RECENT PHARMACEUTICAL RESEARCH ON HYDRAZINE DERIVATIVES

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The chemistry of hydrazine derivatives had its beginnings in 1863 when Hofmann successfully converted azobenzene to hydrazobenzene thus synthesizing the first hydrazine derivative. In 1877 Emil Fischer was able to synthesize phenylhydrazine which was subsequently used by Knorr, his assistant at that time, for reactions with acetoacetic acid esters. The result was the production of antipyrine and later, thanks to the investigations of Stolz, amidopyrine. Antipyrine immediately aroused great interest and, during the influenza epidemic of 1889/90, its efficacy and practical value as an antipyretic was clearly demonstrated.

In 1887 Curtius produced hydrazine sulphate, Lobry de Bruyn prepared the pure, anhydrous base in 1894 and, finally, in 1907 Raschig described his ingeniously simple hydrazine synthesis. Several compounds of practical therapeutic value resulted from these investigations and they unleashed such a spate of chemical research in this field, that, already in 1913, H. Wieland maintained in his excellent monograph "Die Hydrazine" that the hydrazine field had been fully explored and was a closed chapter. He commented that in the short time which had elapsed since the discovery of the base, the number of derivatives, as well as their diversity, already exceeded those of the organic ammonia derivatives which had been known for a considerably longer time.

Wieland's opinion was later to be proved wrong for, although thousands of hydrazine derivatives were already known at that time, research received a new impulse as recently as two decades ago, so that the field again expanded to an unexpected extent. At the end of the 1940's, a new pyrazolidine derivative found practical application as an anti-rheumatic and, under the name of phenylbutazone, attained a leading position in the therapy of rheumatism. In the early 1950's, a simple hydrazine derivative, isonicotinic acid hydrazide was introduced into therapy as a tuberculostatic. As a result of its outstanding successes in the treatment of this disease it provided the impulse for the synthesis of further hydrazine derivatives.

In the last 15 years, a further 100 or so hydrazine derivatives have found practical medical application. A continuous stream of publications and patent specifications testifies to the synthesis of new hydrazine compounds, with interesting and novel pharmacodynamic properties.

Manifestly the chemical, pharmacological and clinical research in this field is more intensive than ever. An attempt will be made here to review the hydrazine compounds. The hydrazines which are in current usage will

be considered first, whereafter the newest developments of synthetic pharmaceuticals derived from hydrazine will be discussed.

Table 1 gives a survey of the most important hydrazine derivatives used as pharmaceuticals. They may be classified into the following four main groups:

Alkyl and aryl hydrazines;
Acylated hydrazines;
Derivatives of aldehydes and ketones and
cyclic hydrazine derivatives.

Table 1 shows that the hydrazine derivatives vary tremendously, not only as to modifications in structure but also as regards their therapeutic indications. Many of the hydrazines and hydrazides having a simple structure are bacteriostatically active compounds which may be used as tuberculostatics; others are monoamine oxidase inhibitors which find application as antidepressives. Angina pectoris also responds well to some of these compounds. Some hydrazones, semicarbazones, thiosemicarbazones, pyrazole derivatives, derivatives of thiazole and of pyridazine are bacteriostatics, others are tuberculostatics whilst antipyretic activity is primarily found in pyrazole derivatives, particularly pyrazolones and pyrazolidine-diones. A new group of hydrazides, which was developed in our laboratories, has a clinically interesting saluretic activity. This saluretic activity is also exhibited by some thiadiazoles though, in this case, the action may be attributed to inhibition of the enzyme carbonic anhydrase. Finally, some phthalazines are important and very active hypotensives, some triazoles and tetrazoles have an analeptic action, certain thiadiazoles exhibit an antidiabetic activity and a number of novel pyrazole derivatives, with a basic substituent attached to their heterocyclic moiety, have interesting analgesic and very marked serotonin-inhibiting properties. As can be seen from the above, the various hydrazine derivatives have a fantastic diversity of action.

Although hydrazine derivatives whose action occurs outside the central nervous system were also included in *Table 1*, in what is to follow, particular attention will be paid to pharmaceuticals affecting the central nervous system.

Although the compounds summarized in *Table 2* are currently used as anti-depressants in psychiatry, a close connection with the tuberculostatic, isoniazid becomes apparent from their formulae. The discovery of these anti-depressants is also closely connected with research in the field of tuberculostatics for, in 1952, Zeller and co-workers discovered proniazid (1-isonicotinyl-2-isopropylhydrazine) which inhibits the enzyme monoamine oxidase and, after investigations by Kline, Saunders and Loomer, this compound was introduced into psychiatry in 1957 for the treatment of depressive states. In the same year Cesarmans discovered the beneficial action of iproniazid in angina pectoris.

As the scope of this review must necessarily be limited, an exhaustive treatment of the biochemical aspects of these monoamine oxidase inhibitors is not possible. It should, however, be mentioned in passing that their antidepressive action is currently attributed to the inhibition of the enzyme

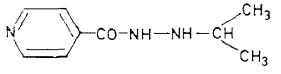
Table 1. Therapeutic application of hydrazine derivatives

Chemical groups		*Typical structure*	*Therapeutic uses*
Aliphatic and aromatic derivs.	Hydrazines	$-\underset{\vert}{CH}-NH-NH_2$	Antidepressants (MAO inhibitors)
Derivatives of carboxylic acids	Hydrazides	$-CO-NH-NH-$	" Angina pectoris, Tuberculostatics, Diuretics
	Semicarbazides	$H_2N-CO-NH-NH-$	Antipyretics
Derivatives of aldehydes and ketones	Hydrazones	$-CH=N-N<$	Tuberculostatics, Bacteriostatics
	Semicarbazones	$H_2N-CO-NH-N=C<$	Tuberculostatics, Bacteriostatics, Haemostatics
	Thiosemicarbazones	$(-C\,S-)$	
Cyclic derivatives of hydrazine	Pyrazoles		Bacteriostatics, Antiphlogistics, Serotonin inhibitors
	Pyrazolones		Antipyretics, Analgesics, Serotonin inhibitors
	Pyrazolidine-diones		Antiphlogistics
	Thiadiazoles		Bacteriostatics, Diuretics, Antidiabetics
	Triazoles		Analeptics
	Tetrazoles		
	Pyridazines		Bacteriostatics
	Phthalazines		Hypotensives

monoamine oxidase and the resulting accumulation of the biogenic amines in the brain. The main indications of these compounds are psychic depression, angina pectoris and severe forms of hypertension. Whilst the compounds in *Table 2* are similar as regards their antidepressive action, variations do exist as regards their strength, dosage, side effects and onset of

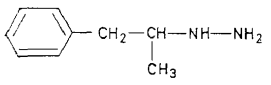
Table 2. Antidepressants

Iproniazid



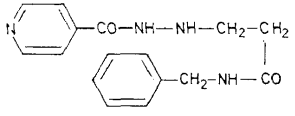
H.H. Fox,
J.T. Gibas.
(1953)

Catron®



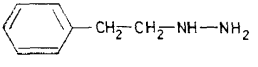
J.H. Biel, A.E. Drukker,
P.A. Shore, S. Spector,
B.B. Brodie.
(1958)

Nialamide



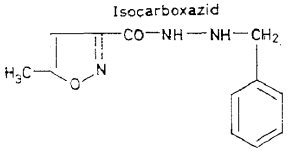
B.M. Bloom, R.E. Carnahan. (1959)

