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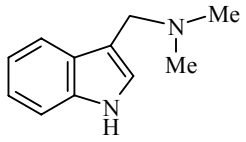
# METHODS FOR THE SYNTHESIS OF ISOGRAMINES AND THEIR CHEMICAL PROPERTIES. (REVIEW)

**B. B. Semenov[1] and M. A. Yurovskaya[2]**

*Published data on methods for the synthesis of indole derivatives (isogramines) containing a dimethylamino group at positions 1, 2 and also at various positions of the benzene ring in the indole bicycle and their chemical properties are reviewed.*

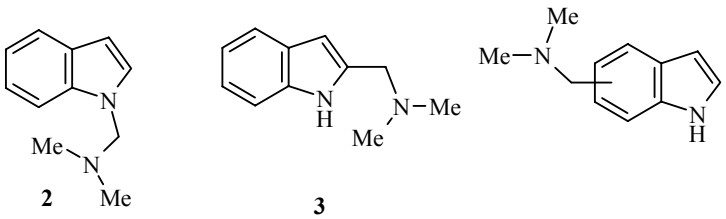
**Keywords:** benzo(dimethylamino)methylindole derivatives, 1-dimethylaminomethylindole, 2-dimethylaminomethylindole, synthesis, chemical properties, Mannich reaction.

Gramine (donaxine, 3-dimethylaminomethylindole) (**1**), one of the indole alkaloids present in the giant reed *Arundo donax*, native to Central Asia, is widely known. It was first isolated by A. P. Orekhov, and in 1935 Euler isolated gramine from certain forms of barley. In chemistry gramine acquired significance as an alkylating amine and a Mannich base, by means of which it was possible to introduce a skatyl residue preparatively into various organic compounds. Gramine has been synthesized by the Mannich reaction from indole, formaldehyde, and dimethylamine.



**1**

There is much less information in the literature on the isomeric derivatives of indole containing a dimethylaminomethyl group at other positions of the indole bicycle, for which we have used the general name of isogramine.



**2** **3**

Isogramines

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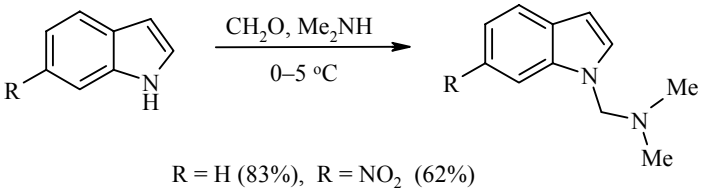
Although such compounds are of undoubted interest, no reviews have been published on their synthesis and chemical properties.

## 1. METHODS FOR THE SYNTHESIS OF ISOGRAMINES

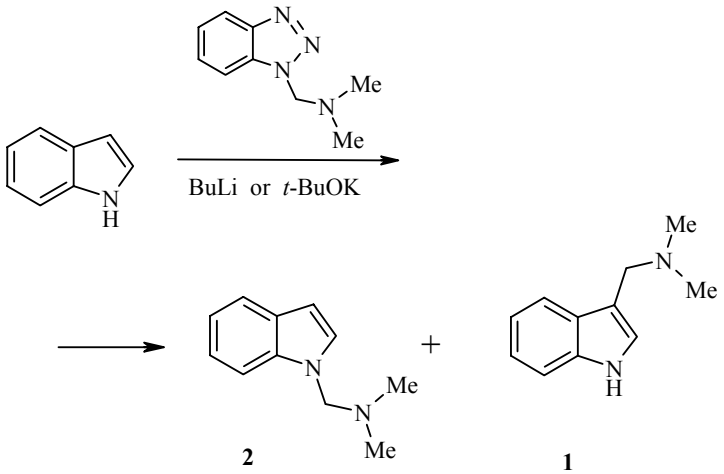
### 1.1. Synthesis of 1-Dimethylaminomethylindoles

One of the main methods of introducing a dimethylaminomethyl group into activated aromatic systems is Mannich aminomethylation. The first type of synthesis of isogramines is based on the electrophilic insertion of a dimethylaminomethyl group into the indole ring. However, it is well known that electrophilic substitution in indoles takes place mainly at position 3. In fact, for unsubstituted indole the Mannich reaction under standard conditions at 10-25 °C leads to the regioselective formation of gramine (with a yield of more than 90%) [1]. It was found that the reaction conditions have a substantial effect on the direction of the process. Thus, it is possible to obtain high yields of 1-dimethylaminomethylindoles by decreasing the reaction temperature to 0-5°C [2-4].

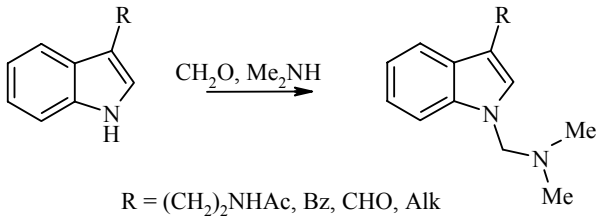



R = H (83%), R = $NO_2$ (62%)

In a number of cases aminomethylation in 1,3-unsubstituted indoles takes place nonselectively with the formation of a mixture of 1- and 3-dimethylaminomethyl derivatives. The use of 1-dimethylaminomethylbenzotriazole in the presence of strong bases (BuLi or *t*-BuOK) as aminomethylating agent leads to the formation of isomeric aminomethylindoles [5]. With *t*-BuOK isogramine (**2**) is mostly formed, the yield of the mixture of isomers amounts to 96%, and the ratio of the isomers **2**:**1** is 89:11.

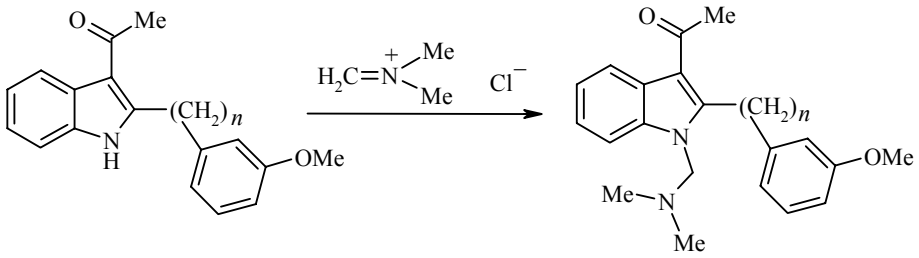



With 3-substituted indoles as substrates the Mannich reaction naturally takes place at position 1 [6-9].



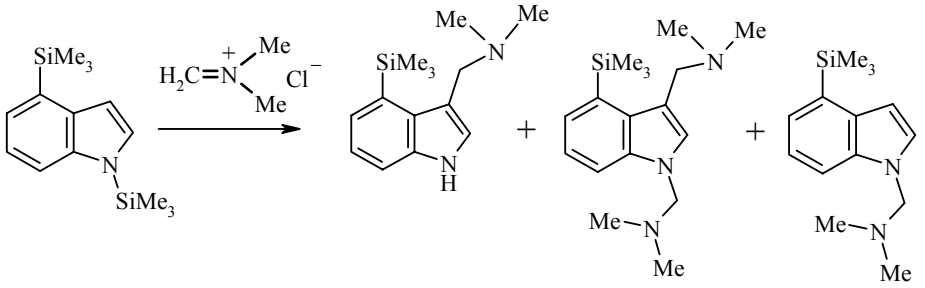

R = $(CH_2)_2NHAc$, Bz, CHO, Alk

The dimethylaminomethylation of 2,3-disubstituted indoles by the action of the crystalline Mannich reagent dimethylmethyleneammonium chloride takes place smoothly and with good yields at position 1 [10].

