생 약 학 회 지
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Natural Products as Model for the Synthesis of Potential New Drugs from Simple Amino Acids

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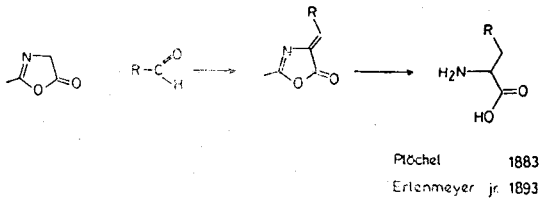
It is a well known fact that amino acids are the universal building stones for the specific proteins of all animals. For the function of a living cell the enzymes built from amino acids as well as special receptors constructed from special proteins for the hormones are very important switches. Therefore it is not astonishing that very potent drugs react with the receptors or imitate respectively block up the hormones and influence the metabolism of the cells decisively. To attack morbific agents, you need toxic compounds for the bacterials or viruses, which are not toxic for the human organism. A known recipe to find out potent drugs is to use natural products of the morbific agents or the human organism as model. Very often a characteristic toxicity of a natural product has used as model for design a new drug and a lot of time later the similarity of the natural product to specific structures of the organism has been recognized, so that the natural products imitate these structures interfering so with the normal metabolism. For example ephedrine interferes with adrenaline and leads so to the development of sympathomimetics; morphine was the model for a lot of analgesics, later on the similarity to enkephaline was recognized; eserine acting as cholinesterase inhibitor leads to the parasympathomimetics and so on.

Although the natural structures of an enzyme or a human receptor are still unknown, it was possible to develop a lot of potent drugs by derivation of natural products. As successful was the derivation of natural and essential compounds of the human organism for the design of new drugs, for example the vitamin folic acid leads to methotrexate with antitumor activity, or a lot of steroidal hormones derivatives, which are important in the dermatology or important as immunsuppressant.

Since a lot of years we are working with amino acids and with heterocycles, which are derived from these amino acids and which—demonstrating very often a similarity to natural products—are proved as leading structures for the development of new drugs. Using natural products as model and synthon as well we also hope to find out new drugs with interesting and improved activity. Hearing the catchword "amino acid" the chemist usually think of proteins, peptides and their synthesis too, which include reactions at the carboxyl- and amino-groups in the building stones of the peptides makes the chemistry of these compounds most attractive.

On the other hand you think less of the third reactive place of the amino acids, the α-C-atom, which can react nucleophil because of its C-H-acidity after simultaneous deactivation of the amino- and carboxyl-group. In the same manner as in the last years the amino acids got cheaper and were available as synthons in greater amounts, they are used for the synthesis of a lot of interesting compounds especially because of



Scheme 1.

the C-H-acidity of the α-C-atom.

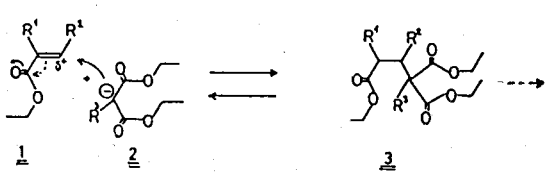
But this α-C-reactivity of the aminoacids has been known for a long time at least since E. Erlenmeyer Jr. has cleared up the azlactone-synthesis which was found from J. Plöchel in 1883 and which is useful to get e.g. phenylalanine and benzaldehyde.

Recently for example B. Schöllkopf[1] has shown impressively that from 2, 5-dioxopiperazines changed in bislactime-ethers optical active amino acids are available from glycine by enantiomeric reaction at the α-C-atom. Heterocyclic derivatives from amino acids such as oxazolidines, hydantoines and piperazindiones possess similar reactivity but these compounds are used more seldom, because of their C-H-acidity.

The cyclization before is not the conditio sine qua non,—you can start similar reactions at the α-C-atom also with esters of N-acylamino acids, Schiff bases and copper complexes of the amino acids.

Such reaction, which are followed by cyclization for example to pyrrolidones seem to be especially attractive. This heterocycles is part of a lot of pharmaceutically interesting natural product and synthetic compounds.

Therefore one can expect similarities of such substituted pyrrolidones with therapeutically used compounds relatively often. We discovered by



Scheme 2.

chance that simple N-acylamino acids are potent donators for the Michael-reaction which result α-pyrrolidones directly. Michael addition of compounds with a reactive acidic C-H group to unsaturated carbonyl compounds is well known as a versatile base-catalysed equilibrium reaction for enlarging carbon skeletons by several C-atoms.