Phenelzine



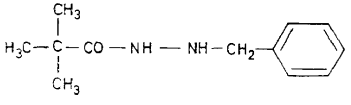
E. Votocek,
O. Leminger.
(1932)

Isocarboxazid



T.S. Gardner, E. Wenis, J. Lee. (1958

Pivazide



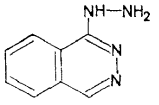
H. Gutmann, O. Straub, P. Zellor. (1957)

action. Exhaustive clinical and pharmacological investigations have shown that the monoamine oxidase inhibitors primarily affect the symptoms of psychic depression, resulting in a lifting of the mood and an increase of drive. Patients feel less tired, mental and physical activity as well as appetite increase and the patients adapt themselves to their surroundings and once more take part in what goes on about them. In the most responsive cases the depressive symptoms may even be partly eliminated. Although, as has already been briefly mentioned above, this antidepressive action and the inhibition of the enzyme monoamine oxidase are thought to be causally related, this has not been conclusively proved. In passing, mention should be made of the fact that MAO-inhibitors also have a prophylactic action on pain in angina pectoris and in many cases successfully lower the systolic and, in some cases, even the diastolic blood pressure. Again the action mechanism in these two indications has not been satisfactorily explained[1].

Of the remaining hydrazine derivatives used in medicine, mention should be made of the hypotensives, the diuretics and antidiabetics. As may be seen from *Table 3*, the hypotensives belong to the phthalazine group of compounds, the diuretics are derivatives of amino-thiadiazoles and *N*-amino-heterocyclic compounds and the antidiabetics are obtained from amino-thiazoles.

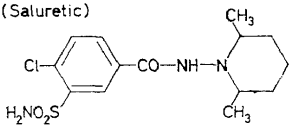
Table 3. Varia (hypotensives, diuretics, antidiabetics)

Hydralazine
(Hypotensive)



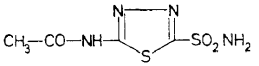
J. Druey, B.H. Ringier.
(1951)

Brinaldix ®
(Saluretic)



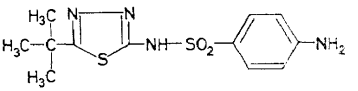
E. Jucker, A.J. Lindenmann, E. Schenker.
(1960)

Acetazolamide
(Diuretic)



R.O. Roblin, J.W. Clapp.
(1950)

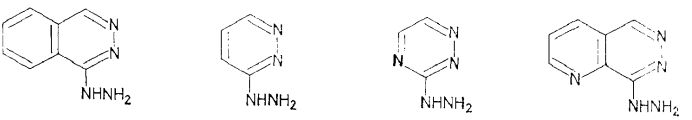
Glybuthiazol
(Antidiabetic)



A. Loubatières.
(1958)

Of these compounds, the phthalazinohydrazines were developed by Druey and colleagues[2]. They were amongst the first synthetic compounds to be used for the treatment of high blood pressure. Not only was this the first medicinal use of phthalazine derivatives, it was also the first time that compounds having free hydrazine radicals were used in medicine.

Of interest also is the fact that phthalazines of this type have only a slight toxicity and produce few side effects. Interesting relationships between the structure and action of these hydrazines became apparent from the investigations of Druey and his colleagues and it was found that the blood pressure lowering effect was particularly marked in compounds with the following basic structures:



The pharmacological properties of hypotensives of the above type were investigated by Gross and his co-workers; their action appears to be mainly peripheral, central action being only marginal.

The diuretic action of the thiadiazole derivatives can be attributed to

carbonic anhydrase inhibition. A further compound with saluretic activity, Brinaldix®, was recently developed in our laboratories. The compound is interesting in that it contains an *N*-amino-heterocyclic group as a structural element. This series of compounds will be discussed in greater detail in what is to follow. The antidiabetic produced from aminothiadiazole is mentioned only for the sake of completeness as this indication is generally limited to sulphonyl urea compounds, so that this hydrazine derivative is a curiosity.

In synthesizing antipyrine in 1883, Knorr produced the first synthetic pharmaceutical having an antipyretic action. Modification of antipyrine subsequently yielded amidopyrine, which is still one of the most important mild analgesics, and later phenylbutazone, the most widely used antiphlogistic and antirheumatic drug. The field of pyrazolones and pyrazolidinediones has been investigated most thoroughly since the discovery of antipyrine and in the search for analgesics and antiphlogistics many thousands of compounds have been synthesized[3]. It was found that amidopyrine, as well as phenylbutazone, has an extraordinarily high specificity of structure, very slight changes yielding compounds which are no longer effective. In spite of all the investigations in this field only half a dozen or so analgesics and anti-inflammatory agents of practical use have been produced, and these are similar in their structure to the two prototypes.

A new development occurred a few years ago when a novel group of basically substituted hydrazines was developed by the author and his co-workers, which when modified to cyclic compounds, yields interesting analgesics, antiphlogistics, spasmo-analgesics and serotonin-inhibitors. These preparations are summarized in *Table 4*.

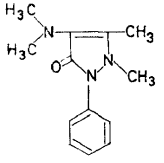
Piperylone and benzpiperylone both find practical application and the clinical preparation MF 389 is undergoing further careful examination. A characteristic of all these compounds is a basic substituent on an *N*-atom of the heterocyclic moiety, this substituent being in fact necessary for their pharmacological actions.

Most of the preparations we have considered thus far are already in clinical use. In the last ten years however, a vast number of compounds, having interesting pharmacodynamic properties, have been described which are not yet ripe for practical application but are still undergoing intensive pharmacological or clinical trials. Although some representatives of this new series of compounds do not comply with the stringent requirements at present demanded from a synthetic drug, the active research worker is, nevertheless, interested in the possibilities offered by the various hydrazine compounds, as these may give a lead for further investigations. Consequently, the latest hydrazine research has been dealt with in the second part of this review and the work done in this connection in our own research laboratories is discussed at greater length.

When we began to take an interest in hydrazine chemistry some years ago, we set out to produce a novel type of hydrazine. The characteristic feature of this group is that the carbon radical bearing the hydrazine radical is also attached to another basic nitrogen group. The carbon radical may, for example, be an alkyl chain and may furthermore form a heterocyclic radical with this further nitrogen group. So as to illustrate the above, a review of these various types of basically substituted hydrazines is given in *Table 5*.

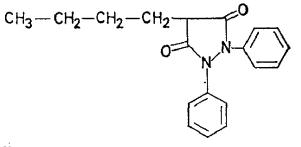
Table 4. Analgesics and antiphlogistics

Amidopyrine



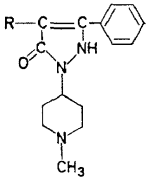
F. Stolz.
(1896)

Phenylbutazone



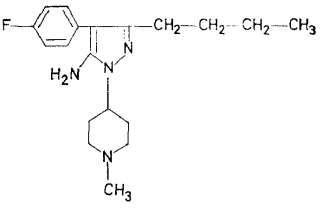
H. Stenzl.
(1946)

Piperylon: $R = C_2H_5$
Benzpiperylon: $R = CH_2{-}C_6H_5$



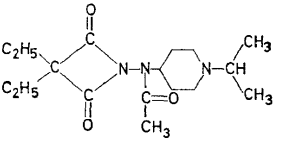
E. Jucker, A.J. Lindenmann,
A. Ebnöther.
(1956)

