Chemistry of 4-Amino-1*H*-1,5-benzodiazepine-3-carbonitrile

Yoshihisa Okamoto [a] and Kaname Takagi*[b]

[a] School of Pharmacuetical Sciences, Kitasato University, Shirokane, Minato-ku, Tokyo 108, Japan

[b] Central Research Laboratories, Zeria Pharmaceutical Co., Oshikiri, Konan-machi, Osato-gun, Saitama 360-01, Japan

Received February 19, 1987

J. Heterocyclic Chem., **24**, 885 (1987).

Contents.

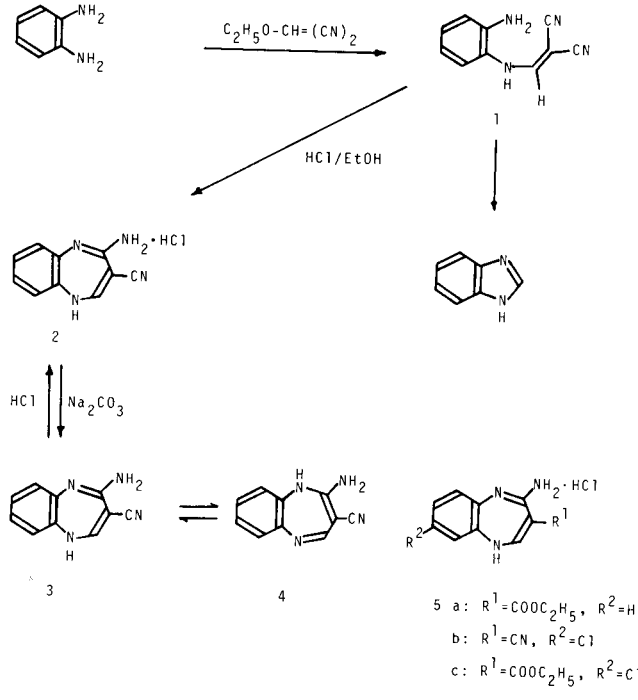
I. Introduction
II. Synthesis and Spectral Properties
III. Oxidation and Reduction
IV. Hydrolytic Reaction
V. Addition of Nitrogen Nucleophiles
1. Addition of Amines
2. Addition of Hydroxylamines
3. Addition of Hydrazines
4. Addition of Amidines
VI. Addition of Active Methylene Compounds
VII. Acylation
VIII. Synthesis of Pyrimidine Derivatives from 4-Acylamino-1*H*-1,5-benzodiazepine-3-carbonitriles
IX. Synthesis and Ring Transformation of 4-Dimethylaminomethyleneamino-1*H*-1,5-benzodiazepine-3-carbonitrile
X. Reaction with Isocyanates and Isothiocyanates

I. Introduction.

Many investigations have been reported on the chemistry of 1,5-benzodiazepines [1] since the first preparation of the 2,4-dimethyl derivatives in 1907 by Thiele [2], and some of the 1,5-benzodiazepine derivatives were found to have the interesting pharmacological properties [3-5]. In general, 1,5-benzodiazepines are synthesized by the reaction of *o*-phenylenediamines with β-dicarbonyl compounds or their analogues [1,6]. The reaction of *o*-phenylenediamine with dimethyl allene-1,3-dicarboxylates are also reported to afford 1*H*-1,5-benzodiazepine derivatives [7]. 4-Amino-1*H*-1,5-benzodiazepine-3-carbonitrile was first prepared in 1973 by our research group from the reaction of *o*-phenylenediamine with ethoxymethylene malononitrile [8]. We have investigated various reactions of this new benzodiazepine ever since and found that the enaminonitrile moiety (N-C=C-CN) in the diazepine skeleton acts like an efficient Michael acceptor to nucleophiles: 4-Amino-1*H*-1,5-benzodiazepine-3-carbonitrile reacts with the nucleophiles with concomitant N^1-C^2 bond cleavage. Moreover, this benzodiazepine is regarded as an *o*-aminonitrile of diazepine, which could become a starting material of fused tricyclic benzodiazepine ring system. Thus, this 1,5-benzodiazepine-*o*-aminonitrile is thought to be a compound with various possibilities in the synthetic chemistry. The purpose of this review is to present a survey of the synthesis, properties and reactions of 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile and its utilization for the synthesis of various heterocyclic compounds.

II. Synthesis and Spectral Properties.

The reaction of *o*-phenylenediamine with ethoxymethylene malononitrile has been reported to afford *o*-(2,2-dicyanovinyl)aminoaniline (**1**), which was readily converted to benzimidazole on heating [9,10]. However, Okamoto and Ueda [8,11] found that when the hydrochloride of the enaminonitrile **1** was refluxed in ethanol, orange needles of 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile monohydrochloride (**2**) was obtained in almost quantitative yield (Scheme 1). The benzodiazepine **2** was also prepared by



Scheme 1

heating of **1** in ethanol saturated with dry hydrogen chloride. The hydrochloride readily gave the free base **3**, when treated with sodium carbonate in cold water [11].

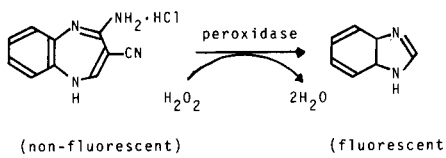
The intramolecular cyclization of the enaminonitrile **1** to the benzodiazepine **2** is apparently dependent on acidity of the reaction media, under which *o*-phenylenediamine condensed with β-dicarbonyl compounds to give 1,5-benzodiazepines [1].

The method for synthesizing **2** has been applied to the preparation of ethyl 4-amino-1*H*-1,5-benzodiazepine-3-carboxylate hydrochloride (**5a**) by using *o*-phenylenediamine and ethyl ethoxymethylene cyanoacetate [8,11]. In the same manner, the 8-chloro derivatives **5b** and **5c** were also synthesized [11].