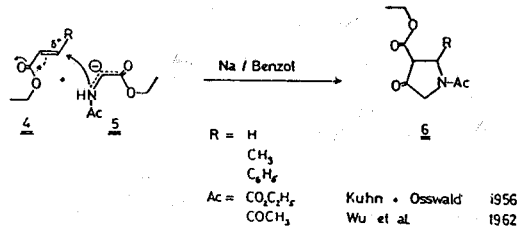
Often, it is even an advantage that the accumulation of reactive groups enables further reactions, for instance cyclizations, to follow subsequently. That the substituents R-1, R-2 and R-3 should strongly influence the course of a Michael addition by steric and inductive effects will come as no surprise.

So far the esters of N-acyl-α-amino acids of weak C-H acidity have not been able to serve as donors for such Michael additions—leaving aside compounds such as acetaminomalonic acid esters with a C-H acidity considerably enhanced by the additional ethoxycarbonyl group.

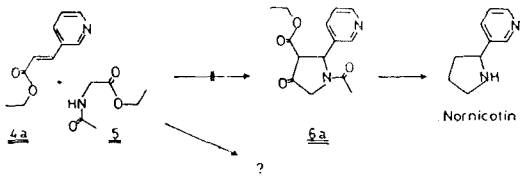
In 1956 Richard Kuhn et al.[2] were first to describe reaction conditions under which relatively simple acylamino acid esters, as sodium salts, can also undergo Michael addition to β-pyrrolidone derivatives.[6]

The Scheme 3 shows this for the example of N-ethoxycarbonyl-glycine ester.[5]

This N-C Michael addition accompanied by simultaneous Diekmann cyclization to β-pyrrolidones **6** was used in 1962 by Wu et al.[3] for preparing a whole series of analogous compounds. Finally, they succeeded also in reacting the especially readily accessible N-acetylglycine



Scheme 3.



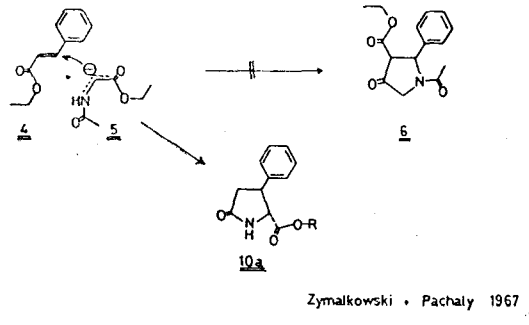
Scheme 4.

ester to give such β-pyrrolidones.

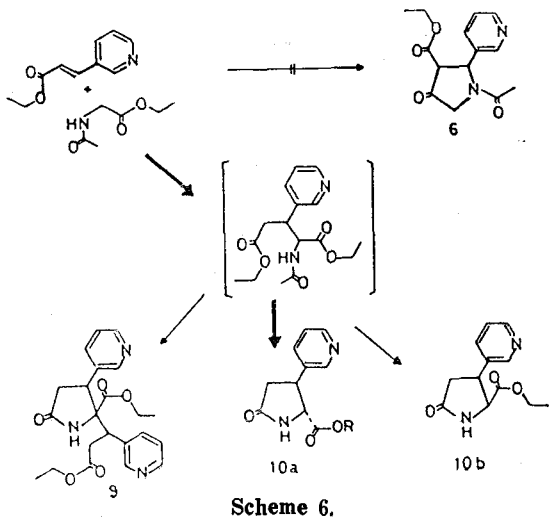
At that time we were interested in preparing substantial amounts of nornicotine, which should be obtainable without difficulty via this Kuhn N-C Michael cycloaddition from 3-pyridylacrylic acid ester and N-acetylglycine ester. To our surprise, however, we isolated only a glass-clear resin of complex composition containing everything but the anticipated β-pyrrolidone **6a**. We finally synthesized our desired nornicotine by entirely different route.

At the beginnings of the 1960's the preparative use of chromatography was only in its infancy, and in Germany a pharmaceutical faculty could be proud if it had its own IR equipment. Under these analytical circumstances our experiment featured as a failure and an unexplained happening in the laboratory record book for the time being, until we re-examined the matter some years later.

This time we employed ethyl cinnamate as acceptor component, and on proceeding analogously we were able to isolate a carboxylic acid[4] which was found to be identical with the 2-carboxy-3-phenyl-5-pyrrolidone (**10a**) already described by Harrington in 1920.[5] The NMR spectrum of the corresponding ethyl ester and its chemical behaviour demonstrated that the corresponding trans-compound **10a** was involved. Instead of the expected N-C Michael addition followed by Diekmann ring closure to β-pyrrolidone, we thus obtained an α-pyrrolidone carboxylic acid by C-C addition and cyclotransamidation. The acetyl group is split off as ethylacetate—if hippuric acid ester is used in place of aceturic acid ester as donor, ethylbenzoate is obtained as side product. Also the initial 25% of α-pyrrolidone **10a** was moderate, we regarded the stereoselective formation of the trans-compound as noteworthy. From such trans-3-aryl-2-carboxy-pyrrolidones or their esters simple acid hydrolysis should correspondingly make available erythro-3-aryl-glutamic acids and, by reduction of these pyrrolidones aryl-substituted prolines. As potential amino acid antagonists these compunds possess pharmacological interest. Our reaction—albeit under more severe conditions—had proceeded quite analogously to a known glutamic acid synthesis with N-acetamidomalonic acid ester via corresponding 2,2-bisethoxycarbonyl-pyrrolidones, but, unlike our variant this latter gives only diastereoisomer mixtures. Following these investigations the



Scheme 5.