MF 389



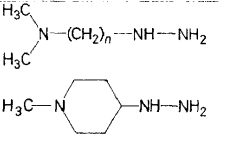
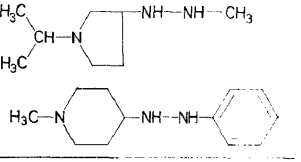
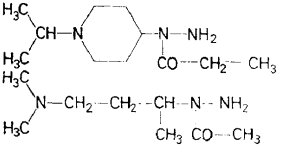
E. Jucker, A.J. Lindenmann,
E. Rissi.
(1958)

XA 99



E. Jucker, A. Ebnöther, E. Rissi,
A. Vogel, R. Steiner.
(1957)

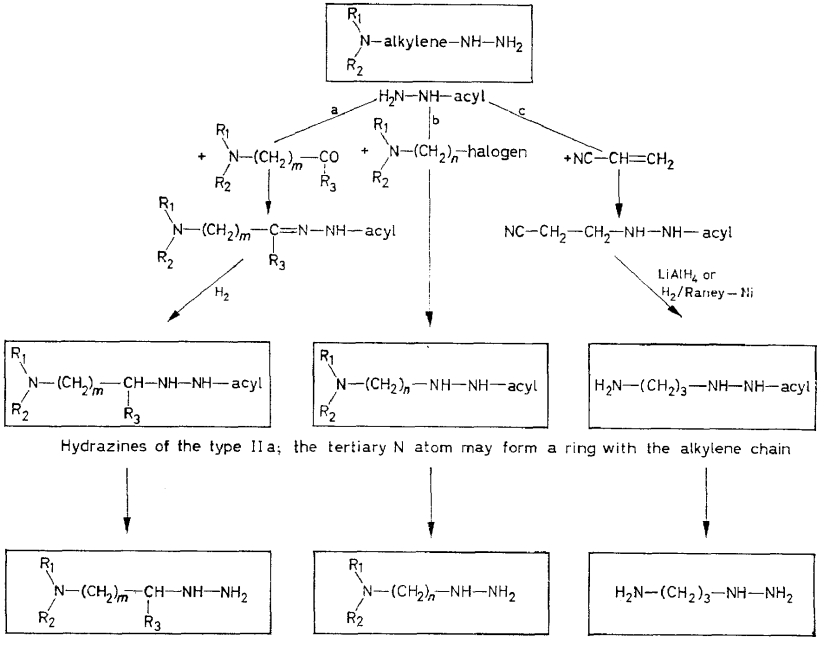
Table 5. Basically substituted hydrazine derivatives

Chemical series	*Examples*
(I) Monosubstituted hydrazines N-alkylene - NH - NH_2	
(II) 1,2 - Disubstituted hydrazines N-alkylene - NH - NH - acyl (II a) or alkyl, aryl (II b)	
(III) 1,1 - Disubstituted hydrazines N-alkylene - N(acyl) - NH_2	

The hydrazines of *Table 5* may be produced in a number of ways and various patterns of synthesis are shown in *Tables 6, 7* and *8*:

Some of these hydrazines have appreciable monoamine oxidase inhibiting actions. However, their real importance lies in the fact that they may be used as starting materials for the production of 4-, 5- and 6-membered heterocyclic compounds. These compounds are novel in that they contain radicals

Table 6. Synthesis of hydrazines of the type I

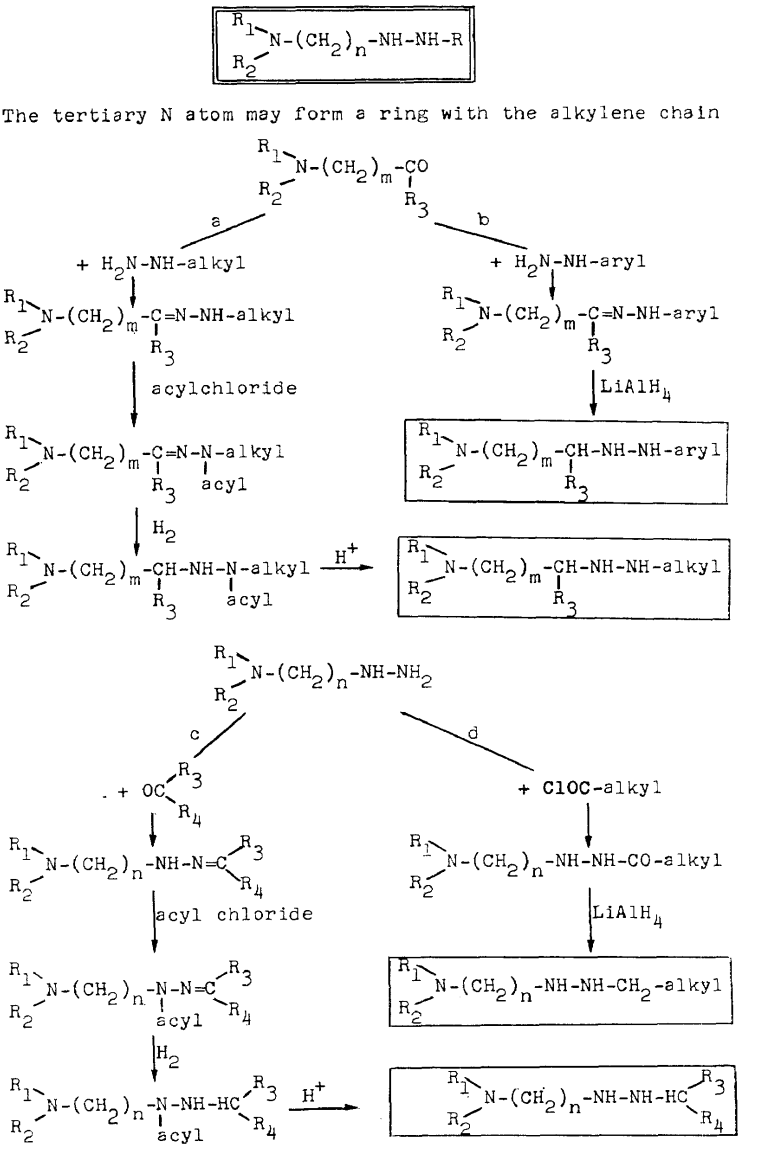


having a basic nitrogen atom as a substituent on a ring nitrogen atom. Prototypes of ring systems which we have produced using the new hydrazines as starting materials are shown in *Table 9*.

Before discussing these new developments in detail, mention should be made of the fact that the new derivatives, the *N*-amino-azetidine diones show marked antiphlogistic actions while the aminopyrazoles have been found to possess an interesting and very wide spectrum of action including, in addition to their narcosis-potentiating effect, analgesic, antiphlogistic, serotonin-inhibiting, adrenolytic and blood-pressure lowering properties. The pyrazolones are important mainly because of their analgesic, spasmo-analgesic and serotonin-inhibiting actions which are of practical value; the latter two properties have not hitherto been observed in hydrazine derivatives, so that this represents a new break-through. Basically substituted pyrazolidinediones showed good antiphlogistic properties in pharmacological tests, but proved unsatisfactory in clinical trials, mainly because of various side effects. Pyridazine diones are characterized by their analgesic properties.

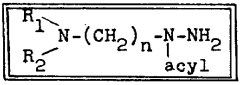
The latest trends in hydrazine chemistry will now be illustrated in such a

Table 7. Synthesis of hydrazines of the type IIb



manner as to encompass our own research within a larger framework, in order that relationships between structure and action may be better demonstrated. The first group of compounds to be discussed is the 5-membered heterocyclic group of compounds containing 2–3 *N*-atoms; these compounds are summarized in *Table 10.* Basically substituted pyrazolones of this type are not in the table as some of the interesting prototypes of this group will be treated separately later.