The ir spectrum of **3** showed three absorption bands at 3400, 3330 and 3230 cm^{-1} attributed to N-H stretching vibration, in addition to a strong cyano absorption band at 2223 cm^{-1}. The ^{1}H-nmr spectrum of **3** in DMSO-d_6 showed a sharp singlet signal due to the olefinic proton at 7.03 ppm and broad multiplets due to the aromatic and the amino protons in the field of 6.33 to 7.43 ppm. The hydrochloride **2** also showed a multiplet signal due to aromatic protons at 6.73-7.27 ppm a singlet signal due to olefinic proton at 7.37 ppm and three broad peaks due to amino protons at 9.30-10.93 ppm which were exchangeable with deuterium oxide. Although the spin-coupling constant between the olefinic proton and the N^1-proton could not be observed in these compounds **2** and **3**, the spectra still support the structures of **2** and **3** as well as its tautomer **4**, because no coupling constant was also observed between those protons in *N*-(2-pyridyl)aminomethylene malononitrile (R-NH-CH = $C(CN)_2$)) [12]. Hereafter, we will use the structure **2** (hydrochloride) or **3** (free base) as the title compound.

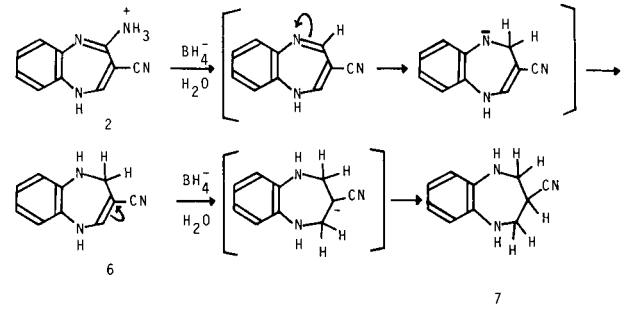
III. Oxidation and Reduction.

The oxidative degradation of **2** with hydrogen peroxide was found to give benzimidazole in very poor yield [13]. Although there is no discussion for the reaction mechanism in this report, the reaction is applicable for the fluorometric determination of hydrogen peroxide, because the



Scheme 2

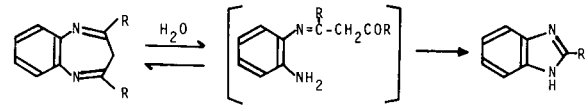
reaction product, benzimidazole, has a strong fluorescence (Scheme 2). The reduction of **2** with sodium borohydride in aqueous solution afforded a mixture of two deaminated compounds: 3-cyano-4,5-dihydro-1*H*-1,5-benzodiazepine (**6**) and 3-cyano-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (**7**), which could be separated by column chromatography [14] (Scheme 3). The structures of **6** and **7** were determined on the basis of ^{1}H- and ^{13}C-nmr, ms and ir spectral data which were discussed in detail.



Scheme 3

IV. Hydrolytic Reaction.

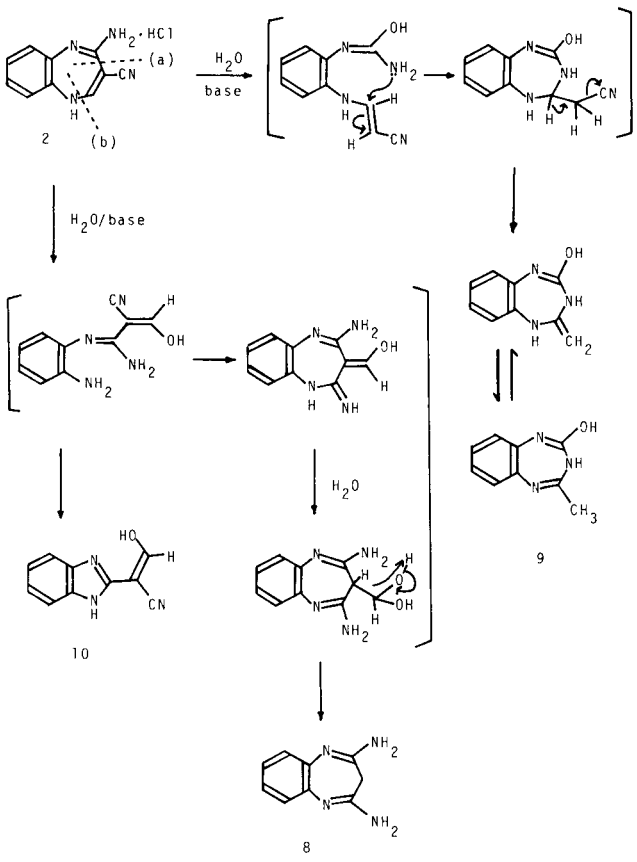
Generally 1,5-benzodiazepines undergo ring contraction by hydrolysis to give benzimidazoles [2,15-18]. The reaction involves ring opening of the diazepine nucleus by attack of the hydroxide anion at 2- or 4-position to give an intermediary monoanil, followed by recyclization to give a five membered ring (Scheme 4).



Scheme 4

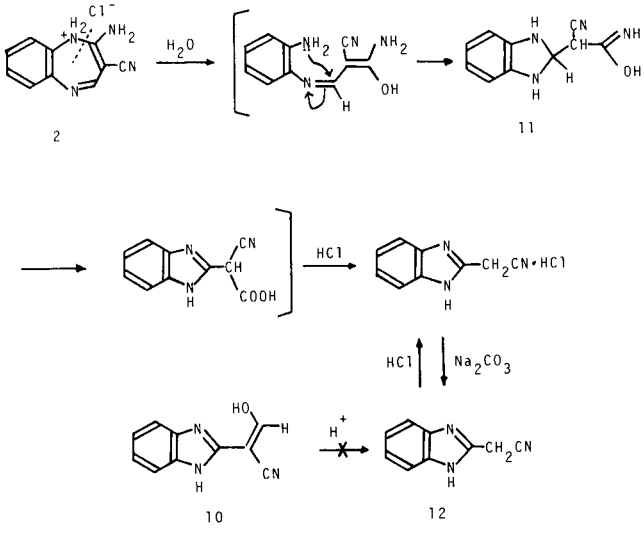
The benzodiazepine **2** is also susceptible to the nucleophilic attack of hydroxide anions [8,11]. When **2** was heated in 3% aqueous sodium hydroxide solution on a water bath for 15 minutes, 2,4-diamino-3*H*-1,5-benzodiazepine (**8**) was obtained. On the other hand, heating of **2** in 0.3% aqueous sodium hydroxide solution (*p*H 8.5) afforded another hydrolyzed product, 2-hydroxy-4-methyl-3*H*-1,3,5-benzotriazepine (**9**). Moreover, when heated in water, in aqueous ammonia or in an aqueous solution of 2-aminopyridine, **2** was transformed into 2-(1-cyano-2-hydroxyvinyl)benzimidazole (**10**). Possible reaction mechanisms were proposed [11] for the formation of **8**, **9** and **10**, which involve cleavage of either a C-C bond (a) or a C-N bond (b) of the diazepine ring in **2** (Scheme 5). The cleavage probably depends on the basicity of the base used. The ^{1}H-nmr spectral study revealed that methyl-methylene tautomerism exists in the triazepine **9**.