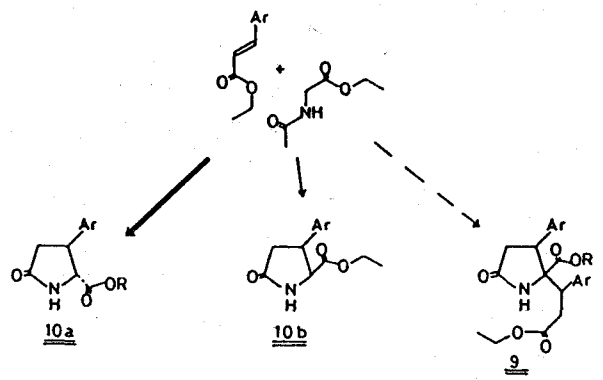


Scheme 6.

explanation for our first abandoned reaction with 3-pyridylacrylate—and considered a failure —was close at hand.

Here as well, unlike in the Kuhn synthesis, stereoselective C-C Michael addition with cyclotransamidation to the pyrrolidone derivative **10a** is observed.[6] In this case, however, up to 60% bis-addition product **9** is formed as side product when equimolar amounts are used as starting materials. Evidently the pyridyl group increases the readiness to undergo addition of acrylic ester so much that Michael addition occurs to this considerable extent. But this side reaction can be substantially suppressed by using one molar excess of acetylglycine ester. An initial decisive obstacle to the elucidation of this reaction was the separation of the resinous reaction mixture. It was finally succeeded surprisingly well by means of column chromatography on Sephadex LH 20—a lipophilic dextrane gel—which also enabled the cis/trans isomers **10a** and **10b** to be split.

It is necessary to postulate as common non-isolatable intermediate product of an open-chain addition product **8**, because from the corresponding **10a** (Ar=3-pyridyl-3) or **10b** no bis-addition product **9** could be obtained under the reaction conditions.



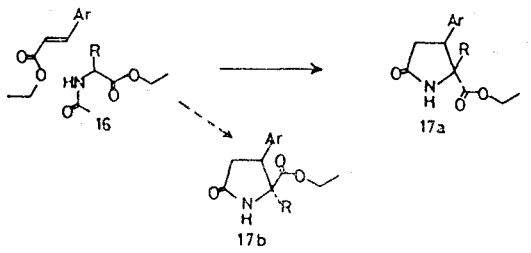
Ar	% 10a R=H	% 10a R=C_2H_5	% 10b	% 10a/b	% Stereoselektivität 10a	
	-	4,8	0,8	5,6	70	
	28	1,7	2,1	31,8	87	
	31	13	5,7	49,7	76	
	38	9,9	4,9	52,8	86	
	11,6	41	7,7	60,3	74	6,5 % 9
	13,6	22,5	5,2	41,3	74	22 % 9
	11,5	57,5	0,9	69,9	98	
	-	-	-	-		17 % 9
	48	-	7	55	87	
	12	5		17	61	
	46,8	5		51 8	≤ 100	

Scheme 7 and Table I.

We have been able to transfer this reaction to a whole series of aryl acrylates and always obtained the same fundamental result.[7~8]

Table I shows that the yields evidently correlate with the Hammet constants of the aryl substituents. The trans-aryl-pyrrolidones **10a** are obtained either as esters in the lipophilic phase or, depending on the nature of the method of working-up, as free acid directly from the aqueous phase. What small proportion of cis-compound **10b** is formed is all obtained as ester in the chloroform phase and is separated by column chromatography. At 60~98% the trans compound stereoselectivity is relatively high. Michael addition to the non-isolatable N-acetyl-3-aryl-glutamate 8 is the confiuration-determining reaction step. The C-3 atom of α,β-unsaturated trans-ester selectively receives the spatially favourable erythro-configuration from the attack by the nucleophilic partner; ring clousure then gives the trans-compound **10a**. It was found that N-acetylamino acid esters other than aceturic acid ester can be used as donor to give corresponding 2, 3-disubstituted 2-carboxy-5-pyrrolidone derivatives.[9]

