1,4-Benzodiazepines. Chemistry and Some Aspects of the Structure-Activity Relationship

By Leo H. Sternbach[*]

Numerous clinically used compounds having favorable tranquilizing and toxic properties possess the 1,4-benzodiazepine skeleton. This group of active substances is readily accessible, e.g. by ring enlargement of quinazoline derivatives, by ring contraction of benzoxadiazocines, and by synthesis from aminobenzophenones, constructing the seven-membered ring in many cases in one step. The relationships between type and position of substituents and the pharmacological properties are illustrated using 1,3-dihydro-5-phenyl-1,4-benzodiazepin-2-ones as examples.

1. General Introduction

This review is meant to give a short outline of the history of the discovery and further development of the chemistry of tranquilizers of the 1,4-benzodiazepine type. It will be limited with very few exceptions to published and also unpublished work carried out in our laboratories[**]. It will concern itself mainly with the most important synthetic routes leading to pharmacologically and clinically interesting types of 1,4-benzodiazepines, and will contain also a short discussion of the pharmacological properties of these compounds.

In view of this, the main subject will be 5-phenyl-1,4-benzodiazepine derivatives which are the most extensively studied group. It should, however, be pointed out that most of the reactions have been used for the synthesis and transformations of 1,4-benzodiazepine derivatives bearing substituents other than phenyl on C-5.

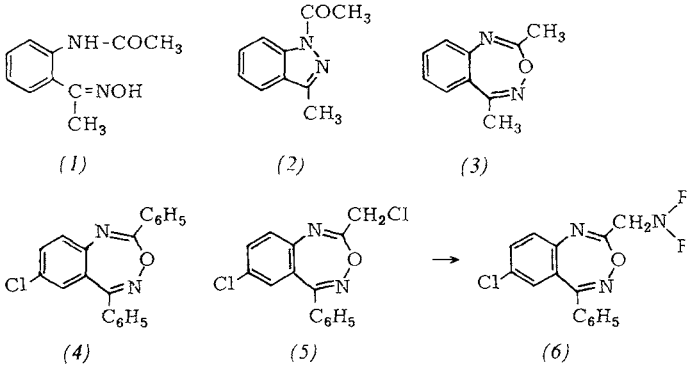
2. Introduction

In the search for a new class of drugs possessing tranquilizing properties similar to those of meprobamate and chlorpromazine, it was decided in the middle 1950's to investigate new types of heterocycles which might ultimately lead to compounds showing the desired properties. As a rather neglected group of chemically interesting compounds, we selected the benzheptoxdiazines, as they were called in the German scientific literature.

The first compounds of this type were obtained in 1891 by *von Auwers* and *von Meyenburg*[1] by dehydration of *o*-acylamino ketoximes *(1)* or aldoximes with a Beckmann mixture. At that time they were considered to be acylindazoles *(2)*.

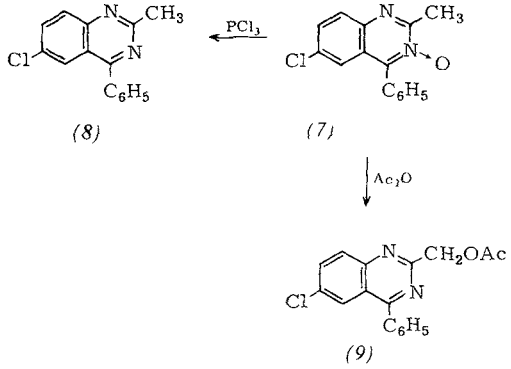
These compounds were further studied in 1893[2] and reinvestigated in 1924[3] when it was agreed upon that they are best represented by structure *(3)*.

In the mid thirties, a few further members of this class of compounds were prepared, specifically compound *(4)*[4] and close analogs thereof. They were relatively easy to synthesize, crystallized very well, and were easy to purify. These were the reasons which made this group of heterocycles so attractive for further exploration. Derivatives to which basic substituents could be attached, as illustrated by conversion of *(5)* into *(6)*, appeared to be particularly interesting.



(1) *(2)* *(3)* *(4)* *(5)* *(6)*

Closer chemical study of these compounds led to the conclusion that the so called "benzheptoxdiazines" did not have the structure originally assigned to them, but were in fact quinazoline 3-oxides of type *(7)*. The transformations shown below illustrate the structural proof[5]. The *N*-oxide oxygen could be readily removed by treatment with phosphorus trichloride or by catalytic hydrogenation to yield the quinazoline *(8)*. On the other hand, treatment with acetic anhydride resulted in the



(8) *(7)* *(9)*

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[**] For a complete review see *G. A. Archer* and *L. H. Sternbach*, Chem. Rev. *68*, 747 (1968).

[1] *K. von Auwers* and *F. von Meyenburg*, Chem. Ber. *24*, 2370 (1891).

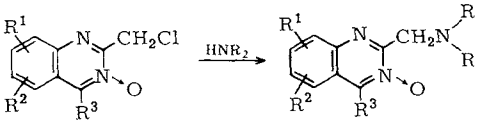
[2] *A. Bischler*, Chem. Ber. *26*, 1891, 1901 (1893).

[3] a) *J. Meisenheimer* and *A. Diedrich*, Chem. Ber. *57*, 1715 (1924); b) *K. von Auwers*, *ibid. 57*, 1723 (1924).

[4] *K. Dzieworiski* and *L. H. Sternbach*, Bull. Intern. Acad. Polonaise, Classe Sc. Math. Nat. Ser. A, 333–348 (1935); Chem. Abstr. *30*, 2972 (1936).

[5] *L. H. Sternbach*, *S. Kaiser*, and *E. Reeder*, J. Amer. Chem. Soc. *82*, 475 (1960).

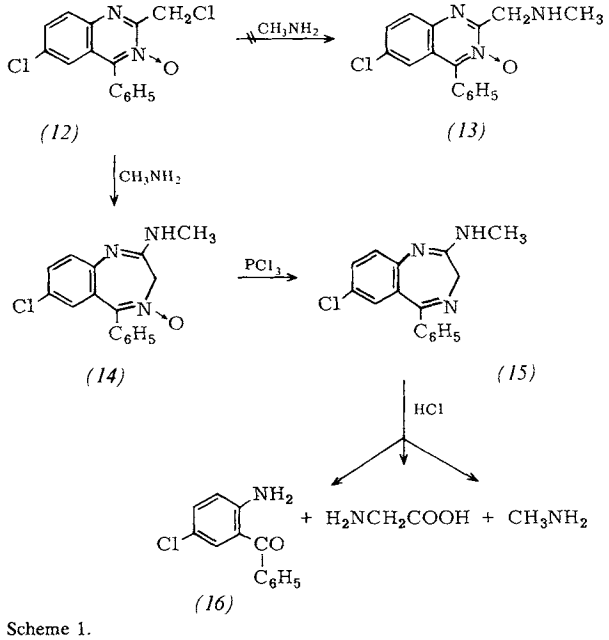
formation of the acetoxy derivative *(9)*, a transformation analogous to that of picoline *N*-oxide[6]. The interesting novel structure of these compounds lending itself to a variety of transformations led to intensified studies. These resulted first in the synthesis of a number of quinazoline 3-oxides of the general formula *(10)* and their transformations with various amines. Secondary amines generally yielded normal substitution products of type *(11)*, which showed no particularly interesting biological properties. The reaction with primary amines or ammonia, however, resulted in the formation of pharmacologically very attractive compounds.