Acid hydrolysis of **2** has also been studied [19]. When a solution of **2** in 0.1 *N* hydrochloric acid was heated on a water bath, 2-cyanomethylbenzimidazole (**12**) was obtained in good yield. Since the benzimidazole **10** which was formed by hydrolysis of **2** in a weak alkaline solution, was not converted to hydrochloride of **12** by heating in hydro-



Scheme 5

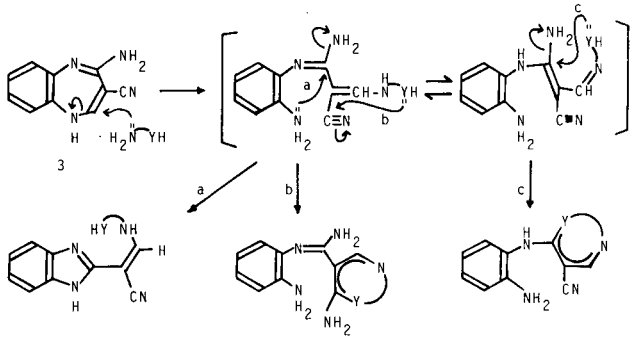
chloric acid (*p*H 1), the formation of **12** was rationalized by C^4-N^5 bond fission of **2**, followed by cyclization to the benzimidazole nucleus **11**, and finally air oxidation and decarboxylation (Scheme 6).



Scheme 6

V. Addition of Nitrogen Nucleophiles.

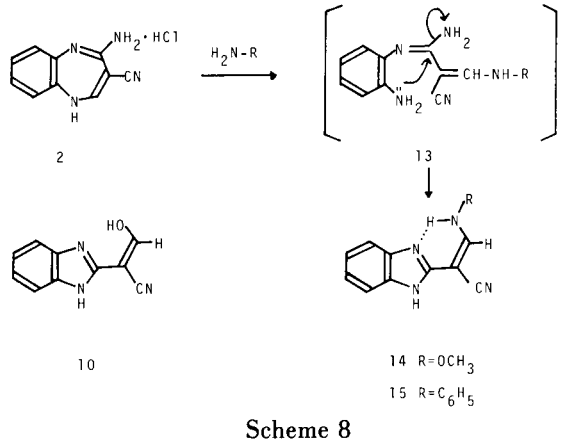
The diazepine **3** is considered to have three electron deficient sites, C-2, C-4 and nitrile carbon. The first one obviously has the most electrophilicity compared with the other two centers. Thus, the diazepine **3** plays like an efficient Michael acceptor at 2-position to nucleophiles ($H_2N^{\frown}YH$) such as amines, hydroxylamines, hydrazines or amidines. The reaction of **3** with these nucleophiles initially leads to intermediates of the ring-opened adducts (Scheme 7). The intermediates might be possible to recyclize in different orientations (a, b, c) which depend on the nature of external group (YH). Thus, the diazepine **3** can be converted to various heterocycles. A general mechanism for the reaction of **3** with nitrogen nucleophiles is outlined in Scheme 7.



Scheme 7

V-1. Addition of Amines.

No reaction of **2** with any simple aliphatic amine has been reported as yet. However, interaction of **2** with methoxyamine hydrochloride in hot water has been described to give a mixture of 2-(1-cyano-2-methoxyaminovinyl)-benzimidazole (**14**) (36% yield) and **10** as a byproduct (4% yield) [19] (Scheme 8). Compound **14** should be produced when ammonia is liberated from a presumed intermediate (**13**, R = OCH_3). Competition between the nucleophilic reaction with methoxyamine and hydrolysis of **2** may be responsible for the low yield of **14**.

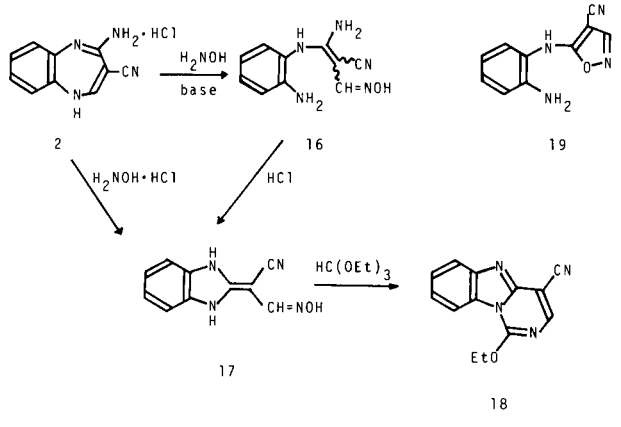


Scheme 8

An aromatic amine reacts with **2** in a similar mode. Heating of **2** with an excess of aniline without solvent gave 2-(2-anilino-1-cyanovinyl)benzimidazole (**15**) [20] (Scheme 8). The ^{1}H-nmr spectral data of **14** and **15** suggest that an olefinic proton and a methoxyamino proton or a phenylamino proton are in a *trans* relation, and that the amino protons form a hydrogen bond with the nitrogen of the imidazole ring.

V-2. Addition of Hydroxylamine.

The reaction of **2** with hydroxylamine hydrochloride in a hot aqueous sodium hydroxide solution (*p*H 8.5) provided a ring-opened hydroxylamine adduct, 3-amino-3-(*o*-aminoanilino)-2-cyano-2-propenal oxime (**16**). When the reaction was done in ethanol using triethylamine as a base, **16** was obtained in a better yield. Compound **16** was readily converted to a benzimidazolidine derivative **17** quantitatively with 10% aqueous hydrochloric acid at room temperature. When **2** was heated with hydroxylamine hydrochloride in water, only the compound **17** was obtained in excellent yield (Scheme 9). The structure **17** was confirmed by derivation to **18**. These results suggest that the formation of **17** should depend on the acidity of the reaction media. *N*-Methylhydroxylamine (both the hydrochloride and the free base) did not react with **2** under the same conditions. Herein, we would like to revise a result described in our previous paper [19] where the wrong structure **19** was proposed instead of the structure **17**.

