamine) **47** by hydroxylation and decarboxylation.

It occurs in the serum of warm-blooded animals as a vasoconstrictor, it is one of the agents responsible for maintaining vascular tone.

Moreover, it acts as a neurotransmitter, i.e. it is essential for conducting impulses between nerve cells.



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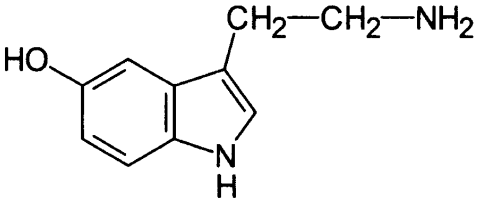
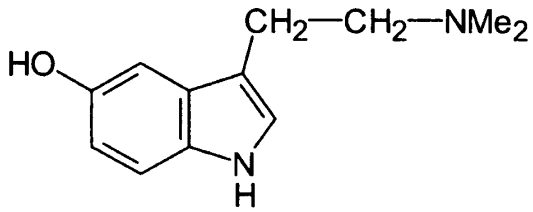


47

Bufotenin **48**, a poison occurring in the skin of toads, causes a rise in blood pressure and paralyses the spinal and cerebral motor centres.

Psilocin **49**, the psychoactive substance in the Mexican mushroom Teonanacatl, increases excitability and causes hallucinations:



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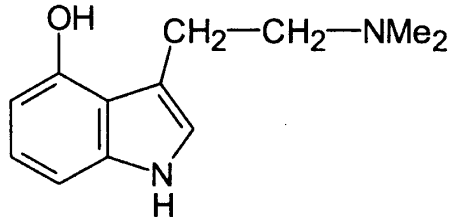
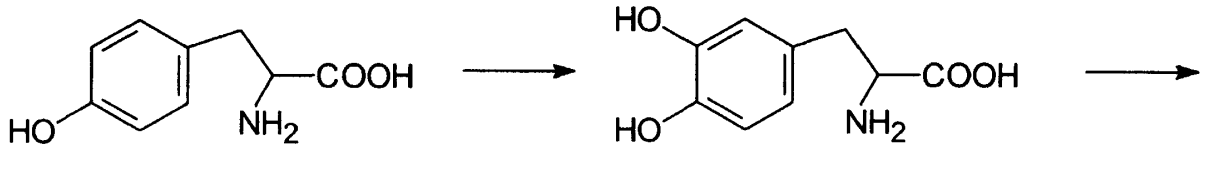
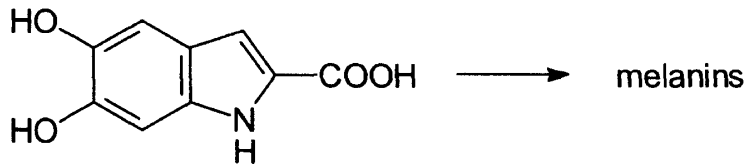


49

Melanin, the black and brown hair and skin pigment in humans and animals, also contains indole units, in particular 5,6-dihydroxyindole. It is derived from the amino acid tyrosine via DOPA (3,4-dihydroxyphenylalanine):

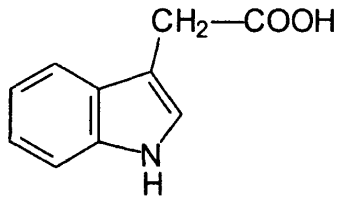




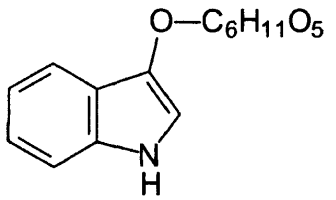
Melanins are produced by specialized cells, the melanocytes. An accumulation of these cells causes moles. If these cells become malignant, a melanoma develops, a type of skin cancer which requires immediate surgery.

The class of indole alkaloids is so large that only a few of those that are physiologically active and pharmacologically important natural products can be mentioned here, e.g. strychnine, brucine, yohimbine, reserpine, vincamine, ergotamine and lysergic acid. Some antibiotics are also derived from indole.

Indole-3-acetic acid **50**, also known as heteroauxin, is a phytohormone. It is mainly formed in buds, seeds and in young blossoms and is a plant growth regulator.



