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# SYNTHESIS OF TRYPTAMINES BY THE FISCHER METHOD USING SYNTHETIC PRECURSORS AND LATENT FORMS OF AMINOBUTANAL (REVIEW)

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*Information on the synthesis of tryptamines using the Fischer reaction is reviewed. A comparative analysis is made of the methods of production and the reactivity of the various synthetic precursors and latent forms of aminobutanal – the carbonyl component in the synthesis of tryptamines by the Fischer method.*

**Keywords:** acetals, acylaminobutanals, 1-acyl-2-hydroxypyrrolidines, 1-acyl-2-alkoxypyrrolidines, 1-acylpyrrolines, aminobutanal, chlorobutanal, cyanopropanals nitrobutanals, 5-sulfamidoalkyltryptamines, tryptamines, tryptophans, hydroformylation of N-allylacylamides, Fischer reaction.

Tryptamines (3-aminoethylindoles) are important biologically active compounds. By acting on various receptors they participate in the regulation of biological processes, and they are widely used in medicine and medical chemistry. In this connection there is currently increased interest in tryptamines and methods for their synthesis. A large number of different approaches to the synthesis of tryptamines have been described in the literature, but there is a shortage of suitable preparative procedures.

The general method for the synthesis of indoles (including tryptamines) by the Fischer method occupies a special place in the chemistry of indoles. It is highly universal and makes it possible to obtain substituted indoles with various substituents in the benzene ring direct from substituted phenylhydrazines. As aldehyde the synthesis of tryptamines by the Fischer method requires synthetic precursors or latent forms of aminobutyraldehyde, the synthesis of which has many specific fine points. In spite of the fact that the first synthesis of tryptamine by the Fischer method was realized about a hundred years ago [1], in the general case the choice of the best reagents and optimum conditions has not been fully studied, and the synthetic potential of all the precursors and latent forms of aminobutanal has not been fully established. Similar methods frequently lead to poorly predictable results (in some cases, possibly, on account of nonidentical isolation procedures). In recent years a series of publications on this subject from various research groups has appeared. During the choice of methods for the synthesis of tryptamines by the Fischer reaction the investigator comes up against an abundance of diverse extremely disconnected material. There are a few reviews [2-7], which either have become

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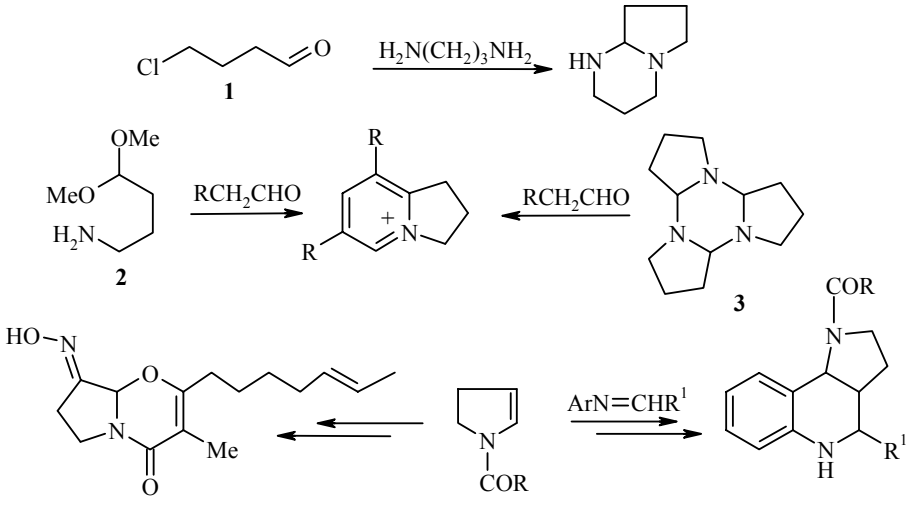
extremely outdated and hardly touch at all on the problem of synthesis of the difficultly obtainable aldehyde component or are largely superficial.

For this reason there is a need for a review that covers the incomplete and the recently published data. The aim of the present applied review was to examine the strategies and methods for the production of the most widely used synthetic precursors and latent forms of aminobutyraldehyde and make a comparative analysis of the use of these compounds in the synthesis of tryptamines by the Fischer method. The presented additional information about the conditions of the processes and the methods of purification of the obtained substances will help to navigate more effectively among the various procedures. Since preparative procedures are given in most of the papers that we examined and the obtained substances have been reliably characterized, we hope that this review will become an important practical guide for the selection of methods for the production of equivalents of aminobutanal and the synthesis of tryptamines by the Fischer method.

Methods for the Fischer synthesis of 2-substituted tryptamines and homotryptamines (see, for example, the recent papers [8-10]) will hardly be discussed at all this review since on the whole they have fewer limitations [2]. Methods for their synthesis have also been examined in the reviews [2, 5, 11-14].

We will not consider the series of methods for the production of tryptamines (see the review [2]) using the Japp–Klingemann reaction, in which the Fischer synthesis is used for the intermediate production of the esters [15-17,18] or intramolecular cyclic amides of tryptamine-2-carboxylic acids. Among these methods the most popular is the Abramovich–Shapiro modification [19, 20], in which the Fischer reaction is used for the formation of 1-oxo-1,2,3,4-tetrahydro-β-carbolines, which are also produced by the indolization of the hydrazones of N-substituted 3-formyl-2-pyrrolidones [21-23]. The hydrolysis and decarboxylation of these carbolines lead to tryptamines. A large number of examples of such a synthetic approach can be found in the review [2] and also, for example, in the papers [24-26]. These methods can have definite advantages in comparison with the single-stage method, since the more readily available anilines are used in the reaction and the indolization stage goes smoothly. (The accepting group at position 2 of the indoles prevents the side processes that reduce the yields of the 2-unsubstituted tryptamines (see below)). However, these advantages are often leveled out by the multistage character of the process and difficulties at the stage of decarboxylation of the tryptamine-2-carboxylic acids [16-20, 24, 27-30], which can only be overcome by the introduction of additional protecting groups [18, 27, 30].

Of greatest practical significance among the latent forms and synthetic precursors of aminobutanal are derivatives with a latent aldehyde function – acetals, bisulfite derivatives, and also heterocyclic intramolecular aminals and enamines. Free aldehydes are usually unstable and often cannot be isolated, and they therefore have to be used quickly or converted into stable derivatives. In this review special attention will be paid to the aldehyde components essential for the synthesis of N-acyl- and N-alkyltryptamines.

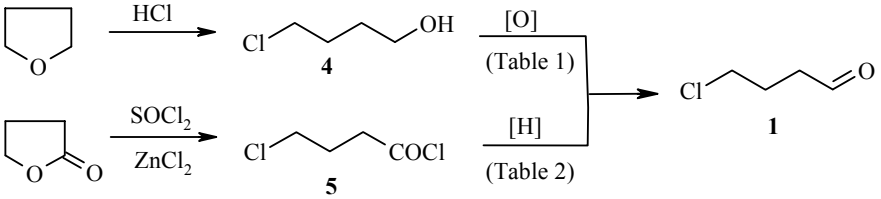


The latent forms of aminobutyraldehyde, found in plants, participate in the biosynthesis of alkaloids [31-33]. 4-Chlorobutanal (**1**) [31], the acetals of 4-aminobutanal **2** [32, 34, 35], and their equivalent trimers 1-pyrrolines **3** [33, 36, 37] are therefore used widely for the synthesis of alkaloids. 1-Acylpyrrolines [36, 38] and also 2-alkoxy- [39-41] and 1-acyl-2-hydroxypyrrolidines [42] have found widespread use in the synthesis of alkaloids and various other nitrogen heterocycles.

## 1. SYNTHESIS OF THE CARBONYL COMPONENT

### 1.1. 4-Chlorobutanal and its Acetals

4-Chlorobutanal **1** and its acetals are the most frequently used precursors of aminobutanal. In spite of this there are a number of difficulties in the production of these compounds and their use in the synthesis of tryptamines. The starting compounds for the synthesis of the aldehyde **1** are the widely used solvent THF and the fairly readily obtainable 4-butyrolactone.




**5** a) 55°C, 22 h (65-70%[a])* [43]; b) 36 h (80%[a]) [44]

If gaseous HCl is passed into boiling THF an equilibrium mixture containing chlorobutanol is formed with yields of 54-59%[a] (yield on the reacted THF 65-70%) [45-49]. Chlorobutanol is also obtained with a total yield of ~60%[a] in the reaction of THF with acetyl chloride in the presence of $ZnCl_2$ followed by transesterification of the acetyl derivative with methanol [47, 50].

The 4-butyrolactone ring is easily opened by the action of $SOCl_2$ in the presence of $ZnCl_2$. Other methods for the synthesis of the acid chloride **5** [51-53] are complicated in experimental execution and do not have preparative significance.

Several standard methods for the oxidation of chlorobutanol have been described in the literature (Table 1). Of these it is worth singling out oxidation in the presence of catalytic amounts of oxammonium salts, which makes it possible to use inexpensive oxidizing agents and does not require absolute solvents.

The reduction of the acid chloride **5** to the aldehyde **1** was carried out according Rosemund method with $Pd/BaSO_4$ as catalyst in the presence of catalyst poison "S/quinoline" [64] or with the addition of a small excess of 2,6-lutidine with Pd/C catalyst.

Hydrogenation in boiling benzene leads to trimerization of a significant part of the chlorobutanal. At higher temperatures (130-140°C) the trimer is not formed [44]. It should be noted that chlorobutanal **1** is extremely unstable. It can be kept at -2°C for only 3-4 h [44], soon undergoes trimerization [44] and oxidation [58], and must therefore be used soon after preparation. Alcohol solutions, in which chlorobutanal exists in the form of the hemiacetal [44], are more stable. The bisulfite derivative, formed with a yield of 96% (it contains

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* Here and subsequently the letters after the yields indicate the method of purification: [a]distillation; [b]chromatography; [c]recrystallization and crystallization from mother liquor; [d]without purification; [e]not indicated.

TABLE 1. Production of Chlorobutanal by Oxidation of Chlorobutanol

| Method | Yield, % | Reference | Method | Yield, % | Reference |
|---|---|---|---|---|---|
| According to Swern [54] | 85 * | [55, 56] | *[2], e-chem. | 70[a] | [61] |
| PCC, $CH_2Cl_2$ | 77[b] | [57] | *[2], $Br_2$ | 60[a] *[3] | [61] |
| | 60[b] | [31] | *[2], NaOCl | 70[a] | [61] |
| | 48[a] | [58] | | | |
| | 54[a] | [59] | | | |
| | 61[a] | [60] | | | |

* Without the procedure, an indication of the method of production.
*[2] 2,2,6,6-Tetramethyl-4-benzoyloxypiperidine 1-oxide, NaBr, $NaHCO_3$, $CH_2Cl_2$–$H_2O$, 20°C, modification of method in [62], see also [63].
*[3] Reaction with cooling according to the method in [62, 63], yield 75%.

TABLE 2. Production of Chlorobutanal by Hydrogenation of the Acid Chloride **5**

| Solvent | Additional conditions | Yield, % | Reference |
|---|---|---|---|
| Benzene | 12 h, Δ | 42[a] * | [44] |
| Benzene | Based on method [44, 51], Δ | 56[a] *[2] | [70] |
| Толуол | The reaction end by titration with HCl | 46[a] | [51] |
| Toluene | Based on methods [51] | 38[a] | [65] |
| Toluene | 6.5 h, Δ | 86[a] | [66] |
| Xylene – toluene, 7:3 | 1.3 atm, 6 h, 120°C | 76[a] | [53] |
| Xylene | 8 h, Δ | 45[a] | [67] |
| Tetralin | 3 h, 130-140°C | 58[a] | [44] |
| Tetralin | Based on methods [44, 51] | 58, 65[a] *[2] | [68, 69] |
| THF, 2,6-lutidine | 4 atm, 6 h | 65[a] | [71] |

* In boiling benzene a mixture of the monomer and trimer (45:55) was obtained.
*[2] Without procedure, an indication of production method.

90% of the main compound) when an ether solution of the aldehyde **1** is stirred with an aqueous solution of sodium bisulfite, is stable during storage [44, 72]. The instability of the free aldehyde **1** may explain the spread of the yields and the poor reproducibility of certain procedures [73].

The acetals of 4-chlorobutanal are also stable equivalents of the aldehyde. During their preparation the yields are increased considerably if the aldehyde is converted into the acetal without being isolated [51] (Table 3).

Other methods for the production of the chlorobutanal (**1**) include the reduction of ethyl 4-chlorobutyrate with a yield of 75%[d] [65] by diisobutyl aluminum hydride (Dibal-H) [43, 80]. The aldehyde can also be obtained with a yield of ~50%[a] by the oxidation of 5-chloropentane-1,2-diol (synthesized by hydrolysis of the product from the reaction of tetrahydrofurfuryl alcohol with acetyl chloride) with $NaIO_4$ (or $Pb(OAc)_4$) [81, 82].

4-Bromobutanal and its acetals are formed similarly (e.g., see [83, 84]) but are on the whole less stable and are hardly ever used for the synthesis of tryptamines.

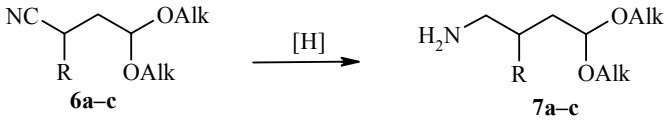
TABLE 3. Preparation of 4-Chlorobutanal Acetals

| Method of production of aldehyde | Acetalization | Yield, % | Reference |
|---|---|---|---|
| $Pd/BaSO_4$, cat. poison, PhMe | EtOH, $CaCl_2$ | 55[a] *,*[2] | [51] |
| $Pd/BaSO_4$, cat. poison, PhMe, Δ | $(CH_2OH)_2$, $H_2SO_4$ | 64[a] * | [74] |
| By the method in [51] | By the method in [51] | 45[a] | [79] |
| On the basis of [74] PhH *[3] | $(CH_2OH)_2$, TsOH, PhH, Δ | 68[a] * | [78] |
| On the basis of [74] $Pd/BaSO_4$, cat. poison, PhH, $H_2$:$N_2$ = 1:1 | MeOH, $H_2SO_4$ | 53[a] * | [73] |
| 1.15 equiv. of 2,6-lutidine, Pd/C, 2.7 atm $H_2$, MeOAc, 23°C, 3.5 ч | MeOH, $H_2SO_4$ | 76[a] * | [77] |
| PCC, $CH_2Cl_2$ | By the method in [74] | 67[a] * | [75] |
| PCC, $CH_2Cl_2$ | PhH, $(CH_2OH)_2$, TsOH | 47[b] * | [76] |
| — | EtOH, $CaCl_2$ | 63[a] | [51] |
| — | $Me_2C(OMe)_2$ | 50[a] | [53] |

* Total yield of two stages.
*[2] With the intermediate isolation of the aldehyde the total yield was 29%.
*[3] High rate of purging of hydrogen, or a mixture with nitrogen, to remove HCl.

## 1.2 Derivatives of 4-Aminobutanal

**1.2.1. 4-Aminobutanal Acetals. Reduction of 3-Cyanopropanal Acetals.** The reduction of cyanopropanals **6** is the most widely used method for the synthesis of the acetals of aminobutanals **7**.