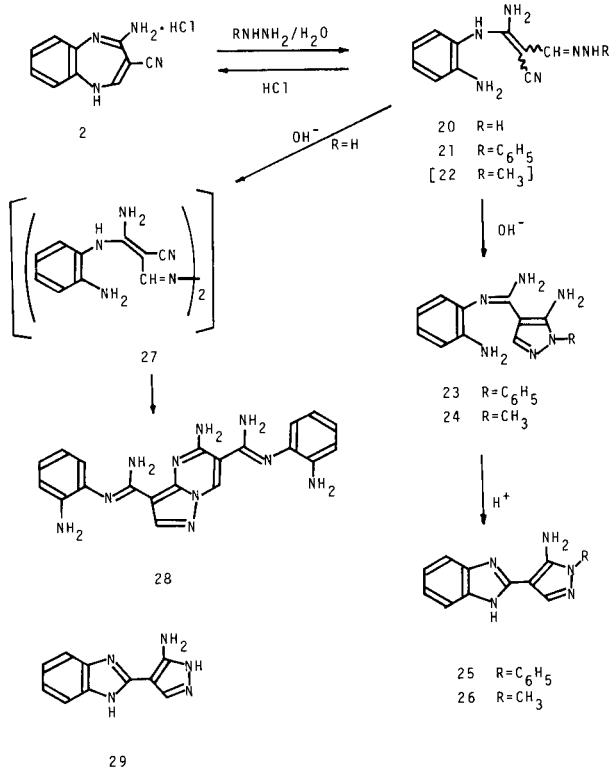


Scheme 9

V-3. Addition of Hydrazines.

The reactions of **2** with hydrazine and mono-substituted hydrazines have been studied in some details [21]. The reactions gave interesting results (Scheme 10) which were different from those obtained by reaction of **2** with hydroxylamine [19] and by the reaction of other 1,5-benzodiazepines with hydrazines [2,16,22,23].

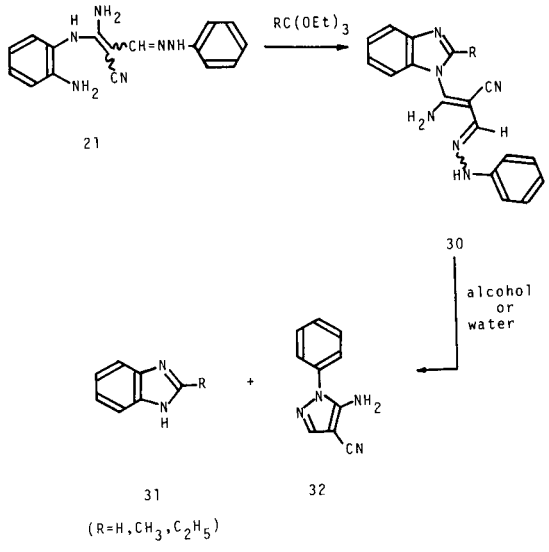
Upon treatment with excess amounts of hydrazine hydrate or phenylhydrazine in water at room temperature, the diazepine **2** immediately converted to a yellow powder of 3-amino-3-(*o*-aminoanilino)-2-cyano-2-propenal hydrazone (**20**) or -phenylhydrazone (**21**) in good yields. Compound **20** reverted to **2** with 10% aqueous hydrochloric acid, while compound **21** afforded a mixture of **2** and 5-amino-4-[*N*-(*o*-aminophenyl)amidino]-1-phenylpyrazole (**23**) as a hydrochloride in 26 and 44% yields, respectively. On treatment with 10% aqueous sodium hydroxide solution, **20** provided 3,6-bis[*N*-(*o*-aminophenyl)amidino]pyrazolo[1,5-*a*]pyrimidine (**28**), presumably *via* diazane **27** as an intermediate. The structure **28** was determined on the basis of its ^{13}C-nmr data. Treatment of **21** with alkaline solution afforded **23** in good yield. The reaction of **2** with methylhydrazine in the presence of an alkali directly gave 5-amino-4-[*N*-(*o*-aminophenyl)amidino]-1-methylpyrazole (**24**), probably *via* an intermediate **22** which could not be isolated. Compounds **23** and **24** were converted to the corresponding benzimidazoles **25** and **26**, respectively, by heating in diluted hydrochloric acid. Recently, we confirmed that prolonged heating of **2** with an excess of hydrazine hydrate in ethanol directly gave 2-(3-aminopyrazol-4-yl)benzimidazole (**29**) [20].



Scheme 10

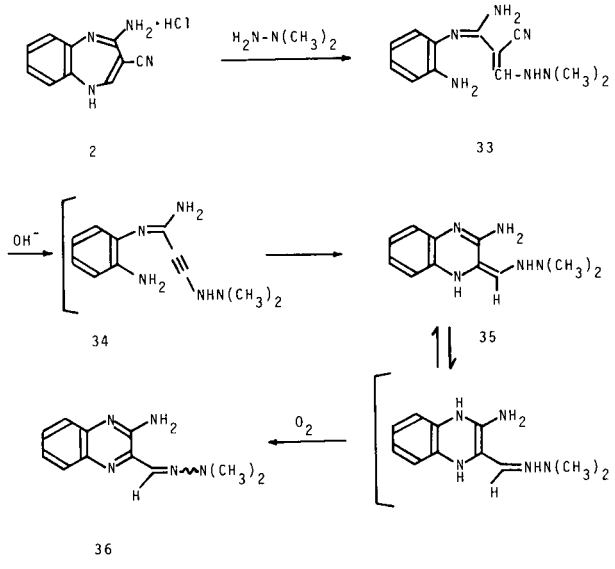
The reaction of the phenylhydrazone **21** with orthoesters gave the benzimidazole derivatives **30** which were readily converted to 2-substituted benzimidazoles **31** and 5-amino-4-cyano-1-phenylpyrazole (**32**) when heated in a protic solvent such as butanol and water above 100°

(Scheme 11). This degradation reaction was explained by hydroxyl group-promoted C-N bond fission [24].