(10) *(11)*

3. Ring Enlargement of Quinazoline 3-Oxides by Treatment with Amines

The products obtained on treatment of compounds of type *(10)* with primary amines were the result of an unusual, novel ring enlargement. Scheme 1 shows the first compound *(14)* thus obtained, and gives a short outline of the structural proof[7].



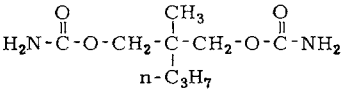
Scheme 1.

Compound *(14)* had the expected composition, was monomolecular, contained an *N*-oxide function and a secondary methylamino group. The UV and IR spectra indicated, however, that the quinazoline 3-oxide molecule must have undergone very profound changes and that the reaction product could not be *(13)*, the simple substitution product. This was confirmed by chemical studies which showed ultimately that the compound had the structure of a 1,4-benzodiazepine 4-oxide *(14)*, and was a representative of a novel group of heterocycles.

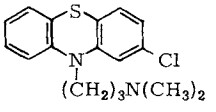
The structure was established by classical methods before the widespread use of NMR and mass spectroscopy became commonplace. It consisted in the acid hydrolysis of the deoxy derivative *(15)* which gave an excellent yield of the aminobenzophenone *(16)*. In addition, glycine and methylamine were formed, which, after benzoylation, were isolated from the hydrolysis mixture in over 60% yield. The normal substitution product *(13)*, on oxygen removal and hydrolysis, would have yielded *N*-methylglycine and ammonia in addition to the aminobenzophenone (see Scheme 1).

4. Pharmacology of Chlordiazepoxide

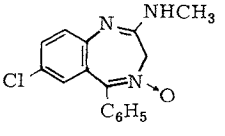
This compound *(14)*, which later obtained the generic name chlordiazepoxide was, as mentioned above, the first product to show desirable pharmacological properties. It was a sedative, muscle relaxant, and anticonvulsant resembling in many respects meprobamate and chlorpromazine, the then most used tranquilizers. Extended pharmacological and later, clinical studies confirmed these properties and led to its introduction in 1960 as the active ingredient of the specialty Librium®. Table 1 shows the comparison of its pharmacological properties and toxicity with those of the two aforementioned tranquilizers.



Meprobamate



Chlorpromazine



(14)

The top row shows the primary tests which were and are generally used in our Pharmacology Department to demonstrate sedative and "tranquilizing" properties. The first test (Inclined Screen) indicates sedation and muscle relaxation in mice, the second (the fighting mice test) a taming effect, and the third measures muscle relaxation in cats. The antimetrazole (Cardiazol) shock test is a measure of sedation and anticonvulsant activity, whereas the two electroshock tests indicate pure anticonvulsant properties[8]; the last column shows the toxicity. The figures in the table indicate the amounts of material (mg/kg) needed to achieve the desired effect. Therefore, small numbers indicate high potency and high numbers low activity[*].

[6] *V. Boekelheide* and *W. J. Linn*, J. Amer. Chem. Soc. *76*, 1286 (1954); *O. H. Bullitt Jr.* and *J. T. Maynard*, *ibid. 76*, 1370 (1954).

[7] *L. H. Sternbach* and *E. Reeder*, J. Org. Chem. *26*, 1111 (1961).

[8] *L. H. Sternbach*, *L. O. Randall*, *R. Banziger*, and *H. Lehr* in *A. Burger:* Drugs Affecting The Central Nervous System. Marcel Dekker, New York 1968, Vol. 2, Chap. 6.

[*] All the pharmacological data reported subsequently will be presented in the same manner in tables containing the same tests in the same order. The toxicity data will be omitted since all benzodiazepine derivatives of the type discussed show a very low toxicity. In view of the wide variations found in biological tests, differences of ± 50% are meaningless. For detailed descriptions of the tests see [8].

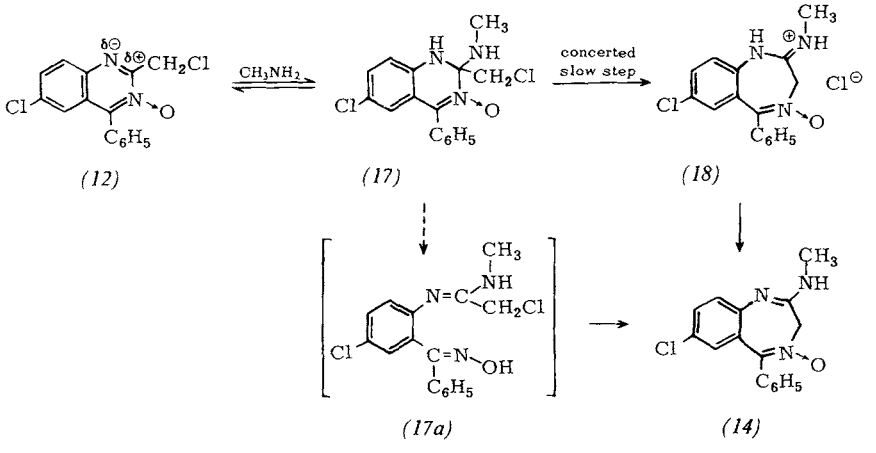
Table 1. Pharmacological and toxic properties of meprobamate, chlorpromazine, and chlordiazepoxide. For explanation see text.

Compound	Incl. Screen	Fighting Mice	Cat	Anti-Met.	Electroshock Max.	Min.	LD_{50} p.o.
Meprobamate	250	250	100	150	200	167	1450
Chlorpromazine	17	20	2.5	42	150	600	75
Chlordiazepoxide	100	40	2	18	92	150	620

As can be readily seen, the new compound was, across-the-board, more potent than meprobamate and resembled chlorpromazine in many of the tests. In addition, it showed, on further study, a very pronounced taming effect on Rhesus monkeys. The interesting properties of this substance started intensive activity with this, at that time quite unexplored, group of heterocyclic compounds. It resulted in the development in our laboratories of a number of new synthetic approaches and in the synthesis of nearly 1500 benzodiazepines of various types, and about 4000 intermediates.

5. Mechanism of Ring Enlargement

The study on the first method for the synthesis of pharmacologically active 1,4-benzodiazepines, *i. e.* the ring enlargement, suggested the mechanism shown below.