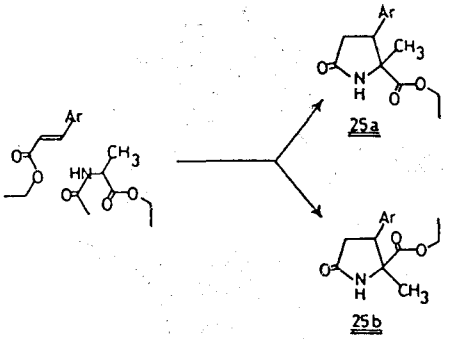
Table II shows that alanine, phenylalanine,



R	Ar	% 17a	% 17b
-H		52	7
$-CH_3$		73	•
$-CH_2-C_6H_5$		52	-
$-CH_2-CH(CH_3)_2$		80	-
$-CH(CH_3)_2$		13	-

Pachaly 1976

Scheme 8 and Table II.



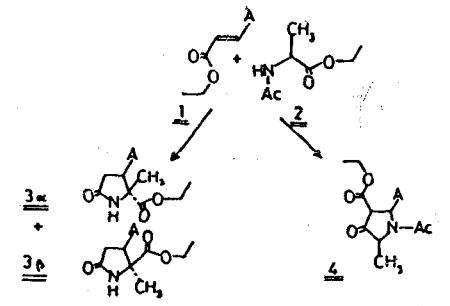
Ar	% 25a	% 25b
	26	
	35	
	51,5	
	30	
	73	+
		42
	18,5	18,5
	38	
	46	

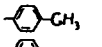
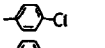
Gottschalk, Pachaly u. Schleypen 1979

Scheme 9 and Table III.

leucine and valine can also be used successfully; the result is once more highly stereoselective. Identification of a trans-methyl compound **17b** was succeeded only by column chromatographic separation of several batches. However, the relatively good yield with N-acetyl-alanine ester led us to check the reactivity of this acetylamino acid with other aryl acrylates[10~11] (Gottschalk et al., 1979).

Yields and stereoselectivity are substantially the same for the first examples as for 3-pyridyl-acrylates. What is surprising is the sudden reversal of stereoselectivity in 4-pyridyl-acrylate where we were able to isolate only the corresponding trans-2-methyl-pyrrolidones derivative **25b**. One important question concerning our type of reaction has not been answered, however. Why do Richard Kuhn et al. obtain β-pyrroldones with acylamino acid esters by N-C



A	Ac	% Ausb. 3α	3β	4
	$-CO_2C_2H_5$	–	–	34
"	$-CO_2C(CH_3)_3$	–	–	3,7
"	$-CO_2CH_2$- 	–	–	4,7
	$-CO-CH_3$	26	–	–
	"	35	–	–
	"	51	–	–
	"	29	–	–
	"	73	+	–
	"	–	42	–
	"	–	–	6,2
$-CH_3$	"	–	–	49
$-H$	"	–	–	62

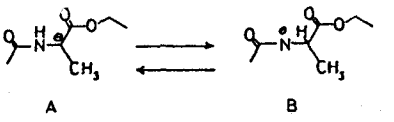
Gottschalk u. Pachaly 1979

Scheme 10 and Table IV.

Michael addition, while we always find C-C addition to α-pyrrolidones under the same reaction conditions? One likely reason is the acyl-group-dependent nucleophilism of the amino-acid nitrogen.

Simple acyl groups (such as acetyl) evidently suppress the nucleophilism of the nitrogen of such kind that only C-C addition can take place and therefore α-pyrrolidones **3** are to obtain.[11] Only if the nitrogen carries an alkoxy-carbonyl group instead of the simple acyl group, the nucleophilism of the nitrogen is some less suppressed because of the additional alkoxy group and now N-C Michael addition takes place and β-pyrrolidones **4** are obtained.

Surprisingly the alkyl-substituted ethyl acrylates on the end of this list yield now only the β-pyrrolidones **4**. Therefore the nucleophilism



Scheme 11.

of the nitrogen cannot be the only important factor of the reaction.

The proton NMR spectroscopy examination of the sodium compound from N-acetyl-alanine ethyl ester with deuterobenzene as solvent shows the presence of two tautomeric forms.[11] The carbanion A can be found with nearly 33%. Both forms (A and B) explain that C-C addition as well as N-C addition are possible. Now the reason for the different place of reaction on the donator-molecule according as the substitution of the acceptor-molecule could be different routes of the reaction, yielding on the one hand α-pyrrolidones **3** and on the other hand the β-pyrrolidones **4**. The complete Micheal reaction of the acylamino acid esters can now be explained in the following way:

The Michael reaction as first step has to be understood as a balance between two intermediate-products I and II by simultaneous C-C and N-C addition.

