

## SYNTHESIS OF HETEROCYCLES USING AMINOACETALS

James M. Bobbitt and André J. Bourque<sup>1</sup>

Department of Chemistry, University of Connecticut, Storrs, CT 06268, U.S.A.

**Abstract** — The use of 2-aminoacetaldehyde acetals as C-C-N synthons in heterocyclic synthesis is summarized. The Pomeranz-Fritsch synthesis of isoquinolines and its modifications since 1970 are described. Coverage of the synthesis of other heterocyclic systems using the acetals is given.

The acetals of 2-aminoacetaldehyde (**1**), usually simply called aminoacetals, are convenient synthons for placing a C-C-N unit in a molecule and have been used extensively in heterocyclic chemistry. The ethyl and methyl acetals are commercially available. The molecules have a nucleophile, the nitrogen, at one end and a blocked electrophile, the aldehyde at the other. Thus, one can attach the nitrogen by alkylation to a number of functional groups and then free the electrophilic aldehyde by hydrolysis. The aldehyde can react with a nucleophile to fully incorporate the synthon. The nucleophile may be an aromatic ring as in most of the isoquinoline syntheses or a negative atom as is the case in most of the other heterocyclic systems.

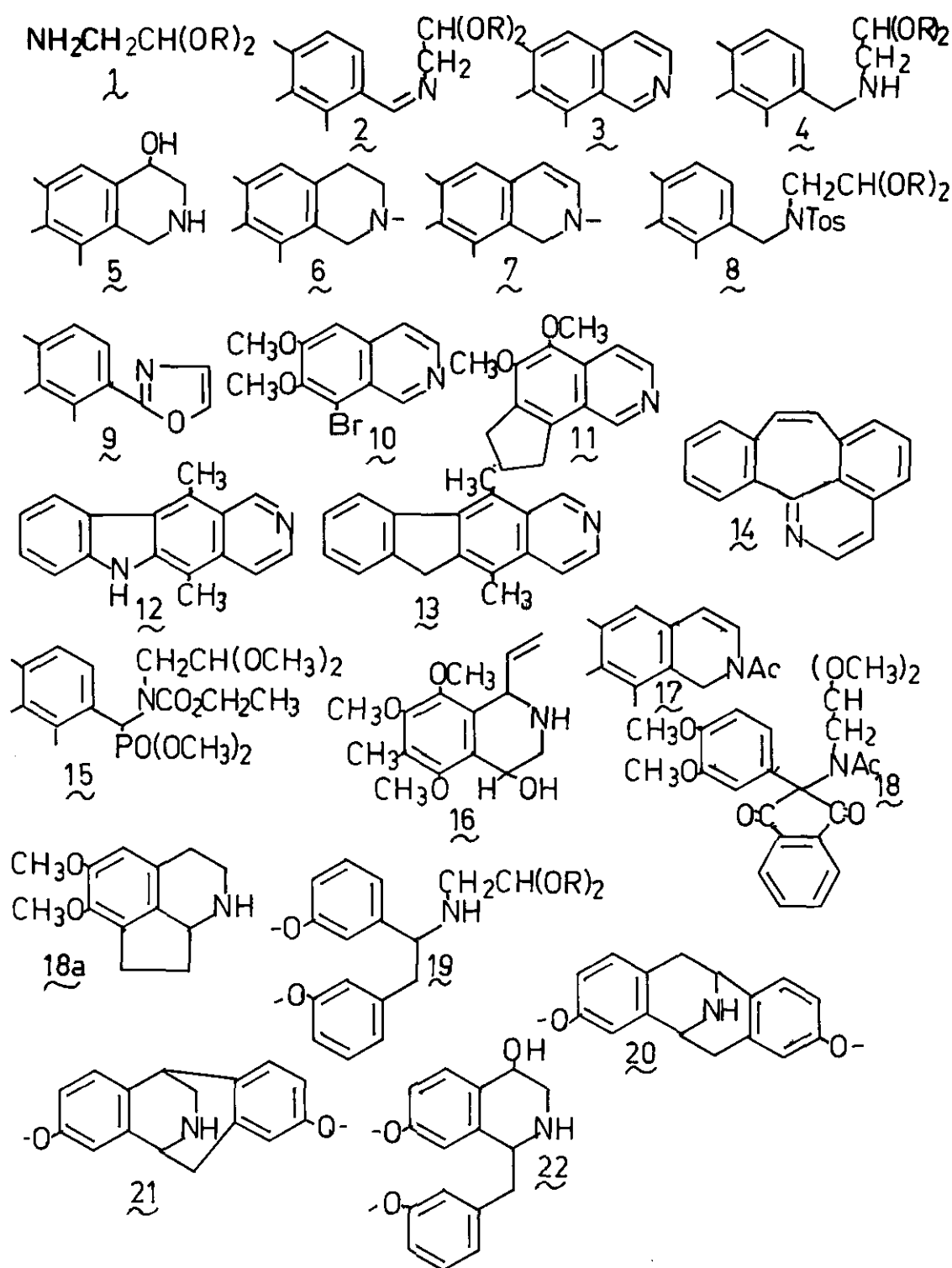
Isoquinoline Systems

Work in this area has been summarized by Gensler,<sup>2</sup> Dyke,<sup>3</sup> and Bobbitt.<sup>4</sup> Thus, only work published after 1970 or especially pertinent papers before that time will be cited. Furthermore, those papers which involve, primarily, reactions of 4-hydroxy-1,2,3,4-tetrahydroisoquinolines and 1,2-dihydroisoquinolines will be cited only if they are especially pertinent to the discussion.