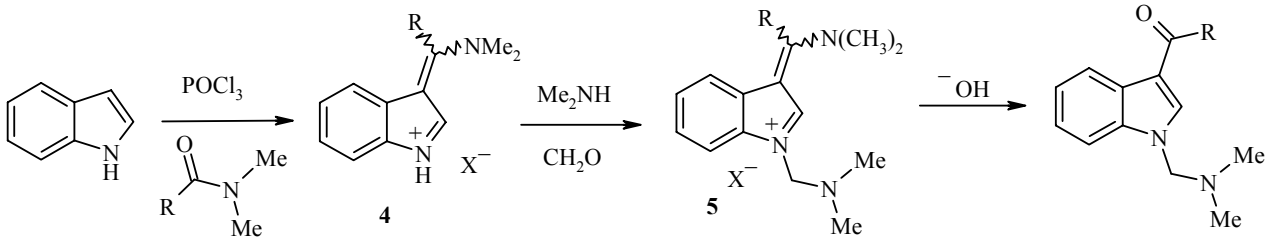



*n* = 1 (92%), *n* = 2 (88%), *n* = 3 (90%)

With a readily eliminated group such as N-trimethylsilyl at the indole nitrogen atom dimethylaminomethylation takes place selectively with the formation of a mixture of 1- and 3-aminomethyl and 1,3-diaminomethyl derivatives [11].



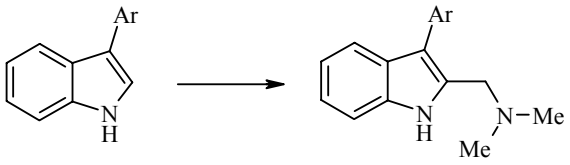

An original one-pot method for the synthesis of 3-acyl-1-dimethylaminomethylindoles requires successive Vilsmeier and Mannich reactions without isolation of the intermediates **4** and **5** [12].



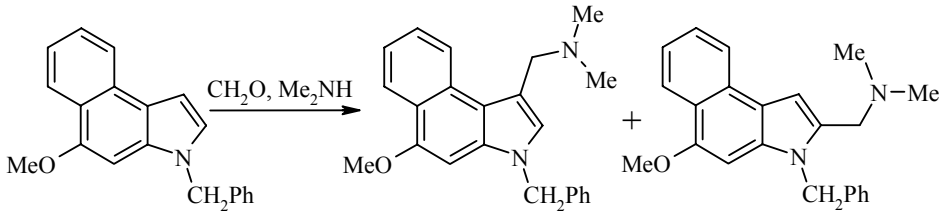

R = Alk

### 1.2. Synthesis of 2-Dimethylaminomethylindoles

A much more complicated problem is presented by the synthesis of 2-dimethylaminomethylindoles, since cases of direct electrophilic substitution in indoles at position 2 are extremely rare and require a specific structure for the indole substrates. Thus, for example, it was possible to realize 2-dimethylaminomethylation in 3-arylindoles [13].



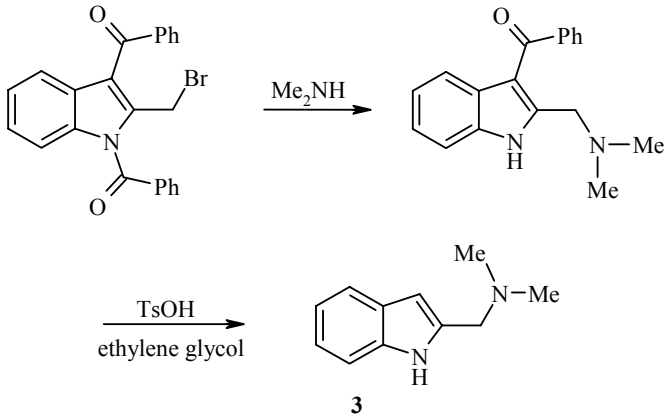

Another example is the nonregioselective aminomethylation of 1,5-disubstituted benzo[4,5]indoles, in which the 2-isomer is formed in mixture with the corresponding 3-dimethylaminomethyl derivative [14].




5 : 3

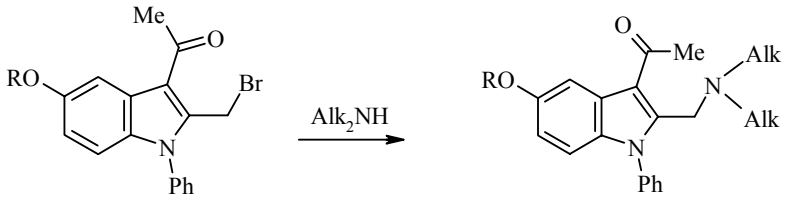
This situation motivated the development of methods for the synthesis of 2-isogramines without direct aminomethylation. These methods can be divided into two groups: The first includes the modification of various functionally substituted derivatives of indole, and the second involves the formation of the indole ring from fragments containing a dimethylaminomethyl group in active or latent form.

Methods of the first group include, for example, nucleophilic substitution of the halogen atom in 2-halogenomethylindoles. Thus, the action of aqueous dimethylamine on 2-bromomethyl-1,3-dibenzoylindole leads to the initial formation of 3-benzoyl-2-dimethylaminomethylindole, the debenzoylation of which with *p*-toluenesulfonic acid in ethylene glycol gives unsubstituted 2-isogramine [15].



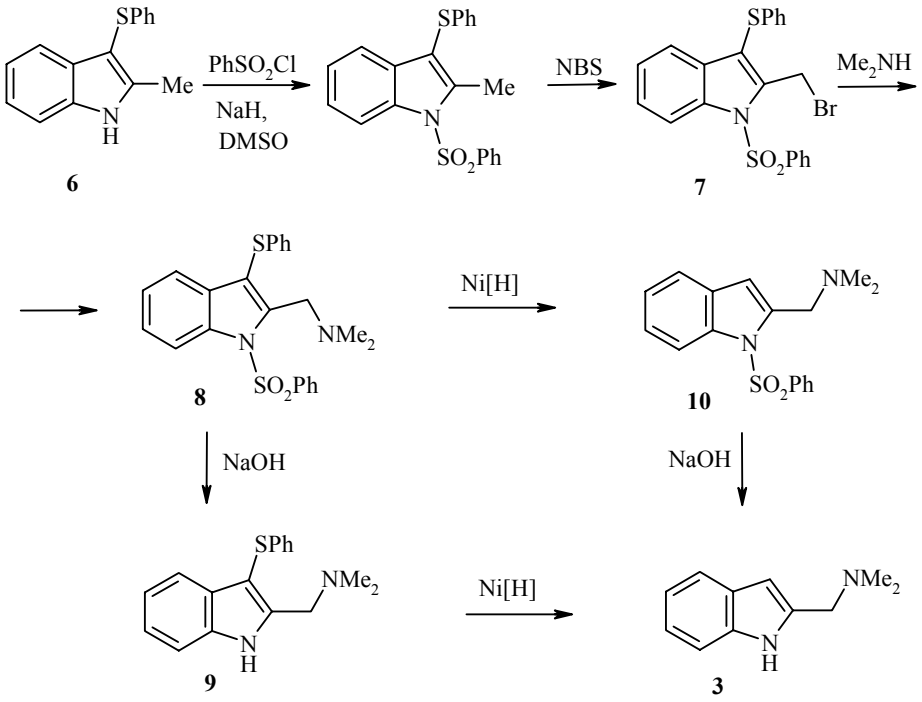

**3**

The corresponding 2-dialkylaminomethyl derivatives were obtained by the analogous reaction of substituted 2-bromomethylindoles with dimethylamine [16-21] and diethylamine [22, 23].