If acetylamino-malonic ester is the donator then the C-H acidity is relatively high in contrary to the nucleophilism of the nitrogen-K-1 will be high compared to K-2-and indepenent of A in the acceptor molecule we obtain glutamic acid derivatives or α-pyrrolidones **3**. If the donator **2** is a acylamino acid ester and simultaneously B an alkoxy group, the nucleophilism of the nitrogen prevails the C-H acidity, -K-2 will be higher or in the same range as K-1. Therefore both intermediates I and II are present and α-and β-pyrrolidones **3** and **4** are obtained at which **4** usually prevails.

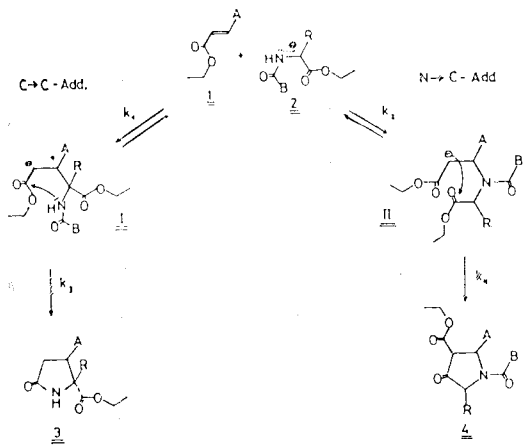
But if the donator **2** carries an N-acetyl group and instead of R and hydrogen or alkyl group, then the substituent A of the acceptor **1** will

determine the route of reaction: If the substituent A is an aryl group, the negative charge of the intermediate I cannot diminish the carbonylactivity because the – I effect of this aromatic substituent, so that in the second step the nucleophil attack of the nitrogen at the acceptor carbonyl-group will split off ethylacetate by yielding the α-pyrrolidone **3**. On the other hand, the influence of the– I effect on the negative charge in intermediate II will prevent the Diekmann cycliszation to the β-pyrrolidone **4**.

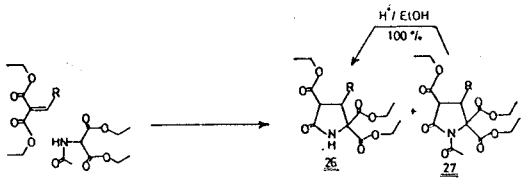
If A of the acceptor is an alkyl group of hydrogen, this mentioned influence of an – I effect is absent, therefore now the cyclization of the intermediate I is prevented, meanwhile the cyclization of the intermediate II will be made easy and result the β-pyrrolidones **4**.

In this manner one can explain all hitherto known results of Michael additions with N-acylamino acid esters.

In respect of the use of several times substituted pyrrolidones for synthesizing condensed heterocycles, we succeeded also in using arylidenmalonic acid esters and α-cyano-cinnamic acid esters as Michael acceptors. The reactions proceed analogously and roughly as well as our previous ones, but a clear-cut stereoselectivity



Scheme 12.



R	% 26	% 27	% 26+27
p-OCH₃	16,5	18,7	35,2
p-CH₃	17	26,4	43,4
H	13,3	17	30,3
p-Cl	15,1	48,2	63,3
p-N	11,1	42	53,1

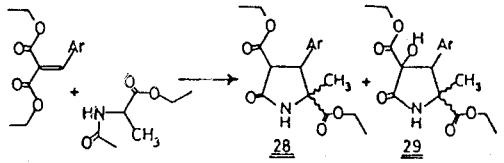
Pachaly u. Westfeld 1976

Scheme 13 and Table V.

by virtue of accumulation of the substituents could not longer be observed.

Here, the initial results shown are those during synthesis of 3-aryl-2, 2, 4-tris-ethoxycarbonyl-pyrrolidones[12]. Strangely enough, we suddenly obtained N-acetyl-pyrrolidones as well-previously the N-acyl group had always been cleaved quantitatively. Brief heating with ethanolic hydrochloric acid enables the N-acetyl derivatives **27** to be deacetylated quantitatively to **26**. Table V shows the results with acetyl-alanine ester.

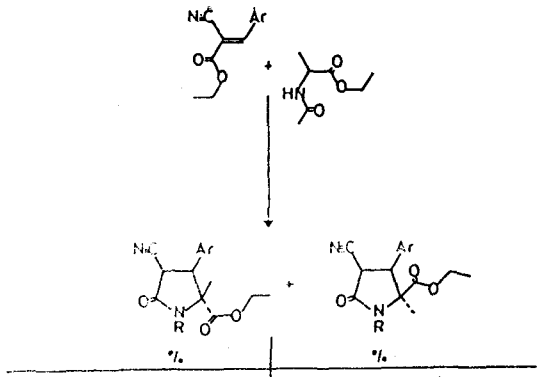
Although the individual reactions still proceed moderately stereoselectively, a uniform line is



Ar	% 28 cis/trans	% 29	% Stereoselektivität (cis-Methyl)
p-OCH₃	26,4	7,5	-36
p-CH₃	45,2	1,7	+24
H	23,1		-26
p-Cl	32,9		+ 6
p-N	5,5		+28

Pachaly u. Westfeld (1977)

Scheme 14 and Table VI.