**6a–c** **7a–c**

**6**, **7 a** R = H (see. Table 4); **b** R = Ph, (85%[a]), THF, $LiAlH_4$, $H_2SO_4$ [85];
**c** R = $CO_2Me$ (80%[b] in the form of the N-acetyl derivative),
$Ac_2O$, $H_2$, 3.4 atm, 20 h, Ni-Ra (Raney nickel) [86, 87]

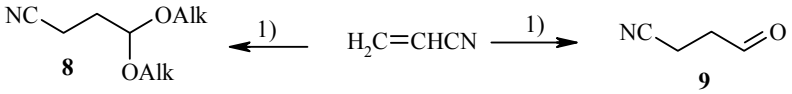
TABLE 4. Reduction of the Acetals of Cyanopropanal **6a**

| $Alk_2$ | [H] | Yield, % | Reference | $Alk_2$ | [H] | Yield, % | Reference |
|---|---|---|---|---|---|---|---|
| $(CH_2)_2$ | $LiAlH_4$ | 79[a] | [35] | $Et_2$ | $LiAlH_4$ | 56[a] | [89] |
| $(CH_2)_2$ | $LiAlH_4$ | 90* | [34] | $Et_2$ | $H_2$*[2] | 91[a] | [90] |
| $Me_2$ | NiAl, NaOH | 62[a] | [88] | $Et_2$ | Na, EtOH | 50[a] | [91] |
| $Me_2$ | Na, EtOH | 78[a] | [32] | $Et_2$ | Na, EtOH | 85[a],*[3] | [92] |
| $Me_2$ | $LiAlH_4$ | 62[a] | [32] | | | | |

* By the method in [35].
*[2] 4 atm, Ni-Ra, in ammoniacal ethanol.
*[3] 10% solution in ethanol; 0.5 mol of nitrile, 6 mol of Na.

The principal starting compounds for the synthesis of the acetals **6a** are such widely used reagents as acrolein and acrylonitrile.

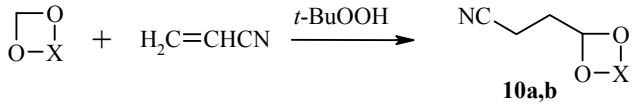
**1.2.1.1. Synthesis of 3-Cyanopropanal Acetals from Acrylonitrile**. The hydroformylation of acrylonitrile to cyanopropanal **9** was used at one of the stages in the industrial production of glutamic acid [93]. The best yields are obtained in polar solvents [94, 95], and the selectivity of the formation of the unbranched aldehyde **9** amounts to ~90 [96, 97]. The yields on the reacted acrylonitrile are high, but the reaction mixture only contains 16% of compound **9** [98].




1) CO, $H_2$, 1% $Co_2(CO)_8$, 100-300 atm, 100-130°C

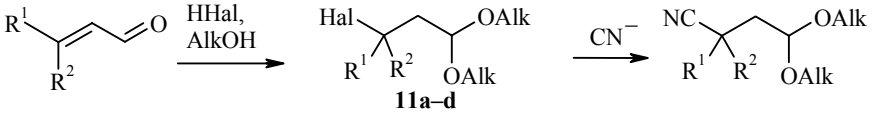
**8 a** Alk = Me (70–90%); anhydrous MeOH [96, 97]; **9** (80%); acetone [98];
for the interconversion of the acetals **8** and aldehyde **9**, see [93].

The derivatives of 1,3-dioxolanes add to acrylonitrile by a radical mechanism with the formation of the acetals **10**.




**10 a** X = $(CH_2)_2$ (30%); 150°C, in an ampule, separation on a preparative GLC column [99];
**10b** = *o*-$C_6H_4$ (66%[a] on the reacted dioxolane); photochemical reaction, 20°C [100].

**1.2.1.2. Synthesis of 3-Cyanopropanal Acetals from Acrolein.** The acetals **11** are obtained by passing a stream of gaseous hydrogen halide into an alcohol solution of the respective unsaturated aldehyde:




**11 a** $R^1$,$R^2$ = H,H (Table 5);
**b** Hal = Cl, $(Alk)_2$ = $(CH_2)_3$, $R^1$,$R^2$ = Me,H (100%[a]); in the presence of 0.5 equiv. of $Bu_4N^+Cl^-$ [101];
**c** Hal = Cl, $(Alk)_2$ = $(CH_2)_3$, $R^1$,$R^2$ = Me,Me (68%[a]); in the presence of 0.5 equiv. of $Bu_4N^+Cl^-$ [101];
**d** Hal = Br, $(Alk)_2$ = $Et_2$, $R^1$,$R^2$ = Me,H (65%[d]) [102]

TABLE 5. Production of halo acetals **11a**

| Hal | $Alk_2$ | Yield, % | Reference | Hal | $Alk_2$ | Yield, % | Reference |
|---|---|---|---|---|---|---|---|
| Br | $Me_2$ | 52[a] * | [32] | Cl | $Et_2$ | 34[a] | [105, 106] |
| Br | $Me_2$ | 45[a] * | [103] | Cl | $(CH_2)_2$ | 58[a] | [107] |
| Br *[2] | $Me_2$ | 42[a] * | [104] | I | $(CH_2)_2$ | 60[b],*[3] | [108] |
| Br | $Et_2$ | 80[d] | [102] | Br | $(CH_2)_2$ | 61-62[a] | [109, 110] |
| | | | | Br | $(CH_2)_3$ | 60-65[a] | [111, 112] |

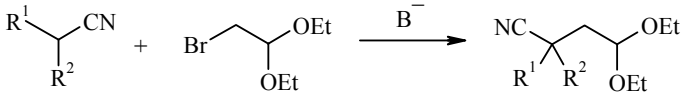
* The 1,1-dialkoxy-3-halopropane was isolated intermediately, the yield on the acrolein.
*[2] Compound **11a** was obtained similarly (Hal = Cl, $Alk_2$ = $Me_2$, $Et_2$) [104].
*[3] Concentrated aqueous HI was used.

The halogen in the acetals **11a** is easily substituted by a nitrile group.


**11a** **12a-d**

**12 a** Hal = Br, $(OAlk)_2 = (OMe)_2$ (86%[a]); $Bu_3N$, $H_2O$ [32] (by the method in [113]); **b** Hal = Br, $(OAlk)_2 = (OCH_2)_2$ (81%[a]); $BnNMe_3^+Cl^-$, $H_2O$ [35]; **c** Hal = Cl, $Alk_2 = (OEt)_2$ (60%[a]); 0.1 equiv. KI, EtOH–$H_2O$, in an autoclave [114]; **c** (the yield was not given); DMSO, NaCN [115] (by the method in [116]); **d** Hal = Br, $Alk_2 = (OEt)_2$ (40–60%[a]); KI (cat.), methanol, Δ [92]

The acetals **13** are also produced by the alkylation of the α-anions of nitriles with bromoacetal.

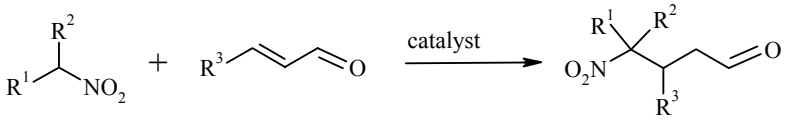



**13a–i**

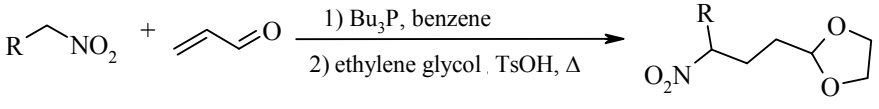
**13 a** $R^1 = R^2$ = Me (62%[a]); $(i\text{-Pr})_2NLi$, [37]; **b–d** $R^1$ = H, ($R^2$ = Ph, *s*-Bu, *i*-Bu) 71-79%[a]; $(i\text{-Pr})_2NLi$, –78°C, THF [117]; **e** $R^1R^2 = (CH_2)_5$; 71-79%[a]; $(i\text{-Pr})_2NLi$, -78°C, THF [117]; **f** $R^1$ = H, $R^2 = CO_2Me$ (32%[a]); NaH, DMF – PhH [86, 87]; **g** $R^1$ = H, $R^2$ = Ph (75%[a]); *t*-BuOK, $Et_2O$ [85]; **h** $R^1$ = Me, $R^2 = CO_2Me$ (80%[a]); $K_2CO_3$, DMF, 110°C, 24 h [118]; **13h → 13i** $R^1$ = Me, $R^2$ = H (96%[a]); AcOK, DMSO, 160°C, 14 h [118]

**1.2.2. Synthesis of Derivatives of 4-Nitrobutanal**. The aliphatic nitro group is easily reduced to an amino group [119] and the acetals of 4-nitrobutanals can be used as precursors of aminobutanals.

4-Nitrobutanal derivatives are produced by the Michael addition of nitroalkanes to acrolein. A large excess of nitroalkane is usually required in order to suppress the formation of polyaddition products. However, with the use of mild catalysts ($Al_2O_3$, and also Amberlyst A-27 [120]) it is possible to conduct the reaction without an excess of nitroalkanes and without solvents.




The acetals **14** are conveniently obtained by the one-pot addition of nitroalkanes (in a fivefold excess) to acrolein in the presence of catalytic amounts of tributylphosphine, using the general method in [126]:




**14a–h**

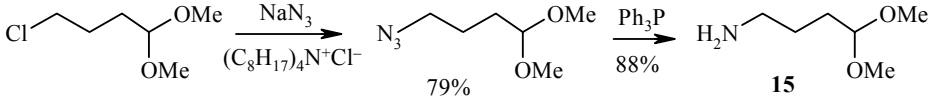
**14 a** R = H (43%[б]) [127], with an eightfold excess of $MeNO_2$ yield 62%[a] [128]; **b–h** R = Me (72%[a]), Et (70%[a]), Pr (72%[a]), *i*-Pr (73%[a]), Bu (70%[a]), *i*-Bu (75%[a]), *i*-$C_5H_{11}$ (80%[a]) [126]

TABLE 6. Production of Nitrobutanal Derivatives

| $R^1$,$R^2$ | $R^3$ | Catalyst | Solvent | T, °C | Excess of nitroalkane | Yield, % | Reference |
|---|---|---|---|---|---|---|---|
| $H_2$ | H | KF | MeOH | -35 | 50 | 48[a] | [121] |
| $H_2$ | H | MeO(K/Na) | MeOH | -20 | 100/100 | 40/32[a] | [122] |
| $Me_2$ | H | $BnNMe_3^+OH^-$ * | *[2] | -20 | 10/1.1 | 49/11[a] | [122] |
| $Me_2$ | H | EtONa | EtOH | 5 | 1 | 33[a] | [123] |
| Me,H | H | $BnNMe_3^+OH^-$ * | *[2] | -20 | 30/40/15 | 51/32/15[a] | [122] |
| Me,H | H | $Al_2O_3$ | *[2] | 0 | 1 | 50[b] | [124] |
| Me,H | H | $Al_2O_3$ | *[2] | 0 | 1 | 27[b] | [125] |
| Et,H | H | EtONa | EtOH | 5 | 1 | 30[a] | [123] |
| Et,H | H | $Al_2O_3$ | *[2] | 0 | 1 | 54[b] | [124] |
| Bu,H | H | $Al_2O_3$ | *[2] | 0 | 1 | 51[b] | [124] |
| $C_5H_{11}$,H | H | $Al_2O_3$ | *[2] | 0 | 1 | 50[b] | [124] |
| $H_2$ | Me | $Al_2O_3$ | *[2] | 0 | 1 | 18[b] | [125] |
| $Me_2$ | Me | EtONa | EtOH | 5 | 1 | 34[a] | [123] |

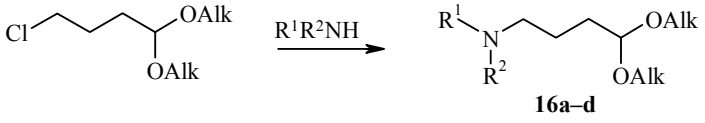
* In the form of a 40% aqueous solution.
*[2] Without a solvent.

**1.2.3. Syntheses Based on Chlorobutanal Derivatives**. 4-Chlorobutanal dimethyl acetal can be converted into the aminoacetals **15** by the successive action of sodium azide (in the presence of a phase-transfer catalyst) and triphenylphosphine [32].




The acetal **15** was also obtained [129] by hydrolysis (57%[a]) of the methoxycarbonyl derivative, synthesized by the Hoffmann rearrangement (69%[a]) from dimethoxyglutaramide (obtained in turn by a multistage synthesis from caprolactam [130]). The production of aminoacetals by the action of an excess of ammonia on halo acetals is well known (e.g., see [91, 131]).

**1.2.4. N-Alkyl Derivatives of Aminobutanal**. Heating of 4-chlorobutanal acetals with amines leads to the formation of the acetals **16**.

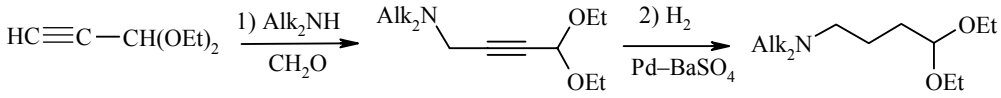



**16 a** $R^1$,$R^2$ = Me,Me; Alk = Me (87%[a]); aqueous $Me_2NH$ (6,7-fold excess), 62°C [77];
**b** $R^1$,$R^2$ = Bu,H; Alk = Et (87%[a]); butylamine (16- fold excess), Δ [132];
**c** $R^1R^2NH$ = (*R*)-3-(benzyloxy)pyrrolidine (and other 3- and 2-substituted pyrrolidines); Alk = Me (44%[b]); equivalent ratio, $K_2CO_3$, THF, Δ [133]; **d** $R^1R^2NH$ = 3-(N-benzyl-N-methyl)aminomethylpyrrolidine; Alk = Me (44%[b]); equivalent ratio, NaI, $Na_2CO_3$, dimethoxyethane, Δ [134]

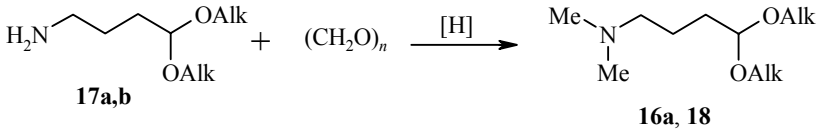
TABLE 7. Preparation of Dialkylaminobutanal Acetals

| $Alk_2$ | 1st yield, % | 2nd yield, % | $Alk_2$ | 1st yield, % | 2nd yield, % |
|---|---|---|---|---|---|
| $Et_2$ | 69[a] | 67[a] | Bn,Me | 71[a] | 65[a] |
| *i*-$Pr_2$ | 69[a] | 41[a] | $(CH_2)_4$ | 65[a] | 82[a] |
| $(HO(CH_2)_2)_2$ | 63[a] | 44[a] | $(CH_2)_5$ | 70[a] | 75[a] |
| $Bn_2$ | 56[a] | 53[a] | Morpholino | 62[a] | 73[a] |

A large series of 4-dialkylaminobutanal acetals was synthesized from propargyl acetal [135, 136] by the Mannich reaction [137] (Table 7).



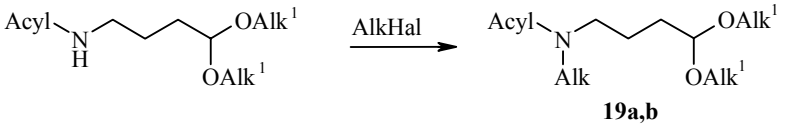

The acetals **16a** and **18** are obtained during reductive amination.