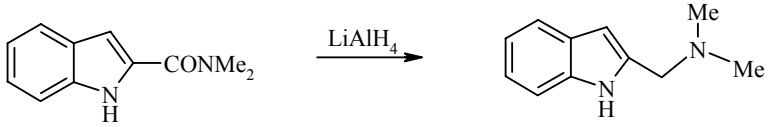

Alk = Me, Et; R = H, Ac

By this procedure it is possible to obtain unsubstituted 2-isogramine (**3**) from 2-methyl-3-phenylthioindole (**6**) using the following sequence of transformations [16]:

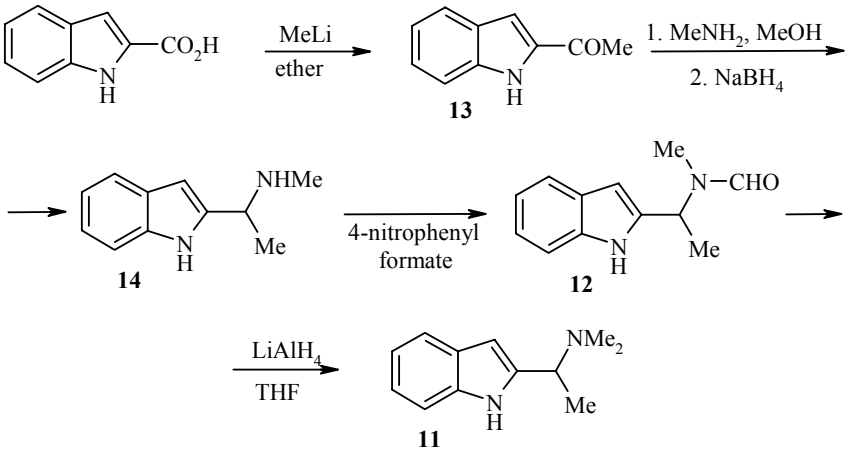



An activating phenylsulfonyl group is introduced at the nitrogen atom in 2-methyl-3-phenylthioindole. The 2-methyl group is then brominated radically with N-bromosuccinimide in the presence of catalytic amounts of benzoyl peroxide, and the 2-bromomethyl derivative **7** undergoes nucleophilic substitution of the halogen atom by an amino group. Further transformations can be carried out in any order: Hydrolytic removal of the phenylsulfonyl group followed by reductive desulfurization (**8** to **9** and then to **3**) and *vice versa* (**8** to **10** and then to **3**).

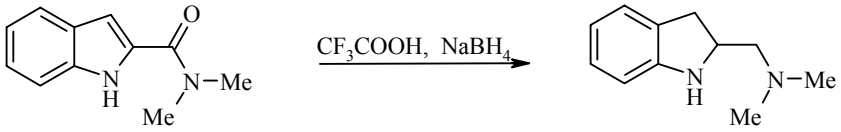
Reduction of the readily obtainable dimethylamides of indole-2-carboxylic acids with lithium aluminum hydride also provides a convenient method for the synthesis of 2-dimethylaminomethylindoles [24-31].



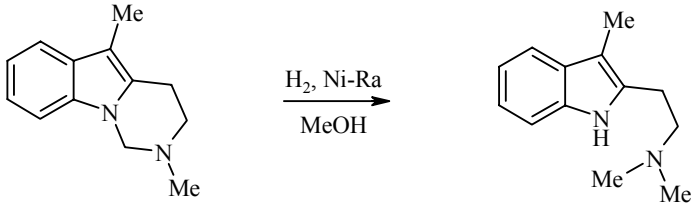

Reduction of the formyl derivative **12**, obtained in turn by successive transformation of indole-2-carboxylic acid into 2-acetylindole (**13**) with methyllithium, reductive amination to the amine **14**, and formylation [32], was also used at one of the stages in the production of the 2-isogramine analog 2-(1-dimethylaminoethyl)indole (**11**).



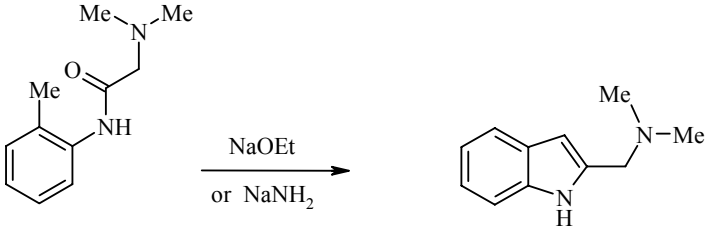

If sodium borohydride in trifluoroacetic acid is used as reducing agent the $C_{(2)}$–$C_{(3)}$ bond of the indole is reduced at the same time as the amide group [33]:



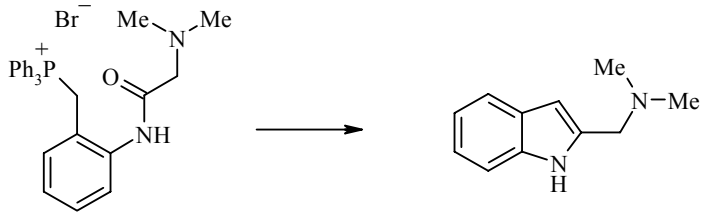

By reductive cleavage of the six-membered hydrogenated ring in the cyclic analog of 2-isogramine – 2,5-dimethyl-1,2,3,4-tetrahydropyrimido[3,4-*a*]indole – in the presence of Raney nickel in methanol it is possible to obtain 2-dimethylaminoethyl-3-methylindole [34].




As mentioned above, the second approach to the synthesis of 2-isogramine involves construction of the indole ring from acyclic fragments. Actually, 2-isogramine was first obtained by the Madelung method from N-(dimethylaminoacetyl)-*o*-toluidine in the presence of sodium ethoxide [35] or sodium amide [36].

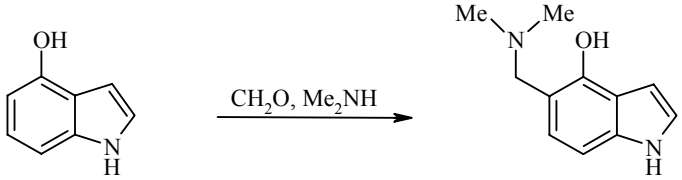



The activation of the *o*-methyl group in the aniline substrate often used in the Madelung reaction (with the corresponding triphenylphosphonium salt) also gave good results in the synthesis of 2-isogramine [37].