Table 8. Synthesis of hydrazines of the type III



The tertiary N atom may form a ring with the alkylene chain

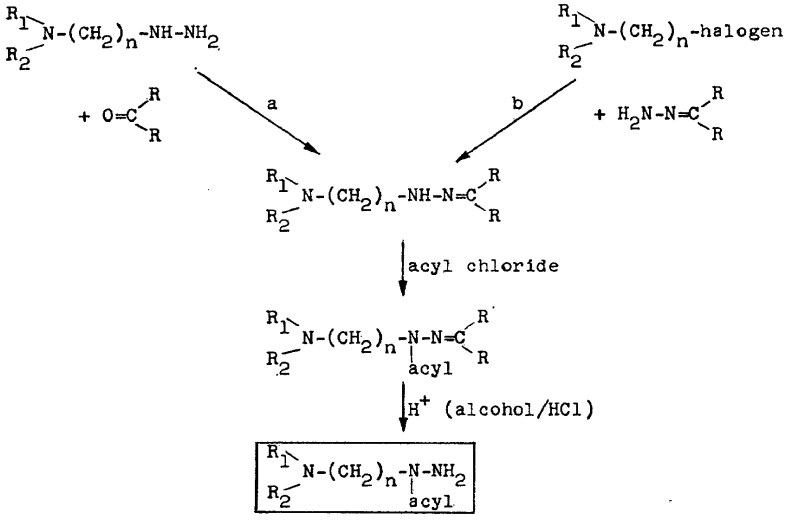


Table 9. New heterocyclic series derived from basically substituted hydrazines

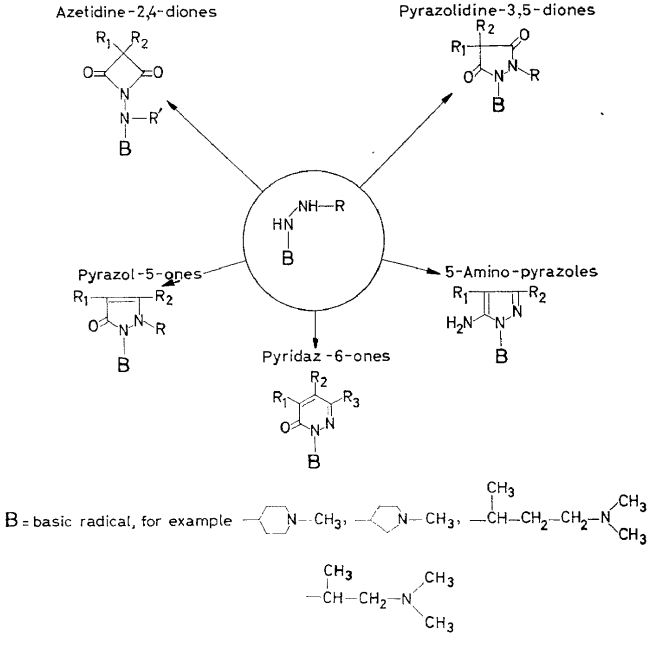
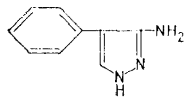
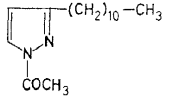


Table 10. Novel pyrazoles and related compounds (excluding pyrazolones and pyrazolidines)



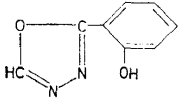
3-Amino-4-phenylpyrazole
(Muscle relaxant)

M.L.Cook.
(1959)



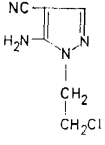
1-Acetyl-3-undecyl-pyrazole
(Anticonvulsive)

G.C.Somerville, W.Oroshnik.
(1958)



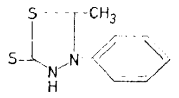
2-(*o*-Hydroxyphenyl)-1,3,4-oxadiazole
(Hypnotic)

J. Maillard, M. Vincent, R. Morin, M. Bernard.
(1959)



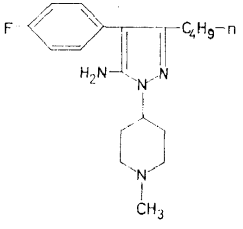
2-(β-Chloroethyl)-3-amino-4-cyanopyrazole
(Tranquillizer)

J. Druey, P. Schmidt, K. Eichenberger, M. Wilhelm.
(1958)



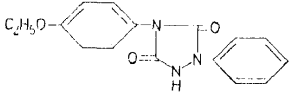
4-Phenyl-5-methyl-1,3,4-thiadiazolidine-2-thione
(Antiphlogistic)

Ed. Geistlich and Sons.
(1959)



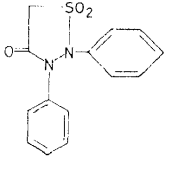
1-(1'-Methyl-4'-piperidyl)-3-n-butyl-4-(*p*-fluorophenyl)-5-aminopyrazole (MF 389)
(Serotonine inhibitor, antiphlogistic)

E. Jucker, A.J. Lindenmann, E. Rissi.
(1958)



1-Phenyl-4-(*p*-ethoxyphenyl)-3,5-dioxo-1,2,4-triazolidine
(Antiphlogistic)

H. Ruschig, K. Schmitt, L. Ther, W. Pfaff.
(1960)



2,3-Diphenyl-1,1,4-trioxo-1,2,3-thiadiazolidine
(Antiphlogistic)

R.M. Dodson, P. Ridge, V. Papesch, M. Grove.
(1959)

As may be seen from this summary, simple 3-amino-4-phenyl-pyrazoles exert muscle-relaxing effects, 1-acetyl-pyrazoles may have anticonvulsive properties, oxodiazole derivatives hypnotic actions and 3-amino pyrazoles, having further substituents on the ring structure, a tranquillizing effect. Triazolidine derivatives may have an antiphlogistic action and a basically substituted 5-aminopyrazole is characterized by very interesting serotonin-inhibiting and antiphlogistic properties. As the serotonin-inhibiting action in the case of basically substituted pyrazoles was first observed by Cerletti, Taeschler and co-workers in our Medical–Biological Laboratories and constituted an interesting new aspect, this novel group of basically substituted 5-amino-pyrazoles will be discussed at greater length.

Whilst pyrazolones and pyrazolidine diones have been investigated chemically at a tempo which, since the discovery of antipyrine, has practically never slackened, the pyrazole group has received considerably less attention. This may be due to the fact that up to the present time very few pyrazole derivatives have attained any practical importance as pharmaceuticals and those which have, do not compare in importance with antipyrine, amidopyrine and phenylbutazone.