**16a** Alk = Me (57%[a]), Pd/C, $H_2$, 114 atm [138]; **18** Alk = Et (92%), ratio of reagents:
**17b** $(CH_2O)_n$ – (*i*-PrO)$_4$Ti – $NaBH_4$, 1:4:2:1.5, absolute diglyme, 60°C [139]

It is also known that the acetal **18** is produced with a yield of 45%[a] by exhaustive methylation with methyl iodide followed by demethylation of the quaternary salt by boiling in ethanolamine [140]. N-Methylaminobutanal was obtained with a yield of 68%[a] by the reduction of methoxycarbonylaminobutanal dimethyl acetal with lithium aluminum hydride [129].

The N-monoalkyl derivatives **19** were produced during the alkylation of N-acylaminobutanals. The acetal, produced qualitatively during the hydrolysis of compound **19b**, is used in the biomimetic synthesis of various alkaloids with an indolizidine fragment [32].




**19 a** AlkHal = MeI, Acyl = Ts, $Alk^1$ = Et (88%[d]), NaOH, EtOH [141];
**b** AlkHal = $(MeO)_2CHCH_2CH_2Br$, Acyl = $COCF_3$, $Alk^1$ = Me (74%[b]), KH, 18-crown-6 [32]

### 1.3. Acylaminobutanals

**1.3.1. Acylation of Aminobutanal Acetals**. Acylaminobutanal acetals are produced by the acylation of aminobutanal acetals under mild conditions (Table 8).

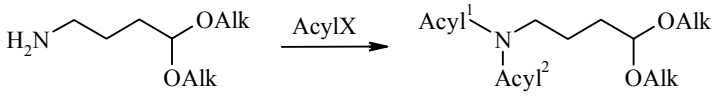


TABLE 8. Acylation of 4-Aminobutanal Acetals

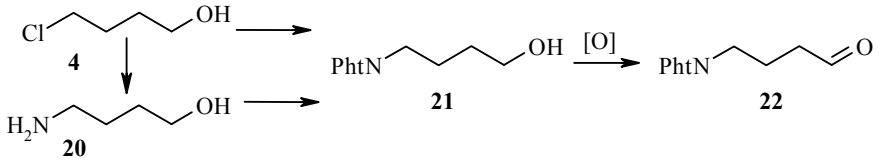
| Alk | AcylX | Conditions | Acyl[1], Acyl[2] | Yield, % | Reference |
|---|---|---|---|---|---|
| Et | $Ac_2O$ | Aqueous 5% $NaHCO_3$, 0°C | Ac, H | 62[a] | [142] |
| Et | Acyl*Cl | *i*-$PrNEt_2$, $Et_2O$, 0-25°C | Acyl*, H | 85[d] | [38] |
| Me | $PhtNCO_2Me$ *[2] | EtOH, Δ | Phthalyl | 93[d] | [88] |
| Et | $PhtNCO_2Et$ | Aqueous $NaHCO_3$, 20°C | Phthalyl | 97[d] | [143] |
| Et | $PhtNCO_2Et$ | Aqueous $NaHCO_3$, 20°C | Phthalyl | 95[d] | [144] |
| Me | $(CF_3CO)_2O$ | $Et_3N$, $Et_2O$, 0°C | $CF_3CO$, H | 93[a] | [32] |
| Et | TsCl | Aqueous NaOH | Ts, H | 91[d] | [141] |

* *o*-Iodobenzoyl.

*[2] Can be obtained from potassium phthalimide and $ClCO_2Me$ in DMF (45%[d] [88]) or in benzene (73-82%[c] [145]).

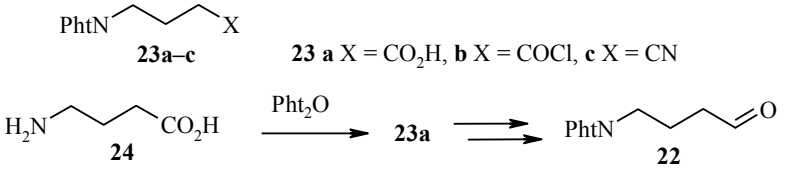
**1.3.2. 4-Phthalimidobutanal.** It is worth mentioning 4-phthalimidobutanal specially, since it has a fully protected amino group. This makes it possible to conduct the Fischer reaction with it under more rigorous conditions and then to obtain tryptamines by hydrazinolysis [88].

There are several synthetic approaches to the production of phthalimidobutanal. The first is based on the oxidation of phthalimidobutanol, which is produced from chlorobutanol or from the poorly available aminobutanol (see its production [146-148], the synthesis of homologs from nitrobutanals [123], and also the synthesis of N-alkylbutanols from 4-butyrolactone [149]).



**4** → **20** (62–64%[a]); liquid $NH_3$, 40-50°C (the N-alkyl derivatives were obtained similarly) [146]; **20** → **21** (91%[d] [150, 151], 76%[d] [153]), PhtO, 140°C, 3 h; **4** → **21** (95%[d]), PhtNH, $K_2CO_3$, DMF, Δ, 12 h [150, 151]; **4** → **21** (46%[c]), PhtNK, DMF, 70°C, 4 h [152]; **21** → **22** a) DMSO/$(COCl)_2$ (80%[d]) [150, 151]; b) $CrO_3$·Py (yield not given) [154]

Another path involves the reduction of derivatives of 4-phthalimidobutyric acid **23b**,**c**. The aldehyde **22** is fairly unstable and decomposes with time. It trimerizes during attempts at crystallization [144].

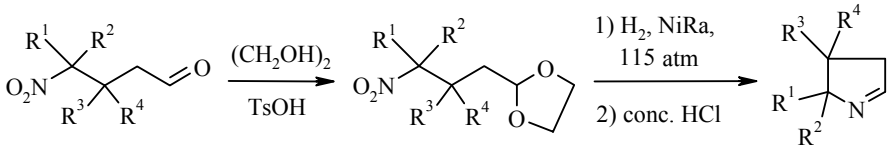


**24** → **23 a** (87%[c]/ 94%[d]) [155] / [88]; **23a** → **23b** (90–100%[d]) $SOCl_2$ [155, 88]; **23a** → **23c** (95%[d]) 1) $SOCl_2$, 2) $NH_3$, 3) $SOCl_2$, Δ [156]; **23c** → **23** (75–80%[d]) 1) $SnCl_2$, $Et_2O$, 2) $H_2O$ [156, 157]; **23b** → **22** (88–96%[d]) $H_2$, $Pd/BaSO_4$, xylene, Δ [88]

## 1.4. Heterocyclic Equivalents of Aminobutanals

**1.4.1. 1-Pyrrolidines and Their Trimers**. Hydrolysis of the acetals of aminobutanals [132, 158], N-alkyl-aminobutanals [132], and N-dialkylaminobutanals [77] in an acidic medium leads to their heterocyclic equivalents.

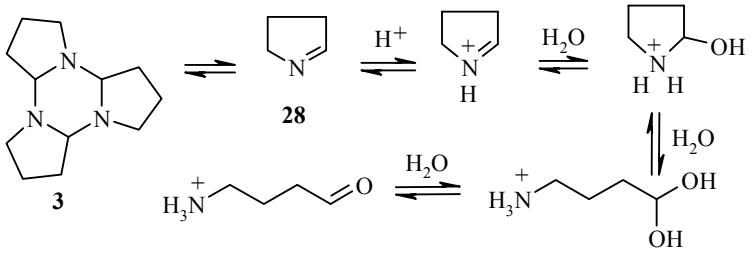
The reductive cyclization of the acetals of substituted nitrobutanals **26a**,**b** [158] and the diethyl acetal of 4-cyano-3,3-dimethylpropanal [37] leads to the production of the pyrrolines **27a**,**b** and **27c** ($R^1 = R^2 = H$, $R^3 = R^4 = Me$) respectively.




**25a,b** **26a,b** **27a,b**

**25a** → **26a** $R^1 = R^2 =$ Me, $R^3 = R^4 = H$ (75%); **26a** → **27a** (53%);
**25b** → **26b** $R^1 = R^2 = R^3 =$ Me, $R^4 = H$ (63%); **26b** → **27b** (61%)

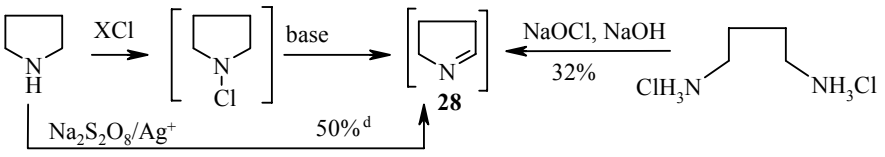
The 1-pyrroline (**28**) formed during the hydrolysis of aminobutanal acetals is unstable and trimerizes with the formation of the trimer **3**, which is depolymerized reversibly when heated. Similar behavior has been recorded for dimethylpyrroline **27c** [37]. Recent investigation of the equilibria existing in an aqueous solution of the pyrroline **28** showed that the trimer **3** predominates in an alkaline medium with the monomer **28** as impurity. Decrease of pH leads to the monocyclic protonated forms, which exist in equilibrium with the acyclic forms [132]. The trimer **3** is unstable in the presence of mineral acids and forms the products from aldol condensation [132, 159]. For more details about the properties of the trimer **3**, its isolation methods, and its purification, see [132, 159-161].




**3** **28**

In chemical transformations the trimer **3** acts like a latent form of aminobutyraldehyde [33, 162, 163].

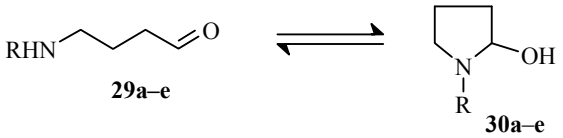
Early methods for the synthesis of the trimer **3** involved the reaction of pyrrolidine and tetramethylenediamine with hypochlorites by a modification of the procedure in [164] and also hydrolysis by a methanol solution of 1-formyl-2-methoxypyrrolidine hydrochloride (44%[a] of **3** together with 16%[a] of aminobutanal dimethyl acetal) [165]. A method with oxidation of pyrrolidine in an aqueous alkaline medium with sodium persulfate has preparative significance [159, 166].




**28**

a) XCl = NaOCl; base = NaOMe, 35%[a] **3** [160]; b) XCl = *t*-BuOCl, N-chlorosuccinimide, NaOCl, $Ca(OCl)_2$; base = KOH in MeOH [164, 162]

**1.4.2. 2-Hydroxy- and 1-Acyl-2-alkoxypyrrolidines.** Acylaminobutanals **29** can exist in equilibrium with 2-hydroxypyrrolidines **30**. The dependence of the constant and rate of establishment of equilibrium on the conditions has been investigated little.



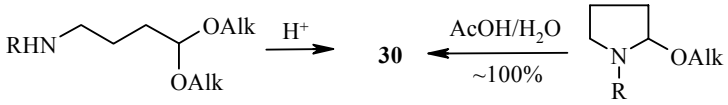

**29a–e** **30a–e**

**29**, **30 a** R = $CO_2Bn$, **b** R = Ac, **c** R = $CO_2Bu$-*t*, **d** R = Ts, **e** R = *o*-iodobenzoyl

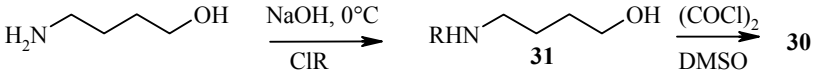
Thus, according to the $^{13}C$ NMR spectra [167] the isomers **29a**/**30a** [167] and **29b-d**/**30b-d** [168] isolated in individual form exist as 2-hydroxypyrrolidines **30**. According to data from the $^{1}H$ NMR spectra [167], the isolated mixture **29e**/**30e** contains 1.5% of the linear form **29e** [38]. At the same time the toluene solution of acetylaminobutanal **29b** [169] contains a relatively small amount of the isomer **30b** [169].

The existence of the equilibrium between the isomers **29** and **30** in the solution gives rise to the higher chemical activity of 2-hydroxypyrrolidines **30** compared with 2-alkoxypyrrolidines [170]. However, 2-hydroxypyrrolidines **30** (R = Et, Bn, Allyl) can be obtained quantitatively by the hydrolysis of 2-alkoxypyrrolidines with a 50% aqueous solution of acetic acid at room temperature [170] (see the procedure in [171]).

2-Hydroxypyrrolidines **30** can be obtained by hydrolysis of the acetals of acylaminobutanals and also by Swern oxidation of acylaminobutanols **31**.

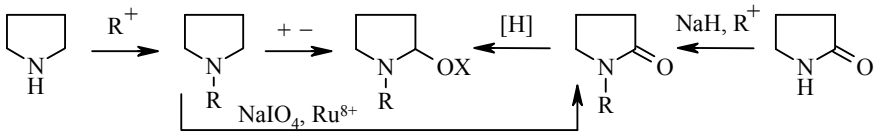



**30 b** (45%[a]), $H^+$ = dilute $H_2SO_4$ [172]; **e** (74%[б]), $H^+$ = 4% aq. HCl–THF, 1:1, 25°C, 5 min [38]




**30 a** 98%[d] / 87%[b] [173] / [167]; **31 a** 64%[c] / 90%[c] [173] / [167]

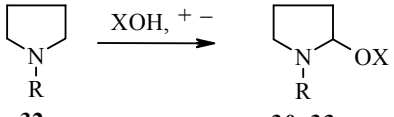
In the most widely used methods for the synthesis of 2-hydroxy- and 2-alkoxyacylpyrrolidines pyrrolidine or pyrrolidone are used as starting compounds with electrochemical oxidation (subsequently denoted by + − in the schemes) and reduction by hydrides respectively at the key stages. Electrochemical oxidation is suitable for compounds with a wide range of substituents at the nitrogen atom and easily obtained reagents are used, but it requires more complicated experimental realization, whereas reduction with hydrides is probably unfeasible for compounds with R = COAlk and COAr [174] and uses more costly reagents.




X = H, Alk

Pyrrolidine is easily acylated with the formation of acylpyrrolidines (e.g., see [165, 175, 176]). 1-Alkoxycarbonyllactams are obtained with yields of 60-80% by acylation of lactams in the presence of sodium hydride (e.g., see [174, 177]) or by oxidation of the readily obtainable alkoxycarbonylpyrrolidines with periodates in the presence of catalytic amounts of a ruthenium salt [171, 176].

**1.4.2.1. Anodic Oxidation of N-Acylpyrrolidines.** The anodic oxidation (see the review [178]) of an aqueous or alcohol solution of the readily obtainable N-acylpyrrolidines **32** (in the presence of tetraalkylammonium salts as electrolyte) is a general method for the production of the pyrrolidines **30** and **33**. Thus, electrolysis of the pyrrolidines **32** (R = Ac, $CO_2Me$, $CO_2Bu$-*t*) in aqueous acetonitrile leads to 2-hydroxypyrrolidines **30** [42, 179]. The most popular method is methoxylation of the pyrrolidines **32** (see [175, 180]), which is easily realized for large loads. The yields of the other 2-alkoxy derivatives are lower [180]. Characteristic examples of the synthesis of compounds **33** are given in Table 9.