The classical Pomeranz-Fritsch synthesis<sup>2</sup> involves the treatment of a benzalaminoacetal such as **2** with H<sub>2</sub>SO<sub>4</sub> to yield an isoquinoline such as **3**. Since the benzalaminoacetals are Schiff bases, easily obtained from **1** and aromatic aldehydes, an important ring system would appear to be available in two steps. Unfortunately, yields are low and not always repeatable. Conc. H<sub>2</sub>SO<sub>4</sub> tends to destroy **2** while dilute acids tend to hydrolyze it to its components. The problem has been attacked in three ways.

The first is to improve the classical method, mainly by developing better acid cyclizing reagents and obtaining a better understanding of the reactions. The second and third involve modifications of the synthesis in which **2** is reduced to a benzylaminoacetal, **4**, which can be safely cyclized in dilute acid.

In the first modification (the Bobbitt modification),<sup>4</sup> **4** is treated with 6 N HCl to yield a 4-hydroxy-1,2,3,4-tetrahydroisoquinoline, **5**, which can be used in various reactions<sup>3,4</sup> or hydrogenolyzed to a tetrahydroisoquinoline, **6**. Compounds such as **5** can also be converted to 1,2-



dihydroisoquinolines, 7, which undergo numerous interesting reactions.<sup>3</sup> In the second modification (the Jackson modification,<sup>5,6</sup> 4 is converted to an N-tosyl-(N-p-toluenesulfonyl) derivative, 8, which can be converted to the completely aromatic isoquinoline, 3, in acid. Both modifications take place in good yield, but both require an activating group, an oxygenated function, in an ortho or para position to the point of ring closure. They are complementary in that one leads to reduced isoquinolines and one leads to aromatic isoquinolines.

#### The Pomeranz -Fritsch Synthesis

There is little doubt that, for sufficiently activated systems, one of the above modifications works best for the synthesis of isoquinoline derivatives. However, for the less activated systems, the classical synthesis is the only choice. When the synthesis fails, the product, if any, is usually an oxazole such as 9.<sup>6a,6b</sup> A study of the degree of activation and the isoquinoline/oxazole ratio has been reported by Brown.<sup>7</sup> The reactions were carried out in H<sub>2</sub>SO<sub>4</sub> and P<sub>2</sub>O<sub>5</sub>. o-, m-, and p-Methylbenzaldehydes gave poor yields, 18-22%, of product which was almost entirely isoquinoline (95/5). The corresponding chlorobenzaldehydes gave poor yields, 9-25%, of a mixture of isoquinoline/oxazole (2/1 for o, 2/3 for p, 3/1 for m). The nitrobenzaldehydes gave reasonable yields of oxazoles and no isoquinolines.

A series of chloro, dichloro, and trichloroisoquinolines has been prepared<sup>8,9</sup> in yields varying from 6-55%. The method of Uff<sup>10</sup> using BF<sub>3</sub> in acetic acid with and without (CF<sub>3</sub>CO)<sub>2</sub>O has been used for making 10,<sup>11</sup> 11,<sup>12</sup> and a series of 6,7-dialkoxyisoquinolines.<sup>13</sup>

Various forms of phosphoric acid, polyphosphoric acid,<sup>14,17</sup> "super" polyphosphoric acid,<sup>18</sup> and orthophosphoric acid<sup>15,16,19</sup> have been used to make derivatives of ellipticine, 12,<sup>16,16a,19</sup> (by adding the fused pyridine ring), pyridofluorenes such as 13,<sup>18</sup> and other fused systems such as 14.<sup>17</sup>

Finally, a convenient method has evolved<sup>20</sup> in which a benzalaminoacetal is treated with ethyl chloroformate and trimethyl phosphite to yield a derivative, 15, which can be cyclized to an isoquinoline with titanium tetrachloride. The reactions can be carried out sequentially in one flask. Although activation is required for ring closure, the method works when free phenol groups are present.

The Bobbitt Modification.<sup>4</sup> Straightforward syntheses of 5-methoxy-7,8-methylenedioxy-,<sup>21</sup> 5,7,8-trimethoxy-,<sup>21</sup> 8-hydroxy-7-methoxy-1-methyl-<sup>22</sup> (the alkaloid arizonine), and 7,8-methylenedioxy-<sup>23</sup> 1,2,3,4-tetrahydroisoquinolines have been reported as well as a highly substituted derivative, 16, used in the synthesis of naphthridinomycin alkaloids.<sup>24</sup>

The need for activation in the benzene ring has been obviated in two ways. The first involves putting a methylthio group in the 3-position of 4 (leading to a 7-methylthiotetrahydroisoquinoline).<sup>25</sup> After ring closure, the sulfur containing group can be removed with nickel boride. Yields are good, but a mixture of isomers was obtained (5- and 7-methylthio-). The second way involves acetylation of the benzylaminoacetal to yield an N-acetyl derivative which can be closed with AlCl<sub>3</sub> to give N-acetyl-1,2-dihydroisoquinolines such as 17.<sup>26</sup> The compound was reduced and deacetylated to 6 or allowed to react with dichlorocarbene to yield, eventually, an azepine. The yields of dihydroisoquinolines in a series of chlorocompounds was fair.