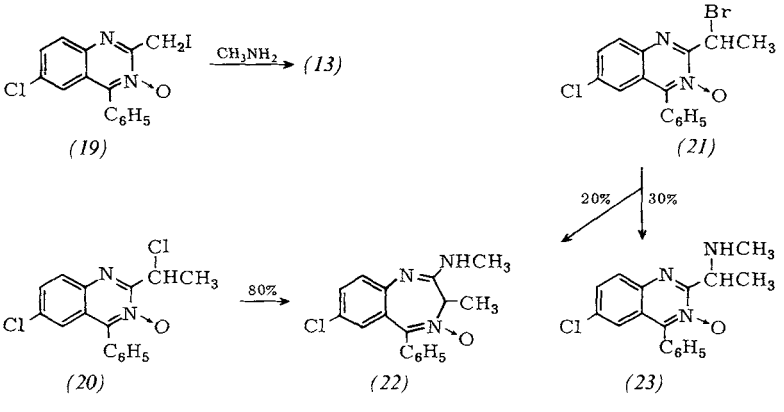


Compound *(12)*, which carries a partial positive charge on C-2 of the quinazoline nucleus, reacts with the nucleophile to form an adduct of structure *(17)*, the reaction being in reversible equilibrium. This adduct in turn, in a concerted reaction, as indicated in formulas *(17)* and *(18)*, undergoes fission between C-2 and N-3, elimination of the chlorine, and formation of a new bond between the exocyclic methylene and the *N*-oxide nitrogen. A short-lived intermediate of structure *(17a)* could also be postulated, which in turn would undergo cyclization to *(14)*. The existence of such an intermediate is suggested by the results of other reactions which will be discussed later.

Further studies showed that we were faced here with two competing reactions, normal substitution and ring enlargement. Good leaving groups, steric hindrance, and substituents in the aromatic nucleus which decrease the positive charge on C-2 led to formation of the normal substitution products. The selection of solvents also affected the course of the reaction. Polar solvents resulted in normal substitution whereas non-polar solvents favored ring enlargement.

5.1. Effect of Leaving Groups[9]

The above effect is well illustrated by the difference in the course of the reaction as determined by the character of the halogen group on the exocyclic methylene group.



The chloromethylquinazoline derivative *(12)* gives, as already mentioned, the ring enlarged benzodiazepine *(14)* in almost quantitative yield. The corresponding iodo derivative *(19)* (obtained readily by treatment of *(12)* with sodium iodide), on the other hand, yields prevalently the normal substitution products *(13)*. The "intermediate" bromo derivative gives, as might be expected, both the normal substitution product *(13)* and the ring enlarged product *(14)*, which were isolated in yields of 30 and 20% respectively. In order to exclude a possible steric effect, caused by the exocyclic methyl group, the behavior of the chloro derivative *(20)* was also studied, and this showed almost quantitative ring enlargement.

In order to obtain comparable data, these reactions were all carried out under identical conditions (methanol as solvent, room temperature, large excess of methylamine). In every case the yields indicate the amounts of isolated crystalline material.

5.2. Effects of Substituents and of Solvents[9]

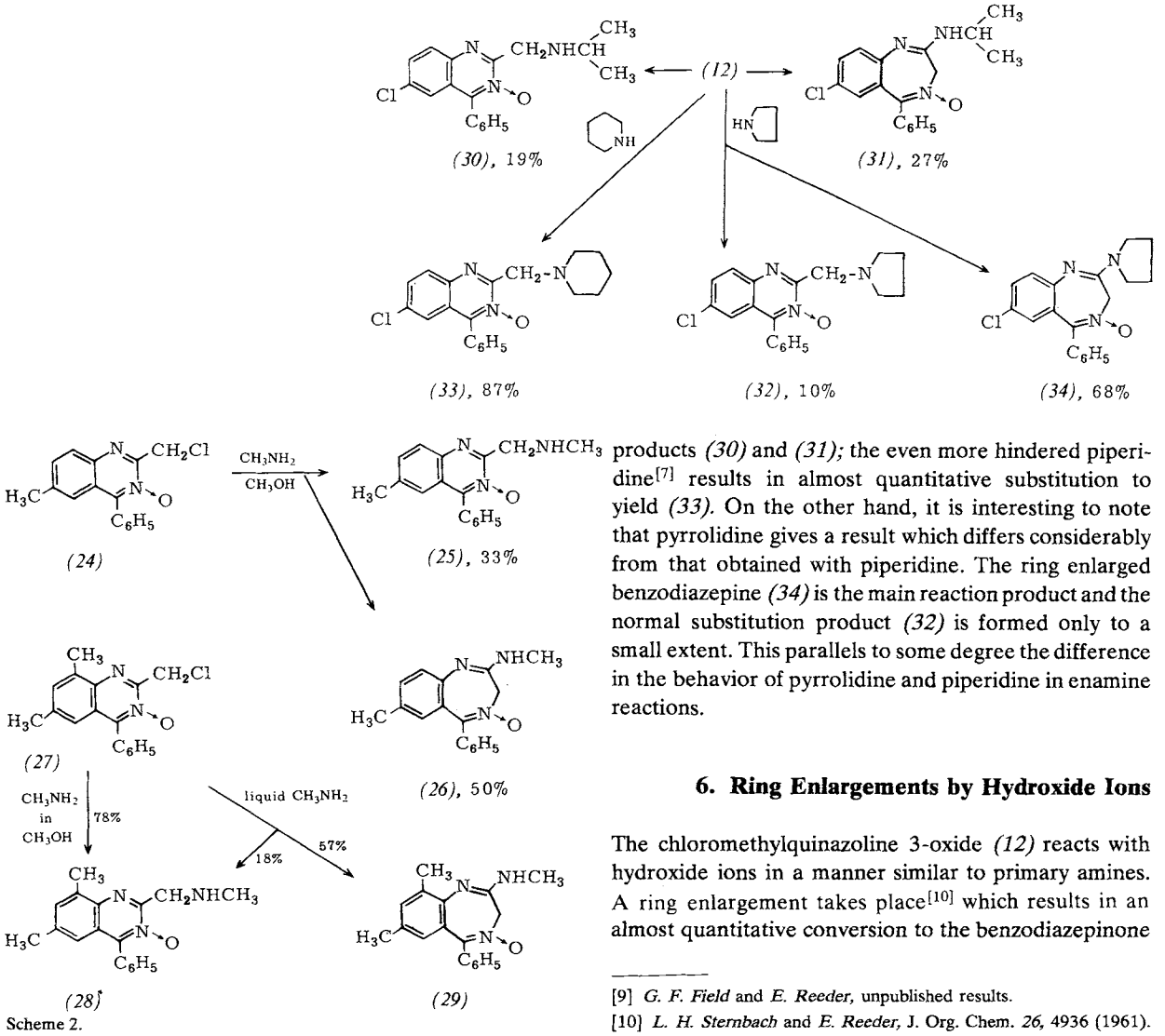
Whereas electron withdrawing substituents (Cl, NO_2, CF_3 *etc.*) on C–6 of the quinazoline nucleus favor ring enlargement, almost to the complete exclusion of normal substitution, electron releasing substituents have the opposite effect. Due to the decrease of the partial positive charge on C–2, the normal substitution offers strong competition, as shown in Scheme 2.