Scheme 11

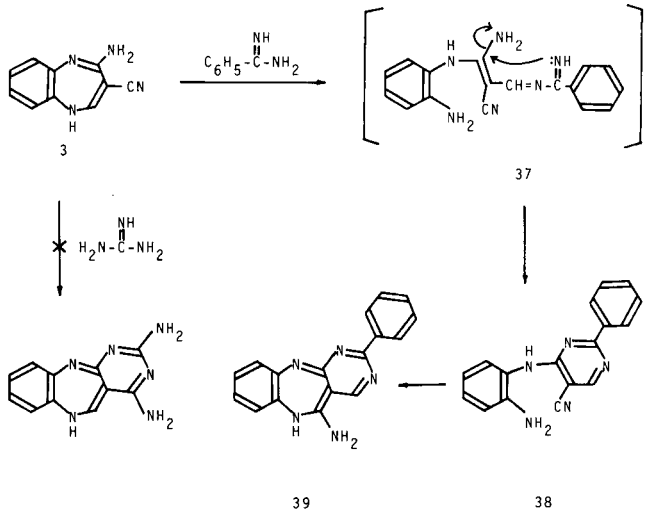
The reaction of **2** with *N,N*-dimethylhydrazine in alkaline media characteristically gave *N*-(2-amino-3-quinoxalinylmethylene)-*N'*,*N'*-dimethylhydrazine (**36**) in 32% yield [21]. The reaction pathways were explained as follows: the ring-opened hydrazine adduct **33** is initially formed, then loss of hydrogen cyanide gives **34**, whose intramolecular cyclization affords dihydroquinoxaline ring compound **35**. The latter and its tautomer are readily oxidized by air to give **36** (Scheme 12).



Scheme 12

V-4. Addition of Amidines.

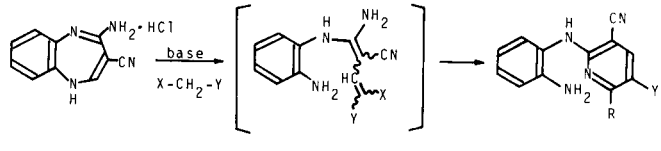
The reaction of **2** with guanidines in an aqueous solution was attempted to obtain fused benzodiazepines. However, the reaction afforded an alkaline hydrolyzed product **8** [8,11]. We also tried the reaction of **3** with guanidine, acetamidine or benzamidine in anhydrous media, and found that only benzamidine provided, on treatment with **3** in dimethylformamide at 60°, 4-(2-aminoanilino)-2-phenylpyrimidine-5-carbonitrile (**38**) as a crystalline product in 39% yield [25]. This reaction probably proceeds by initial attack of benzamidine at 2-position of **3** to give a ring-opened intermediate **37** which then undergoes intramolecular cyclization with loss of ammonia (Scheme 13). The compound **38** can serve for the formation of a fused tricyclic benzodiazepine. When heated in ethanol containing triethylamine, **38** was converted to 5-amino-2-phenylpyrimido[4,5-*b*][1,5]benzodiazepine (**39**) in 54% yield [25].



Scheme 13

VI. Addition of Active Methylene Compounds.

Several active methylene compounds react with the diazepine **2** at 2-position in the presence of an appropriate base. When **2** was heated with ethyl acetoacetate in ethanol in the presence of triethylamine, ethyl 2-(*o*-aminoanilino)-3-cyano-6-methylpyridine-5-carboxylate (**41a**) was ob-



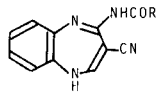
Compound 41	R	Y	Yield(%)
a	CH_3	COOEt	47
b	NH_2	CN	72
c	NH_2	$CONH_2$	67
d	NH_2	2-benzimidazolyl	46

Scheme 14

tained in 47% yield. Similarly, other active methylene compounds reacted with **2** to give pyridine derivatives **41b-d** (Scheme 14). The reaction involves N^1-C^2 bond cleavage of the diazepine ring, followed by recyclization of the ring-opened adduct **40** to give pyridine derivatives **41** [26].

VII. Acylation.

The benzodiazepine **3** can readily be acylated to the corresponding 4-acylamino derivative as in the acylation of simple aromatic *o*-aminonitrile [27]. The reaction of **3** with ethyl chloroformate in ethanol in the presence of triethylamine at room temperature provided a deep red crystalline solid of 4-ethoxycarbonylamino-1*H*-1,5-benzodiazepine-3-carbonitrile (**42a**) [20,28]. The acylation takes place selectively at the 4-amino group of **3**. Analogous selectivity was observed in preparation of 4-acylamino-1*H*-1,5-benzodiazepine-3-carbonitriles **42b-d** which were obtained by the reaction of **3** with acid anhydrides [29] (Scheme 15). The acylaminobenzodiazepines obtained by these reactions are useful for synthetic chemistry because of their conversion to pyrimidines and fused pyrimidines as described in the following section.



42a-d

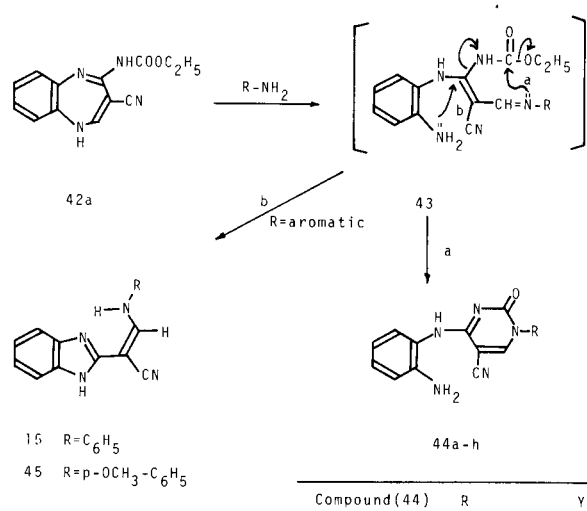
R	Yield(%)
a: OC_2H_5	62
b: CH_3	68
c: C_2H_5	69
d: C_6H_5	75

Scheme 15

VIII. Synthesis of Pyrimidine Derivatives from 4-Acylamino-1*H*-1,5-benzodiazepine-3-carbonitriles.

The N^1-C^2 bond of acylaminobenzodiazepines **42** was readily cleaved with amines, and this reaction supplied a new synthetic approach to a variety of pyrimidines.

The reaction of **42a** with aliphatic primary amines in ethanol at room temperature gave 1-alkyl-4-(2-aminoanilino)pyrimidine-2(1*H*)-one-5-carbonitriles **44a-h** [20,28] (Scheme 16). The pathway to the pyrimidines **44** can be rationalized by ring opening of **42a** with amines to give intermediates **43**, followed by liberation of ethanol from **43** to afford **44** (reaction a). The reaction of **42a** with aromatic primary amines such as aniline and anisidine took place under reflux in ethanol, and resulted in the formation of the benzimidazoles **15** and **45**. These benzimidazoles should be produced by route b from the intermediates **43** (R = C_6H_5 or C_6H_4-*p*-OCH_3) of which the intramolecular cyclization by route a could not take place because of the low nucleophilicity of the aromatic amine.