Acetylation of the benzylamine nitrogen has been used in another case to prevent deamination of a 2-amino-1,3-diketone.<sup>27</sup> Thus, compound 18 could be cyclized smoothly with dilute HCl to an N-acetyl-1,2-dihydroisoquinoline whereas the N-H compound deaminated to the diketone. The benzyl-oxy-carbonyl group<sup>28</sup> and the N-carbethoxy group<sup>28a</sup> have also been used to prevent unwanted reactions in ring closures.

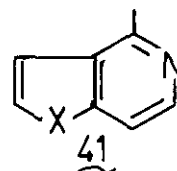
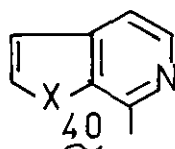
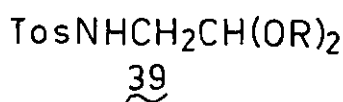
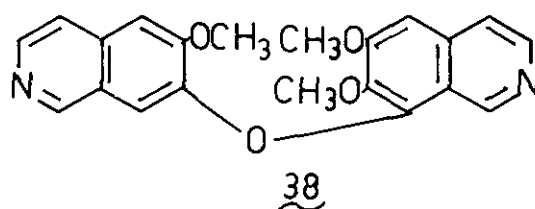
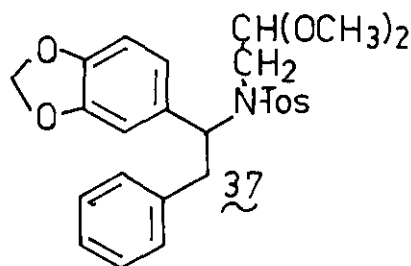
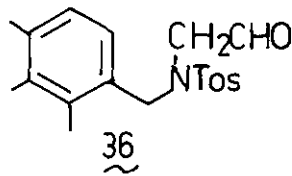
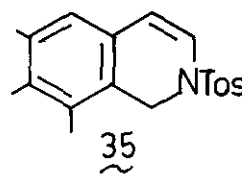
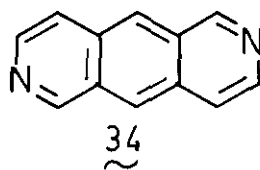
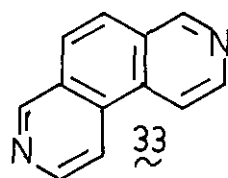
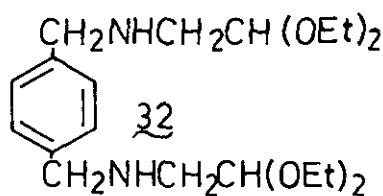
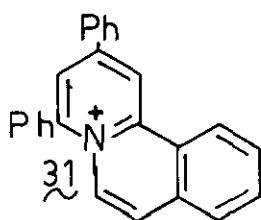
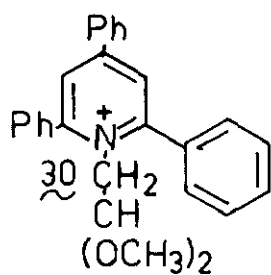
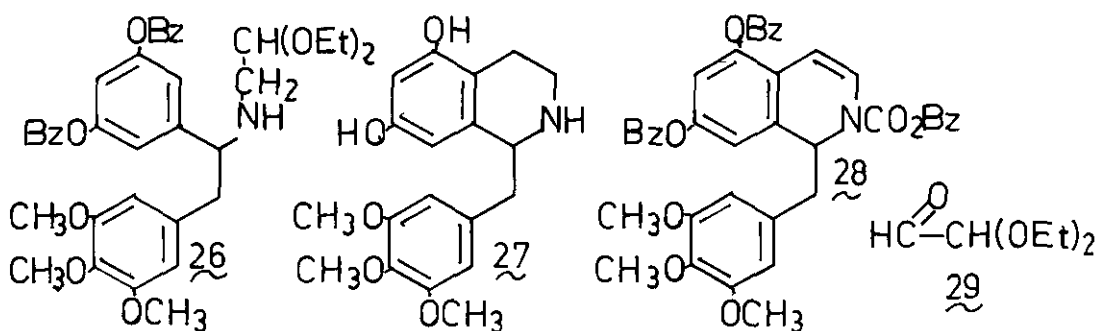
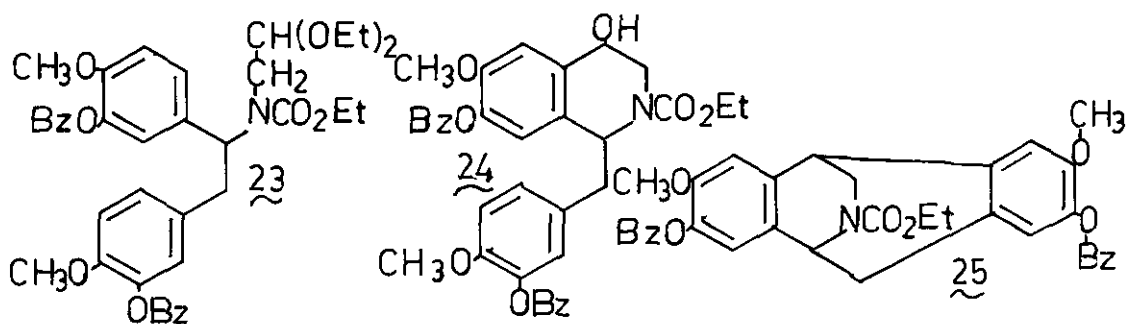
The construction of a nitrogen ring from a ketone Schiff base rather than an aldehyde Schiff base has been used less frequently, but some caution is required. Huffman<sup>29</sup> was able to prepare the reduced Schiff base leading to 18a only under careful anhydrous conditions. Similar work has been reported by others with tetralones<sup>30</sup> and a deoxybenzoin.<sup>31</sup> In the former case, ring closure was caused by HCl in tetrahydrofuran while in the latter case, conc. HCl was used.