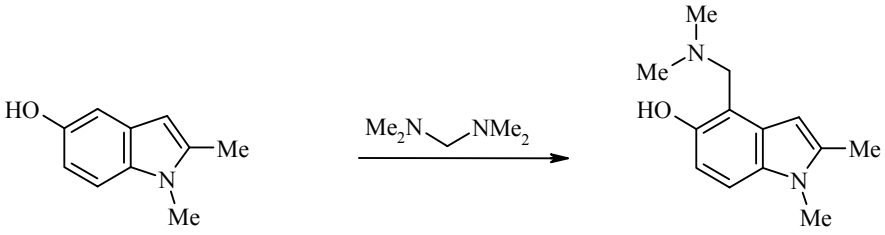


### 1.3. Synthesis of Indole Derivatives Containing a Dimethylaminomethyl Group in the Benzene Ring

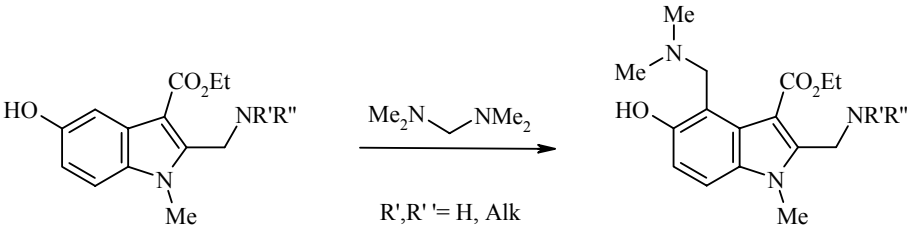
Direct electrophilic introduction of the dimethylaminomethyl group into the benzene ring of indoles is only possible in the presence of a strong activating donor group (such as a hydroxyl or methoxy group). In fact, for 4-hydroxyindole the Mannich reaction takes place at position 5 even if position 3 is free [38].



In principle the presence of an activating group at position 5 of the benzene ring creates two possibilities for regioorientation of entry of the dimethylamino group at the two *ortho* positions 4 or 6. As a rule, for 5-hydroxyindoles the Mannich reaction goes preferentially at position 4. Actually, in the absence of substituents at position 3, for example, aminomethylation with bisdimethylaminomethane goes regioselectively at position 4 with yields close to quantitative [39-41], which could apparently be determined by purely steric factors.

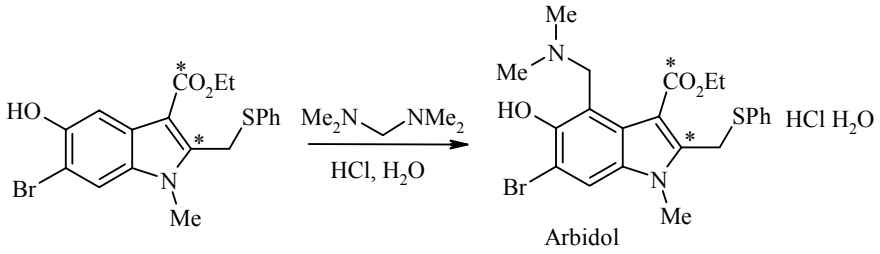


However, formation of the corresponding 4-isogramine (which has been proposed as an anti-inflammatory agent) was also noticed for the 3-substituted 5-hydroxyindole 3-acetyl-5-hydroxy-2-(sulfanylmethyl)indole, in spite of the presence of the acetyl group at position 3 [42]. Regioselective dimethylaminomethylation at position 4, including cases where position 6 was free, has also been observed for a series of 1,2,3-trisubstituted 5-hydroxyindoles [43-45].



At the same time there are data indicating that the reaction of certain 2,3-disubstituted 5-hydroxyindoles with bisdimethylaminomethane leads to simultaneous aminomethylation at positions 4 and 6 [20].

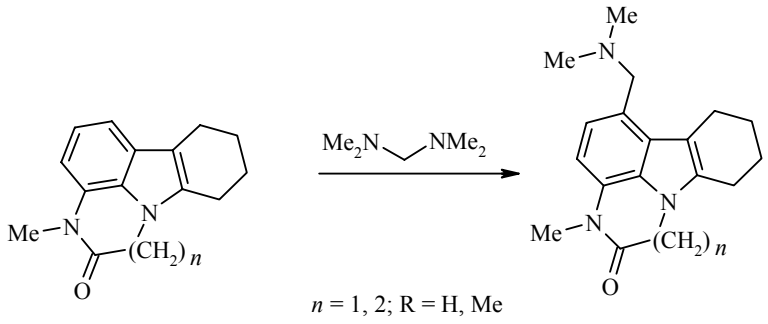
Of course, the only possibility for 1,2,3,6-tetrasubstituted [46-52] and 1,2,3,6,7-pentasubstituted [18] 5-hydroxyindoles is dimethylaminomethylation at position 4. This method was used for the synthesis of arbidol, labelled with $C^{14}$ at position 2 and at the ethoxycarbonyl group, in order to study its pharmacokinetics [53].



Arbidol

It should be noted that if there is a methoxy group instead of a hydroxyl group in the benzene ring dimethylaminomethylation with bisdimethylaminomethane in acetic acid takes place exclusively at position 6 [54].

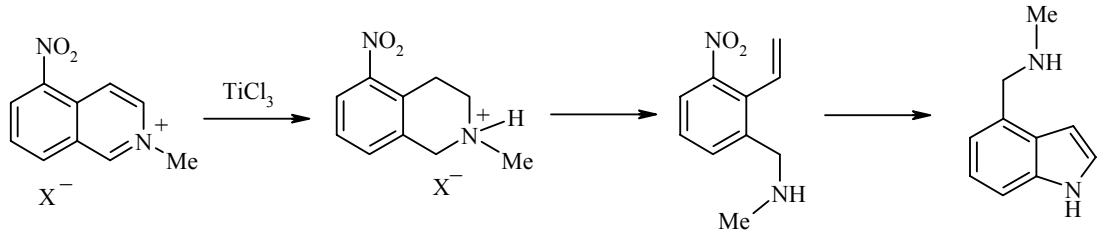
The 4-dimethylaminomethylation of certain tetracyclic derivatives of 1,2,3,4-tetrahydrocarbazole was proved by NMR with shift reagents and is not subject to any doubts [55].



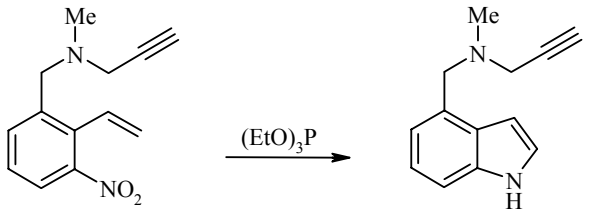
*n* = 1, 2; R = H, Me

Cases where 7-isogramines are formed from 5,6-disubstituted 4-hydroxyindoles [56] and 1,2,3-trisubstituted 6-hydroxyindoles [57] are known.

An example of the production of a 4-isogramine analog without the Mannich reaction is the elegant recyclization method for the transformation of 5-nitroisoquinoline methiodide or its hydrochloride into 4-methylaminomethylindole by the action of $TiCl_3$ [58-60]. This method includes reduction of the quaternized pyridine ring of the isoquinoline, Hoffmann cleavage with the formation of the corresponding *o*-nitrostyrene, and subsequent reductive cyclization of the latter. By modifying the experiment it was possible to produce macroquantities of these extremely difficultly obtainable indole derivatives.