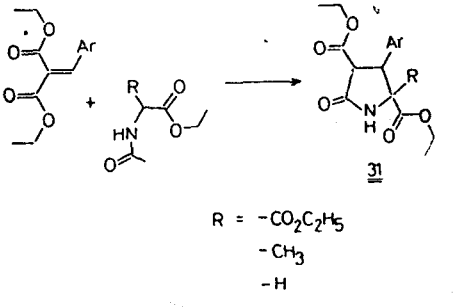
Ar	R = -COCH$_3$	-H	R = -COCH$_3$	-H
	%.		%.	
-OCH$_3$	17.6		33.0	
-CH$_3$	31.4	5.2	19.5	5.8
	26.0		5.2	

Scheme 15 and Table VII.

no longer evident. Table VI shows the corresponding results with some alpha-cyano-cinnamic esters[13].

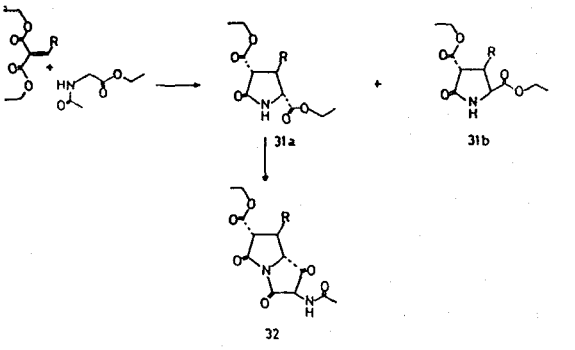
Here, too we find N-acetyl-pyrrolidones **30a** and **30b** without the earlier uniform stereoselectivity.

Just like with acetamido-malonic ester and acetyl-alanine we also anticipated α-pyrrolidones during the corresponding reaction with acetyl-glycine esters. Unexpectedly, however, we initially isolated from the reaction mixture merely a novel condensation product **32**, evidently formed by reaction of one equivalent arylidene-malonic ester with two equivalents acetyl-glycine



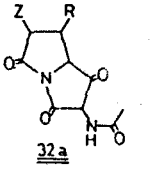
R = -CO$_2$C$_2$H$_5$
-CH$_3$
-H

Scheme 16.



Scheme 17.

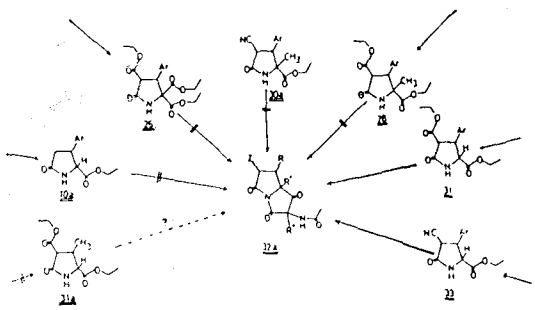
ester[14]. Unlike the anticipated compounds of type **31**, our condensation product gave a violet colour with ferric chloride-as we had also observed with β-pyrrolidones. Looking at the overall result of this combination of Michael addition and cyclisation, it is found that initally like in previous Michael additions of acetylglycine esters to aryl acrylate derivatives-the reaction again leads to the trans compound **31a** with 74~88% stereosectivity, which evidently



Z	R	%. d.Th.
-CO$_2$C$_2$H$_5$		34.6
"	-CH$_3$	49
"	-OCH$_3$	49
"	-Cl	46.3
"	-CH$_3$	—
-C≡N		46
"	-CH$_3$	35
"	-OCH$_3$	17.5
"	-Cl	30

Pachaly • Westfeld
1978

Structure 1 and Table VIII.



Scheme 18.

forms the pyrrolizidines **32a** particularly readily with excess acetylglycine ester. By contrast, we were unable to discover a corresponding pyrrolizidine from the cis-compound **31b**.

Since the pyrrolizidine ring skeleton is found in alkaloids of numerous Leguminosae, Compositae and Boraginaceae which have cytotoxic properties, we have investigated the use of this reaction for the directed synthesis of pyrrolizidines. The result is shown in Table VIII.

The yield when arylidene-malonic esters are used is quite substantial. It is also possible to replace the carbethoxy-group by the cyano group[14].

This single-stage pyrrolizidine synthesis is evidently strongly dependent on the substituents of the reaction partners as shown in Scheme 18.

In principle all pyrrolidone derivatives shown here should be able to form corresponding pyrrolizidines **32** with the excess acylamino acid esters; but this is confirmed only in the pyrrolidones **31** and **33**.