When an oxygenated  $\alpha$ -benzylbenzylaminoacetal such as 19 is treated with acid, three products are possible;<sup>3,4,32</sup> a pavinane type, 20, an isopavinane type, 21, or a 4-hydroxytetrahydroisoquinoline, 22. In fact the simple ring closure to 22 is seldom found, a severe limitation in the synthesis of 1-benzylisoquinoline alkaloids.

McDonald and his coworkers<sup>28a</sup> were able to partially solve this problem using different ring closure conditions on an N-carbethoxybenzylaminoacetal, 23. Treatment of 23 with 6 N H<sub>2</sub>SO<sub>4</sub>/acetone (3:5) gave 4-hydroxytetrahydroisoquinoline, 24, in 89% yield. In pure HCO<sub>2</sub>H, 23 yielded the isopavine, 25, in quantitative yield. In a similar paper, Iwakuma and coworkers<sup>28</sup> have defined conditions which will produce any one of the desired products, at least with benzylaminoacetal, 26. Thus, treatment of 26 with oxalic acid in the presence of H<sub>2</sub> over 10% Pd/C gave 60% of 27, a tetrahydroisoquinoline derived by reduction of a type 22 compound. Apparently, the mild acid carried out the first ring closure rapidly, and the intermediate alcohol was hydrogenolyzed before the second ring closure could take place. When 26 was N-acylated with benzyloxy-carbonyl chloride, and the N-acyl derivative was treated with formic acid, an acylated isopavinane derivative corresponding to 21 was obtained in 80% yield, presumably by the reaction of the 4-hydroxy compound, 22. When N-acylated 26 was treated with HCl in tetrahydrofuran, the N-acyl-1,2-dihydroisoquinoline, 28 was obtained which could be converted to the pavine type corresponding to 20 in 80% yield with more concentrated HCl. Catalytic hydrogenation of 28 in the presence of oxalic acid also led to 27. The use of H<sub>2</sub>SO<sub>4</sub>/acetone and formic and oxalic acids may be especially important in future work.

Benzylaminoacetals have been made using 2,2-diethoxyacetaldehyde, 29, to reductively alkylate amino groups already in place,<sup>33,34</sup> and an efficient preparation of 29 has been described.<sup>34</sup> The dehydrogenation of a 4-hydroxy-5,6,7-trimethoxytetrahydroisoquinoline over 10% Pd/C led to a 4-hydroxyisoquinoline.<sup>35</sup> One would have thought the hydroxyl group would be lost. Fluoroboric acid, HBF<sub>4</sub>, was used to close pyrrilium salts such as 30 to quinolizinium salts such as 31.<sup>36</sup> Fuming H<sub>2</sub>SO<sub>4</sub> was used to close a double benzylaminoacetal, 32, to 33 and 34,<sup>37</sup> a reaction reminiscent of some early work by Fischer.<sup>38</sup> Yields of 33 and 34 were low.

The Jackson Modification. Although the reactions described above are convenient for the preparation of reduced isoquinolines, aromatic isoquinolines were still difficult to obtain directly until the techniques developed by Jackson and his coworkers appeared.<sup>5,6</sup> These involve the tosylation of benzylaminoacetals to give derivatives such as 8. In the first paper,<sup>5</sup> these tosyl



derivatives were closed to N-tosyl-1,2-dihydroisoquinolines such as 35 which were converted to isoquinolines such as 3 with potassium tert-butoxide. In a later pair of papers,<sup>6</sup> it was observed that the conversion of 8 to 3 could be done in one step with 6 N HCl in dioxan, although in some cases the two step acid-base process was still needed. The tosyl group is removed as a sulfonic acid which was isolated. When the benzene ring was not activated by an oxygen in position 5 or 7 (of the potential isoquinoline), the free aldehyde, 36, was obtained which, on further acid treatment, led to N-tosylbenzylamines. Yields of isoquinolines are excellent. In later work,<sup>39</sup> it was found that ring closure of tosylated  $\alpha$ -benzylbenzylaminoacetals such as 37 resulted in a low yield of desired benzylisoquinoline along with a large amount of 6,7-methylenedioxyisoquinoline formed by loss of the benzyl group. In at least one case<sup>6</sup> (8-hydroxy-7-methoxyisoquinoline) a free phenol group does not interfere with the reaction.

The method has been used to make a number of simple isoquinoline systems such as 8-benzyloxy-7-methoxy-,<sup>6,40,41</sup> 7,8-dimethoxy-,<sup>6,42</sup> 7,8-methylenedioxy-,<sup>6,42</sup> 7-methoxy-,<sup>6</sup> 5-methoxy-,<sup>6</sup> 5,7-dimethoxy-,<sup>6,43</sup> 6,7,8-trimethoxy-,<sup>6</sup> 5,6,7-trimethoxy-,<sup>6</sup> 8-hydroxy-7-methoxy-,<sup>6</sup> 5,8-dimethoxy-,<sup>6</sup> 6-methyl-7-methoxy-,<sup>44</sup> 5,7-dibenzyloxy-,<sup>45</sup> 7,8-dibenzyloxy-,<sup>45</sup> and 6-methoxy-7-hydroxyisoquinoline.<sup>46</sup> A double ring formation was brought about by Knabe<sup>47</sup> to give 38. The reaction has been used by several groups to make the pyridine ring of ellipticine, 12, and its derivatives.<sup>48-51</sup>

Two examples have appeared in which the N-tosylbenzylaminoacetals have been prepared from a benzyl halide or mesylate and N-tosylaminoacetal, 39. In one case, the sodium salt of 39 was prepared with sodium hydride<sup>52</sup> and several isoquinolines were made in good yield. In the other case,<sup>45</sup> potassium carbonate in dimethylsulfoxide was used as a base to condense 39 with a halide.