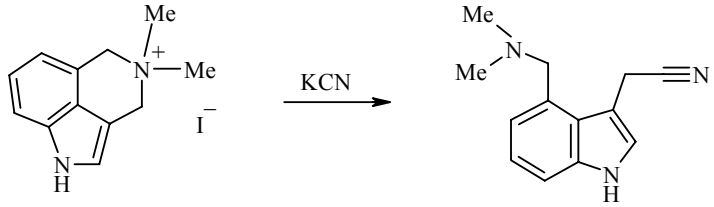


In the case of N-methyl-N-(2-propynyl)-N-(2-vinyl-3-nitrobenzyl)amine it was possible to realize cyclization of the analogous *o*-nitrostyrene with $(EtO)_3P$ and obtain an analog of 4-isogramine **15** with a propynyl group at the exocyclic nitrogen atom [61]:




**15**

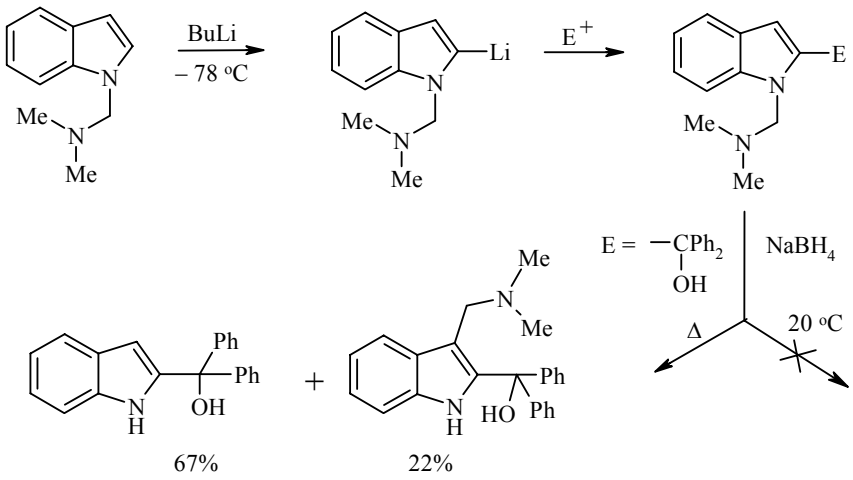
In another condensed derivative of isoquinoline – 4-methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]-isoquinoline – opening of the hydrogenated quaternized six-membered ring with KCN in DMF leads not only to the formation of 4-isogramine but also to functionalization at position 3 of the indole ring [61].




## THE CHEMICAL PROPERTIES OF ISOGRAMINES

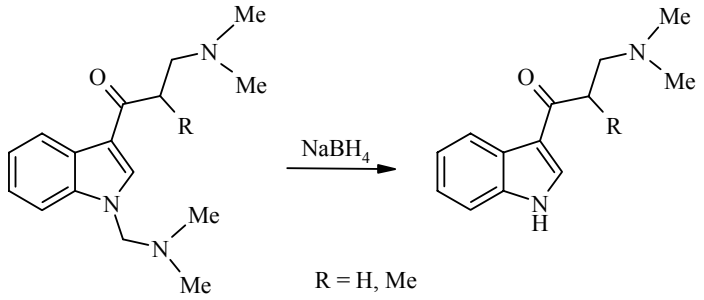
### 2.1. Metallation of 1-Isogramine

In contrast to electrophilic substitution reactions, which usually take place at position 3 in unsubstituted indoles, the lithiation of N-dimethylaminomethylindole makes it possible to insert the most diverse substituents at position 2 of the indole ring, which is of fundamental significance. Lithiation of 1-isogramine with BuLi in ether at -78°C leads to the 2-lithium derivative, which during treatment with various electrophiles (carbonyl compounds, alkyl halides, disulfides) gives the corresponding 2-substituted 1-isogramines with yields of 51-87% [2].



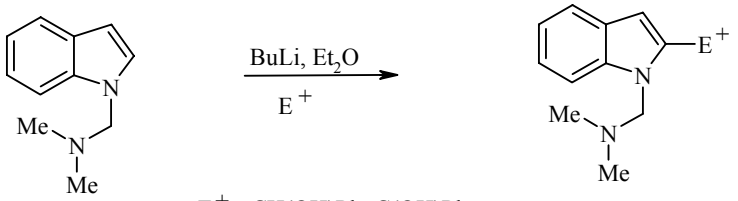
Of course, the possibility of removing the dimethylaminomethyl group by reduction substantially raises the synthetic importance of the method. Only in one case (with the presence of a diphenylhydroxymethyl group at position 2) was this process not completed under the influence of sodium borohydride and not accompanied by partial migration of the dimethylaminomethyl group to position 3.

The reaction also took place quite successfully for other 2-substituted 1-isogramines under the same conditions, and only small amounts of the rearrangement products were formed. One example is the successful removal of the dimethylaminomethyl group in 3-acyl-1-isogramines [62].



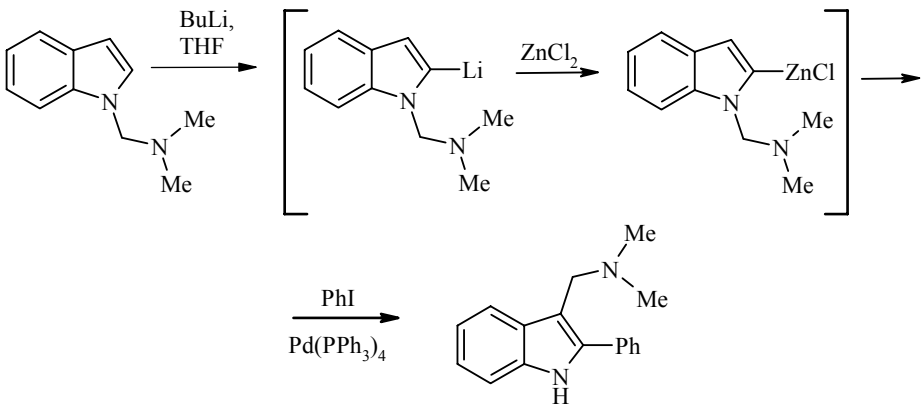

R = H, Me

The use of aldehydes and ketones as electrophilic agents in reaction with 2-lithio-1-isogramines leads to the smooth formation of the corresponding secondary and tertiary alcohols [63].



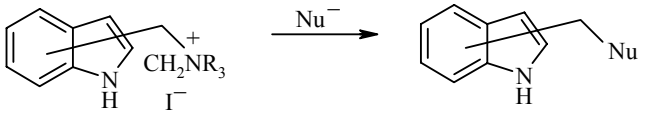

$E^+$ = CH(OH)Ph, $C(OH)Ph_2$

Transmetallation occurs when the 2-lithio derivative of N-isogramine is treated with $ZnCl_2$, and cross-coupling of the intermediately formed organozinc compound with iodobenzene catalyzed by $Pd(PPh_3)_4$ is accompanied by migration of the dimethylaminomethyl group to position 3 [64, 65].



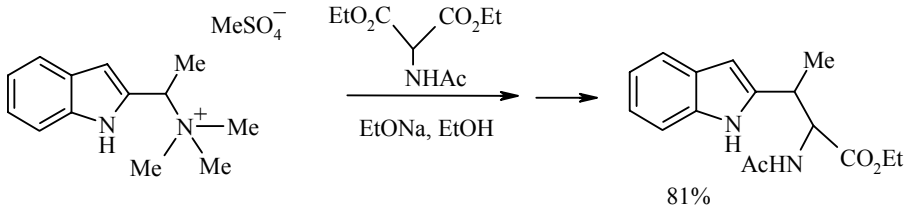
## 2.2. Reaction of Isogramines with Nucleophiles

Like gramine quaternized isogramines are capable of reacting with the most varied types of nucleophilic agents. First, quaternization of isogramines increases the positive charge at the methylene group linking the indole bicycle to the ammonium group. Second, it creates a good leaving group, i.e., the tertiary amine. Together, this leads to successful nucleophilic substitution.

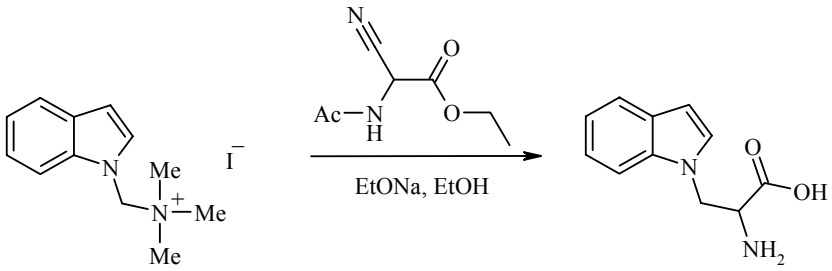



Such reactions in the isogramine series provide an effective means of introducing functional substituents at various positions of the indole ring.