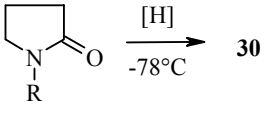

**32** **30**, **33**

**30** X = H, **33** X = Me

TABLE 9. Production of 2-Methoxypyrrolidines **33**

| R | *Q*, F/mol | Electrolyte | Yield, % | Reference |
|---|---|---|---|---|
| CHO | 2.0 | $Me_4NBF_4$ | 87[a] | [165] |
| Ac | 2.0 | $Me_4NBF_4$ | 80/92[a] | [165] / [180] |
| Ac | 3.7 | $Et_4NOTs$ | 45[a] | [41] |
| $CO_2Me$ | 2.3 | $Et_4NOTs$ / $Me_4NBF_4$ | 78–83/94[a] | [175, 41] / [180] |
| $CO_2Me$ | 2.0 | $Et_4NOTs$ | 65[a] | [181] |
| $CO_2Bn$ | — | $Et_4NOTs$ | 65[b] | [39] |
| $CO_2Ph$ | 2.0 | $Me_4NBF_4$ | 91[b] | [180] |
| Ts | 3.5 | $Et_4NOTs$ | 79[e] | [182, 183] |
| COBn | 2.5 | $Et_4NOTs$ | 85[b] | [41] |
| COPh | 2.0 | $Me_4NBF_4$, $Et_4NOTs$ | 75-97[e] | [180, 183] |

**1.4.2.2. Reduction of 1-Acyllactams by Metal Hydrides.** Another method for the production of hydroxypyrrolidines **30** involves the reduction of acyllactams **34** by metal hydrides. Mild reducing agents ($LiEt_3BH$ and Dibal-H) lead to high yields of the hydroxypyrrolidines **30**.




**30**

**34**

**30 a** R = $CO_2Bn$ (88[b] / >84[d]); Dibal-H / $LiEt_3BH$; THF [171] / [177]; **c** R = $CO_2Bu$-*t* (90-95[b]); Dibal-H ($LiEt_3BH$); THF [171, 184]; **d** R = Ts (94[b]); Dibal-H; $CH_2Cl_2$ [185]

The result from the reduction of lactams **34** with a large excess of $NaBH_4$ depends on the reaction conditions.

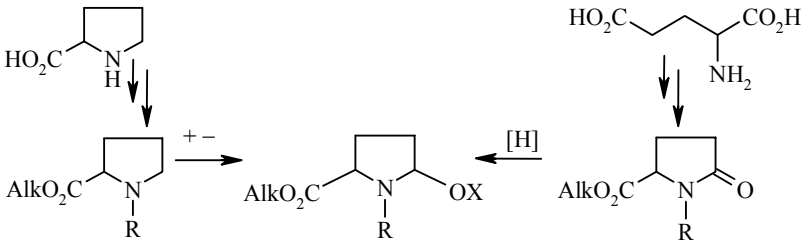

**30** **35a-e**

**35 a** R = $CO_2Me$ (80%[a]), **b** $CO_2Et$ (83%[a]), **c** $CO_2Bn$ (83%[a]), **d** $CO_2Bu$-*t* (88%[a]), **e** $CO_2Allyl$ (88%[a]); [174]

If a constant weakly acidic medium in ethanol is maintained reduction leads to 2-ethoxypyrrolidines **35a-e** [174, 186]. Realization of the reaction both in aqueous solution and with the lactams **34** (R = Ac, COPh) leads to acylaminobutanals [174, 187].

In a neutral methanol solution at −10°C [171, 188] 2-hydroxypyrrolidines **30** are formed. Compared with reduction by $LiEt_3BH$ or Dibal-H this procedure leads to smaller yields (by 10-40%), but it is preferred for economic reasons if the reaction is carried out on larger scales [171].

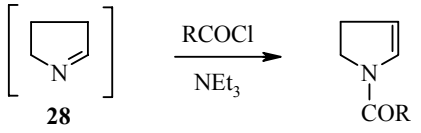
Various aldehyde components **36** needed for the synthesis of tryptophans, including L-tryptophan, were synthesized from derivatives of amino acids (proline and glutamic acid) using such methodology.




**36a–g**

**36** X = Alk = Me, **a** R = Ts (98%[e], +–, 5.8 F/mol), **b** R = COPh (94%[b], +–, 3.0 F/mol) [182];
**36 c, d** X = H, Alk = *t*-Bu, **c** R = $CO_2$Bu-*t* (98%[e]), **d** R = $CO_2$Bn (80%[e]), $LiEt_3BH$ [189];
**36d** (91%[d]) $LiEt_3BH$ [177]; **36 e**, **f** X = H, Alk = Me, **e** R = $CO_2$Bu-*t* (84%[b]), **f** R = $CO_2$Me (72[e]) Dibal-H [171];
**36g** X = H, Alk = Me, R = $CO_2$Et (85–90%[b]); $LiEt_3BH$, Dibal-H [184]

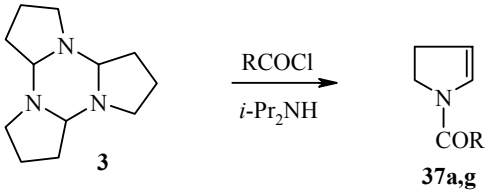
**1.4.3. 1-Acyl-2-pyrrolines.** One of the methods for the production of N-acylpyrrolines **37** may be distillation of a 0.1 M solution of the pyrroline trimer **3** in THF into a flask cooled to -78°C followed by the addition of an acylating agent [161].




**28** **37a-f**

**37 a** R = Me (71%), **b** R = OMe (78%), **c** R = OEt (79%); **d** R = BnO (74%),
**e** R = $ClCH_2$ (57%), **f** R = $CCl_3CH_2O$ (39%)

In a modified procedure the pyrrolines **37** are produced by adding the acylating agent dropwise to a boiling solution of the trimer **3** in THF [177].




**3** **37a,g**

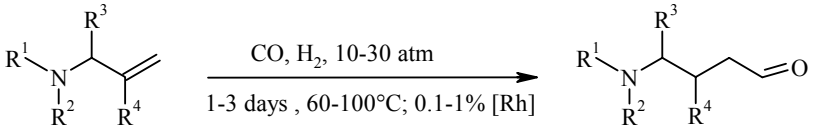
**37 a** R = Me (58%), **g** R = Ph (67%)

The acylpyrrolines **37a** and **37h** (R = *t*-Bu) were also obtained by isomerization [190] of the difficultly obtainable (e.g., see [191, 192]) 1-acyl-3-pyrrolines by the action of $RhH(CO)(PPh_3)_3$.

The pyrrolines **37a** (38%[e], cat. $SiO_2$ [193]) and **37h** (91%[a], cat. $NH_4Cl$ [193], see also [171]) were obtained by thermal splitting of methanol from 2-methoxypyrrolidines **33** in the presence of various catalysts. The dehydration of 2-hydroxypyrrolidines **30** is often complicated by side reactions, but there are a large number of different successful procedures [38, 169, 171, 177, 184].

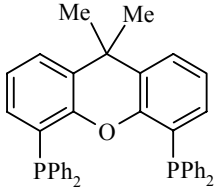
## 1.5. Hydroformylation: A General Method for the Synthesis of Derivatives of 4-Aminobutanal and their Latent Forms from Allylamines

The hydroformylation of allylamines is a promising method for the production of derivatives of 4-aminobutanal and their latent forms. The low selectivity of the catalysts used in the earlier papers gave rise to a large amount of side products, preventing the realization of a preparative synthesis of the aldehydes **39a** [172, 194-196].



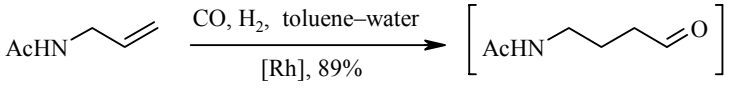

**39 a** $R^4$ = H, **b** $R^4$ = Alk (Ar) **39a,b**

The aldehydes **39b** are obtained selectively during hydroformylation in the presence of rhodium complexes (usually $Rh(acac)(CO)_2$) [168, 197, 198]. The presence of diphosphine ligands with sterically separate phosphorus atoms is necessary in order to suppress the formation of the isomeric branched aldehyde **39a** [168, 169, 197-199]. The most widespread of such ligands was xantophos (4,5-bisdiphenylphosphino-9,9-dimethylxanthene) [200]. The addition of a 5-12-fold excess of it to the rhodium catalyst effectively suppresses the formation of branched aldehydes [168, 169, 199].

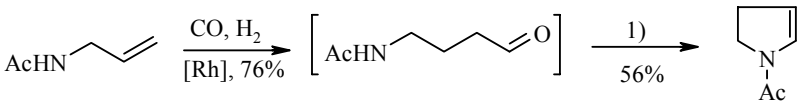



Xantophos

By hydroformylation of N-allylacetamide in a two-phase system it is possible to separate quantitatively the reaction product from the toluene solution of the catalyst and to use the regenerated catalyst not less than five times without loss of activity [199]. The yield of the aldehydes amounts to 96% with a 15:1 ratio of linear to branched aldehyde. The aldehyde is used without isolation for the synthesis of melatonin (N-acetyl-tryptamine) in aqueous solution [199].



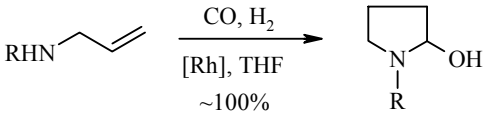
A mixture containing the cyclic latent forms of acetylaminobutanal in addition to the linear form is formed during the hydroformylation of N-allylacetamide in toluene. During optimization of the conditions for the hydroformylation process [169] it was found that it is reasonable for preparative procedures to reduce the amount of the costly rhodium to 0.0002% with a simultaneous increase of the xantophos-rhodium ratio to 12:1 and to preactivate the catalyst in an atmosphere of hydrogen at increased temperature. This makes it possible to realize the reaction with an acceptable small loss in the degree of conversion, regioselectivity, and rate of reaction. The obtained optimum conditions were used for a one-pot preparative synthesis of 1-acetylpyrroline.




**37a**

1) Toluene, 3 Å molecular sieves, 150°C, 12 h, then azeotropic distillation of water (threefold repetition of the cyclization procedure). Overall yield on the allylacetamide 41%[a].

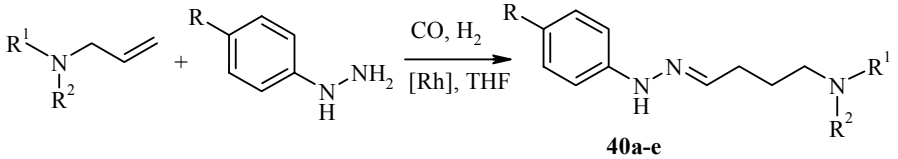
The pyrrolidines **30b-d** are isolated quantitatively under similar conditions [168].




**30b–d**

**30 b** R = Ac, **c** R = $CO_2$Bu-*t*, **d** R = Ts

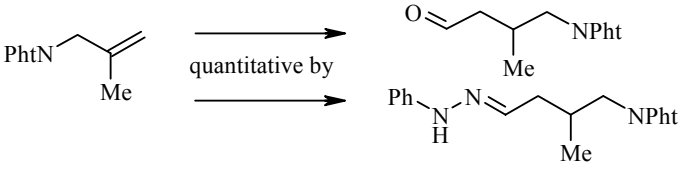
If hydroformylation is realized in the presence of arylhydrazines with a wide range of functional groups the hydrazones **40** are formed. Their yield is on the whole higher than during isolation of the free aldehydes [198].




**40a-e**

**40 a** $R^1 = R^2 = Me$, R = H (~100%[d]); **b** $R^1R^2 = (CH_2)_5$, R = H (97%[d]); **c** $R^1R^2 = (CH_2)_5$, R = OMe (93%[d]); **d** $R^1 = R^2 = Me$, R = CN (90%[d]); **e** $R^1R^2 = (CH_2)_5$, R = $NO_2$ (80%[d])

The presence of both phthalyl protection and substituents at the β–position in the allylamines led to higher yields from hydroformylation [168, 172, 197].



A large number of varied methods for the production of the above-mentioned allylamines are found in the accompanying material of the articles [168, 197-199].

The presented methods for the production of synthetic precursors and latent forms of 4-aminobutanal include both highly preparative reliable methods of synthesis and dubious and rarely used methods. Often there is a choice between the accessibility of the reagents, the complexity of practical realization, and the multistage character of the process, and this is determined by the specific aims and resources.

## 2. FISCHER SYNTHESIS OF TRYPTAMINES

### 2.1. From 4-Aminobutanal Acetals and Arylhydrazines by the Action of $ZnCl_2$

The first syntheses of tryptamines by the Fischer method were conducted by heating arylhydrazines with the acetals of aminobutanals to 180°C in the presence of anhydrous zinc chloride. Later modifications involved relaxation of the reaction conditions – indolization at lower temperatures and in inert solvents. The tryptamine is isolated in the form of the hydrochloride after precipitation of the zinc with hydrogen sulfide or in the form of the base from an alkaline solution. In some cases the tryptamines are converted into acyl derivatives in order to facilitate separation from impurities. The presence of donating groups in the benzene ring of the hydrazine leads to a reduction of the yields on account probably of the thermal lability of the respective hydrazines and hydrazones (Table 10).

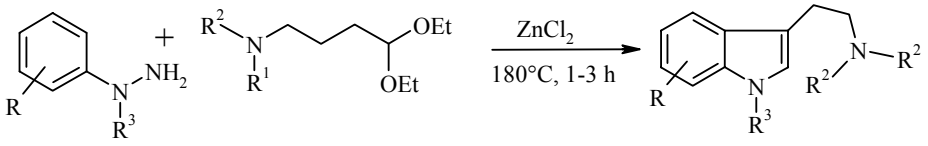



TABLE 10. Synthesis of Tryptamines Using $ZnCl_2$

| R | $R^3$ | $NR^1R^2$ | Yield, % | Reference |
|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 |
| H | H | $NH_2$ | 45[c] (hydrochloride)* | [201] |
| H | H | $NH_2$ | 68[d], 58[a], 51[a,c] | [92] |
| H | H | $NH_2$ | 42 (hydrochloride) | [202] |
| H | H | NHTs | 34 | [141] |
| H | H | NMeTs | 56 | [141] |
| H | Me | $NH_2$ | 48[a] | [203] |
| H | Et | $NH_2$ | 80 | [204] |
| H | Bn | $NH_2$ | 40-50 | [205] |
| 5-OBn *[2] | H | $NH_2$ | 45 | [206] |
| 5-OBn | H | $NH_2$ | 25 (hydrochloride) | [207] |
| 5-OMe | H | $NH_2$ | 20[c] (hydrochloride) | [208] |
| 6-OMe | H | $NH_2$ | 38[a] | [203] |
| 5-OEt | H | $NH_2$ | 29 | [209] |
| 5-OEt | H | NHTs | 26 | [141] |
| 5-OEt | H | NMeTs | 19 | [141] |
| 7-OMe | H | $NH_2$ | 24[a] | [203] |

TABLE 10. (continued)

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| 6-MeO and 4-MeO | H | $NH_2$ | 38[a] (2-isomer) | [210] |
| 5-F | H | $NH_2$ | 49[c] (hydrochloride) | [211] |
| 5-F | H | $NH_2$ | 50[c] (hydrochloride) | [208] |
| 5-Cl | H | $NH_2$ | 37[c] (hydrochloride) | [208] |
| 5-Br | H | $NH_2$ | 51[c] (hydrochloride) | [208] |
| 5-Me | H | $NH_2$ | 50[c] (hydrochloride) | [208] |
| 7-Me | H | $NH_2$ | 39[a] | [212] |
| 6-Br and 5-Br | H | $NH_2$ | 60[b] (3:2) (2-isomer) | [213] |

* After purification of the tryptamine by distillation the yield increased to 75% [210].
*[2] The reaction was carried out in xylene.