The presence of one methyl group on C–6 of the quinazoline nucleus *(24)* results in the formation of both the normal and the ring enlarged products *(25)* and *(26)*, which were isolated in the indicated yields. Even more pronounced is the additive effect of two methyl groups on C–6 and C–8. The predominant reaction product is the quinazoline 3-oxide *(28)* which is formed in very high yield under standard conditions.

The effect of the solvent is apparent when the reaction is carried out in aprotic liquid methylamine; ring enlargement is highly favored and the main reaction product is the benzodiazepine derivative *(29)*. This course of the reaction is not due to the low temperature as was established by parallel experiments in methanol.

5.3. Steric Effects[9]

The following examples illustrate the influence of sterically hindering substituents on the nucleophile. The bulky isopropylamine causes the formation of both products *(30)* and *(31)*; the even more hindered piperidine[7] results in almost quantitative substitution to yield *(33)*. On the other hand, it is interesting to note that pyrrolidine gives a result which differs considerably from that obtained with piperidine. The ring enlarged benzodiazepine *(34)* is the main reaction product and the normal substitution product *(32)* is formed only to a small extent. This parallels to some degree the difference in the behavior of pyrrolidine and piperidine in enamine reactions.



Scheme 2.

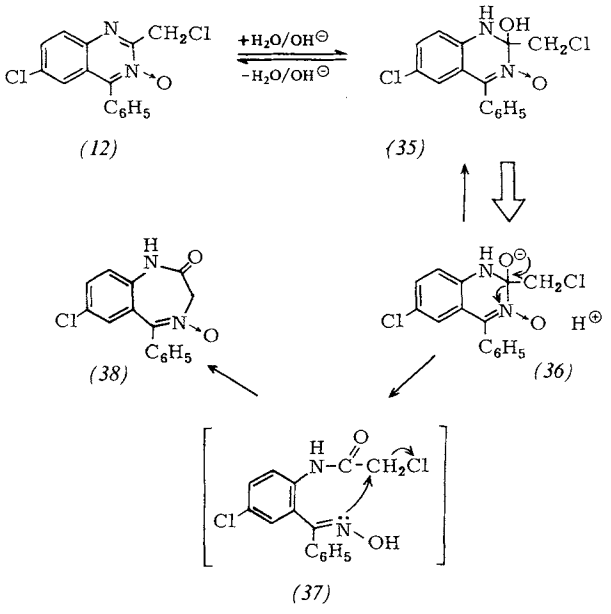
6. Ring Enlargements by Hydroxide Ions

The chloromethylquinazoline 3-oxide *(12)* reacts with hydroxide ions in a manner similar to primary amines. A ring enlargement takes place[10] which results in an almost quantitative conversion to the benzodiazepinone

[9] *G. F. Field* and *E. Reeder*, unpublished results.

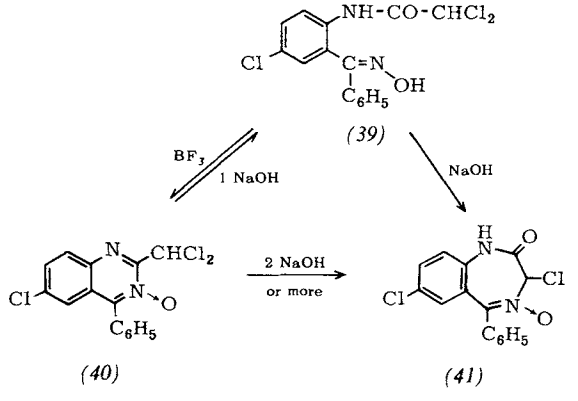
[10] *L. H. Sternbach* and *E. Reeder*, J. Org. Chem. *26*, 4936 (1961).

(38), as shown below. Normal substitution, *i.e.*, replacement of the exocyclic halogen by a hydroxy group was never observed, even with compounds bearing electron releasing substituents in the benzene ring.



This can be explained as indicated above. The first reaction is, in analogy to the reaction with methylamine, addition of OH^- at C–2 of the quinazoline nucleus and formation of the equilibrium intermediate *(35)*. In this intermediate the OH hydrogen has strongly acidic character. This causes immediate ionization to form *(36)*, which cannot revert *via (35)* to *(12)*, but must undergo further reactions, possibly through *(37)*, to *(38)*.

The study of the analogous ring enlargement of the "dichloromethylquinazoline" *(40)*[11] made it plausible that the open compound *(37)* is indeed an intermediate of the reaction *(12)*→*(38)*.



Treatment of *(40)* with 1 mole of alkali yielded the analog of *(37)*, the dichloroacetyl derivative *(39)*, which in this case could be readily isolated. Further treatment of this open compound *(39)* with alkali then gave an excellent yield of the benzodiazepinone *(41)*. Due to the lower reactivity of the chlorines in compound *(39)*, the cyclization to *(41)* does not occur with the speed which made it impossible to isolate the monochloro derivative *(37)* postulated as an intermediate in the preceding reaction. Another indication that in the "monochloromethyl" case the reaction proceeds as formulated is the ease of transformation of the intermediate *(37)* – prepared by unequivocal methods – into *(38)* on treatment with alkali[10].

7. Transformations of Chlordiazepoxide

The interesting biological properties of chlordiazepoxide *(14)* led to intensive study of its chemistry. These investigations were concerned initially with the structure determination [*(14)*→ *(15)*→ *(16)*[7]], but later the study of the effect of structural changes on the pharmacological properties became our main objective[8].

It was found that the readily accessible acetyl derivative of chlordiazepoxide *(14 ac.)* could be converted in excellent yield into the *N*-oxide *(38)*[10] and the simple 5-phenylbenzodiazepin-2-one *(42)*. It was of great interest that the benzodiazepinones *(38)* and *(42)* were pharmacologically at least as active as chlordiazepoxide, as can be seen in Table 2. Hydrogenation of *(42)* in the presence of a platinum catalyst led to a tetrahydro derivative *(43)* with considerably decreased pharmacological activity. This latter finding proved to be a general rule and was confirmed in all cases in which 4,5-dihydrobenzodiazepine derivatives were compared with the corresponding unhydrogenated compounds.