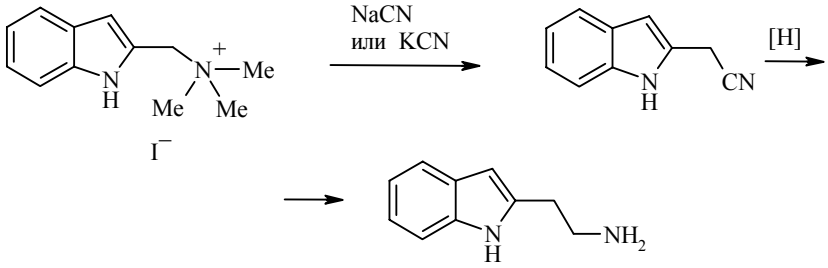
The reaction of quaternized isogramines with C-nucleophiles can be illustrated for the reaction of 2-isogramine methosulfate with acetylaminomalonic ester in the presence of sodium ethoxide. This process leads after hydrolysis and decarboxylation to high yields of ethyl 2-(acetylamino)-3-(2-indolyl)butyrate [34].



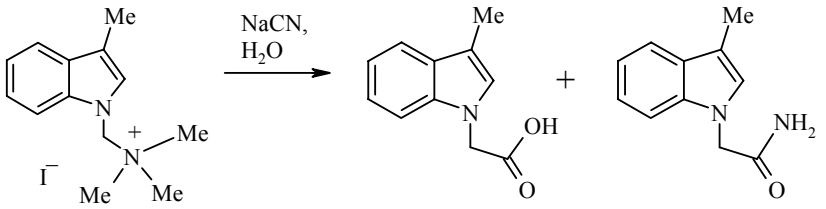

The analogous reaction of 1-isogramine methiodide with acetamidocyanoacetic ester gives the nucleophilic substitution product, the hydrolysis of which leads to 2-amino-3-(1-indolyl)propionic acid [9].



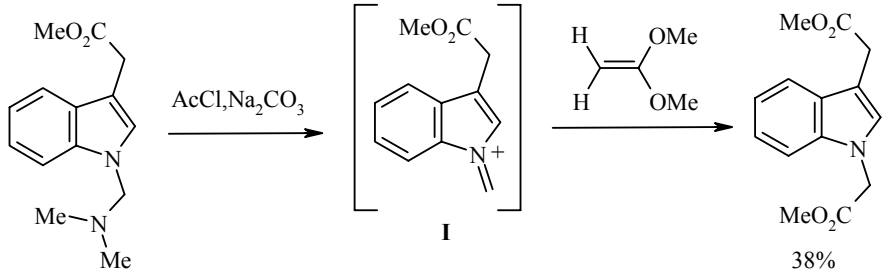

As known, alkali metal cyanides provide excellent sources of C-nucleophiles. In fact, the reaction of 2-isogramine methiodide with sodium [29] and potassium [30] cyanide gives 2-indolylacetonitrile, the reduction of which gives 2-isotryptamine.



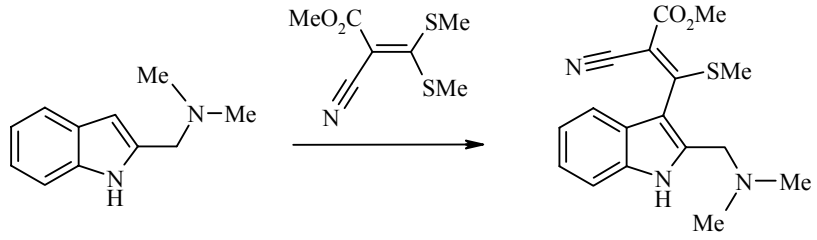
In the case of 3-methyl-1-isogramine methiodide the reaction with sodium cyanide in water is accompanied by hydrolysis of the nitrile group with the formation of a mixture of the corresponding amide and acid [9].



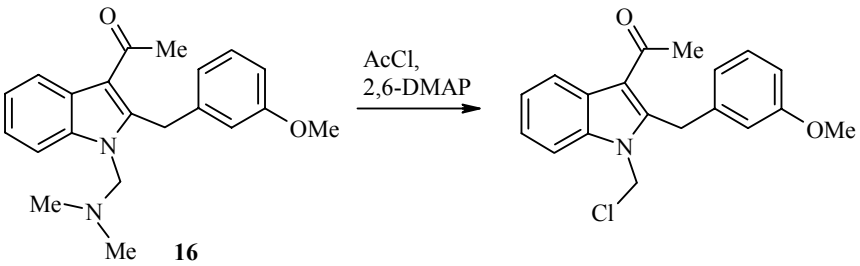

The use ketene dimethyl acetal, the reaction of which with methyl 1-dimethylaminomethyl-3-indolylacetate leads to substitution of the dimethylamino group by methylethoxycarbonyl, as C-nucleophile has been described [66]. It is curious that in this case 1-isogramine and not its methiodide was used as substrate. Since the reaction was carried out in the presence of acetyl chloride, there are grounds for supposing that nucleophilic substitution is activated as a result of the intermediate formation of the acylium salt of gramine, although the authors postulate the formation of the intermediate **I** at the first stage of the reaction.




Nucleophilic substitution of the dimethylamino group does not occur in isogramines that are not activated by quaternization. An example is nucleophilic substitution of the SMe group in 3,3-bis(methylthio)-2-cyanoacrylate by the 3-indolyl fragment during reaction with 2-isogramine without affecting the dimethylaminomethyl group [67].

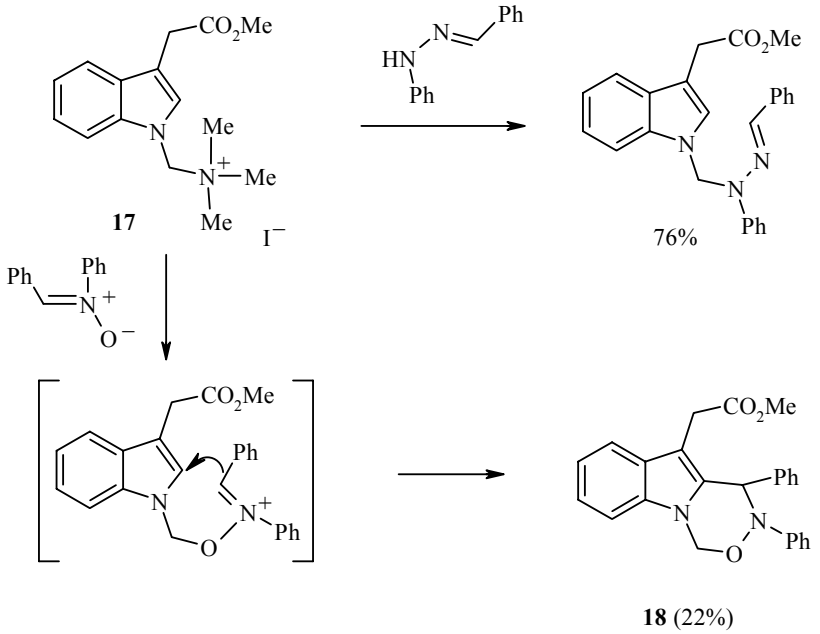



It was possible to substitute the dimethylamino group in the substituted 1-isogramine **16** by a chlorine atom by the action of acetyl chloride in the presence of 2,6-dimethylaminopyridine (2,6-DMAP) [10].