## 2.2. From the Acetals of 4-Aminobutanals and Arylhydrazine Hydrochlorides

In the development of the work in [206, 207] it was found that it is impossible to isolate the hydrazones during the reaction of the hydrochlorides of arylhydrazines containing donating substituents with the acetals of

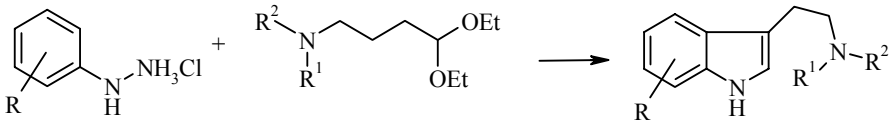


TABLE 11. Synthesis of Tryptamines with Donating Substituents

| R | $NR^1R^2$ | Conditions | Yield, % | Reference |
|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 |
| 5-OBn | $NH_2$ | 50% EtOH – 5% HCl, 4:1, 4 h, Δ | 68[c] (hydrochloride) | [142] |
| 5-OBn | $NH_2$ | 25% AcOH, 80°C, 2 h | 68[c] (hydrochloride) | [142] |
| 5-OEt | $NH_2$ | 25% AcOH, 80°C, 2.5 h | 35 (picrate) | [215] |
| 5-OMe | $NH_2$ | 25% AcOH, 80°C, 2 h | 35 (picrate) | [142] |
| 5-OMe | $NMe_2$ | 25% AcOH, 80°C, 2.5 h | 74/76 (picrate) * | [140] |
| 5-OMe | $NEt_2$ | 25% AcOH, 80°C, 2.5 h | 61 (picrate) | [140] |
| 5-OMe | N(*i*-Pr)$_2$ | 25% AcOH, 80°C, 2.5 h | 57 (picrate) | [140] |
| 5-OMe | NMeBn | 25% AcOH, 80°C, 2.5 h | 52/21[b] (picrate) * | [140] |
| 5-OMe | $N(CH_2)_4$ | 25% AcOH, 80°C, 2.5 h | 76 (picrate) | [140] |
| 5-OMe | $N(CH_2)_5$ | 25% AcOH, 80°C, 2.5 h | 79 (picrate) | [140] |
| 5-OMe | $N(C_2H_4)_2O$ | 25% AcOH, 80°C, 2.5 h | 45 (picrate) | [140] |
| 5-OBn | $NMe_2$ | 25% AcOH, 80°C, 2.5 h | 42/52 ( hydrochloride) * | [140] |
| 5-OBn | $NEt_2$ | 25% AcOH, 80°C, 2.5 h | 49/51[6] (oxalate) * | [140] |
| 5-OBn | N(*i*-Pr)$_2$ | 25% AcOH, 80°C, 2.5 h | 35/36[b] (oxalate) * | [140] |
| 5-OBn | NMeBn | 25% AcOH, 80°C, 2.5 h | 58/40[b] (oxalate) * | [140] |
| 5-OBn | $N(CH_2)_4$ | 25% AcOH, 80°C, 2.5 h, 2 equiv. HCl | 65 (hydrochloride) | [140] |

TABLE 11. (continued)

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| 5-OBn | $N(CH_2)_5$ | 25% AcOH, 80°C, 2.5 h, 2 equiv. HCl | 83 (hydrochloride) | [140] |
| 5-OBn | $N(C_2H_4)_2O$ | 25% AcOH, 80°C, 2.5 h, 2 equiv. HCl | 73 (hydrochloride) | [140] |
| 5-SBn | $NH_2$ | AcOH–EtOH–$H_2O$, 1:2:1, 80°C, 4 h | 45 (hydrochloride) | [216] |
| 7-OMe | $NH_2$ | 25% AcOH, 80°C, 2.5 h | 8[b] (picrate) | [215] |
| 7-OMe | $NEt_2$ | 25% AcOH, 80°C, 2.5 h | 20[b] (picrate) | [215] |
| 7-OMe | $N(CH_2)_4$ | 25% AcOH, 80°C, 2.5 h | 18[b] (picrate) | [215] |
| 7-OMe | $N(CH_2)_5$ | 25% AcOH, 80°C, 2.5 h | 15[b] (picrate) | [215] |
| 5-OBn | NHCOPh | 25% AcOH, 80°C, 2.5 h | 70[c] | [215] |
| 5-OBn | NHAc | 25% AcOH, 80°C, 2 h | 68[b] | [217] |
| 5-OEt | NHAc | 25% AcOH, 80°C, 2.5 h | 41[b] | [215] |
| 5-OMe | NHAc | 25% AcOH, 80°C, 1 h | 26[c] | [142] |
| 5-OMe | NHAc *[2] | AcOH–EtOH–$H_2O$, 2.5:3.5:4, 40°C, 12 h | 61[c] (87[d]) | [214] |

* The second figure represents the yield for the reaction in the presence of 2 equiv. of HCl.

*[2] The acetyl acetal was obtained by acetylation and was used in the reaction without isolation.

aminobutanals in a weakly acidic medium – the reaction leads directly to the tryptamines [142]. Indolization takes place readily in dilute mineral acids and also in 25% acetic acid at 85°C (Table 11), and in the last case the reaction products are easier to purify than in the Fischer reaction with $ZnCl_2$ [142]. In order to facilitate the isolation of the crystalline hydrochlorides of the tryptamines in some cases it is necessary to use several equivalents of HCl, while addition of the acid at the beginning of the reaction can have a negative effect on the yield of the tryptamine [140].

In the synthesis of melatonin under similar conditions (AcOH–EtOH–$H_2O$, 2.5:3.5:4) at 40-45°C the reaction time is increased, but the lower temperature makes it possible to avoid side processes. If free hydrazine is used under such conditions instead of its hydrochloride the reaction does not occur; if aminobutanal acetal is used instead of its N-acetylated derivative the yield of the respective tryptamine is very low [214].

Tryptamine is not formed from *m*-benzyloxyphenylhydrazine under the reaction conditions [142]. After prolonged boiling in a 5% ethanol solution of HCl aminobutanal 2,4-dinitrophenylhydrazone does not form even traces of tryptamine [142]. 7-Methoxytryptamines are formed with very low yields. The possibility of substitution side reactions during cyclization of the *o*-derivatives of hydrazones is a common complication of the Fischer reaction [4, 7].

Halo-5-methoxytryptamines were obtained by analogous methods:

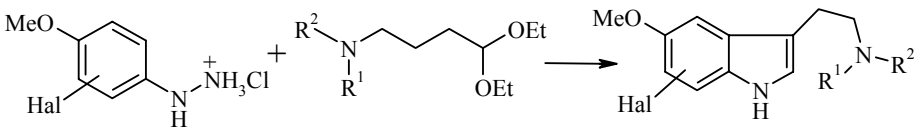


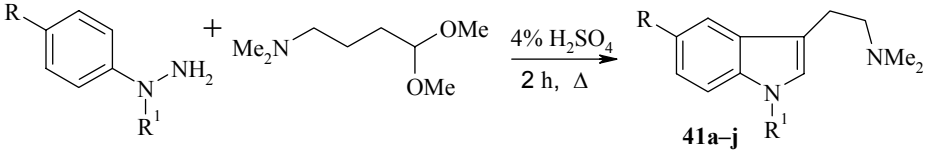
TABLE 12. Synthesis of Halo-5-methoxytryptamines

| Hal | $NR^1R^2$ | Reaction conditions | Yield, % | References |
|---|---|---|---|---|
| 6-Br and 4-Br | NHAc | 25% AcOH, 80 °C, 1 h 30 min | 82[b] (3:2) | [218] |
| 6-F<br>4-F | $NMe_2$* | 24% AcOH, 85°C, 28 h | 49[b]<br>7[b] | [219] |
| 7-F | NHAc*[2] | AcOH–EtOH–$H_2O$, 2.5:3.5:4, 40°C, 12 h | 27[b] | [24] |
| 7-F | $NH_2$ | 5% HCl–EtOH, 1:1, 40 °C, 12 h *[3] | 31[b] | [24] |
| 4,6-$F_2$ | NHAc*[2] | AcOH–EtOH–$H_2O$, 2.5:3.5:4, 40°C, 12 h | 68[b] | [24] |
| 4,6-$F_2$ | $NH_2$ | 5% HCl–EtOH, 1 : 1, 40 °C, 12 h *[3] | 45[b] | [24] |

* In the form of the dimethyl acetal.
*[2] The acetyl acetal was obtained without isolation by acetylation before the reaction.
*[3] Or 10 min of microwave treatment at 100°C.

## 2.3. N,N-Dimethyltryptamines. Indolization by the Action of Acids

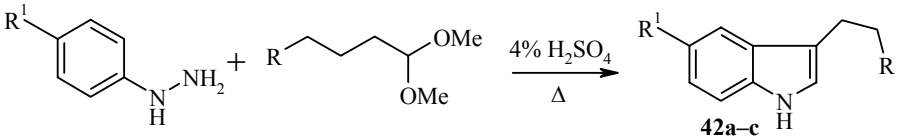
During optimization of the conditions for the production of tryptamine **41a** [77] it was found that the most effective catalyst was a 4% aqueous solution of $H_2SO_4$. The yield of the tryptamine **41a** in 8% trifluoroacetic acid was somewhat lower, while in 8% hydrochloric acid the reaction was complicated by the formation of aniline derivatives. The tryptamine **41b** was formed with the smaller yield when the reaction was carried out in 25% acetic acid [140], while the synthesis of the tryptamine **41a** was complicated by the formation of side products [77].



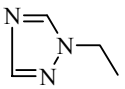
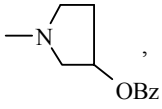
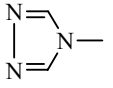

**41a–j**

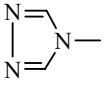
**41 a–h** $R^1$ = H, **a** R = $CH_2CN$ (76%[c] 5 mol load); **b** R = OMe (85%[e]); **c** R = H (86%[e]); **d** R = Me (89%[e]); **e** R = *i*-Pr (91%[e]); **f** R = F (100%[e]); **g** R = Cl (82%[e]); **h** R = Br (93%[e]); **i**, **j** $R^2$ = *p*-chlorobenzyl, **i** R = *i*-Pr (91%[e]); **j** R = (2-quinolinyl)methoxy (88%[e])

The extension of this method to the synthesis of series of dialkyltryptamines **42** led to less successful results:




**42a–c**

**42 a** R= $NMe_2$, $R^1$ =  , **b** R =  , $R^1$ =  ,

**c** R= $NMe_2$, $R^1$ = 

**42 a** 2 h, 37%[b] [220]; **b** 48 h, 22%[b] [133] (boiling for 60 h reduces the yield to 10% [134]); **c** 40 h, 45%[b] [221]

## 2.4. Synthesis of Tryptamines Using Derivatives of 4-Phthalimidobutanal

Phthalyl protection for the amino group of aminobutanal, used successfully for the synthesis of many tryptamines, is also suitable for their subsequent modifications. The hydrazones **43**, containing electron-accepting groups, readily undergo cyclization in a mixture of acetic and sulfosalicylic acids [88]. (The reaction does not go during boiling in acetic acid or with sulfosalicylic acid in ethanol.) The phthalyl protection is easily removed by hydrazinolysis.

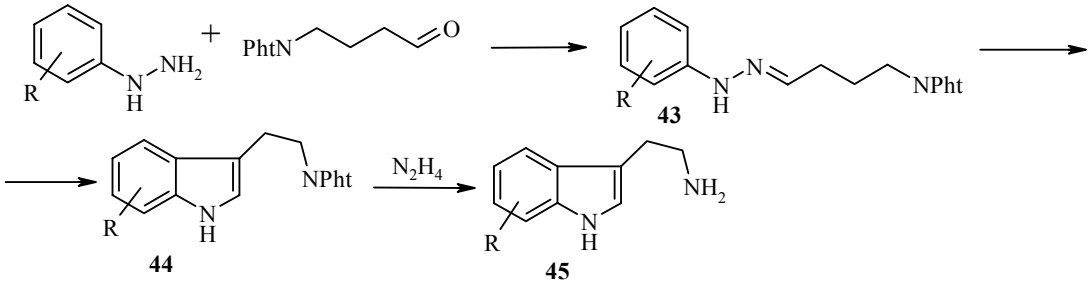



TABLE 13. Synthesis of Tryptamines Using Derivatives of Phthalimidobutanal

| R | Indolization conditions | Yield, % | | | Reference |
|---|---|---|---|---|---|
| | | **43** | **44** | **45** | |
| 5-Et | EtOH–HCl, 140:1, Δ, 14 h | * | 48[b] | 94[b] | [143] |
| 5-(*i*-Pr) | EtOH–HCl, 140:1, Δ, 14 h | * | * | 25[b] | [143] |
| 5-(*t*-Bu) | EtOH–HCl, 140:1, Δ, 14 h | * | * | 52[b] | [143] |
| 5- Cyclohexyl | EtOH, 60 °C, 30 min *[2] | * | 67[b] | 96[b] | [143] |
| 7-F | EtOH, Δ, 2 h *[2] | * | * | 12[b] | [71] |
| 7-MeO | EtOH, Δ, 2 h *[2] | * | * | 37[b] | [71] |
| 7-Cl | EtOH–5 N HCl, 200:1 *[2] | * | * | 25[b] | [71] |
| 5-Me, 7-Cl | EtOH–5 N HCl, 200:1 *[2] | * | * | 34[b] | [71] |
| 6,7-Benzo | EtOH–5 N HCl, 200:1 *[2] | * | * | 17[b] | [71] |
| 6-Me, 7-Cl | EtOH–5 N HCl, 200:1 *[2] | * | * | 24[b] | [71] |
| 5-Br, 7-Me | EtOH–5 N HCl, 200:1 *[2] | * | * | 56[b] | [71] |
| 5-MeO, 7-$NO_2$ | SSA*[3], AcOH, Δ, 20 min | ~89[c] | 84[c] | 83[c] | [88, 222] |
| 5-$NO_2$, 7-MeO | SSA*[3], AcOH, Δ, 20 min | 92-94[c] | 49[c] | 76[c] | [88, 222] |
| 5-Cl, 7-$NO_2$ | SSA*[3], AcOH, Δ, 20 min | 76[c] | 84[c] | 86[c] | [88, 222] |
| 4-$NO_2$, 7-MeO *[4] | SSA*[3], AcOH, Δ, 20 min | 82[c] | 82[c] | 83[c] | [88] |
| 5-BnO | EtOH–$H_3PO_4$, 50:1, Δ, 4 h | * | 74[c] | 66[c] *[5] | [88] |
| 5-$(CH_2)_3CO_2H$ | AcOH–$H_2O$, 1:3, Δ, 1 h *[2] | * | 63[b] | — | [223] |
| 5-$(CH_2)_2CO_2H$ | AcOH–$H_2O$, 1:3, Δ, 2 h *[2] | * | 52[b,c] | — | [223] |
| 5-$CH_2CO_2H$ | 25% AcOH, 70-80°C, 2 h 48 min *[2] | * | 33[b] | 50[b] | [224] |
| 5-$CH_2CONH_2$ | 25% AcOH, Δ, 30 min *[2] | * | 69[c] | 64[c] | [224] |
| 5-CH(Me)$CONH_2$ | 25% AcOH, Δ, 1 h *[2] | * | 19[b,c] | 81[c] | [224] |
| 5-$CH_2CONMe_2$ | 25% AcOH, Δ, 30 min *[2] | * | 81[c] | 86[c] | [224] |
| 5-$CH_2CN$ | 25% AcOH, Δ, 2 h *[2] | * | 56[c] | — | [224] |

* The hydrazone or phthalyltryptamine was not isolated or was used in the crude state.