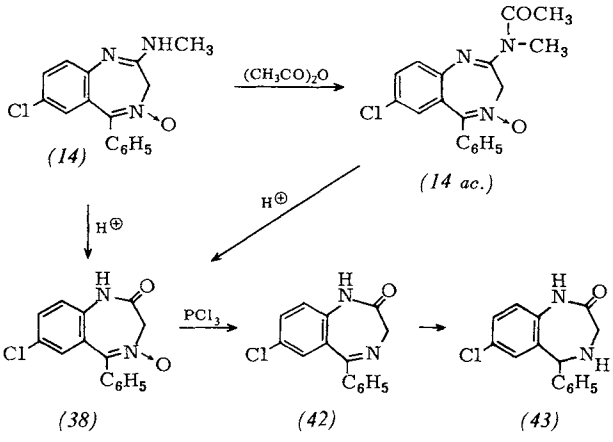


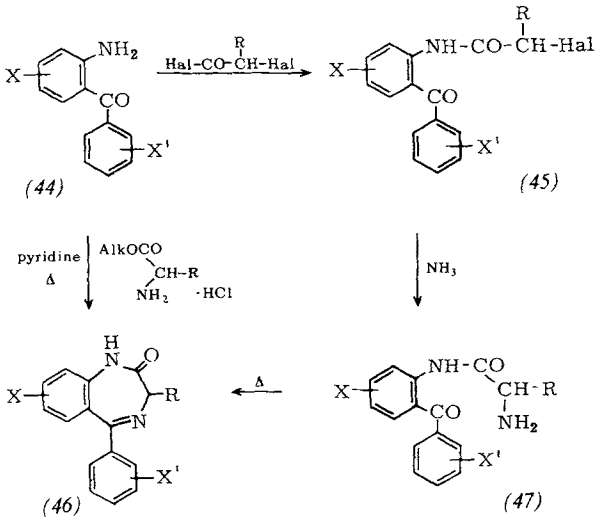
Table 2. Pharmacological properties of a few 1,4-benzodiazepine derivatives.

Compound	Incl. Screen	Fighting Mice	Cat	Anti-Met.	Electroshock Max.	Min.
(14)	100	40	2	18	92	150
(14 ac.)	100	20	2	15	150	150
(38)	75	40	1	6	52	400
(42)	75	20	1	6	25	61
(43)	300	40	10	9.2	36.7	106

8. Methods for the Synthesis of 1,3-Dihydro-1,4-benzodiazepin-2-ones

The benzodiazepine 4-oxides of type *(38)* were relatively readily accessible by treatment of quinazoline 3-oxides such as *(12)* with alkali. This led to a fairly extensive pharmacological investigation of members of this group of compounds bearing different substituents in the phenyl rings.

[11] *A. Stempel, E. Reeder,* and *L. H. Sternbach,* J. Org. Chem. *30,* 4267 (1965).

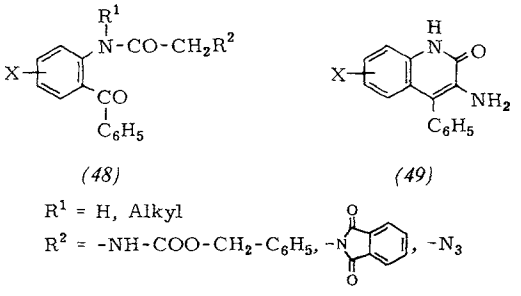


More attractive, however, were benzodiazepinones of type *(42)*, which, as mentioned before, possessed even more pronounced pharmacological activity. Their simple structure induced the search for less involved synthetic approaches and resulted in alternative methods which enabled us to prepare a large number of compounds of this type[12]. The only limiting factor was the accessibility of the 2-aminobenzophenones or 2-aminoacetophenones which were used as starting materials. Our one-step method involves the treatment of an aminobenzophenone *(44)* with glycine ester hydrochloride in pyridine and results in the formation of the benzodiazepinone of type *(46)*, generally in yields of about 50%.

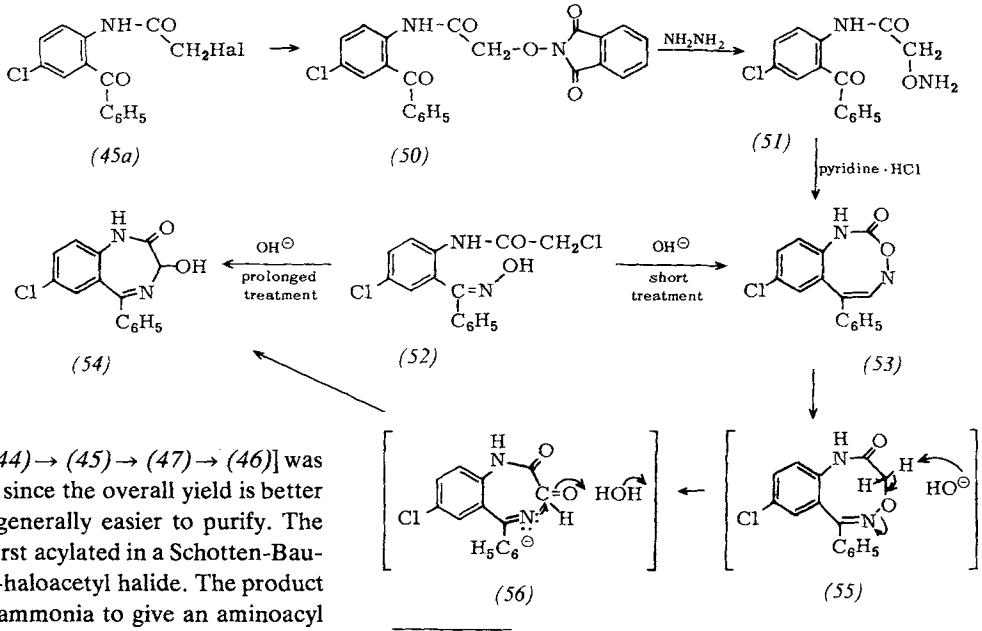
The multistep method [*(44)* → *(45)* → *(47)* → *(46)*] was preferable in most cases, since the overall yield is better and the end-product is generally easier to purify. The aminobenzophenone is first acylated in a Schotten-Baumann reaction with an α-haloacetyl halide. The product of acylation reacts with ammonia to give an aminoacyl derivative which can be readily cyclized. The overall yield in these three steps frequently exceeds 70%. These two methods made the 1,3-dihydro-1,4-benzodiazepin-2-ones the most readily accessible members of this group of heterocyclic compounds.

Another approach used *N*-protected glycine derivatives such as the benzoxycarbonyl[13], the phthaloyl[14] or azido[15] derivatives for the synthesis of intermediates of type *(48)* and the subsequent construction of the seven membered ring.

The ease of formation of this seven membered ring is quite remarkable. Competitive reactions, such as *e. g.* the formation of the aminopyridones[12] of type *(49)* were observed only in rare cases.



Another method for the synthesis of benzodiazepinone derivatives consists in ring contraction of a benzoxadiazocine *(53)*[16a] by treatment with alkali. It leads to 3-hydroxy derivatives such as *(54)*, a class of compounds which was first described by *Bell* and *Childress*[16b][*].



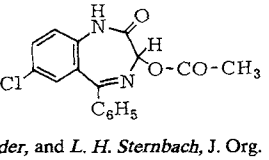
[12] *L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy,* and *A. Stempel,* J. Org. Chem. *27,* 3788 (1962).

[13] *S. C. Bell, T. S. Sulkowski, C. Gochman,* and *S. J. Childress,* J. Org. Chem. *27,* 562 (1962); *A. Stempel* and *F. W. Landgraf, ibid. 27,* 4675 (1962).

[14] Netherlands Patent 6500446 (1966), Delmar; Chem. Abstr. *64,* 5120 (1966).

[15] *J. B. Petersen* and *K. H. Lakowitz,* Acta Chem. Scand. *23,* 971 (1969).