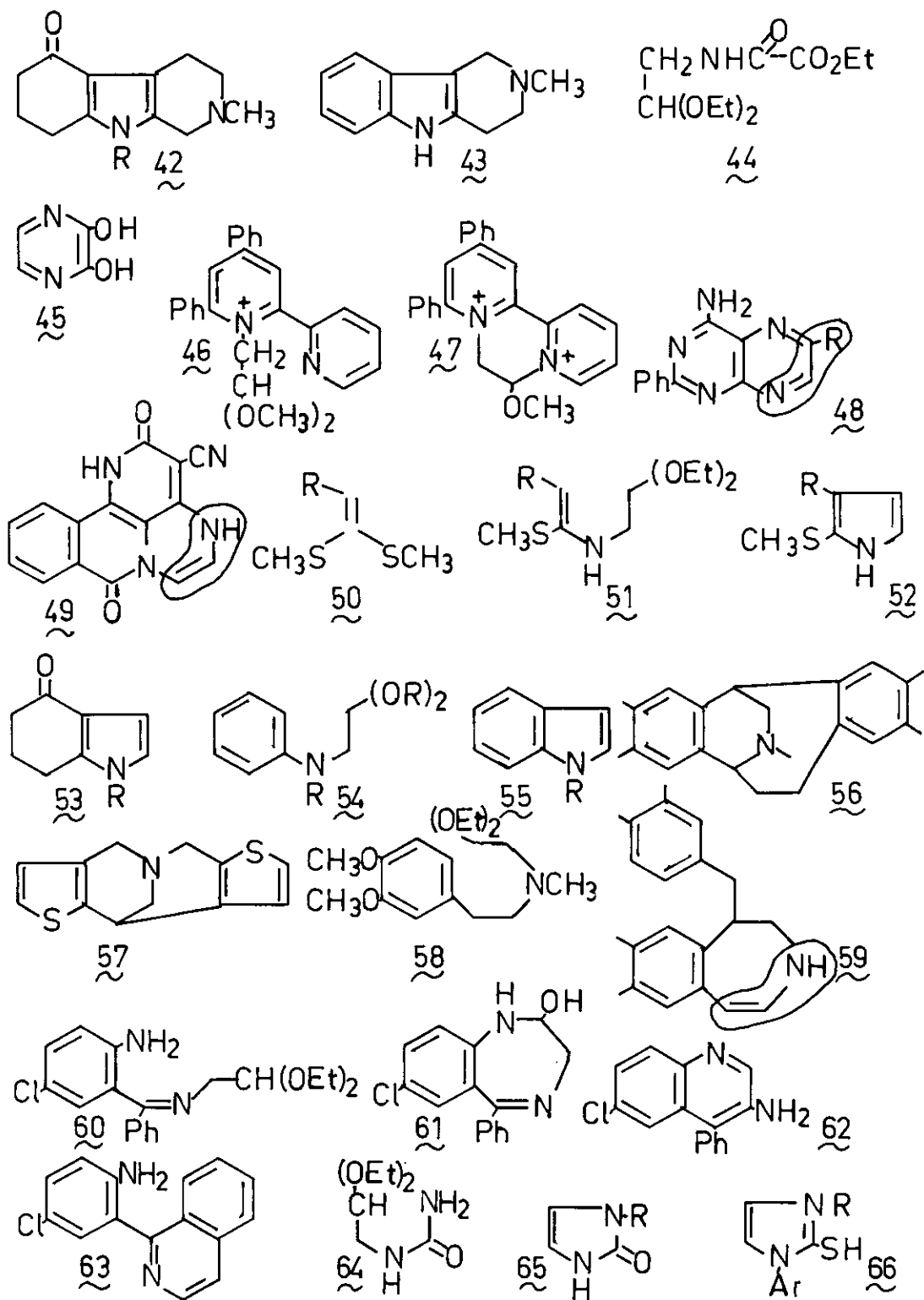
A reaction which may be similar to the Jackson sequence involves the treatment of benzylaminoacetals with chlorosulfonic acid to obtain numerous isoquinolines in fair yields.<sup>53</sup> No activation of the benzene ring is needed. The reaction is also reminiscent of the early work of Fischer using fuming sulfuric acid.<sup>38</sup>

#### Systems Containing Fused Pyridine or Reduced Pyridine Rings (Other Than Isoquinoline)

Several cases which should be in this group were mentioned previously as parts of the earlier discussion, such as the ellipticines and compounds 13, 14, 31, 33, and 34.