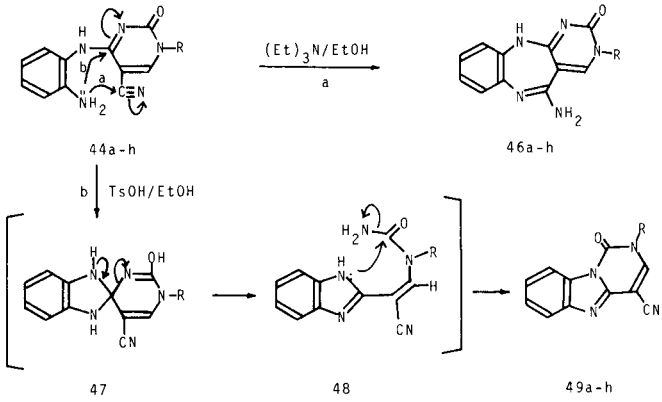
15 R=C_6H_5

45 R=p-OCH_3-C_6H_5

44a-h

Compound(44)	R	Yield(%)
a	CH_3	72
b	C_2H_5	50
c	n-C_3H_7	43
d	iso-C_3H_7	56
e	n-C_4H_9	3
f	$CH_2CH{=}CH_2$	60
g		53
h		49

Scheme 16



44a-h 46a-h

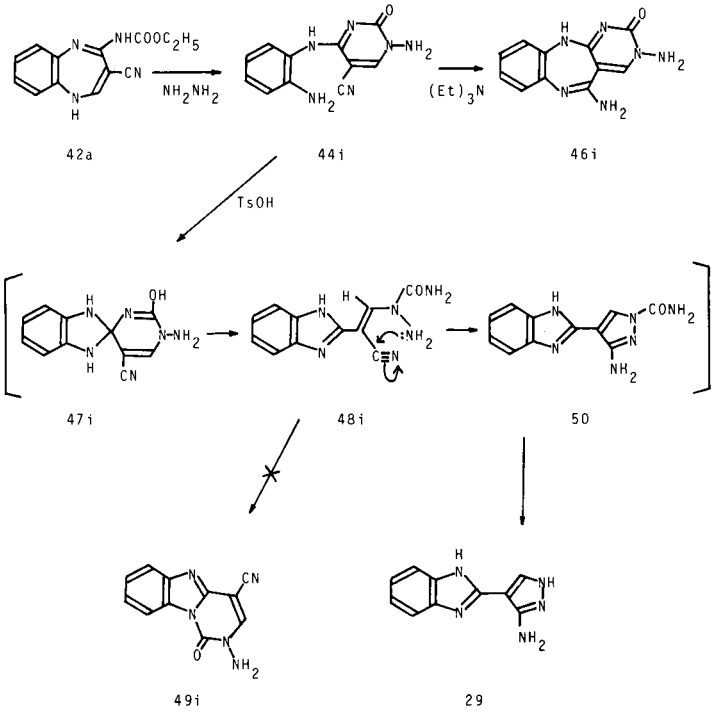
47 48 49a-h

Compound (44)	R	Yield(%) (46)	(49)
a	CH_3	55	69
b	C_2H_5	66	80
c	n-C_3H_7	55	79
d	iso-C_3H_7	32	90
e	n-C_4H_9	59	71
f	$CH_2CH{=}CH_2$	59	80
g		75	83
h		73	94

Scheme 17

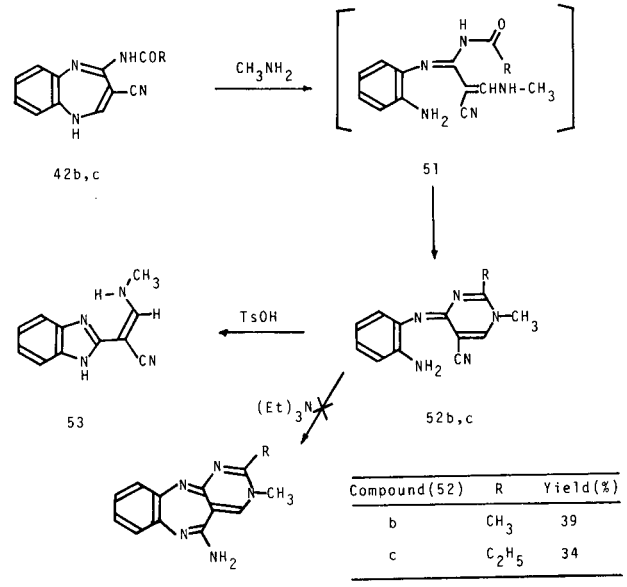
It is worth noting that pyrimidines **44** underwent two different intramolecular cyclizations depending on the reaction conditions. Thus, refluxing of **44a-h** with triethylamine in ethanol gave 3-alkyl-5-aminopyrimido[4,5-*b*][1,5]-benzodiazepin-2(3*H*,11*H*)-ones **16a-h**, while refluxing of **44a-h** in ethanol in the presence of *p*-toluenesulfonic acid afforded 2-alkylpyrimido[1,6-*a*]benzimidazol-1(2*H*)-one-4-carbonitriles **49a-h** [20,28] (Scheme 17). Namely, the interaction between the cyano group and the *o*-amino group in **44** is predominant in the base-catalyzed cyclization (reaction a). Whereas in the acid-catalyzed cyclization, the *o*-amino group attack at 4-position of pyrimidine nucleus in **44** (reaction b) to give spiro-intermediate **47** which is readily converted to **48**, and recyclization of **48** gives **49** with loss of ammonia. The proposed pathway **44**→**49** is reasonable because analogous acid-catalyzed cleavage of pyrimidine ring was reported by Andrews and Tong [30].

Hydrazine hydrate readily reacted with **42a** in ethanol at room temperature in a similar mode to that of aliphatic primary amines to give the pyrimidine **44i** in 78% yield, which was converted to the pyrimido[4,5-*b*][1,5]benzodiazepine (**46i**) by heating in ethanol containing triethylamine. On the other hand, treatment of **44i** with *p*-toluenesulfonic acid in boiling ethanol afforded the pyrazole **29** in 80% yield. No formation of pyrimido[1,6-*a*]benzimidazole (**49i**) was observed [20]. The above result was explained by the interaction between the cyano group and the hydrazino group of an intermediate **48i** to give a pyrazole ring **50**, which was hydrolyzed to **29** (Scheme 18).