[*] *Bell* and *Childress* used as starting material the *N*-oxide *(38)*, which after subjection to a type of Polonovsky rearrangment and hydrolysis of the 3-acetoxy derivative is converted into *(54)*.

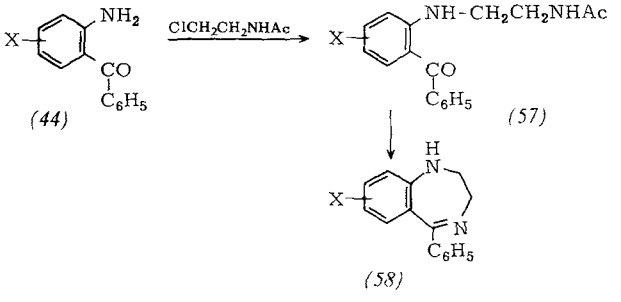


[16] a) *A. Stempel, I. Douvan, E. Reeder,* and *L. H. Sternbach,* J. Org. Chem. *32,* 2417 (1967); b) *S. C. Bell* and *S. J. Childress, ibid. 27,* 1691 (1962).

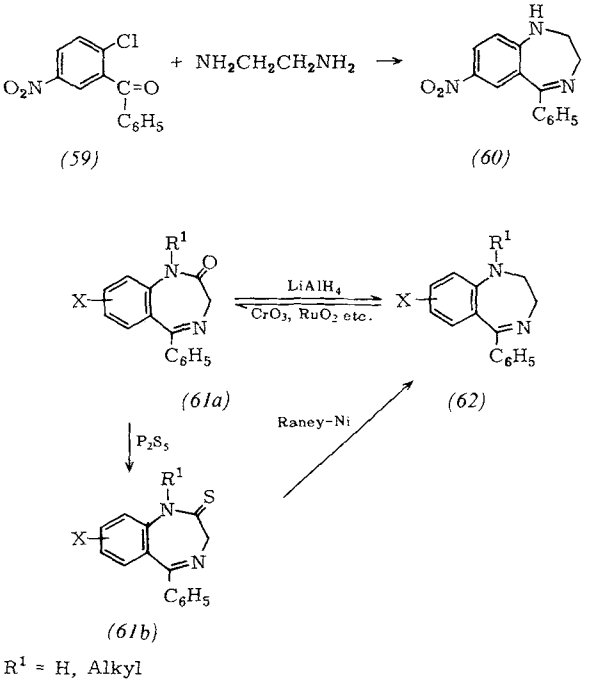
Two methods for the synthesis of the starting material *(53)* are outlined above. One approach, the transformation of *(50)* and related benzophenone derivatives, *via (51)*, into compounds of type *(53)* served as an unequivocal proof for the structure of *(53)*. Another method consists in the alkali treatment of *(52)* under mild conditions. On prolonged treatment with alkali, compound *(52)* was directly converted into *(54)* in about 60% yield. The mechanism indicated, *via (55)* and *(56)*, explains this transformation. It is interesting to note that under practically the same reaction conditions, the isomeric *anti* oxime derivative *(37)* gives the *N*-oxide *(38)* in excellent yield.

9. 2,3-Dihydro-1*H*-1,4-benzodiazepines

Further studies in the benzodiazepine series led to compounds of type *(58)*. The finding that these products also possessed valuable pharmacological properties resulted in a number of synthetic approaches.



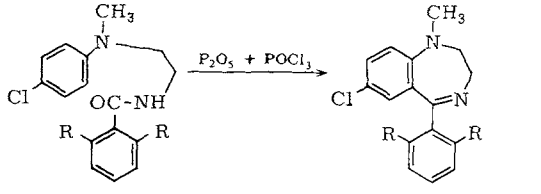
The simplest route consisted in the introduction of the acylaminoethyl moiety into the *o*-aminobenzophenone molecule to yield *(57)*[17], which on hydrolysis gave the desired product *(58)*. The unsubstituted aminoethylamino ketone was not isolated in these cases since it cyclized immediately to form the very stable benzodiazepine derivative *(58)*.



R^1 = H, Alkyl

Another method for the synthesis of benzodiazepine derivatives of this type is by reaction of an appropriately substituted *o*-halobenzophenone with ethylenediamine[18]. The yield in these reactions is generally very good. The nitro group in compound *(60)* could be reduced to the amino group, which, *via* Sandmeyer transformations, led to a variety of 7-substituted benzodiazepines. Another method for the preparation of benzodiazepines is the reduction of the 2-one *(61a)* or desulfurization of the thione *(61b)*[17,19][*].

A Bischler-Napieralski type cyclization proved very useful[21]. This method led in some cases to compounds which were otherwise difficult to synthesize, *e. g.* compound *(66)*[9]. The yields in most cases were very good.



10. 1*h*- and 3*H*-1,4-Benzodiazepines

Compounds of this type are most readily accessible by ring enlargements of 1,2-dihydroquinazoline 3-oxides. In this connection it is amusing to mention how our first dihydroquinazoline *N*-oxide[22] was discovered. At the beginning of our studies when only small quantities of aminobenzophenone oximes were available, attempts were made to recover the last amounts of crystalline material from the oxime mother liquor – which consisted of a dark syrup. A variety of solvents was tried without success. Finally, when in despair we used acetone, a solvent we had previously always gingerly avoided, a large amount of a beautiful yellow crystalline material was obtained, which, however, was quite definitely not the desired oxime.

Closer investigation showed that an unexpected reaction had occurred: the oxime had condensed with the acetone to yield the dihydroquinazoline derivative *(67)*. Further studies showed that the reaction was quite general and that *anti*-oximes of type *(68)* react very readily with aldehydes or ketones to yield dihydroquinazolines[22].

[17] *L. H. Sternbach, E. Reeder,* and *G. A. Archer,* J. Org. Chem. *28,* 2456 (1963).

[18] *L. H. Sternbach, G. A. Archer,* and *E. Reeder,* J. Org. Chem. *28,* 3013 (1963).

[19] *G. A. Archer* and *L. H. Sternbach,* J. Org. Chem. *29,* 231 (1964).

[*] Compounds of type *(62)* could be reoxidized to *(61a)* by various oxidizing agents [20].