This result is of interest from two points of view. First, it serves as an example of the very effective and successful generation of an active Cl-nucleophile. Second, it indirectly confirms our idea that nucleophilic substitution in isogramines can be activated with the use of acetyl chloride.

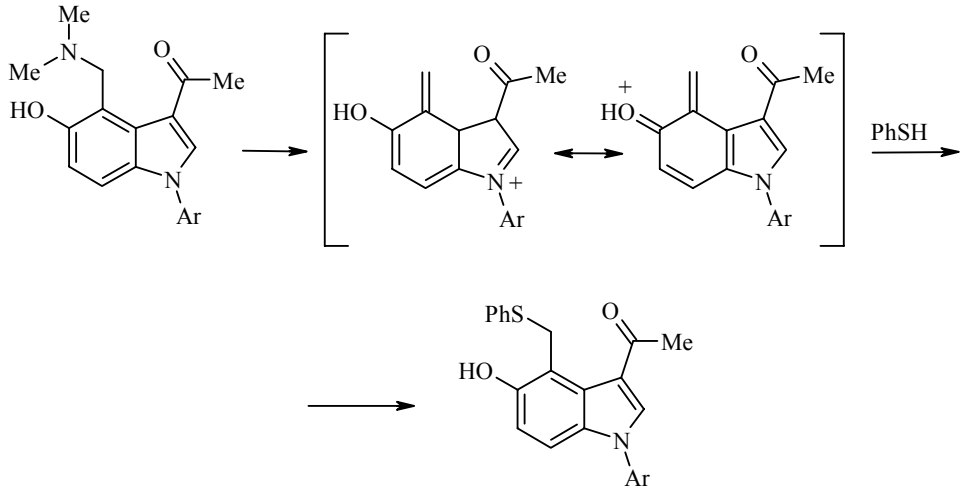
Substitution by an N-nucleophile can be illustrated in the reaction of 1-isogramine methiodide **17** with benzaldehyde phenylhydrazone [68].



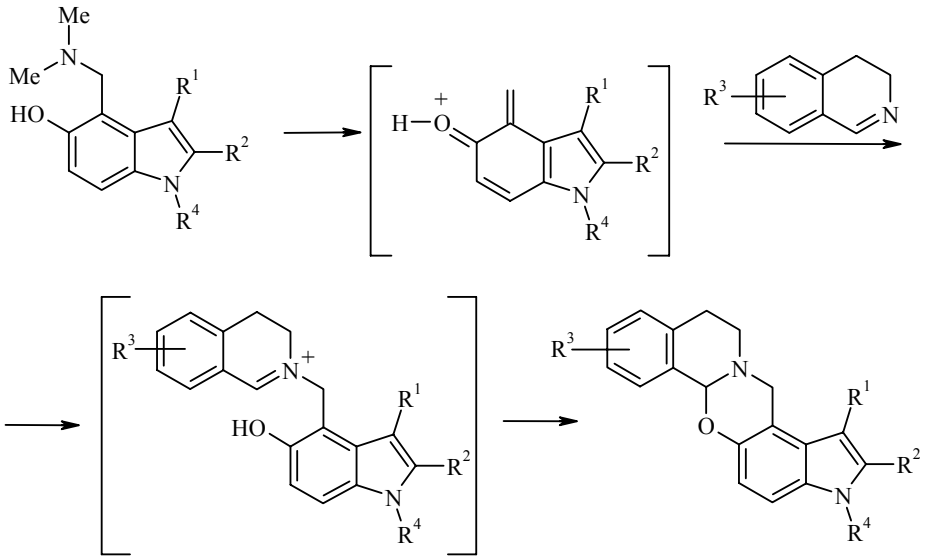
**18** (22%)

The formation of the 1,2-diphenyl-1,2-dihydro[1,2,5]oxadiazino[5,4-*a*]indol-10-ylacetate (**18**) in the reaction of the same methiodide **17** with diphenyl nitrone in DMSO at 120°C [68] can be represented as a two-stage process, the first stage of which is nucleophilic substitution of the trimethylammonium group by the O-nucleophile, while the second is intramolecular electrophilic attack by the formed intermediate cation at position 2 of the indole fragment.

The ease of substitution of the dimethylamino group in unquaternized 1,2,3-trisubstituted 5-hydroxy-4-isogramines by an S-nucleophile (thiophenol) [69] can be explained by the realization for such structures of an elimination–addition mechanism [70] similar to that proposed earlier for gramine [71, 72].

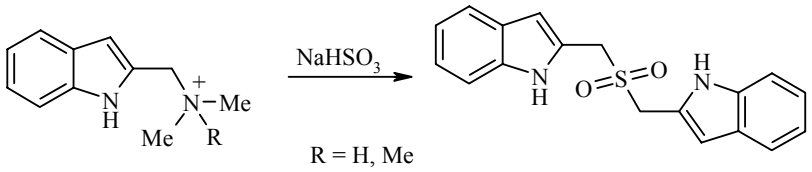


The reaction of substituted 5-hydroxy-4-isogramines with 3,4-dihydroisoquinolines, which leads to the complex conjugated 3,11,12,14-tetrahydroindolo[4',5:5,6][1,3]oxazino[2,3-*a*]isoquinoline system, may take place by a similar mechanism [73].



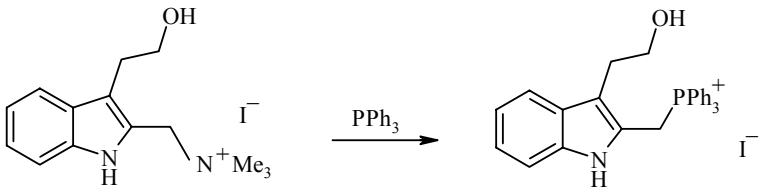
$R^1 = CO_2Alk$, $R^2 = Alk$, $R^3 = Hal, OMe, SMe$, $R^4 = Alk$

Another example of an S-nucleophile is sodium bisulfite, the reaction of which with 2-isogramine hydrochloride or methiodide leads to the double alkylation product bis(2-indolylmethyl) sulfone [74].



R = H, Me

If the P-nucleophile triphenylphosphine is used, it is possible to phosphorylate the methiodides of 2-dimethylaminotryptophol [75] and 2-isogramine [31].

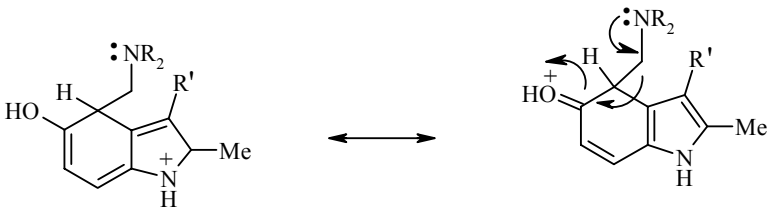


## 2.3. Retro-Mannich Reaction

An alternative though less common direction to nucleophilic substitution for the transformation of Mannich bases is the retro-process, in which the initially formed C–C bond is cleaved, and the original substrate is regenerated [70, 76, 77].

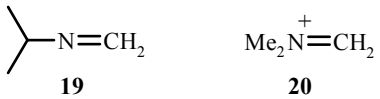
The main publication on the retro-Mannich reaction for 4-dimethylaminomethyl-5-hydroxyindoles dates from 1970 [70]. There are no more recent papers on the subject. The process takes place in the presence of various types of amines in a neutral medium (alcohol) and an inert atmosphere.