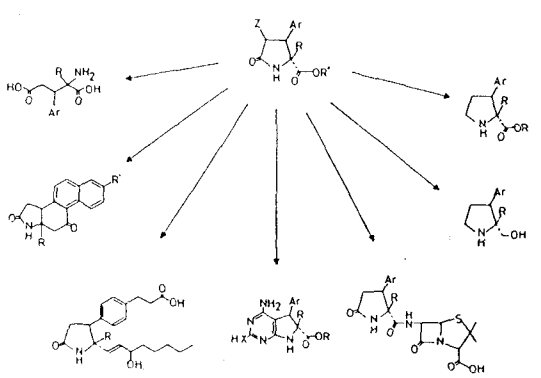
However these investigations have shown that substituted α-pyrrolidones are obtainable by Michael addition with simple amino acids. Scheme 19 demonstrates in which kind these pyrrolidones are to be used as synthons of some potential drugs which are analogs of natural products.

By simple hydrolysis one gets 2-alkyl-3-aryl-glutamic acids which are suggested to antagonize the metabolism of glutamin. By reduction one gets 3-aryl-pyrrolidines which should have adrenergic and analgesic activities. As well as these potential drugs one should get 17-aza-steroids, 7-desaza-7-aryl-purines or β-lactam-antibiotics, which because their substituents at the pyrrolidone-ring should have good β-lactamase stability.

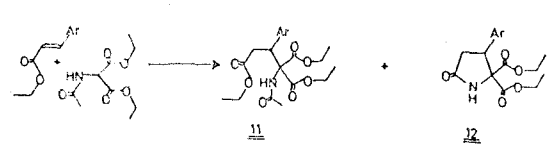
In respect of the biological testing of the glutamic acids accessible from these, it was now desirable to look for a corresponding stereoselective method of preparing the cis-aryl-pyrrolidones **10b**, from which by hydrolysis threo-aryl-glutamic acids are obtainable.

A promising pathway seemed that via reaction products with acetamidomalonic ester, which also correspondingly gives 3-aryl-2, 2-bisethoxycarbonyl-pyrrolidones **12** by Michael addition with aryl acrylates. This bisethoxycarbonyl derivative **12** should also be able to selectively furnish the corresponding cis-compounds **10b** by hydrolysis and decarboxylation if it were possible to isolate the free dicarboxyl compounds or half esters.

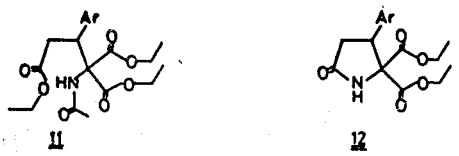
During the analogous preparation of 3-alkyl-



Scheme 19.



Scheme 20.



11 12

Ar	% 11	% 12
	3,3	•
	5,1	27
		34
		69
		45
		53
	10	37
	10	30
	6,8	
		22
		5
		33,5
		10

Pachaly 1971
Pachaly u. Schleypen 1979

Structure 2 and Table IX.

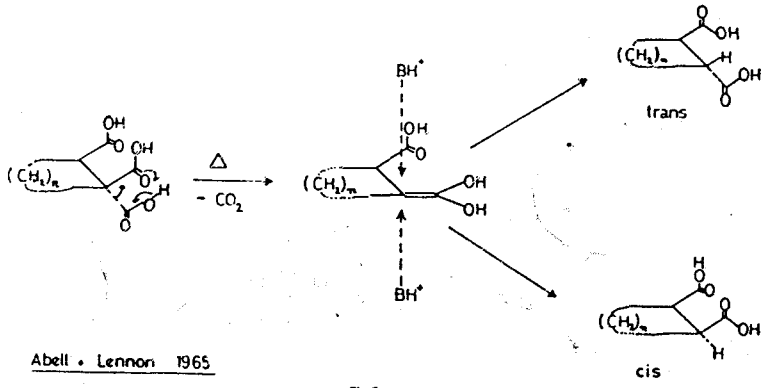
glutamic acids via 3-alkyl-2, 2-bisethoxy-carbonyl-pyrrolidone derivatives such as **12**, other authors had either failed in this objective or had not attempted stereoselective decarboxylation at all.

Although aryl acrylates have intrinsically poorer Michael acceptor properties than analogous alkyl acrylates, Table IX shows acceptable yield during preparation of the malonic ester derivatives 12[15~16].

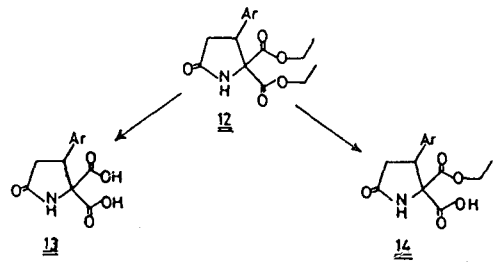
The most favourable Michael reaction results should be abtained at room temperature. In our case, however, with alkyl acrylates the open addition product **11** should form preferentially; it only cyclizes at higher temperatures.