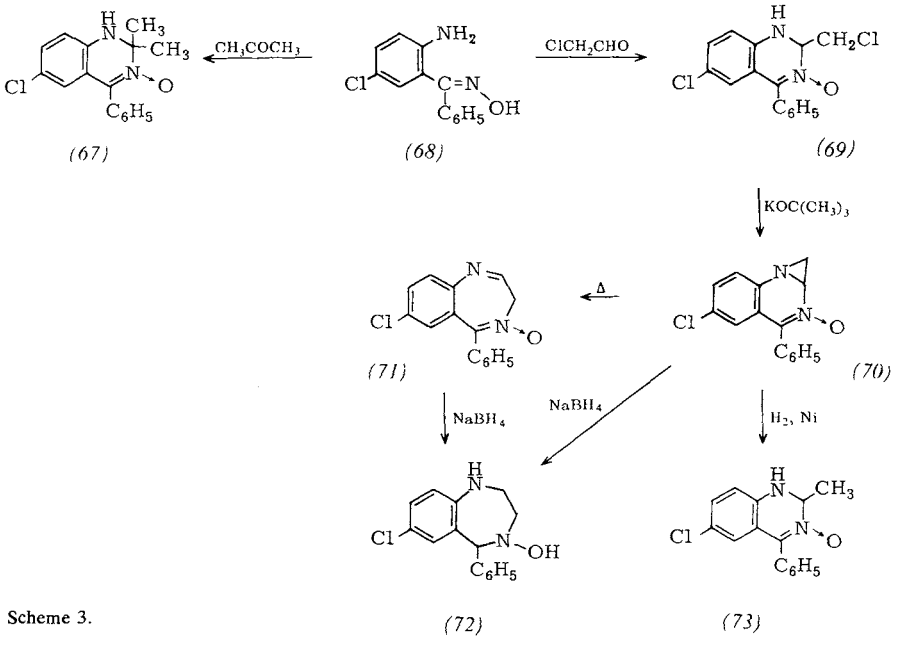
[20] *R. I. Fryer, G. A. Archer, B. Brust, W. Zally,* and *L. H. Sternbach,* J. Org. Chem. *30,* 1308 (1965); *A. M. Felix, J. V. Earley, R. I. Fryer,* and *L. H. Sternbach,* J. Heterocyclic Chem. *5,* 731 (1968).

[21] *H. H. Kaegi,* J. Labelled Compounds *4,* 363 (1968).

[22] *G. F. Field, W. J. Zally,* and *L. H. Sternbach,* J. Org. Chem. *30,* 3957 (1965).

Further study of these compounds showed that dihydroquinazoline derivatives containing exocyclic halogens undergo ring enlargements similar to those studied in the quinazoline 3-oxide series.

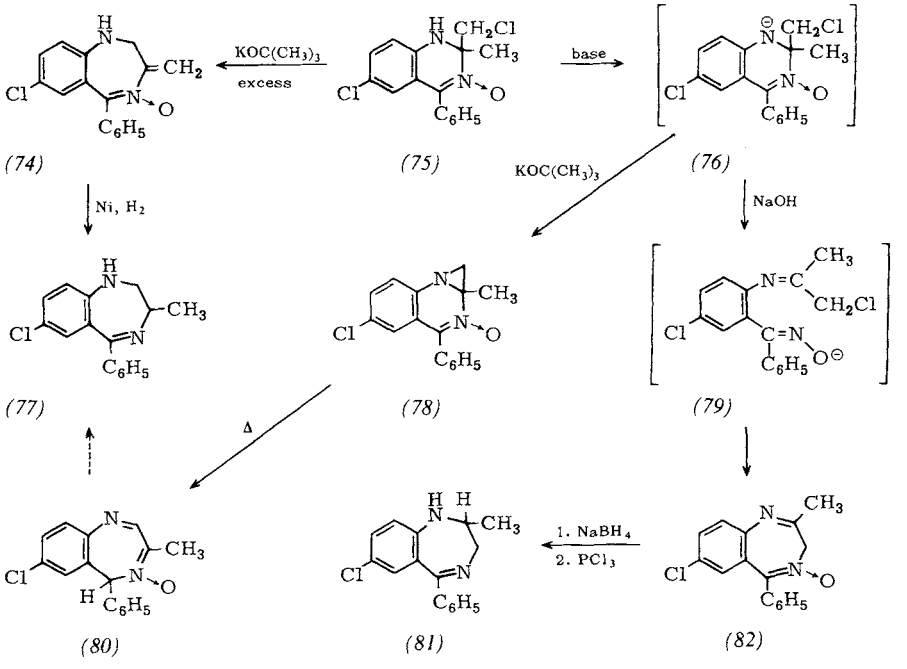
Scheme 3 shows reaction sequences leading to 3*H*-1,4-benzodiazepine derivatives[23]. On treatment of compound *(69)* with potassium *tert*-butoxide the first reaction product is compound *(70)*.



Scheme 3.

The presence of the three-membered ring in *(70)* is shown by the results of reduction experiments. Hydrogenation with Raney nickel as catalyst leads to hydrogenolysis of the bond between the 1-position and the methylene group to yield the 2-methyl-dihydroquinazoline *(73)*. On the other hand, reduction with $NaBH_4$ gave a good yield of the known tetrahydrobenzodiazepine derivative *(72)*. Heating converted compound *(70)* into the valence tautomer *(71)* which could again be reduced in excellent yield to compound *(72)*. The structural assignment for compound *(71)* is based on very convincing spectral evidence (IR, NMR) and is confirmed by the ease of transformation into the known *(72)*.

Investigation of the ring enlargement of a quinazoline 3-oxide *(75)* bearing two substituents on C-2 showed that the course of this reaction depends on the character of the base used and results in the formation of isomeric benzodiazepines. The sequence shown represents an explanation of these reactions. Ion *(76)* is in every case the primary reaction product. If dilute alcohol is used as solvent and sodium hydroxide as base, ring opening occurs to yield a postulated compound *(79)* [similar to *(37)*], which undergoes cyclization to *(82)*. In this reaction sequence the quinazoline *(75)* gives the benzo-



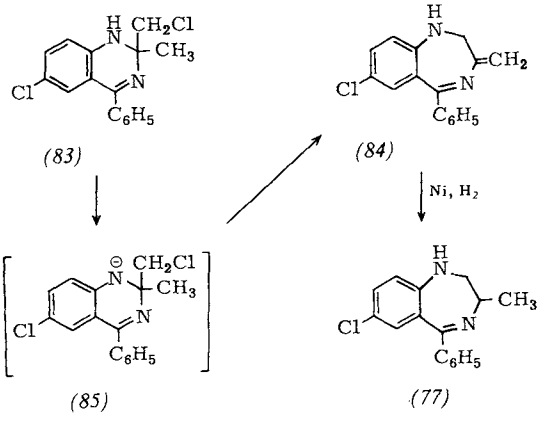
[23] *G. F. Field, W. J. Zally,* and *L. H. Sternbach,* J. Amer. Chem. Soc. *89,* 332 (1967).

diazepine *(82)* (~80% yield), whose structure was indicated by its UV and NMR spectra and confirmed by transformation into the known compound *(81)*.

The reaction of *(75)* with potassium *tert*-butoxide in an aprotic solvent proceeds somewhat differently. The primary reaction product, *i.e.* the ion *(76)*, undergoes intramolecular alkylation to form an aziridino-quinazoline *(78)* whose presence can be easily demonstrated and which on heating transforms into the benzodiazepine *(80)* [*(75)* → *(80)* = 42% yield], the isomer of *(82)*. The structural assignment is based on physicochemical data, UV and NMR spectra (signal for the methyl group) and on the stepwise chemical conversion into the known compound *(77)*.