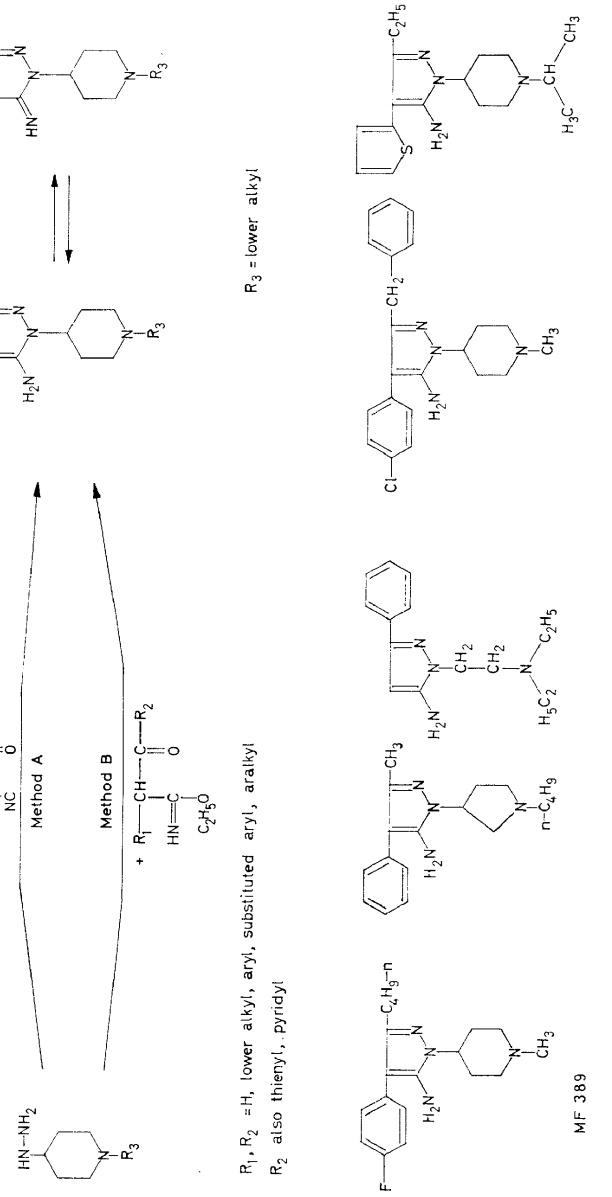
At the commencement of our investigations, aminopyrazoles were still little known and no preparation from this series, aside from a bacteriostatically active sulphonamide derivative, had, to the best of our knowledge, ever been used as a drug. As aminopyrazoles may occur in tautomeric form, they were also of particular interest because it was our desire to investigate, in comparative tests, the relationship between structure and action of these compounds and compare them with the pyrazolones still to be mentioned. As a result of these considerations, we synthesized a large number of 5-aminopyrazoles, all of which were characterized by an extra basic radical at the nitrogen atom in the 1-position. *Table 11* summarizes the most important groups of this new series. The table clearly shows that the substituent at the nitrogen 1 atom comprises an amino-alkyl, pyrrolidyl or piperidyl radical.

The remaining positions of the molecule may also be substituted in diverse ways. Thus, for example, an alkyl, aralkyl, aryl or trifluoromethyl radical may be attached to the C–3 atom, whilst the C–4 atom of our compounds generally has a phenyl, thienyl or *p*-halogeno-phenyl radical attached thereto. Finally, the amino radical in the 5-position, may be free or substituted.

These novel hydrazine derivatives were synthesized by condensing the aforementioned basic substituted hydrazines with a substituted acyl acetic acid nitrile in such a way that the substituents of the nitrile occurred at the C–3 and C–4 atoms of the pyrazole ring.

For obvious reasons each individual group of compounds included in a review of the enormous field of hydrazine drugs cannot be treated in detail. It is for this reason that only particularly characteristic aspects of these aminopyrazoles will be selected and discussed. The wide spectrum of activity of this group of compounds is particularly striking. The investigations of Cerletti, Taeschler and co-workers which were conducted on many aminopyrazoles of the above type, have led to the following conclusions: aminopyrazoles, having one basic substituent at the N–1 atom and aliphatic or

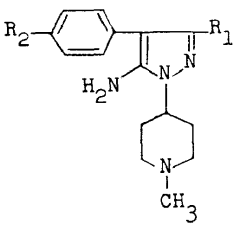
Table 11. Synthesis and examples of 5-amino-pyrazoles



aromatic radicals on the C–3 and C–4 atoms, in general have an analgesic and an adrenaline-inhibiting action, a very strong serotonin inhibition, potentiation of anaesthesia, inhibition of formalin and serotonin oedema, a marked blood pressure lowering effect and an inhibition of nicotine-induced muscle spasm. This spectrum of activity clearly suggests a central nervous action of these preparations. All representatives of this novel group, however, do not possess all the above mentioned effects to the same degree. The most active representatives of the series contain an alkyl radical, preferably containing 3 or 4 carbon atoms, in the 3-position and a *p*-chloro- or *p*-fluorophenyl radical in the 4-position. Compounds having a trifluoromethyl or benzyl radical at the C–3 carbon atom are also very active. Compounds having an *N*-alkyl piperidyl radical at the N–1 atom are the most active preparations whilst amino-alkyl substitution markedly attenuates biological activity. If the individual actions, described for individual prototypes of this series, are compared with typical control compounds, it will be seen that, in every case, the activity is very marked and in some cases specific (*Table 12*).

In discussing *Table 3* it was pointed out that, of the new pyrazolones having an analgesic action and some of those having an antiphlogistic action, those preparations which originate from the series of the basically substituted hydrazines are particularly active[5]. Mention has also been made

Table 12. Relations between structure and effect of some 5-amino-pyrazoles



R_1	R_2	Adrenalin inhibition in vitro x times weaker than DHE	Serotonin inhibition in vitro x times stronger than Piperylon	Potentiation of narcosis ED_{50} mg/kg s.c. (mice)	Inhibition of oedema in rats ED_{20} mg/kg s.c. serotonin oedema[1]	Inhibition of oedema in rats ED_{20} mg/kg s.c. formalin oed.[2]	Inhibition of the nicotine induced muscular spasm in mice ED_{50} in mg/kg s.c.	Acute toxicity (mice) LD_{50} in mg/kg s.c.
CH_3	H	55		41	10	27	7	450
i-C_3H_7	Cl	30	22	3·3	0·3	20	4	180
CF_3	Cl	7·5	4·4	4·4	1·2	7	1·4	250
n-C_4H_9	F	15	130	8·5	0·28	40	2·8	200

of the fact that, hitherto, practically all modifications of the amidopyrine structure yielded ineffective compounds and that, up to now, only some half dozen compounds of the group of classical pyrazolones and pyrazolidine-diones were used as analgesics and antiphlogistics. Consequently, it was even more surprising that a whole series of basically substituted pyrazolones (see *Table 13*) proved to be interesting analgesics, spasmo-analgesics and serotonin-inhibitors of clinical value.

The synthesis of these novel pyrazolone compounds was effected in a number of ways. An example is the conversion of suitably substituted β-keto-carboxylic acids and suitable derivatives thereof with basically substituted hydrazines.

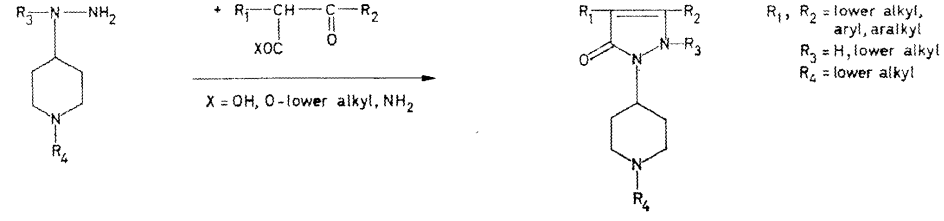
Pharmacological testing has shown that individual representatives of the basically substituted pyrazolones shown in *Table 13* have characteristic analgesic and antiphlogistic actions, but, above all, remarkable serotonin-inhibition. It is this latter action which is practically non-existent in the classical, phenyl substituted pyrazolones, for example, aminopyrine, antipyrine and phenylbutazone. This series of compounds has already produced piperylon, which is a well-tolerated mild analgesic and spasmolytic and benzpiperylon. It is surprising that benzpiperylon, when compared directly on the same organs in a great number of experiments, has proved to be as potent an antiserotonin agent as lysergic acid diethylamide on a weight for weight basis. As regards the analgesic action, benzpiperylon and aminopyrine are roughly equipotent. The low toxicity and the almost complete absence of side effects in the case of piperylon and benzpiperylon is particularly advantageous. Thus, for example, both compounds are virtually devoid of ulcerogenic properties. Pharmacological tests have furthermore demonstrated that both piperylon and benzpiperylon have a central anti-emotional action, manifest from their ability to inhibit emotional defaecation.