*[2] The arylhydrazine hydrochloride was used in the reaction.

*[3] SSA is sulfosalicylic acid.

*[4] During the cyclization of the similar 2-methoxy-4-nitrophenylhydrazones under such conditions a complex mixture of products is formed [225].

*[5] The removal of the phthalyl protection was described in [30].

## 2.5. Synthesis of Tryptamines Using Cyclic Latent Forms of Aminobutanal

The cyclic forms of aminobutanal have also found use in the synthesis of tryptamines and tryptophans (Table 14).

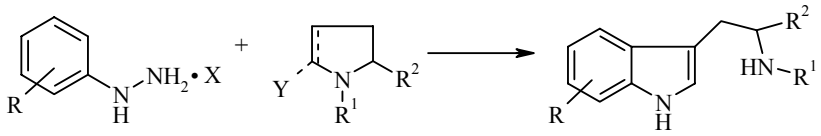


TABLE 14. The Use of Cyclic Latent Forms of Aminobutanal in the Synthesis of Tryptamines

| R | X | Y | $R^1$ | $R^2$ | Conditions | Yield, % | Reference |
|---|---|---|---|---|---|---|---|
| Bn | HCl | 1-ene * | H | H | 2-PrOH, 80°C | 21[a] | [226] |
| 7-MeO | — | 2-OMe | Ts | H | AcOH, 100°C, 5 h | 74[b] | [227] |
| H | — | 2-OMe | Ts | H | $ZnCl_2$, xylene, 1 h 30 min, Δ | 63[b] | [182], [183]*[2] |
| H | — | 2-OMe | COPh | H | $ZnCl_2$, xylene *[2] | 76[e] | [183] |
| 5-MeO | HCl | 2-OMe | COPh | H | *[3], *[2] | 87[e] | [183] |
| H | — | 2-OMe | Ac | H | AcOEt – xylene, $ZnCl_2$*[2] | 60[e] | [183] |
| 5-MeO | HCl | 2-OMe | Ac | H | AcOH–$H_2O$, 25:75, Δ *[2] | 32[e] | [183] |
| H | — | 2-OMe | $CO_2Me$ | H | $ZnCl_2$, xylene *[2] | 41[e] | [183] |
| 5-MeO | HCl | 2-ene | Ac | H | *[3], 20 min, Δ | 75[b] | [177] |
| 5-MeO | HCl | 2-ene | COPh | H | *[3], 20 min, Δ | 85[b] | [177] |
| 5-Br | HCl | 2-ene | COPh | H | AcOH – $Ac_2O$, 20 min, Δ | 30[b] | [177] |
| H | — | 2-ene | Ac | H | $ZnCl_2$, xylene, 20 min, Δ | 62[b] | [177] |
| H | — | 2-ene | COPh | H | $ZnCl_2$, xylene, 20 min, Δ | 65[b] | [177] |
| 5-MeO | HCl | 2-ene | $CO_2Bn$ | H | *[3], 20 min, Δ | 81[b] | [177] |
| 5-MeO | HCl | 2-OH | $CO_2Bn$ | H | *[3], 35 min, Δ | >95[б] | [177] |
| H | — | 2-OMe | COPh | $CO_2Me$ | $ZnCl_2$, xylene, 1 h 30 min, Δ | 74[b] | [182] |
| H | — | 2-OMe | COPh | $CO_2Me$ | $ZnCl_2$, xylene *[2] | 74[e] | [183] |
| H | HCl | 2-OMe | Ts | $CO_2Me$ | AcOH, 100°C, 4 h | 71[b] | [182] |
| H | — | 2-OMe | Ts | $CO_2Me$ | $ZnCl_2$, xylene *[2] | 73[e] | [183] |
| H | HCl | 2-OH | $CO_2Bn$ | $CO_2Bu$-*t* | *[3], 35 min, Δ | >95[b] | [177] |
| H | — | 2-OH | Ac | $CO_2Me$ | 0.1M HCl, Δ | 37*[4] | [228] |

* The trimer of pyrroline **3** with the addition of 1 equiv. of HCl.

*[2] The procedure and the characteristics of the substances were not given.

*[3] Solvent AcOH–EtOH–$H_2O$, 25:35:40.

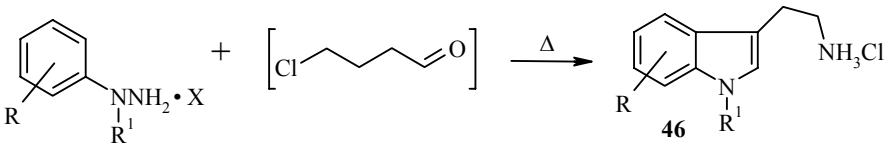
*[4]After hydrolysis to tryptophan.

For the arylhydrazine bases it is better to use $ZnCl_2$ in xylene, and for the hydrochlorides the 25:35:40 AcOH–EtOH–$H_2O$ mixture is usually better [177]. The analogous reactions with optically active derivatives of 2-hydroxy- and 2-methoxypyrrolidine-5-carboxylic acids lead to optically active tryptophan derivatives [177, 182, 183, 228] (see also [229]).

In contrast to the aminobutanal acetals, which were used in the synthesis of tryptamines [24, 142, 215], use of the trimer of both pyrrolidine [226] and piperideine [230] in the Fischer reaction led to unsatisfactory results, which may be explained by their instability in the acidic medium and the need for milder conditions. The success in the use of the trimers of pyrroline **3** in place of aminobutanal acetals in the synthesis of other heterocyclic compounds [33] makes it possible to hope for its successful future application for the synthesis of tryptamines.

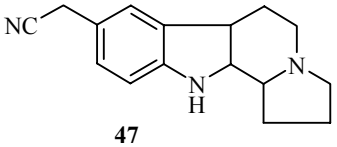
## 2.6. Synthesis of Tryptamines by the Grandberg Reaction

The Grandberg reaction [68, 231] is a widely used general method for the production of tryptamines (Table 15):




**46**

The reaction must be carried out without an acidic catalyst [72], or otherwise derivatives of β-chloroethylindole are formed (see below). The best yields are obtained with the bisulfite derivatives of chlorobutanal, and freshly prepared chlorobutanal and other 4-halobutanals and 4-hydroxybutanal tosylates [231] are less effective [72]. The use of an aldehyde containing significant amounts of the trimer [44] and also arylhydrazine hydrochlorides [72] in the reaction substantially reduces the yields of the tryptamines. Chlorobutanal acetals are stable in a neutral medium [44] and must therefore be hydrolyzed before the beginning of indolization. It is possible to combine their hydrolysis in the acidic medium with the formation of the arylhydrazones [232] followed by a Grandberg reaction in a close-to-neutral medium. During the synthesis of the tryptamine **46** (R = 5-$CH_2CN$) by reaction with chlorobutanal dimethyl acetal the side formation of the condensation product **47** was observed [77] (cf. [233] and [234]).




**47**

Later [235] it was found that the addition of salts that create buffer solutions makes it possible to bring more stable arylhydrazine hydrochlorides into the reaction and to increase the yield of the sulfamidomethyltryptamines significantly (see below in section 2.9), but the possibility for improvement of the yields for other types of tryptamines remains unresolved.

TABLE 15. Synthesis of Various Tryptamines by the Grandberg Reaction

| R | $R^1$ | X | Butanal* | Conditions | Yield, % | Reference |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| H | H | — | A | Aqueous alcohols, Δ | 70-71[a] | [68, 69, 231] |
| H | H | — | B | 60% MeOH, 14 h, Δ | 78[a] | [72] |
| H | Bn | — | A | 90% MeOH, 20 h, Δ | 75[a] | [68, 70] |
| H | Bn | — | B | 60% MeOH, 14 h, Δ | 78[a] | [72] |
| 5-OMe | Bn | — | A | 90% MeOH, 20 h, Δ | 70[a] | [68, 70] |
| 5-OMe | H | — | A | 90% MeOH, 20 h, Δ | 45[a] | [68, 231] |
| 5-OMe | H | — | A | MeOH–$H_2O$, AcONa | 48 | [60] |
| 5-$CH_2CN$ | H | HCl | B | Not indicated | 40[c] | [77] |
| 5-CN | H | — | B | EtOH–$H_2O$, 5:1, 18 h, Δ | 35[c] | [236] |
| 5-CN | H | HCl | B | EtOH–$H_2O$, 5:1, 80 °C | 35[c] | [237] |
| 5-OBn | H | — | B | 60% MeOH, 14 h, Δ | 60[c] | [72] |
| H | Me | $H_2SO_4$ | A | 90% MeOH, 10 h, Δ | 78[a] | [72] |
| H | Me | — | A | 90% MeOH, 8–10 h, Δ | 81[a] | [68] |
| H | Me | — | B | 60% MeOH, 14 h, Δ | 83[a] | [72] |
| H | *i*-Pr | — | A | 90% MeOH, 8–10 h, Δ | 87[a] | [68] |
| H | Ph | — | A | 90% MeOH, 8–10 h, Δ | 56[a] | [68] |
| H | 2-(2-Pyridyl)-ethyl | — | A | 90% MeOH, 8–10 h, Δ | 39[a] | [68] |
| 5-Me | H | $H_2SO_4$ | A | 90% MeOH, 10 h, Δ | 45[a] | [72] |
| 5-Me | H | — | A | 90% MeOH, 8-10 h, Δ | 48[a] | [68] |
| 7-Me | H | — | A | 90% MeOH, 8-10 h, Δ | 33[a] | [68] |
| 7-OMe | H | — | A | 90% MeOH, 8-10 h, Δ | 24[a] | [68] |
| 5-Br | H | — | A | 90% MeOH, 8-10 h, Δ | 80[c] | [68] |
| 7-Br | H | — | A | 90% MeOH, 8-10 h, Δ | 67[c] | [68] |
| 7-Br | H | — | A | MeOH, 95°C, 18 h | 11–23[b] | [71] |
| 5,7-$Br_2$ | H | — | A | MeOH, 95°C, 18 h | 5[b] | [71] |
| 5-Me, 7-Br | H | — | A | MeOH, 95°C, 18 h | 19[b] | [71] |
| 7-OMe | H | — | A | MeOH, 95°C, 14 h | 21[b] | [71] |
| 5,7-$F_2$ | H | — | A | MeOH, 95°C, 15 h | 21[b] | [71] |
| 6-Me, 7-Br | H | — | A | MeOH, 95°C, 15 h | 10[b] | [71] |
| 5-(*t*-Bu) | H | — | A | MeOH, 95°C, 15 h | 39[b] | [71] |
| 4-F, 5-Me | H | — | A | MeOH, 95°C, 15 h | 28[b] | [71] |
| 6,7-Benzo | H | — | A | MeOH, 95°C, 15 h | 38[b] | [71] |
| 5- Cyclohexyl | H | — | A | MeOH, 95°C, 15 h | 6[b] | [71] |
| 4,7-$Me_2$ | H | — | A | MeOH, 95°C, 15 h | 4[b] | [71] |
| 5-(*i*-Pr) | H | — | A | MeOH, 95°C, 15 h | 50[b] | [71] |
| 5,7-$Me_2$ | H | — | A | MeOH, 95°C, 15 h | 15[b] | [71] |
| 4,6-$Me_2$ | H | — | A | MeOH, 95°C, 15 h | 11[b] | [71] |
| 6,7-$Me_2$ | H | — | A | MeOH, 95°C, 15 h | 12[b] | [71] |
| 1,7-$(CH_2)_2$ | | — | A | 90% MeOH, 8-10 h, Δ | 43[b] | [68] |
| 1,7-$(CH_2)_3$ | | — | A | 90% MeOH, 8-10 h, Δ | 74[b] | [68] |
| 1,7-$(CH(Me)(CH_2)_2)$ | | — | A | 90% MeOH, 8-10 h, Δ | 92[b] | [68] |
| 5-$CO_2Et$ | H | HCl*[4] | D*[3] | $H_2O$–MeOH, 1:4, HCl, $Na_2HPO_4$, pH 5, 12 h, Δ | 32[d] | [232] |
| 5-$CO_2Et$*[2] | H | HCl | C | EtOH–$H_2O$, 5:1, 2 h, Δ | 34[b] | [238] |
| 5-$CH_2CONH_2$ | H | *[4] | C | 90% MeOH, 15 h | 23[d] | [224] |

TABLE 15. (continued)

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| 5-$CH_2CONHMe$ | H | — | C | EtOH–$H_2O$, 5:1, 20 h | 41[c] | [224] |
| 5-R*[5] | H | — | C | EtOH–$H_2O$ – 2H HCl, 7:3:1, 2 h, Δ | 8[b] | [236] |
| 5-R*[6] | H | HCl | C+HCl | EtOH–$H_2O$, 5:1, 4 h, Δ | 38[b] | [220] |
| 5-R*[7] | H | HCl | D | EtOH–$H_2O$, 5:1, 2 h, Δ | 23[b] | [239] |

* A = chlorobutanal, B = bisulfite derivative, C = dimethyl acetal; D = diethyl acetal.

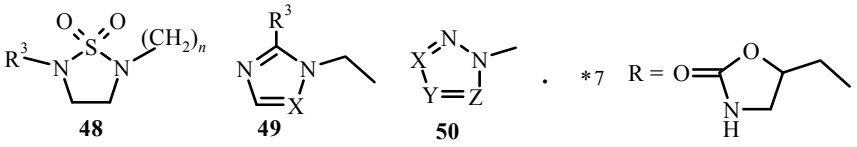
*[2] 5-$CH_2CO_2Et$, 5-$(CH_2)_3CO_2Et$, and 5-$CH_2CN$ were also prepared by this method (yields not given).

*[3] The use of A leads to a large amount of side products [240].

*[4] The hydrazone was isolated intermediately.

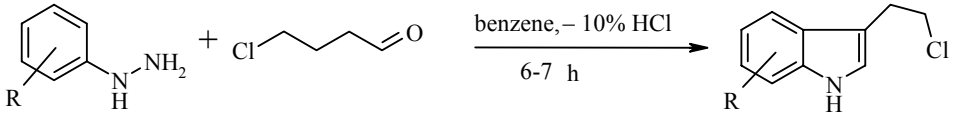
*[5] R = **48**, where $R^3$ = Me, $n$ = 1 (also $R^3$ = Me, $n$ = 0 and $R^3$ = Bn, $n$ = 0 with yields of 8-11%).

*[6] R = **49**, where $R^3$ = H, X = N (and also $R^3$ = H, X = CH; $R^3$ = Me, X = CH; R = **50**, where X, Y, Z = N, CH, CH; CH, CH, N; N, N, CH; N, CH, N with no indication of the yields).