50

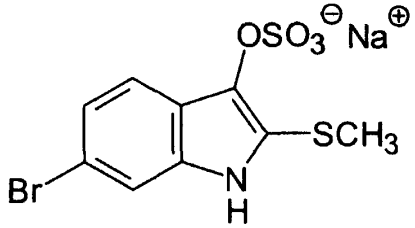


51

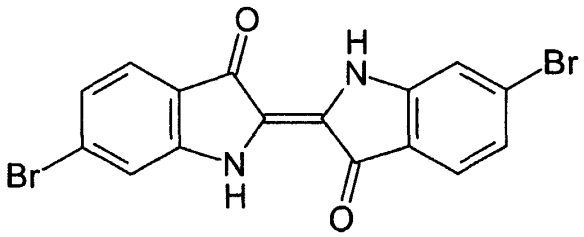
Indican **51**, the β-glucoside of the enol form of indoxyl, occurs in indigo plants (*Indigofera tinctorid*) and in wood (*Isatis tinctorid*). During the extraction of the crushed plant with water, indican is hydrolyzed to give indoxyl and glucose by the action of the enzyme indoxylase, which is also present in these plants.

From antiquity until about 1890, the extraction of indigo from plants was based on this reaction and subsequent aerial oxidation. Thereafter, synthetically produced indigo came to dominate the market.

Among indole compounds occurring in sea organisms, tyrindolsulfate **52** must be mentioned. It occurs in molluscs of the type murex, purpura and dicathais, which are mainly found in the Mediterranean. The tyrian purple of antiquity (6,6'-dibromoindigo **53**) was extracted from these animals:

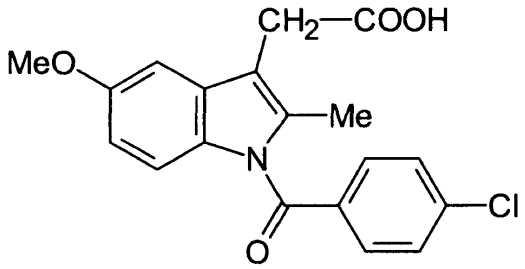


52

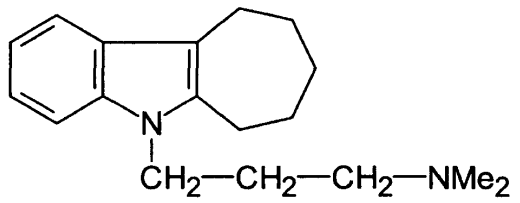


53

The indole ring system forms the basis of several pharmaceuticals, for instance the anti-inflammatory indomethacin **54** and the antidepressant iprindole **55**:

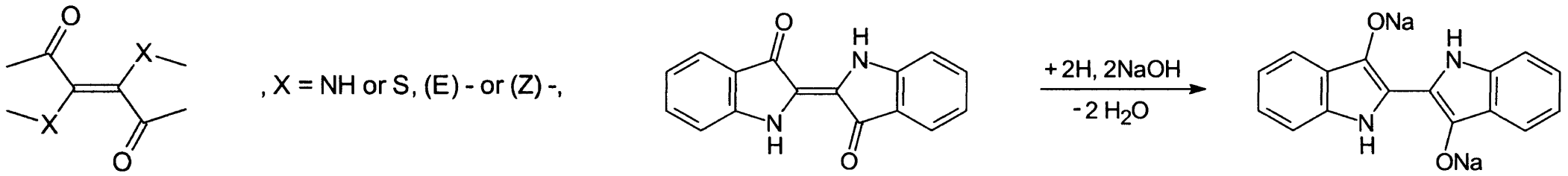


54



55

Indigo and other dyes which contain the chromophore **56** are known as indigoid dyes, and are vat dyes. These water-insoluble compounds are reduced by sodium dithionite and sodium hydroxide and applied as vat dyes, whereby they become soluble as disodium dihydro compounds, e.g.:



56

Before the availability of sodium dithionite (1871), the reduction of indigo was brought about by bacteria with reducing properties (fermentation vat).

The vat of indigo has a brown-yellow color. The cloth is dipped in the vat and then exposed to air to allow reoxidation to indigo which is precipitated and finely distributed onto the fiber. A consequence of this process is the low rubbing fastness of the dyes. It causes the faded appearance of indigo-dyed jeans and makes possible the manufacture of 'faded jeans'.

Since the seventies, indole compounds have lost their importance as textile dyes. They have, however, found application in other fields, e.g. in polaroid photography.