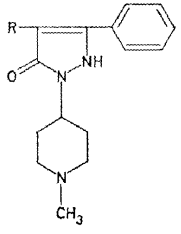
Whilst working on the pyrazolones, which have just been discussed, it seemed natural also to synthesize the corresponding basically substituted pyrazolidine-diones. This class appeared to be particularly interesting at the time and shows some similarity to compounds of the phenylbutazone type. In contrast to the latter compounds, however, hydrazobenzene is no longer a component of the molecule and it is thus to be assumed that different products of metabolism would result from the two series. During the course of this research we produced the groups of pyrazolidine-diones shown in *Table 14*.

The synthesis of these compounds was effected by conversion of suitable malonic acid derivatives with basically substituted hydrazines. The resulting pyrazolidine-diones then underwent exhaustive pharmacological testing. These tests showed various compounds of this series to have a marked antiphlogistic action which was particularly impressive in lower doses in the formalin oedema test on the rat (see *Table 15*).

When converting hydrazines or amines with malonic acids, the corresponding dihydrazides or dioxopyrazolidines and diamides are the primary reaction products. However, in some of our syntheses, which have just been described, a further reaction product was obtained in addition to the expected dioxopyrazolidine. The structure of this further reaction product

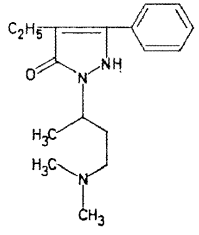
Table 13. Synthesis and examples of pyrazol-5-ones

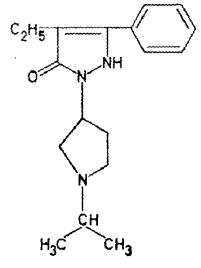


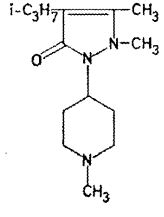


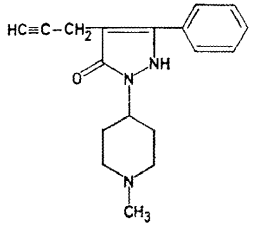
R = C_2H_5 : Piperylon

R = $CH_2-C_6H_5$: Benzpiperylon









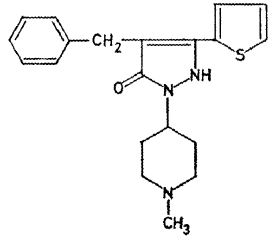
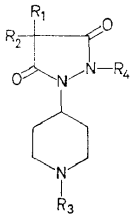
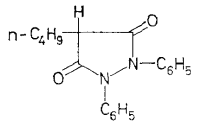


Table 14. Synthesis and examples of pyrazolidine-3,5-diones

x

Table 15. Antiphlogistic action of some pyrazolidine-3,5-diones in formalin oedema test (mice)



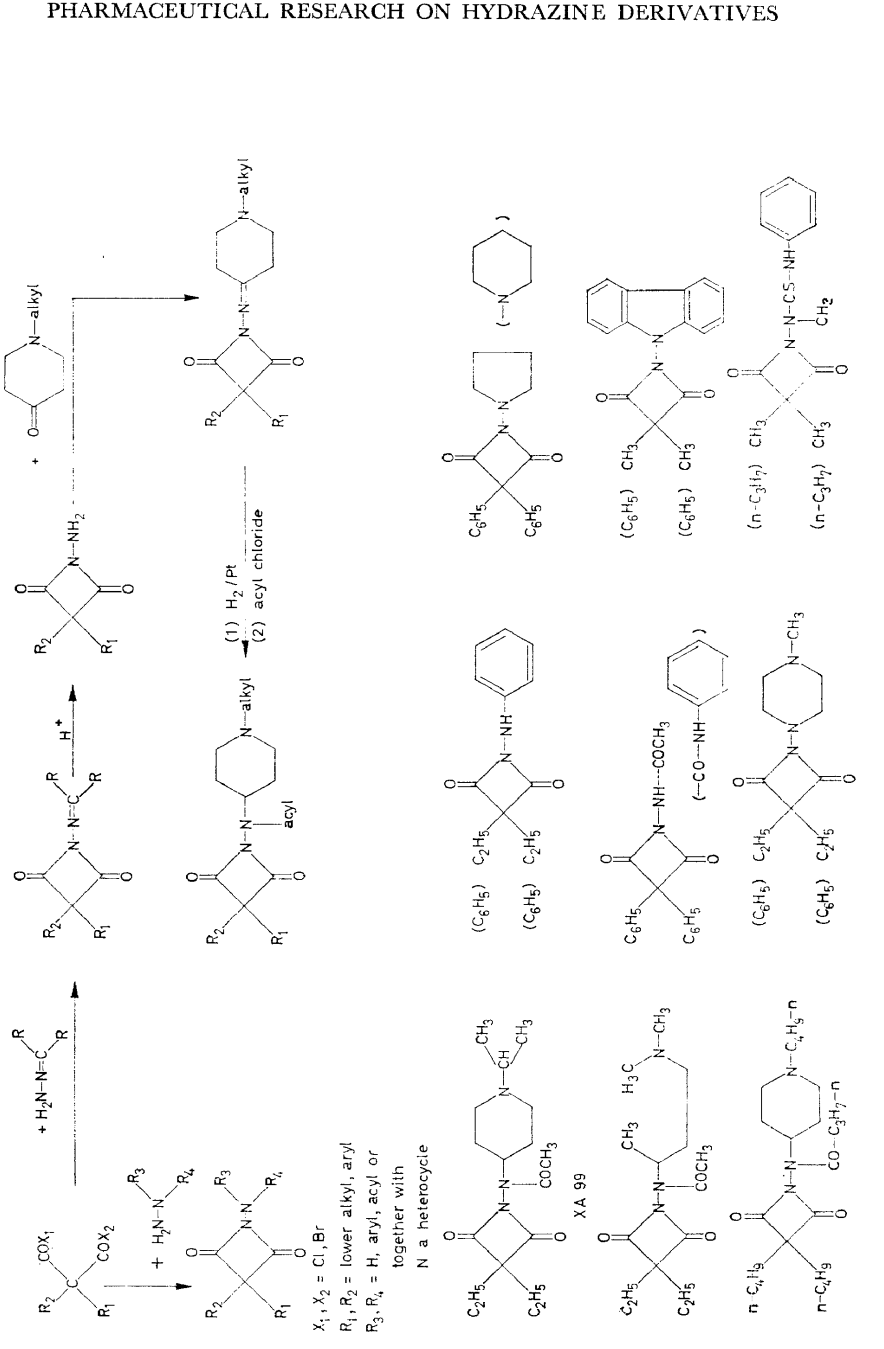
				Dosage (mg/kg)			
R_1	R_2	R_3	R_4	25	50	100	200
n-Propyl	H	Methyl	i-Propyl	−6·4	−8·4	−14·4	−22·0
Cyclohexyl	H	Methyl	i-Propyl	−3·4	−5·7	−8·4	−21·4
Ethyl	Ethyl	Methyl	H	−3·8	−12·8	−10·6	−10·9
Benzyl	Benzyl	Methyl	H	−1·9	−4·8	−6·8	−15·0
Ethyl	Ethyl	Methyl	i-Propyl	−0·5	−10·0	−15·0	−22·3
n-Butyl	n-Butyl	Methyl	i-Propyl	−6·8	−13·0	−20·9	−36·5
Ethyl	Ethyl	Methyl	Acetyl	−5·0	−11·4	−15·9	−13·0
n-Butyl	H	Methyl	Dimethyl-carbamoyl	−7·8	−10·4	−9·0	−14·7
 Phenylbutazone				0	−1·9	−12·1	−28·0