## 2.7. Synthesis of Tryptamines through β-Chloroethylindoles

Indolization of 4-chlorobutanal phenylhydrazones in the presence of acidic catalysts leads to chloroethylindoles. Thus, chloroethylindole is formed when the arylhydrazine **51** (R = 3-$CH_2CONH_2$) is boiled with chlorobutanal in 50% acetic acid [224]. Chloroethylindoles **52** containing accepting groups are formed with low yields. At the same time, for example, in the reaction of 4-chloro-2-pentanone with N-benzyl-5-methoxyphenylhydrazine 1-benzyl-5-methoxy-2-methylchloroethylindole is formed with a yield of 67% during the indolization of the corresponding hydrazone in a 0.4 N ethanol solution of HCl (241).



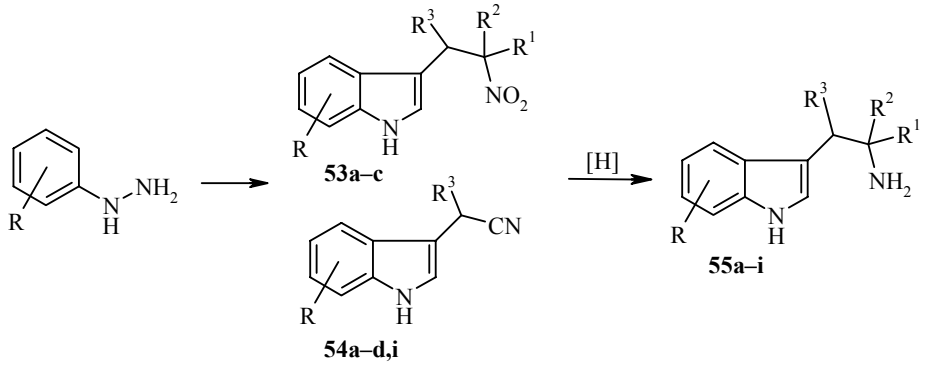

**51** **52a-d**

**52 a** R = 5-$NO_2$, 15%[b] (on the hydrazone) [233]; **b** R = 4-$NO_2$ (7%[b]), **c** R = 6-$NO_2$ (8%[b]) [66]; **d** R = 5-$CO_2Et$, 34%[b] (conc. $H_2SO_4$ is added to a boiling solution in toluene) [240]

In reaction with ammonia and amines the chloroethylindoles form tryptamines (65-88%) and N-alkyltryptamines (50-85%) [66, 233, 240, 241].

## 2.8. Other Examples of the Synthesis of Tryptamines Using the Fischer Method

It is possible to use derivatives of cyanopropanal and nitrobutanal in the Fischer reaction. Reduction of the indoles **53** and **54** leads to the tryptamines **55**




**53 a** R = 5-OBn; $R^1$ = Me, $R^2$ = $R^3$ = H (40%[b,c]); 1) 50% AcOH; 2) benzene–conc. HCl [242];
**53a** → **55a** R = 5-OH; $R^1$ = Me, $R^2$ = $R^3$ = H (~100%[d]); 3.4 atm $H_2$, Pd/C, quantitatively [242];
**53b** R = 4,6-$F_2$, 5-OMe; $R^1$ = Me, $R^2$ = $R^3$ = H (59%[b]); 90% $HCO_2H$; **53b** → **55b** (54%[b]) $LiAlH_4$ [125];
**53c** R = 4,6-$F_2$, 5-OMe; $R^1$ = $R^2$ = H, $R^3$ = Me (39%[b]); 90% $HCO_2H$; **53c** → **55c** (43%[b]) $LiAlH_4$ [125];
**55d–h** $R^1$ = Me, $R^2$ = $CO_2Et$, $R^3$ =H, **d** R = H (20%[c]); **e** R = OBn (47%[d]); **f** R = Me (86%[d]); **g** R = Cl (13%[d]);
**h** R = F (34%[d]); 1) AcOH; 2) 10% SSA – 2-PrOH, 1–10 h, Δ; 3) Ni-Ra, $H_2$, 10 atm; one-pot [243];
**54a** R = H, $R^3$ = $CO_2Me$ (40%[b]); THF, HCl, Δ, 35 min [86, 87];
**54i** → **55i** R = H, $R^1$ = $R^2$ = H, $R^3$ = $CO_2Me$ (95%[b] in the form of the N–Ac derivative); $H_2$, 3.4 atm, 20 h, Ni-Ra; $Ac_2O$ [86, 87]; **55i** (40%[b]); Fischer synthesis from aminobutanal **7c**, THF, HCl, Δ, 35 min [86, 87];
**54a–d** $R^3$ = H, **a** R = 5-OBn (61%[b]); **b** R = 5-OMe (67%[b]); **c** R = 5-OEt (51%[b]); **d** R = 7-OMe (11%[b]);
50% AcOH, 80°C, 2 h 30 min [215]; **54** → **55** see also the preparative methods in [244] ($LiAlH_4$) and [245] ($H_2$, Ni-Ra)

Catalytic hydrogenation of the indoles **54** in the presence of alkylamines leads to N-alkyltryptamines [246, 247]. In the presence of a benzyl group it is possible to combine catalytic reduction with debenzylation [242].

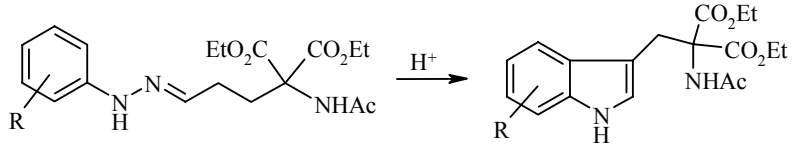
Butanals containing accepting groups and a quaternary carbon atom at position 4 are formed readily and with almost quantitative yields by the addition of the respective carbonyl component to acrolein in the presence of basic catalysts. In many cases this makes it possible to carry out the preparation of the phenylhydrazone (and sometimes even the subsequent indolization) in one pot. The ethyl esters of α-methyltryptophans **55d-h**, from which the α-methyltryptophans are formed during alkaline hydrolysis, were obtained in this way [243].

The carbonyl component required for the production of N-acetyl-α,α-di(ethoxycarbonyl)tryptamines is formed quantitatively during the reaction of acrolein and acetylaminomalonic ester in the presence of sodium methoxide in benzene [248, 249]. If the reaction mixture is acidified with acetic acid and heated with arylhydrazine the hydrazone is formed. Isolation of the hydrazone in the crystalline form simplifies the purification and increases the overall yield of the indole **56** [250]. The best catalyst is 5-10% $H_2SO_4$ in

TABLE 16. Production of N-Acetyl-α,α-di(ethoxycarbonyl)tryptamines **56**

| R | Indolization conditions | Yield of hydrazone, % | Yield of tryptamine, % | Reference |
|---|---|---|---|---|
| 5-OBn | SSA, 90% *i*-PrOH, Δ, 1 h | Without isolation | 70[c] (on the acrolein) | [251] |
| H | 7% $H_2SO_4$, Δ, 5.5 h | 87[c] [248] | 90[c] | [252] |
| 7-Cl | 5% $H_2SO_4$, Δ, 5 h | 84[c] | 99[c] | [249] |
| 5-Br | 5% $H_2SO_4$, Δ, 5 h | Not indicated | 85[c] | [250] |
| 5-F | 5 / 7% $H_2SO_4$, Δ, 5 h | 61[c] [253] | 92[c] / 89[c] | [250]/[253] |
| 5-Cl | 5% $H_2SO_4$, Δ, 5 h | Not indicated | 60[c] | [250] |
| 5-Me | 5 / 7% $H_2SO_4$, Δ, 5 h | 90[c] / ~100[c] | 90[c] / 61[c] | [250]/[254] |
| 4,6-$Me_2$ | 7% $H_2SO_4$, Δ, 4.5 h | 90[c] | 77[c] | [254] |
| 6-Me | 7% $H_2SO_4$, Δ, 4.5 h | 88-93[c] | 16[c] | [254] |
| 4-Me | | | 17[c] | |
| 5-MeO | 5% $H_2SO_4$, Δ, 5 h | Not indicated | >61[c] | [250] |
| 5,7-$F_2$ | 5-10% $H_2SO_4$, Δ, 5 h | 85-90[e] | 12[b] | [255] |
| 7-F | 5-10% $H_2SO_4$, Δ, 5 h | 85-90[e] | 38[b] | [255] |
| 4,7-$F_2$ | 5-10% $H_2SO_4$, Δ, 5 h | 85-90[e] | 36[b] | [255] |
| 5-$NO_2$ | PPA, 110°C | Not indicated | 9[b] | [256] |
| 7-$NO_2$ | PPA, 110°C | 65[d] | 46[d] | [257] |

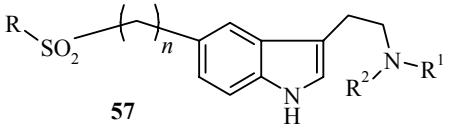
aqueous solution [251]. (In alcohol solution the yield is greatly reduced.) The most characteristic examples are given in Table 16, and a large set of examples was published in [2]. The obtained tryptamines **56** are hydrolyzed and decaeboxylated to acetyltryptophans and then to tryptophans (see [250] and the references in Table 16).




**56**

Various derivatives of glutamic γ-aldehyde [228, 229, 258, 259] are widely used for the Fischer synthesis of derivatives of racemic and L-tryptophans [228, 229, 258].

### 2.9. 5-Sulfamidoalkyltryptamines



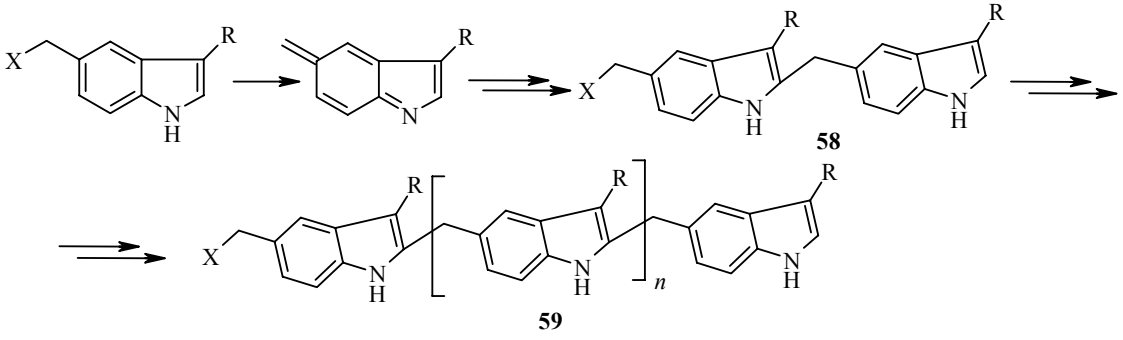

**57**

**57 a** $n$ = 1, R = NHMe, $R^1 = R^2$ = Me – sumatriptan,
**b** $n$ = 1, R = $N(CH_2)_4$, $R^1 = R^2$ = Me – almotriptan

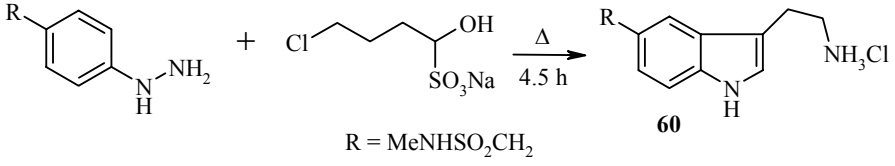
In the series of tryptamines it is necessary to consider 5-sulfamidoalkyltryptamines separately. Many drugs for the treatment of migraine belong to the class of compounds **57** (e.g., **57a** and **57b**) and have been described in detail in the patent literature. The production of these compounds is attended by specific difficulties. Despite the use of a large number of methods their synthesis is typified by low yields. Synthesis by the Abramovich–Shapiro method [16, 260] (see the successful modifications in [16, 30]) and the introduction of

the sulfamide group [232] into existing tryptamines come up against certain obstacles. For biochemical investigations, therefore, the Fischer method is a convenient procedure for the synthesis of large series of compounds. (Among other methods for the construction of the indole ring see, for example, the application of the Heck method [232].)

The sulfamidomethyl group in the tryptamines **57** ($n$ = 1) exhibits increased electrophilicity, e.g., the condensation product **58** can be formed during their recrystallization from the aqueous acid [234]. The formation of alkylation products **58** [261, 262, 240], including high-molecular polymers **59** [262] and other side products, is therefore possible under the conditions of the Fischer reaction, and they greatly complicate the isolation of the desired tryptamines. In order to suppress the formation of the condensation products it is possible to use hydrazines with a sulfamide group in the latent isothiazolone form [261] or protected by an ethoxycarbonyl group [234] in the Fischer reaction. This facilitates purification, and the protecting groups are then easily removed in an alkaline medium. Indolization of the sulfamidomethylphenylhydrazones of δ-substituted pentanals using phosphoric acid in a two-phase system increases the yield of indole and facilitates the separation of the condensation products [262].




During the production of tryptamine **60** by the Grandberg reaction [235] the addition of salts that create buffer solutions and also diatomite (as sorbent) makes it possible to increase the yield significantly and facilitates the isolation procedure (Table 17).



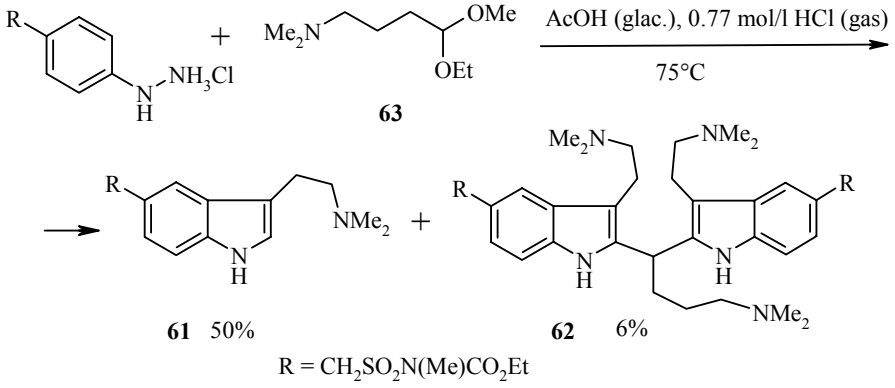

However, it is not known what processes are prevented by the buffer medium. The reactions leading to the side products **58** and **59** or the formation of the product from condensation of the aldehyde and the tryptamine may be suppressed.

During the synthesis of the tryptamine **61** by the Fischer reaction in acetic acid the best catalyst is hydrogen chloride ($H_2SO_4$ and $MeSO_3H$ are almost equivalent to it), whereas the use of $HClO_4$, TsOH, and sulfosalicylic acid and also other solvents significantly reduces the yields of the tryptamine **61**. Together with the tryptamine the condensation product **62**, the mechanism of formation of which is unclear, was also isolated. It was established that it is formed not from the tryptamine **61** but in parallel. (Compound **62** is only formed from the reagents **61** and **63** in small amounts under analogous conditions.) The **62**-**61** ratio is increased to 2:1 if the Fischer reaction is conducted at room temperature [234].