Various other activated rings can be used with aminoacetals to generate compounds having a fused pyridine or a fused, reduced pyridine ring. Given the ready availability of heterocyclic aldehydes, it is surprising that so little work has appeared. Herz<sup>54</sup> and Dressler<sup>55</sup> used the classic Pomeranz-Fritsch synthesis on thiophene aldehydes to make derivatives such as 40 and 41 (X = S). The work has been extended to selenophenes 40 and 41 (X = Se).<sup>56</sup> Polyphosphoric acid was used as a condensing agent, and yields were fair. Maffrand<sup>57</sup> has used the Bobbitt and Jackson modifications to make an extensive series of aromatic and partially reduced thienopyridines (40 and 41, X = S, with the pyridine ring reduced).

We<sup>58</sup> used a Mannich procedure in which N-methylaminoacetal and formaldehyde were condensed with a substituted pyrrole or an indole to make 42 and the  $\gamma$ -carboline, 43. The latter work has been challenged,<sup>59</sup> but we have repeated it successfully several times.



## Pyrazines and Fused Pyrazines

The condensation of ethyl oxalate and aminoacetal gave a monoamide derivative, 44, which, on treatment with ammonia, and subsequent ring closure with 0.5% HCl in acetic acid gave 2,3-dihydroxypyrazine, 45, in 70% yield. Treatment of 46 with conc. HCl gave 47, but the removal of methanol to yield a completely aromatic system was not successful.<sup>61</sup> The aminoacetal synthon has been used to prepare 48<sup>62</sup> (R = H from aminoacetal and R = Me from aminoacetonedimethylacetal) and 49. In each case the aminoacetal was added to a heterocyclic system by transamination. The added atoms in 48 and 49 are enclosed.

## Pyrroles and Indoles

Condensation of aminoacetal and 50 (R = various electronegative groups) gave 51 which could be closed to 52 with dry HCl in EtOH.<sup>64</sup> Condensation of cyclic 1,3-diketones with aminoacetals and N-alkylaminoacetals followed by acid catalyzed ring closure yielded pyrroles such as 53 (R = H and alkyl). Alkylaminoacetals worked best.<sup>58</sup>

The ring closure of anilinoacetals such as 54 to indoles such as 55 is a tantalizing idea since the starting materials are easily available from aniline and haloacetals. The reaction has been tried a number of times, as summarized by Uff<sup>10</sup> and Nordlander.<sup>65</sup> Uff was able to use his  $\text{BF}_3/\text{CH}_3\text{CO}_2\text{H}/(\text{CF}_3\text{CO})_2\text{O}$  method to close N-alkylanilinoacetals in good yield to N-alkylindoles (55, R = Me or Et). N-Hydrogenaniline derivatives, 54, R = H, did not work. The problem appears to have been solved by Jackson<sup>49,51</sup> and Nordlander<sup>65</sup> using, respectively, N-tosyl (54, R = tos) and N-trifluoroacetyl (54, R =  $\text{CF}_3\text{CO}-$ ) derivatives. The tosyl route gave only fair yields, but the trifluoroacetyl route was quite successful. Both the tosyl and acetyl groups were removable, the acetyl being more easily so. No ring activation is needed for ring closure.

## Bicyclic Systems

The double condensation of the aldehyde produced by hydrolysis of a benzylaminoacetal with two aromatic rings, probably sequentially rather than simultaneously, leads, as cited above, to bicyclic systems such as the pavinane, 20, and isopavinane systems, 21. This was first observed by Battersby.<sup>66</sup> The second ring closure is really a reaction of a 1,2-dihydroisoquinoline (to yield the pavinane system)<sup>3</sup> or a 4-hydroxytetrahydroisoquinoline (to yield the isopavinane system)<sup>4</sup> and the products can be controlled in some cases.<sup>28,28a</sup> Some recent examples are the synthesis of some homoisopavine derivatives such as 56<sup>67</sup> and the use of perchloric acid as a ring closure reagent for preparing isopavines.<sup>68</sup> It would appear that the perchloric acid system does not require ring activation for closure as is true for the other reactions of benzylaminoacetals. Maffrand has extended his thiophene work<sup>57</sup> to bicyclic systems such as 57.<sup>69</sup>

## Azepines and Diazepines

Both azepines and certain diazepines should be good candidates for syntheses using aminoacetals, but little success has been reported. Proctor<sup>70</sup> was unable to close 58, but Sainsbury<sup>71</sup> did obtain 59 from a similar reaction. In an attempt to close 60 to the diazepine, 61, with HCl as reported,<sup>72</sup> the quinoline 62 was obtained in 98% yield.<sup>73</sup> The authors cite this as a possible acid-



catalyzed Friedlander synthesis, but the extremely high yield may indicate something more interesting. When 60 was treated with conc.  $H_2SO_4$ , a good yield of the Pomeranz-Fritsch product, 63, was obtained.

### Imidazoles and Fused Imidazoles

4-Imidazolin-2-one, 65 ( $R = H$ ) can be made from potassium cyanate and aminoacetal via 64.<sup>74,75</sup> The reaction has an interesting history which has been summarized.<sup>74</sup> Similar reactions have been reported where the isocyanate is organic, in one case a blocked sugar,<sup>75</sup> and in another case, a carbethoxy group.<sup>76</sup> The products were, respectively, 65 where  $R$  was a 2,3,4-tri-O-benzoyl- $\beta$ -D-ribofuranosyl group and carbethoxy. Dry toluene with a small amount of *p*-toluenesulfonic acid was used to prepare the sugar derivative, and dilute aqueous acid was used in the other cases. Yields were good. In a similar reaction with aryl thiocyanates, a series of 1-aryl-2-mercaptoimidazoles, 66, was prepared.<sup>77</sup> N-Alkyl-2-aminoimidazoles were obtained by the sequence 67-69 ( $R = -CH_2CH_2N-(CH_3)_2$ ) which should be a good general route.<sup>78</sup>