was determined and found to be that of a malonimide. Imides of dicarboxylic acids with 5- or 6-membered rings have been known for a long time and have been intensively investigated. Although several authors had proposed a compound having the malonimide structure, it was only verified in 1914 by Staudinger and co-workers when converting diphenylketene with phenylisocyanate. From that time onwards, until we started our own research, only two further malonimides had been described, namely by Landquist and Stacey in 1953. The fact that these interesting 4-membered ring compounds were readily obtained by reacting di-substituted malonic acid derivatives and hydrazines or primary amines, astounded us and encouraged us to investigate this interesting novel group of compounds thoroughly. During the course of this research there were produced a great number of azetidinediones which originate as shown in *Table 16.*

Some of these compounds showed a very marked antiphlogistic action in pharmacological tests according to the granuloma pouch method (*Table 17*).

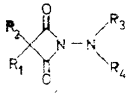
The figures given for the various dosages in this summary pertain to percentage values with reference to exudate inhibition. The test is carried out

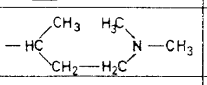
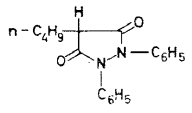
Table 16. Synthesis and examples of azetidine-2,4-diones



in such a manner that an air pocket is formed under the skin on the back of the rats into which a small quantity of croton oil is injected, whereupon a granuloma pouch forms. The inflamed tissues react by forming an exudate and it is thus possible, by administering the compound to be tested and comparing with control animals, to determine the inhibition of exudate formation and to express this as a percentage.

Table 17. Antiphlogistic action of some azetidine-2,4-diones in formalin oedema test (mice)

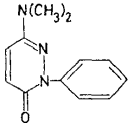


R_1	R_2	R_3	R_4	Inhibition (%) of oedema formation at various dosages (mg/kg)						Effect comparison with that of phenylbutazone
				6.25	12.5	25	50	100	200	
Ethyl	Ethyl	Acetyl		0	0	-5.2	-16.6	-22.5	-32.0	260
Ethyl	Ethyl	Acetyl		0	0	-6.9	-11.9	-23.7	-31.5	250
n-Butyl	n-Butyl	Acetyl		-5.0	-10.2	-21.8	-17.7	-21.0	-30.9	700
Ethyl	Ethyl	Acetyl		0	0	-6.8	-17.4	-28.6	-40.7	280
Ethyl	Ethyl	Acetyl		0	-9.2	-19.2	-23.5	-30.5	-37.7	730
n-Propyl	n-Propyl	Acetyl		-4.6	-16.9	-25.9	-28.1	-28.4	-	1000
Phenylbutazone				0	0	0	-1.9	-21.1	-28.0	100

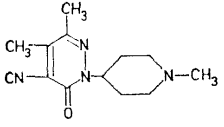
Whilst 5-membered heterocyclic hydrazine derivatives having two nitrogen atoms have been tested quite exhaustively, investigations in the field of 6-membered heterocyclic compounds derived from hydrazine are fewer and of more recent date. The impulse to some of this research was probably provided by the fundamental investigations of Druey and co-workers which led to the above mentioned phthalazines with a hypotensive action. Up to the present time, however, only very few 6-membered heterocyclic compounds containing the hydrazine radical have found practical application; namely the phthalazines already mentioned, and some bacteriostatically active pyridazines. Recently, however, publications have been appearing more frequently and bear witness to increased activity in this field. *Table 18* gives a short review of some of the recently described pyridazones and phthalazones having interesting pharmacodynamic properties.

As may be seen from this table, some pyridazines have analgesic, anticonvulsive, anti-tussive and diuretic properties. The most important actions of the above phthalazines are circulatory and antihistaminic.

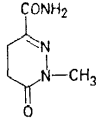
Table 18. Pyridazones and phthalazones



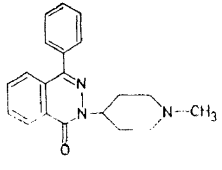
1-Phenyl-3-dimethylamino-pyridazone-(6)
(Antipyretic, analgesic)
J. Druey, A. Hüni, Kd. Meier, B.H. Ringier, A. Staeheli.
(1954)



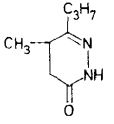
1-(1'-Methyl-4'-piperidyl)-3,4-dimethyl-5-cyano-pyridazone-(6)
(Analgesic)
E. Jucker, R. Süess.
(1959)



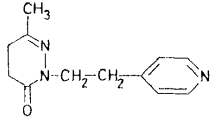
1-Methyl-4,5-dihydro-pyridazine-6-one 3-carboxylic acid amide
(Antitussive)
V. Teotino, G. Maffii.
(1960)



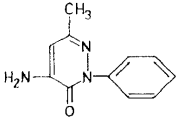
2-(1'-Methyl-4'-piperidyl)-4-phenyl-phthalazone-(1)
(Antihistaminic)
E. Jucker, R. Süess.
(1957)



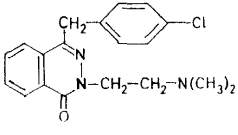
3-Propyl-4-methyl-pyridazine-6-one
(Anticonvulsive)
W.C. Hammann.
(1955)



1-[β-(4' Pyridyl)-ethyl]-3 methyl-4,5-dihydro-pyridazine-6-one
(Potentiates drugs acting on the central nervous system)
G. Gever, J.G Michels.
(1959)



1-Phenyl-3-methyl-5-amino-pyridazone-(6)
(Diuretic)
The Lancet. 1961



2-(β-Dimethylaminoethyl)-4-p-chlorobenzylphthalazone-(1)
(Antihistaminic)
H.J. Engelbrecht, D. Lenke, H. Müller.
(1957)

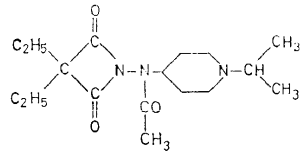
Recently, an unusual group of hydrazine derivatives has aroused considerable interest. The group is that of the *N*-amino-heterocyclic compounds, *e.g.* *N*-amino-piperidine, *N*-amino-morpholine, *etc.* Isolated reports on compounds of this type have been found scattered in the literature for some considerable time and only recently has there been any indication to suggest that this group of compounds might attain importance in therapy. *Table 19* lists a number of derivatives belonging to this *N*-amino-heterocyclic group of compounds. The table includes derivatives of *N*-amino-azetidine-dione which have already been described above, derivatives of *N*-amino-oxazolidine, derivatives of *N*-amino-piperidine, of *N*-amino-quinazolone and of *N*-isoquinoline. To the best of our knowledge, no representative of this group of compounds has, as yet, found practical application; the diuretically active chlorosulphamyl-benzoic acid hydrazides of the *N*-amino-piperidine series have, however, shown sufficient promise in clinical trials that hopes regarding their applicability seem justifiable. For this reason this saluretic group will be discussed in greater detail.