TABLE 17. The Effect of the Conditions of the Grandberg Reaction on the Yield of the Tryptamine **60**

| Form of hydrazine | pH-modif. agent | Solvent | Load | Yield, % |
|---|---|---|---|---|
| Base | — | EtOH–$H_2O$, 3:1 | 23 mmol | 33* |
| Base, 1 equiv. HCl | 0.25 equiv. $Na_2HPO_4$ | EtOH–$H_2O$, 3:1 | 23 mmol | 57* |
| Hydrochloride | 0.25 equiv. $Na_2HPO_4$ | EtOH–$H_2O$, 3:1 | 23 mmol | 67* |
| Hydrochloride | 1.5 g of diatomite | EtOH–$H_2O$, 1:2 | 47 mmol | 53* |
| Hydrochloride | 0.25 equiv. $K_2CO_3$ | EtOH–$H_2O$, 1:2 | 47 mmol | 55* |
| Hydrochloride | 0.25 equiv. $Na_2HPO_4$ | EtOH–$H_2O$, 1:2 | 47 mol | 71* |
| Hydrochloride | 0.25 equiv. $Na_2HPO_4$ | MeOH–$H_2O$, 1:1 | 23 mmol | 71* |
| Hydrochloride | 0.25 equiv. $Na_2HPO_4$ | *i*-PrOH–$H_2O$, 2:3 | 23 mmol | 69* |
| Hydrochloride | 0.25 equiv. $Na_2HPO_4$ | EtOH–$H_2O$, 3:1 | 3 mol | 56*[2] |
| Hydrochloride | 0.12 equiv. $Na_2HPO_4$ 7.5 g of diatomite | EtOH–$H_2O$, 1:2 | 0.4 mol | 64*[2] |

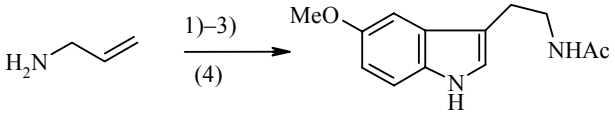
* By chromatography.
*[2] Extraction followed by crystallization.




The most characteristic examples of the synthesis of tryptamines **57** are presented in Table 18.

## 2.10. Hydroformylation of Allylamine Derivatives: One-Pot and Tandem Synthesis of Tryptamines

The choice of conditions for the hydroformylation process was discussed in section 1.5. In the first preparative method of hydroformylation of allylacetamide the obtained solution of acetylaminobutanal was used for a one-pot synthesis of melatonin [199].




1) $Ac_2O$ 0-5°C; 2) CO, $H_2$, [Rh], toluene–water, 1:1; 3) 4-methoxyphenylhydrazine hydrochloride, $H_2O$–AcOH, 50:1, Δ, 10 min; 4) the yield 44% on the 4-methoxyphenylhydrazine (16% on the allylamine)

TABLE 18. Synthesis of Tryptamines **57** by Various Methods

| R | *n* | Form of hydrazine | $NR^1R^2$ | Aldehyde* | Indolization conditions | Yield, % | Reference |
|---|---|---|---|---|---|---|---|
| $NH_2$*[2] | 0 | *[3] | $NH_2$ | A | 140-150°C with $ZnCl_2$ | Not indicated | [260] |
| $NH_2$ | 0 | Hydrochloride | NPht | P | 2 h in 50% AcOH | 6[b] *[4] | [247] |
| Ph | 0 | Base | $NH_2$ | G(C) | MeOH–$H_2O$ 9:1, 4 d, Δ | 48[b] | [263] |
| *p*-$MeC_6H_4$ | 0 | Base | $NH_2$ | G(C) | MeOH–$H_2O$ 9:1, 4 d, Δ | 30[b] | [263] |
| $NH_2$ | 1 | Hydrochloride | $NH_2$ | G(M) | EtOH–$H_2O$, 5:1, 1) 50°C, 1.5 h; 2) $NH_4OAc$, Δ, 3.5 h | 20[b] | [247] |
| $NC_4H_8$ | 1 | Hydrochloride | $NH_2$ | G(E) | 1) HCl, 2) $Na_2HPO_4$, pH 5, $H_2O$–MeOH, 1:6, 12 h, Δ | 58[d] | [232] |
| NHMe | 1 | Hydrochloride | $NH_2$ | G(M) | 1) HCl, 2) $Na_2HPO_4$, EtOH–$H_2O$, 3:1, 4 h, Δ | 45–50[c] | [264] |
| NHMe | 1 | *[3] | $NMe_2$ | D | PPE, $CHCl_3$, 4 h, 20°C | 22[6] (30 on the hydrazone) | [265] |
| NHMe | 1 | Hydrochloride | $NH_2$ | G(M) | EtOH–$H_2O$, 5:1, 2 h, Δ | 32[b] | [247] |
| NHMe | 1 | Hydrochloride | NPht | P | 25% AcOH, Δ, 1 h | 41[d] (83[b]) *[5] | [247] |
| NH-*c*-Hex | 1 | Hydrochloride | $NH_2$ | G(M) | EtOH–$H_2O$, 5:1, 4 h, Δ | 50[b] | [247] |
| NHBn *[6] | 1 | Hydrochloride | $NH_2$ | G(M) | EtOH–$H_2O$, 5:1, 4 h, Δ | 63[b] | [247] |
| NHMe | 2 | *[3] | $NMe_2$ | D | PPE, $CHCl_3$, 8 min, Δ | 34[b] | [246] |
| H | 2 | *[3] | $NMe_2$ | D | PPE, $CHCl_3$, 10 min, Δ | 11[b] | [246] |
| NHMe | 2 | Hydrochloride | $NH_2$ | G(M) | EtOH–$H_2O$, 5:1, 5 h, Δ | 33[b] | [246] |
| NHBn | 2 | Hydrochloride | $NH_2$ | G(M) | EtOH–$H_2O$, 4:1, 2 h, Δ | 17[b] | [246] |

*A = aminobutanal, P = phthalimidobutanal and its acetals, G = by the Grandberg reaction (M, E, and C are the dimethyl acetal, diethyl acetal, and free chlorobutanal respectively), D = dimethyl acetal of dimethylaminobutanal, PPE = polyphosphoric ether.

*[2] Cannot be obtained by the Grandberg reaction in spite of variation of the conditions (a complex mixture of side products is formed) [232].

*[3] The hydrazone was isolated intermediately.

*[4] See also the procedure for preparative dephthalylation [30].

*[5]The yield from dephthalylation is given in parentheses.

*[6]Also obtained under similar conditions with R = NHPh; $NMe_2$; $NHCH_2CH_2Ph$; NHAllyl; NHPr-*i*; NHEt with much lower yields.

This approach was developed further for the tandem synthesis of a series of phthalyltryptamines. Thus, during hydroformylation in the presence of arylhydrazines and toluenesulfonic acid (in toluene or THF) the hydrazones that form are indolized into tryptamines, and the addition of arylhydrazine suppresses the side processes. The yield can be increased by using benzhydrylidene-protected hydrazines, which are produced either directly from benzophenone and arylhydrazine or from aryl bromide and benzophenone hydrazone in the presence of palladium acetate [266, 267, 197].

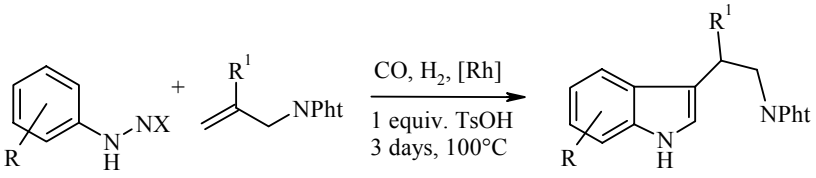
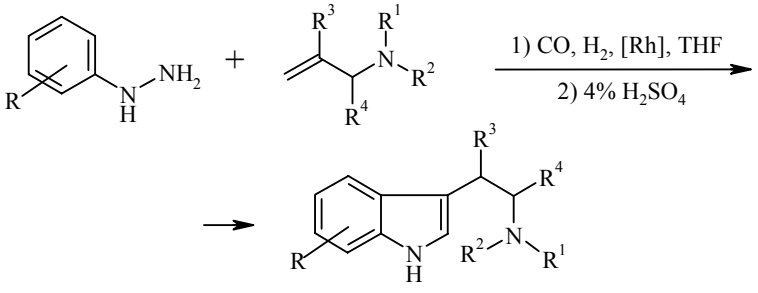



TABLE 19. Tandem Synthesis of Tryptamines in Organic Solvents

| R | $R^1$ | X | Yield, % | Reference | R | $R^1$ | X | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|
| H | H | $H_2$ | 46[6] | [197] | 5-F | Me | $CPh_2$ | 47[b] | [168] |
| H | Me | $H_2$ | 60[6] * | [197] | 5-Cl | Me | $CPh_2$ | 78[b] | [168] |
| 5-Cl | Me | $H_2$ | 60[6] * | [197] | 5-Br | Me | $CPh_2$ | 50[b] | [168] |
| 5-(*t*-Bu) | Me | $H_2$ | 48[6] * | [197] | 7-Me | Me | $CPh_2$ | 48[b] | [168] |
| H | Me | $CPh_2$ | 83[6] | [168] | 7-Cl | Me | $CPh_2$ | 42[b] | [168] |

* The tryptamines were isolated in the form of N(1)–Ts derivatives obtained by the action of TsCl on the reaction mixture in the aqueous NaOH–toluene system.

Since the tandem synthesis of tryptamines in organic solvents is sometimes complicated by the separation of poorly soluble salts of toluenesulfonic acid it is better to conduct the indolization of the arylhydrazones separately. It was found that indolization with 4% $H_2SO_4$ leads to high yields and in some cases does not require further purification of the tryptamines **64**. At the same time the use of alcohol solutions of $H_2SO_4$ leads to low yields of the tryptamines [198].




**64**, **65**

**64** $R^4$ = H, **65** $R^4$ = Ph

TABLE 20. One-Pot Synthesis of Tryptamines **65**

| R | $R^3$ | $R^1$, $R^2$ | Indolization conditions | Yiekld, % | Reference |
|---|---|---|---|---|---|
| H | Me | Et, Ts | THF, 80°C, 2 h | 94[b] | [168] |
| H | Me | Et, COPh | THF, 80°C, 2 h | 85[b] | [168] |
| H | Me | Et, Ac | THF, 80°C, 2 h | 61[b] | [168] |
| H | Me | Et, Boc | THF, 80°C, 2 h | 58[b] | [168] |
| 5-OMe | Me | Pht | THF, 80°C, 2 h | 95[b] | [168] |
| H | Me | Pht | THF, 80°C, 2 h | 38[b] | [168] |
| 5-Br | Me | Pht | THF, 80°C, 2 h | 50[b] | [168] |
| H | H | Ts, H | THF, 80°C, 2 h | 59[b] | [168] |
| H | H | Pht | THF, 80°C, 2 h | 51[b] | [168] |
| 5-OMe * | H | Pht | THF, 80°C, 2 h | 80[b] | [168] |
| H | H | Ts, Et | THF, 80°C, 2 h | 80[b] | [168] |
| H | H | Me, Me | $H_2O$, 100°C, 2 h | ~100[d] | [198] |
| 5-(*p*-$FC_6H_4CONH$)* | H | Me, Me | $H_2O$, 100°C, 2 h | 44[d] | [198] |
| H | H | $(CH_2)_5$ | $H_2O$, 100°C, 2 h | 97[d] | [198] |
| H | H | $(C_2H_4)_2NPh$ | $H_2O$, 100°C, 2 h | 96[d] | [198] |
| H | H | $(C_2H_4)_2NCO_2Et$ | $H_2O$, 100°C, 2 h | 94[b] | [198] |

*Arylhydrazines in the form of α-Boc derivatives, obtained by the reaction [268] of aryl iodides with N-Boc-hydrazine [198].

If optically active α-phenylallylamines are used in the reaction the phenyltryptamines **65** ($R^1 = R^2 = Et$ (85%[b]); $R^1R^2 = (CH_2)_5$ (54%[b])) are obtained with insignificant loss of optical purity [198].

It is possible to combine the hydroformylation and indolization processes in aqueous medium. (When necessary water-soluble sulfo derivatives of phosphine ligands are added.) The use of such a procedure leads to the tryptamine **64** ($R = R^3 = H$; $R^1R^2 = (C_2H_4)_2NCO_2Et$) with a quantitative yield. Both the one-pot methods and the tandem syntheses were extended to the synthesis of derivatives of homotryptamines [198].

Hydroformylation with a subsequent Fischer reaction was examined in detail in [269].

After analysis of existing data on the synthesis of tryptamines using the Fischer reaction it is possible to reach the following conclusions.

**1. Optimum Procedures.** The best and most widely used catalyst for the synthesis of N,N-dialkyltryptamines, N-acetyl-α,α-di(ethoxycarbonyl)tryptamines, and certain acyltryptamines is a 4% solution of $H_2SO_4$. Under such conditions the presence of halogens (F, Cl, Br) in the benzene ring is permitted, and the peptide bonds and carbamate groups are retained [198]. The use of $H_2SO_4$ solutions with a significant alcohol content is probably undesirable [198, 251]. The method of indolization at moderate temperatures [214] in a water–alcohol solution of acetic acid is well recommended for the synthesis of acyltryptamines from arylhydrazines (in the form of hydrochlorides) with electron-donating substituents. The Grandberg reaction often leads to unpredictable results, and the yields of the sulfamidotryptamines in this reaction can be significantly increased if the reaction is carried out in the presence of $Na_2HPO_4$ [235]. Isolation of the crystalline hydrazones in the synthesis of phthalyl- [88] and N-acetyl-α,α-di(ethoxycarbonyl)tryptamines [250], for example, increases the indolization yield and makes it possible to obtain the tryptamines without complicated isolation and purification procedures.

**2. Formation of Side Products.** The formation of products from condensation with the aldehyde was observed during indolization in the HCl–benzene system [233], in acetic acid solutions of mineral acids [234] (and also, possibly, in acetic acid solution at 80°C [214, 77]), and in the Grandberg reaction [77], and this reduces the yields of the indolization products. The presence of a sulfamidoalkyl group can lead to additional

self-polycondensation processes. All these side reactions can reduce the yield to a significant degree and complicate the purification procedures. The synthesis of tryptamines substituted at position 2 does not come up against such limitations (e.g., see [263]).

**3. Dependence of the Yields on the Structure of the Reagents.** On account of the use of various methods and isolation procedures the dependence on the structure of the reagents is not always obvious. Arylhydrazines with accepting groups often require more rigorous indolization conditions and more thorough protection of the amino group and lead to smaller yields of the tryptamines. The use of arylhydrazines containing more than one halogen atom and containing a halogen (particularly fluorine) or alkoxy (aryloxy) groups at the *ortho* position can lead to very low yields of the tryptamines. Arylhydrazines containing sulfamide, heterocyclic, carboxyl, and alkylcarboxyl groups often lead to unsatisfactory yields of tryptamines irrespective of the indolization method. In some cases protection of the sulfamide groups can improve the yield [16, 234]. The synthesis of acetyltryptamines can give reduced yields compared with the synthesis of other acyltryptamines. Tryptamines containing accepting groups at the α-position of the ethylamine fragment are obtained with higher yields.

A large number of synthetic equivalents of aminobutanal derivatives can be used for the synthesis of tryptamines, but far from all of them have found practical application. Of them the dioxolanes derivatives have the lowest while free aldehydes, their dialkyl acetals, and 2-hydroxypyrrolidines have the highest reactivity and popularity. The relation between the form of the aldehyde and the yield of the tryptamine is not totally clear. Thus, in some cases the use of free chlorobutanal in the Grandberg reaction significantly reduces the yield of the tryptamine possibly on account partly of disregard of the extreme instability of this aldehyde. On the whole the heterocyclic equivalents of acylaminobutanals are no less effective than the acyclic compounds in the synthesis of tryptamines but are more rarely used.

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