Scheme 18

The transformation of the acylamino-benzodiazepines **42b,c** to the pyrimidine derivatives has also been studied [29]. When **42b,c** were treated with methylamine in ethanol at room temperature, 2-alkyl-4-(*o*-aminophenylimino)-1-methylpyrimidine-5-carbonitriles **52b,c** were obtained (Scheme 19). These pyrimidine imines, in contrast with the pyrimidines **44**, did not undergo intramolecular cyclization to pyrimido[4,5-*b*][1,5]benzodiazepine by refluxing with triethylamine in ethanol, but the starting materials were recovered. This may be caused by their imino type structure. On the other hand, when heated with *p*-toluenesulfonic acid in ethanol, **52b,c** were converted to the same product, 2-(1-cyano-2-methylaminovinyl)benzimidazole (**53**).

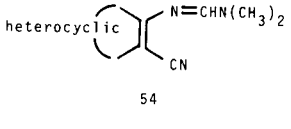


Compound(52)	R	Yield(%)
b	CH_3	39
c	C_2H_5	34

Scheme 19

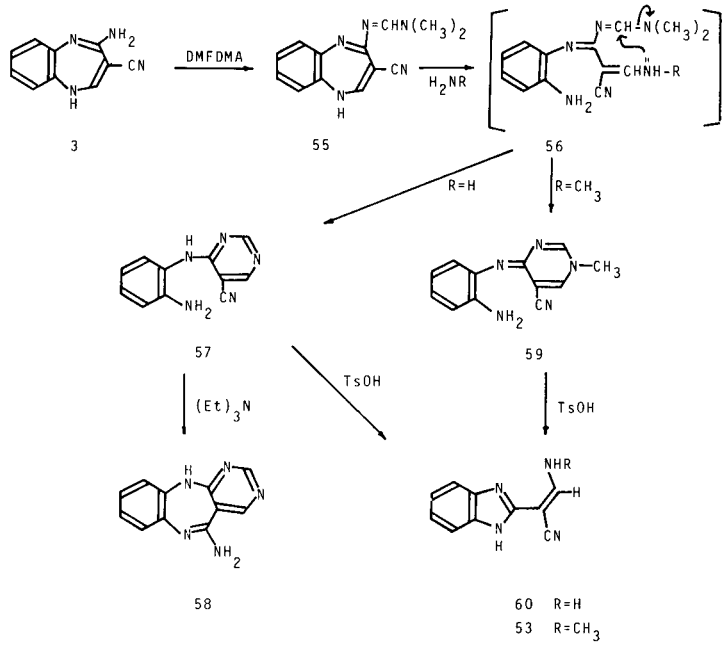
IX. Synthesis and Ring Transformation of 4-Dimethylaminomethyleneamino-1*H*-1,5-benzodiazepine-3-carbonitrile.

The condensation of heteroaromatic *o*-aminonitrile with *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) has been reported to give the formamidine derivatives **54** [31,32,33] (Scheme 20), which could be derived to different condensed heterocycles.



Scheme 20

Similarly, the benzodiazepine **3** was reacted with DMF-DMA in boiling benzene to give 4-dimethylaminomethyleneamino-1*H*-1,5-benzodiazepine-3-carbonitrile (**55**) in good yield [29]. The benzodiazepine **55** readily reacted

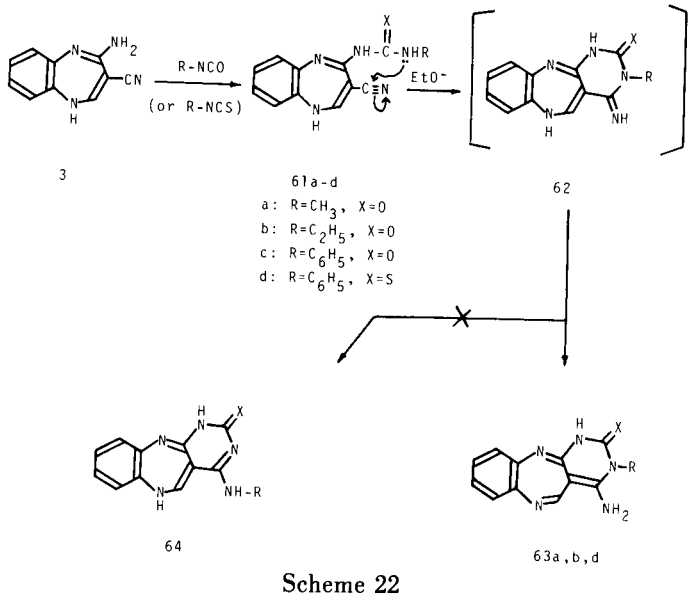


Scheme 21

with ammonia in ethanol at room temperature to give 4-(*o*-aminoanilino)pyrimidine-5-carbonitrile (**57**). The reaction involved ring opening of **55** to generate an intermediate **56** (R = H) which gave **57** with loss of dimethylamine. A similar reaction of **55** with methylamine in ethanol afforded the pyrimidine imine (**59**) (Scheme 21). Intramolecular cyclization of **57** to 5-aminopyrimido[4,5-*b*][1,5]benzodiazepine (**58**) was accomplished by refluxing with triethylamine in ethanol, whereas a similar cyclization of the pyrimidine imine **59** was not successful, as in the case of the imine **52b,c**. Both **57** and **59** were converted into benzimidazoles **60** and **53**, respectively, on heating with *p*-toluenesulfonic acid in ethanol.