During the course of extensive research on new saluretics a few years ago, we also synthesized chlorosulphamyl benzoic acid hydrazides, and it has been found that a number of these relatively simple compounds have very interesting saluretic properties. In further investigating this field, we endeavoured, on the one hand to raise the activity of these hydrazides, if possible, and, on the other hand to lower the toxicity and undesirable side effects, *e.g.* potassium excretion. For this purpose we modified the hydrazine component and, *inter alia*, also introduced *N*-amino-heterocyclic compounds. The first experiments led to interesting compounds and it was thus natural to concentrate on these hydrazine derivatives and investigate every possible variation. As is shown in *Table 20*, a number of these *N*-amino-heterocyclic compounds were synthesized and condensed with chlorosulphamyl benzoic acid.

N-aminopyrol, *N*-aminopyrrolidine, *N*-aminopiperidine, *N*-amino-morpholine, *N*-aminothiomorpholine, *N*-aminopiperazine, *etc.*, as well as mono- and dialkylated derivatives of the above type, were used as the hydrazine component. The pharmacological investigations showed that many of these hydrazides have an appreciable diuretic activity. The potency of the various compounds depends, to a large extent, upon the nature of the hydrazine component. Derivatives of *N*-aminopiperidines are particularly active, especially when positions 2 and 6 are methylated. The pharmacological investigations carried out on rats and dogs led to the conclusion that Brinaldix® has a saluretic action on the kidney. This effect is probably due to a selective inhibition of the reabsorption of sodium and chloride ions in the tubuli. The discovery that the potassium excretion is only very slightly raised and that the acid–base equilibrium is not affected, is of great importance. The active doses of this preparation are at least 100,000 times smaller than the toxic doses. The discovery that the *cis-trans*-isomers vary considerably in their action is also interesting; Brinaldix® is the *cis*-form and is approximately 5 times more active than the *trans*-form.

During the course of research in this field, quite a number of hitherto unknown *N*-amino heterocycles were prepared; these are also shown in the above table. It proved interesting to compare the activities of all these

Table 19. Novel *N*-amino derivatives of heterocyclic compounds

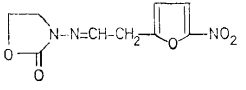


1-[*N*-(1'-Isopropyl-4'-piperidyl)-*N*-acetyl-amino]-3,3-diethyl-azetidine-2,4-dione (XA-99)

(Antiphlogistic)

E. Jucker, A. Ebnöther, E. Rissi, A. Vogel, R. Steiner.

(1958)

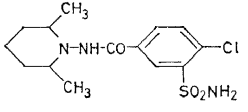


3-[2'-(5''-Nitro-2''-furyl)-ethylidene]-amino-oxazolidine-2-one (NF 219)

(Hypotensive)

J.P. Buckley, A.E. Edlin, W.J. Kinnond, M.D. Aceto.

(1962)



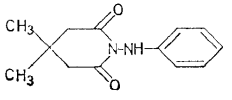
N-(2',6'-Dimethyl-1'-piperidyl)-3-sulphamyl-4-chloro-benzoic acid amide,

Brinaldix ®

(Diuretic)

E. Jucker, A.J. Lindenmann.

(1961)

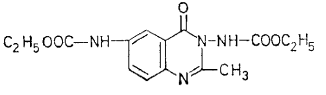


N-Phenylamino-β,β-dimethyl-glutarimide

(Hypnotic)

J. Büchi, M. Mühle, H. Braunschweiger, F. Fabiani.

(1962)

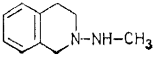


2-Methyl-3,6-bis-(ethoxycarbonylamino)-quinazolone-(4)

(Hypnotic, muscle relaxant)

S. Petersen, H.G. Kroneberg, K. Stoepel.

(1960)



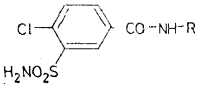
2-Methylamino-1,2,3,4-tetrahydro-isoquinoline

(Diuretic, monoamine oxidase inhibitor)

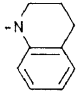
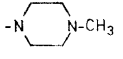
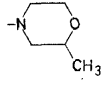
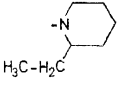
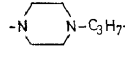
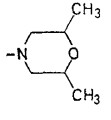
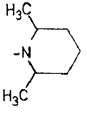
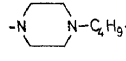
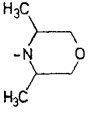
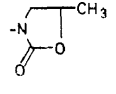
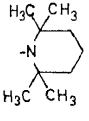
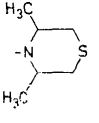
J.H. Biel.

(1960)

Table 20. Novel heterocyclic hydrazides and their relative diuretic potency



(R shown below)

	(+)	Long duration of action 	++		+	Relatively short duration of action 	++
	++		+++		0		+++
	+++		++		(+)		+
	++		*cis*-Form: ++++ (Brinaldix®) *trans*-Form: ++		(+)		
	+		+++			Very short duration of action 	++
							(+)

chloro-sulphamyl benzoic acid hydrazides, for certain aspects of the relationship between chemical structure and physiological activities of these novel groups of substances became evident.

In this lecture, we have tried to show the development over the last hundred years of hydrazine derivatives which can be used as drugs. Until about 1950, only very few heterocyclic derivatives of hydrazine were used as medicinal agents, and these particularly as antipyretics and analgesics. The introduction a few years ago of isonicotinic acid hydrazide, phenylbutazone and phthalazino hydrazines gave a new impulse to hydrazine research and encouraged research workers all over the world to continue or to take up the search for new hydrazines with therapeutic properties. The results of these combined efforts by chemists, biochemists, biologists and clinicians are evident: in the course of the last 15 years, about 100 new hydrazines were introduced for therapeutic application. For those who, in their own research work, are associated with hydrazine, there can be no doubt that this interesting base will yield new derivatives with valuable properties as drugs. Thus, the efforts which Hofmann, Emil Fischer, Knorr, Curtius, Raschig, Wieland and others have invested in hydrazine are justified as it increasingly becomes one of the most important starting materials in drug research.

I am indebted to Drs A. Ebnöther, A. J. Lindenmann, E. Rissi, E. Schenker, Mr R. Steiner, Drs R. Süess and A. Vogel of the Sandoz Pharmaceutical-Chemical Research Department, who have been intimately associated with these chemical developments.

My thanks are also due to Dr J. Bally, Mr A. Bianchetti, Dr M. Frossard and Mr A. Kessler for their valuable assistance in preparing this manuscript.

References

[1] For further details, the reader is referred to the following publications:
(*a*) A. Pletscher, K. F. Gey, and P. Zeller. " Monoaminoxydase-Hemmer ", in *Progress in Drug Research* (Ed. E. Jucker), Birkhäuser, Basle and Stuttgart, **2**, p. 417 (1960).
(*b*) A. Jenni and A. Pletscher. " Monoaminoxydase-Hemmer ", *Schweiz. Apotheker Ztg.* **100**, 177 (1962).
[2] Literature summary see E. Schlittler, J. Druey and A. Marxer. " Antihypertensive agents ", in *Progress in Drug Research* (Ed. E. Jucker), Birkhäuser, Basle and Stuttgart, **4**, p. 295 (1962).
[3] W. Krohs and O. Hänsel. *Pyrazolones and Dioxopyrazolidines*, Editio Cantor, Aulendorf i. Württ. (1961).
[5] *See, for example*, E. Jucker. *Angew. Chem.* **71**, 321 (1959).