Ring enlargement of the 2-disubstituted quinazoline 3-oxide under discussion can also take place *via* a third route[9]. When an excess of potassium *tert*-butoxide is used for the protonation of *(75)* an orange compound having an exocyclic methylene group is formed in 25% yield. It has the structure *(74)*. The mechanism of this reaction is not quite clear, but is certainly dependent on the excess of base which abstracts a proton from the exocyclic methyl group. The structure of *(74)* was proved by its NMR spectrum and its transformation by hydrogenation into the known 3-methylbenzodiazepine derivative *(77)*. Thus, three isomers – namely *(74)*, *(80)*, and *(82)* – can be formed on treatment of *(75)* with base.

Whereas the fully aromatic 2-chloromethylquinazolines underwent normal exchange reactions and needed the 3-oxide function in order to undergo ring enlargements, the 1,2-dihydroquinazolines behaved differently[9].

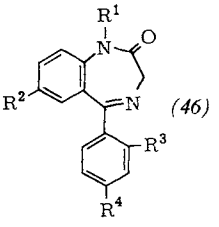


Treatment of *(83)* with a strong base (potassium *tert*-butoxide) resulted again in the formation of an ion of type *(85)*, which then underwent ring enlargement, possibly *via* an oxazirino compound, to yield the benzodiazepine *(84)*. The transformation of *(83)* to *(84)* is relatively clean and occurs with a yield of 60%. The structure of compound *(84)* was established by its physicochemical properties (NMR) and its chemical transformation into the known benzodiazepine derivative *(77)*.

11. Structure-Activity Relationship

Before concluding, a few examples will be given which illustrate some of the rules which could be established in the course of our studies regarding the relation of structure to activity[8].

The 1,3-dihydro-5-phenylbenzodiazepin-2-ones of type *(46)* lent themselves best to these investigations. One reason for this was the ready accessibility of these compounds; more important, however, was the fact that they are the most potent types of benzodiazepines and show,



(46)

Table 3. Pharmacological properties of 1,4-benzodiazepinones.

Cmpd.	R^1	R^2	R^3	R^4	Incl. Screen	Fighting Mice	Cat	Anti- Met.	Electroshock Max.	Min.
(46a)=(42)	–	Cl	–	–	75	20	1	6	25	61
(46b)	CH_3	Cl	–	–	30	10	0.2	1.4	6.4	64
(46c)	–	Cl	Cl	–	100	40	0.1	0.4	13	115
(46d)	–	Cl	–	Cl	>500	>100	–	>800	300	>800
(46e)	–	NO_2	–	–	15	5	0.1	0.5	8.4	132
(46f)	–	CH_3	–	–	>500	>100	–	175	175	>800
(46g)	CH_3	NO_2	F	–	1	0.8	0.02	0.12	12	345

therefore, also the widest variations in activity. They are in this respect more interesting than the 2-amino derivatives of type *(14)*, the tetrahydro-2-ones of type *(43)*, the dihydrobenzodiazepines of type *(62)*, and the last discussed 1*H*- and 3*H*-benzodiazepines.

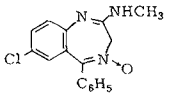
Table 3 shows some compounds of type *(46)* and their pharmacological properties. The substituent on C-7 was found to be of paramount importance, but also substitution on N-1 and in the 5-phenyl ring had a decisive effect on the activity.

Electron withdrawing substituents on C-7 generally imparted high activity, whereas electron donors had the opposite effect.

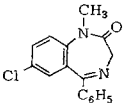
A methyl group on N-1 potentiated the activity, as did a halogen in the *o*-position of the phenyl ring; a substituent in the *p*-position, however, decreased the activity dramatically. The additive character of these effects allowed us to synthesize custom tailored compounds such as, for example, *(46g)* which contained all the features known to impart high pharmacological activity. *(46g)* is indeed the pharmacologically most potent benzodiazepinone known to us.

12. Closing Remarks

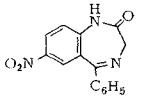
Table 4. 1,4-Benzodiazepines in clinical use.



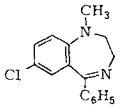
chlordiazepoxide
(Librium®) *(14)*



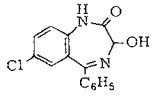
diazepam
(Valium®) *(46b)*



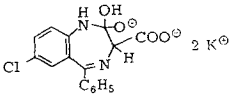
nitrazepam
(Mogadon®) *(46e)*



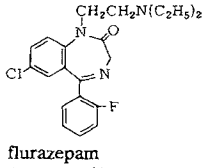
medazepam
(Nobrium®) *(64)*



oxazepam
(Serax®) *(54)*



chlorazepate
(Tranxène®)
(Tranxilium®)



flurazepam
(Dalmane®)

These studies and those of other investigators resulted ultimately in the production of seven 1,4-benzodiazepine derivatives which are now in clinical use as tranquilizers or sleep inducers. Table 4 shows the formulas, the generic names, and also the names of the specialties containing these products.

Additional compounds are being studied and it is to be expected that the number of clinically used 1,4-benzodiazepine derivatives will increase considerably within the next few years.

I wish to acknowledge the dedicated work of my co-workers who contributed so greatly to the development of the chemistry of 1,4-benzodiazepines; in particular, I thank Mr. E. Reeder, Drs. G. Archer, G. Field, R. Ian Fryer, W. Metlesics, G. Saucy, N. Steiger, and A. Stempel. I also want to express my appreciation to the Director of our Pharmacology Department Dr. L. O. Randall and his co-workers for their close co-operation which resulted in the efficient biological evaluation of these compounds.

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Preparative Solid State Chemistry: The Present Position[1,2]

By Harald Schäfer[*]

Dedicated to Professor Wilhelm Klemm on the occasion of his 75th birthday

Two types of reaction are distinguished in solid state chemistry: those in which high mobility of the reactants is aimed at (which can be achieved by the use of high temperatures, by the introduction of defects, by the promotion of surface diffusion, or by means of chemical transport phenomena), and those reactions in which the nature of the products is determined by existing structural elements or lattice defects of the reactants. The importance of paying more attention than hitherto to reaction pathways in preparative solid state chemistry is pointed out.

1. Introduction

The distinction between organic and inorganic chemistry has a historical basis. In some respects it is more meaningful to divide the subject into molecular chemistry and solid state chemistry, a classification that is also useful from the preparative point of view. Theories of reaction mechanism and their practical application are more fully developed in molecular chemistry than in solid state chemistry, for the following reasons:

Molecular chemistry is primarily chemistry in solution. The molecules or ions are so close together in the solution that the diffusion paths (of the order of 10 Å) are of no importance to the course of the reactions, and moreover the diffusion constants are relatively large ($\approx 10^{-5}$ cm^2/sec). Kinetic mechanisms, involving relatively small

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[1] In memory of my late friend *A. D. Wadsley*, of Melbourne, who died on January 7, 1969, and to whom we owe our basic knowledge of the structure relations of the so-called Hägg-Magnéli phases.

[2] Expanded version of an address given at the Colloquium on Preparative Solid-State Chemistry on April 1, 1969 in Aachen (Philips Central Laboratories).