X. Reaction with Isocyanates and Isothiocyanates.

The reaction of aromatic *o*-aminonitriles with phenyl isocyanate and phenyl isothiocyanate has well been studied by Taylor for synthesizing fused pyrimidines [34,35]. This method was applied to the benzodiazepine **3** for synthesizing pyrimido[4,5-*b*][1,5]benzodiazepine ring system [36]. The reaction of **3** with alkyl isocyanates in dry tetrahydrofuran at room temperature provided *N*-(3-cyano-1*H*-1,5-benzodiazepin-4-yl)-*N'*-alkylureas **61a,b** in good yields. Heating of **3** with phenyl isocyanate in dimethylformamide in 130° afforded the phenylurea derivative **61c**. Upon treatment with sodium ethoxide in boiling ethanol, the benzodiazepinylureas **61a,b** underwent intramolecular cyclization to afford 3-alkyl-4-aminopyrimido[4,5-*b*]-[1,5]benzodiazepin-2(1*H*,3*H*)-ones **63a,b**, whereas **61c** did not give the expected tricyclic benzodiazepine (Scheme 22). The reaction of **3** with methyl and ethyl isothiocyanates did not provide the expected benzodiazepinylthioureas. Treatment of **3** with phenyl isothiocyanate in dry tetrahydrofuran under reflux gave *N*-(3-cyano-1*H*-1,5-benzodiazepin-4-yl)-*N'*-phenylthiourea (**61d**) which was converted to 4-amino-3-phenylpyrimido[4,5-*b*][1,5]benzodiazepin-2(1*H*,3*H*)-thione (**63d**) by heating with sodium ethoxide in ethanol [36] (Scheme 22). In the cyclization of **61** to **63**, we could not obtain the isomer **64** at all which might be formed from the imine **62** by the Dimroth type rearrangement [37]. Spectral data of **63a,b,d** suggested that they are in the amino form **63** rather than the imino form **62**.



Scheme 22

REFERENCES AND NOTES

[1] D. Lloyd and H. P. Cleghorn, "Advances in Heterocyclic Chemistry", Vol **17**, A. R. Katritzky and A. J. Boulton, eds, Academic Press, New York, San Francisco, London, 1974, pp 27-43.

[2] J. Thiele and G. Steimming, *Ber.*, **40**, 955 (1907).

[3] L. H. Sternbach, *Prog. Drug Res.*, **22**, 258 (1978) and references cited therein.

[4] K. Hideg and O. Hideg-Hankovszky, *Acta. Chim. Acad. Sci. Hung.*, **75**, 137 (1973).

[5] C. R. Ellefson, C. M. Woo, A. Miller and J. R. Kehr, *J. Med. Chem.*, **21**, 952 (1978).

[6] Recently, interesting synthesis of 1,5-benzodiazepines by reaction of *o*-phenylenediamine with α-oxoketenethioacetals was reported, the latter compounds being nevertheless analogues of β-dicarbonyl compound: A. Ushirogoshi, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Heterocycles*, **14**, 7 (1980) and references cited therein.

[7] J. Ackroyd and F. Scheimann, *J. Chem. Soc., Chem. Commun.*, 339 (1981).

[8] Y. Okamoto and T. Ueda, *J. Chem. Soc., Chem. Commun.*, 367 (1973).

[9] K. S. Sardesai and S. V. Sunthankar, *J. Sci. Ind. Res.* (India), **B18**, 158 (1959).

[10] P. H. Stahl, R. Barchet and K. W. Merz, *Arzneim.-Forsch.*, **18**, 1214 (1968).

[11] Y. Okamoto and T. Ueda, *Chem. Pharm. Bull.*, **23**, 1391 (1975).

[12] Y. Okamoto, Y. Kurasawa, K. Takagi, A. Takada and T. Ueda, *Chem. Pharm. Bull.*, **22**, 243 (1974).

[13] Y. Okamoto, S. Inamasu and T. Kinoshita, *Chem. Pharm. Bull.*, **28**, 2325 (1980).

[14] Y. Okamoto and T. Kinoshita, *Chem. Pharm. Bull.*, **29**, 1165 (1981).

[15] D. Lloyd, R. H. McDougall and D. R. Marshall, *J. Chem. Soc.*, 3785 (1965).

[16] J. A. Barltrop, C. G. Richards, D. M. Russell and G. Ryback, *J. Chem. Soc.*, 1132 (1959).

[17] M. Weissenfels, W. Thust and M. Mühlstädt, *J. Prakt. Chem.*, **292**, 117 (1963).

[18] M. Weissenfels, H. Schuring and G. Hühsam, *Chem. Ber.*, **100**, 584 (1967).

[19] Y. Okamoto, K. Takagi and T. Ueda, *Chem. Pharm. Bull.*, **28**, 567 (1980).

[20] K. Takagi, T. Aotsuka, H. Morita and Y. Okamoto, *J. Heterocyclic Chem.*, **23**, 1443 (1986).

[21] Y. Okamoto, T. Ueda and K. Takagi, *Chem. Pharm. Bull.*, **31**, 2114 (1983).

[22] K. Meguro and Y. Kuwada, *Tetrahedron Letters*, 4039 (1970).

[23] I. L. Finar, *J. Chem. Soc.*, 4049 (1958).

[24] Y. Okamoto, Y. Kurasaw, A. Takada and K. Takagi, *J. Heterocyclic Chem.*, **22**, 1719 (1985).

[25] Unpublished results.

[26] To be published.

[27] E. C. Taylor and A. McKillop, "Advances in Organic Chemistry: Methods and Results", Vol **7**, "The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles", E. C. Taylor, ed, Interscience Publishers, New York, London, Sydney, Toronto, 1970, p 226.

[28] T. Aotsuka, H. Morita, K. Takagi and Y. Okamoto, *Synthesis*, 668 (1986).

[29] K. Takagi, T. Aotsuka, H. Morita and Y. Okamoto, *Synthesis*, in press.

[30] K. J. M. Andrews and B. P. Tong, *J. Chem. Soc.* (C), 1753 (1968).

[31] B. Verček, I. Leban, B. Stanovnik and M. Tišler, *J. Org. Chem.*, **44**, 1695 (1979).

[32] M. Kočevar, B. Stanovnik and M. Tišler, *Heterocycles*, **15**, 293 (1981).

[33] M. Tišler, *Heterocycles*, **20**, 1591 (1983).

[34] E. C. Taylor and R. V. Ravindranathan, *J. Org. Chem.*, **27**, 2622 (1962).

[35] E. C. Taylor, A. McKillop, Y. Shvo and G. H. Hawks, *Tetrahedron*, **23**, 2081 (1967).

[36] K. Takagi, H. Morita, T. Aotsuka and Y. Okamoto, *Heterocycles*, **26**, 175 (1987).

[37] O. Dimroth, *Ann. Chem.*, **364**, 183 (1909), *Idem, ibid*, **459**, 39 (1927). This type of rearrangement was observed in the cyclization products of *o*-cyanophenylureas with an alkali: see references [34] and [35].