Iminoesters, 70, obtained from nitriles by treatment with EtOH/HCl, react with aminoacetals to give 71 which can be converted to 2-alkylimidazoles, 72. In the cases where  $R$  was  $CD_3$ ,<sup>79</sup> or an aromatic residue,<sup>80</sup> conc.  $H_2SO_4$  was used for ring closure. When  $R$  was a large alkyl group, ring closure was made with dilute acid.<sup>81</sup> In a similar reaction, S-methylthioureas such as 73 can be converted to a mixture of 2-arylaminoimidazoles, 75 and 1-aryl-2-aminoimidazoles, 76.<sup>82</sup> Compounds with structure 75 were also obtained from phenylcyanamide and aminoacetal.<sup>82</sup> Several similar reactions have been reported.<sup>83,84</sup>

In a unique reaction,<sup>85</sup> a palladium complex was used to prepare several imidazoles by the sequence 77-80, where  $R$  was *tert*-butyl in most cases, and  $R'$  and  $R''$  were various combinations of H and  $CH_3$ .

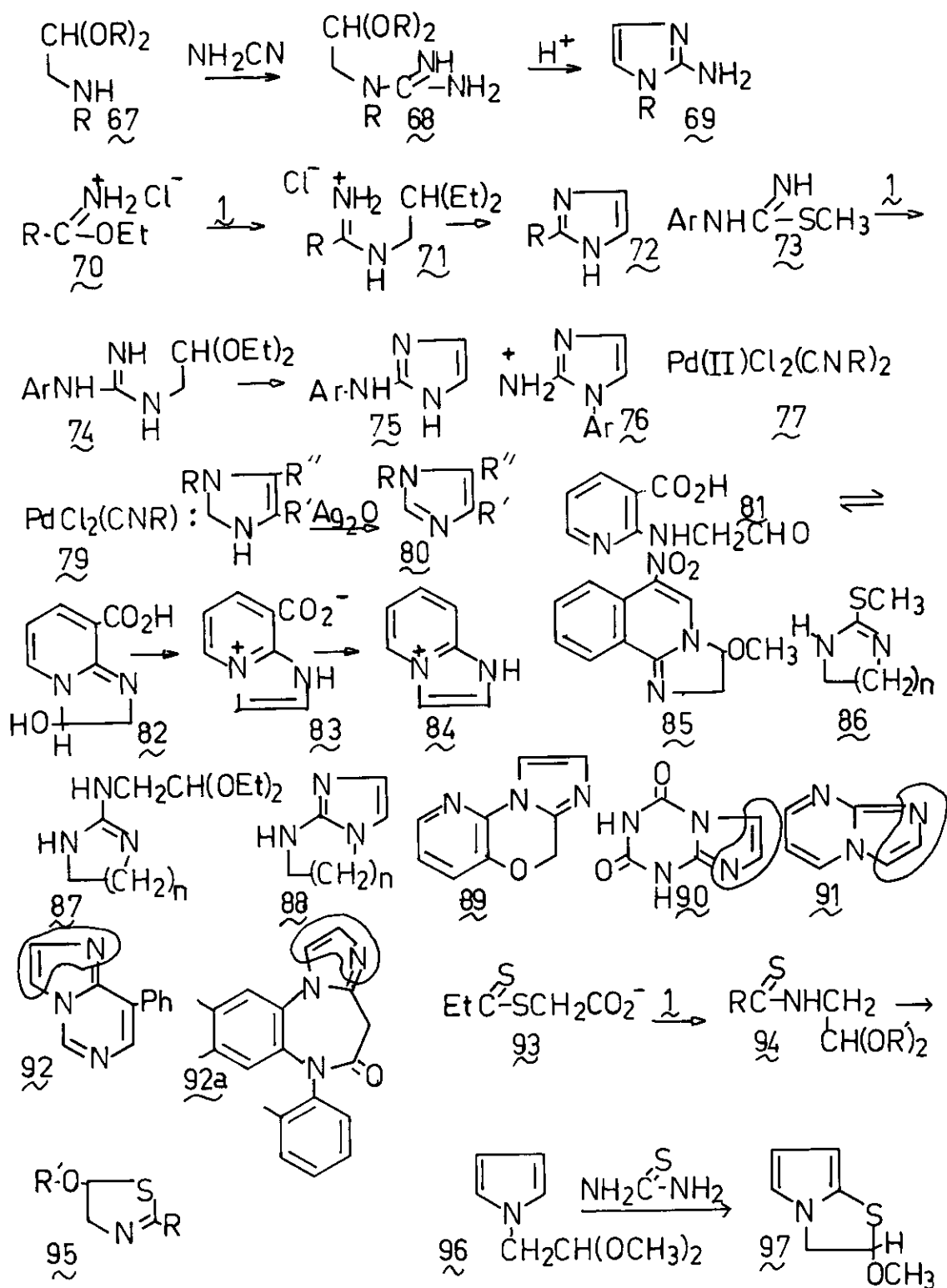
Aminoacetals have been used to build fused imidazole rings onto existing heterocycles in several cases. In general, ring closure conditions are vigorous. In one case, at least, there is evidence of an intermediate hydroxyimidazoline. Specifically, 81, formed by hydrolysis of an appropriate acetal derived from 1 and 2-chloro-3-cyanopyridine, appears to exist in a cyclic form, 82. Treatment of 82 with acetic anhydride/sodium acetate led to 83 in good yield. Compound 83 was decarboxylated to 84. A similar reaction starting with 1-chloro-4-nitroisoquinoline led to an intermediate methoxy derivative, 85.<sup>87</sup> A series of fused imidazoles on imidazoles, pyrimidines, and 1,3-diazepines was prepared as shown in 86-88 ( $n = 1,2,3$ ).<sup>88</sup>