The nature of the amine has a definite role. Thus, primary amines are most effective as catalysts. For example, a quantitative yield of 4-unsubstituted indole was obtained when 4-dimethylaminomethyl-3-ethoxycarbonyl-5-hydroxyindole was boiled with isopropylamine in alcohol, but the yield decreased to 84% with a secondary amine (diethylamine) and to 40% with a tertiary amine (triethylamine). The mechanism proposed by the authors of the method involves protonation at position 4 as key stage with the formation of a resonance-stabilized intermediate.



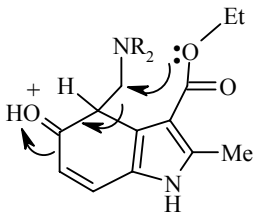
The protonation required for the reaction in this case probably occurs as a result of the phenolic hydroxyl in the substrate molecule.

To explain the special catalytic role of primary amines (such as isopropylamine) in the retro-Mannich reaction the authors assume that transamination occurs initially and that the good leaving group (the neutral imine **19**) is then removed instead of the charged particle **20**, as would occur during removal of the dialkylaminomethyl group.

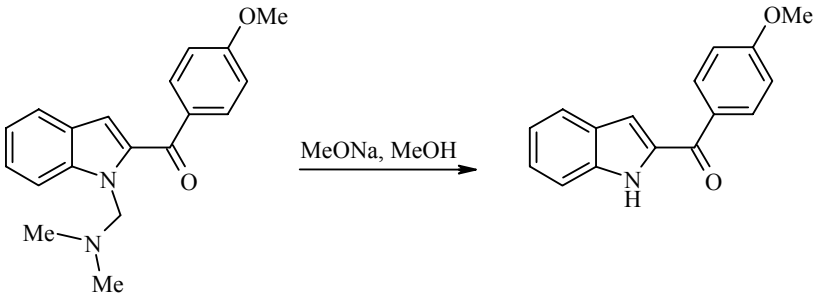


**19** **20**

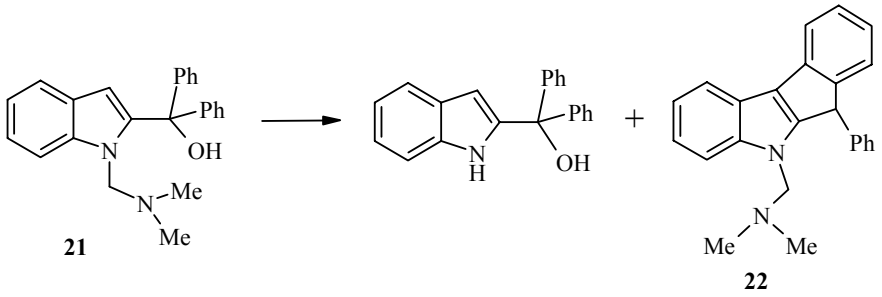
The retro-Mannich reaction takes place more readily for the 3-ethoxycarbonyl derivatives of 5-hydroxy-4-isogramine than for the 3-alkyl-substituted compounds and does not take place at all in the case of the 3-unsubstituted derivatives of 4-isogramine. The authors explain such an effect from the substituent at position 3 of 4-isogramine in terms of electronic and steric factors and reject a deciding role from *peri* interaction of the substituents at positions 3 and 4.



Apart from the reductive removal of the dimethylaminomethyl group in 1-isogramine derivatives mentioned above [2] cases are known where sodium methoxide in methanol was used for such a process [78].



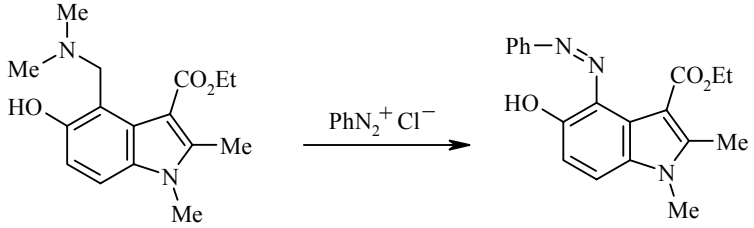

With (1-dimethylaminomethyl-2-indolyl)diphenylcarbinol (**21**) as substrate under the same conditions removal of the $Me_2NCH_2$ group is accompanied by rearrangement with the parallel formation of the tetracyclic structure **22** [78].




An attempt at pyrolytic removal of the dimethylaminomethyl group of 2-isogramine under vacuum at 820°C led together with the production of unsubstituted indole to complete destruction of the molecule and to the products from condensation of the fragments that are formed [79]. As a result dimethylaminoacetonitrile, methylaminoacetonitrile, benzonitrile, quinoline, and *o*-vinylbenzonitrile were formed.

## 2.4. Other Reactions

The only example not included in the classification of the chemical characteristics of isogramines presented above is the extremely unusual substitution of the dimethylaminomethyl group in 4-dimethylaminomethyl-3-ethoxycarbonyl-5-hydroxy-1,2-dimethylindole by a phenylazo group during the action of benzenediazonium chloride [80].




Unfortunately, the authors of this brief communication merely state the fact but make no suggestions about the reaction mechanism. In our opinion the only possible explanation of this process is electrophilic *ipso* attack by the benzenediazonium cation at position 4 followed by aromatization as a result of elimination of the dimethylaminomethyl group.

## 3. PHARMACOLOGICAL CHARACTERISTICS OF ISOGRAMINES

Analysis of published data on the biological activity of isogramines makes it possible to analyze certain qualitative relationships governing their activity and its relation to the structure. It was found that derivatives of 2-isogramine were the most promising in this respect. There are also data on the physiological activity of indole derivatives containing dialkylaminomethyl groups in the benzene ring. There are no published data on the biological characteristics of other isomeric gramines.

The activity most frequently encountered among the derivatives of 2-isogramine is antiviral. Thus, for example, there data on the antiviral activity of 1,3,5-trisubstituted 2-diethylaminomethylindoles [22, 23]. Activity against the influenza virus was exhibited by the hydrochloride of 5-acetoxy-1-benzyl-6-bromo-2-dimethylaminomethyl-3-ethoxycarbonylindole [19].

In the case of the 4-dimethylaminomethyl derivatives of substituted 5-hydroxyindoles it was shown that they also exhibit activity against influenza, but this is no higher than the activity of rimantadine [41, 54]. Another compound of this series arbidol (6-bromo-5-hydroxy-4-dimethylaminomethyl-1-methyl-2-phenylthiomethyl-3-ethoxycarbonylindole) proved a highly effective product with antiviral, interferon-inducing, and immunostimulant activity [81-83]. Study of the pharmacokinetics showed that 90% of the product is removed from the organism in the first 24 h [53].

Antimicrobial properties were discovered in the methosulfate and hydrochloride of 2,2'-bis(dimethylaminomethyl)-5,5'-biindole [25].

2-Dialkylaminomethyl derivatives of 5-nitro-3-phenylindole exhibit clearly defined neuroleptic activity. Thus, they inhibit the action of phenamine and serotonin, intensify the soporific action of hexenal, and intensify the analgesic activity of promedol [17].

There are data on the short-term antihypertensive, antiarrhythmic, antifibrillation, and anticonvulsive activity of the bisdimethylaminomethyl derivative of indole – ethyl 5-hydroxy-4,6-bis(dimethylaminomethyl)-2-methylindole-3-carboxylate [20].

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