The fused systems, 89,<sup>89</sup> 90,<sup>90</sup> 91,<sup>91</sup> 92,<sup>92</sup> and 92a<sup>97</sup> were made from appropriate aminoacetal precursors. The atoms from the acetal are enclosed.

### Oxazoles and Thiazoles

The formation of oxazoles as byproducts of the Pomerantz-Fritsch synthesis with deactivated molecules<sup>6a,6b,7</sup> was discussed earlier. The synthesis does not seem to have been exploited for the formation of oxazoles themselves.

Aminoacetal reacts in water with sodium thiopropionylthioglycolate, 93 to yield 94 ( $R = C_6H_5$ ) which





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#### Patent Addendum

During the course of this literature search, information was obtained about a number of patents involving aminoacetals. Those patents which appear to involve heterocyclic synthesis, as judged from the abstract alone, are given below with Chemical Abstracts citations and a word or two of explanation. Coverage is from volume 77, 1972 and may not be complete.

#### Six-member Rings with One Nitrogen

- 79:31954 Homoisopavine  
84:59230 Dichlorotetrahydroisoquinolines  
84:135620 Thienopyridines  
84:164748 Tetrahydrothienopyridines  
86:55299 Tetrahydroisoquinolines  
86:106409 Tetrahydroisoquinolines  
87:39528 Tetrahydroisoquinolines  
87:102303 Tetrahydroisoquinolines  
89:122925 Alkoxyisoquinolines  
90:72075 Benocyclohepta-isoquinolines  
91:175318 Benzo[b]thieno[3,2-c]pyridines  
92:110987 Benzofuro[2,3-c]pyridines  
93:150128 Dichlorotetrahydroisoquinolines  
94:15947 9-Hydroxyellipticine  
95:43131 Tetrahydroisoquinolines  
95:115605 Thienopyrazine  
98:8182 Thiadiazolotetrahydroisoquinolines

#### Six-member Rings with Two Nitrogens

- 95:115606 Pyrazinoisoindoles  
100:209869 Pyrazinotetrahydroisoquinolines

#### Seven-member Rings with One or Two Nitrogens

- 77:164777 Benzodiazepines  
77:164778 Benzodiazepines (Ref. 72 above)  
78:135856 Benzodiazepines  
90:54994 Aminobenzodiazepines  
93:26300 Benzazepines  
93:186198 Benzazepines  
99:22340 Benzazepines  
101:230367 Benzazepines  
102:6226 Benzazepines

102:203882 Benzazepines  
 103:96022 Benzazepines

Five-member Rings with Two Nitrogens

78:43504 Imidazophthalazines  
 80:37188 Imidazobenzodiazepines  
 81:49293 Imidazoles  
 83:206271 Dibenzoimidazodiazepines  
 84:44062 Dibenzoimidazoazepines  
 85:21368 Imidazolylbenzophenones  
 85:21488 Imidazodiazepines  
 85:63099 Imidazodiazepines  
 85:78177 Imidazodiazepines  
 86:89819 Imidazoles  
 86:89908 Imidazodiazepines  
 86:106597 Imidazoles  
 86:189946 Imidazoles  
 86:189947 Imidazoles  
 87:5975 Imidazoles  
 87:201595 Imidazodiazepines  
 88:37848 Imidazodiazepines  
 88:62431 Imidazodibenzoxazepines  
 89:43488 Imidazoquinazolines  
 89:197615 Imidazobenzodiazepines  
 90:23129 Imidazobenzodiazepines  
 90:132750 Aminoimidazoles  
 91:20554 Imidazobenzotriazepines  
 91:211415 Imidazoles  
 91:211822 Imidazoles  
 93:46411 Imidazoles  
 95:150698 Imidazoquinazolines  
 96:104241 Imidazoles  
 96:162717 Imidazoles  
 96:162759 Imidazobenzothiadiazepines  
 96:199685 Imidazoles  
 97:92283 Imidazoles  
 98:72100 Imidazoles  
 98:197888 Imidazoles  
 99:1754 Imidazopyrimidines  
 99:5557 Nitroimidazoles  
 99:105271 Imidazophthalazines  
 99:139972 Imidazothiadiazepines  
 99:158433 Imidazoles  
 99:158476 Imidazobenzodiazepines  
 100:103288 Imidazopyrimidines

100:103359 Imidazoles  
100:156633 Imidazoles  
100:205000 Imidazoles  
100:209832 Imidazoles  
101:211186 Imidazobenzodiazepines  
102:6053 Imidazoles  
102:132034 Imidazoles  
102:132054 Imidazopyridooxazines  
102:166544 Imidazoles  
102:166752 Pyranoimidazoles  
102:203967 Imidazolines  
103:123531 Imidazopyrrolobenzodiazepines  
103:150898 Imidazoles

Five-member Rings with Nitrogen and Sulfur

101:22812 Thiazoles  
103:141737 Thiazoles

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