On the other hand, too high a temperature must be avoided because otherwise uncontrolled side-reactions occur increasingly.

In our first-time preparation of 3-aryl-2, 2-bisethoxy-carbonyl-pyrrolidones **12**, all that a lengthening of the reaction time-for instance to obtain maximum cyclization of **11**-results a sterically uncontrollable decarboxylation. Cis/trans-mono-ethoxycarbonyl aryl-pyrrolidones **10 a/b** are already found in the reaction mixture. Reacting for 12 hours at 78° represents a compromise for which the yields given here apply. Overall, however, the yields are comparable with those during the reaction with acetylglycine esters. The only difference is that the trans compound is already present stereoselectively there while here everything is still unresolved stereochemically. The malonic ester derivatives **12** obtained had now to be converted into the free carboxylic acids or half esters as conservatively as possible before the actual decarboxylation. Stereoselective decarboxylations of cyclic malonic acid derivatives have been observed in the past, but because of the difficulties at that time of analysing the diastereomer mixtures obtained they were generally only



Scheme 21.



Ar	% 13	% 14
	46	84
	46	90
	58	89
	61	93
	67	93
	60	93
	67	91

Pachaly 1971

Scheme 22 and Table X.

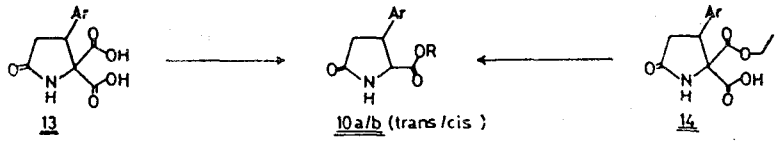
described qualitatively.

A model which applies well to our 3-aryl-2,2-bisethoxy-carbonylpyrrolidones is due to Abell and Lennon[17], who in 1965 reported about the stereochemistry of the decarboxylation of 1,1,2-cycloalkanetricarboxylic acids.

In the absence of solvents decarboxylation leads substantially to the cis-compound, in collidine as solvent the cis-compound is reported likewise to be formed quantitatively, while decarboxylation with hydrochloric acid gives predominantly trans-dicarboxylic acids. This authors postulate that the configuration-determining step is the transfer of the proton to the intermediately formed sp-2 C-atom. The neighbouring substituents of this C-atom determine whether and from which side the proton can attack preferentially. The bulky collidinium cation can transfer the proton more easily from below, so that the cis-compound is formed selectively. By contrast, the smaller hydronium can attack from both sides without difficulty and allows the thermodynamically more stable trans-form to form. In our aryl-substituted bisethoxycarbonyl-pyrrolidones such steric hindrance by the larger aromatic substituents should make itself in the same way.

For this purpose bisethoxycarbonyl-pyrrolidones were saponified with one equivalent barium hydroxide in aqueous/alcoholic solution[18].

The free carboxylic acids **13** or half esters **14** obtained in this way are decarboxylated under various different conditions and the stereo-



	% Stereoselektivität für 10b (cis)				
	aus 13			aus 14	
Ar	ohne Lsgm.	Collidin	$H_3O^{\oplus}$	ohne Lsgm.	$H_3C-N(C_6H_{11})_2$
	24	18	—	30	30
	22	—	24	30	32
	34	22	36	30 — 36	24
	22	12	36	26	24
	-50	-64	-30	+ 32	+ 26
	-60	-60	—	-50	-16
	-58	-54	—	-50	—

Pachaly 1971

Scheme 23 and Table XI.

chemical result is tested for stereosectivity values found are shown in Table XI.

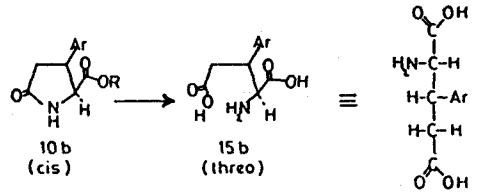
Decarboxylation does indeed proceed stereoselectively to the desired cis-3-aryl-2-carboxy-pyrrolidones **10b** and their ethyl esters[18]. Admittedly, there are a few surprises and the stereoselectivity is very moderate. While the phenyl analogous, in contrast to the findings of Abell and Lennon, invariably and only moderately stereoselectively give the cis-compound **10b** with hydronium ions the exact opposite is observerd with the basic pyridyl compounds:the exceptionally highly stereoselective formation of the trans-compounds is here denoted by the minus sign.

From the cis-half ester **14** decarboxylation via the fundamentally same enol intermediate stage succeeds with the same steric result. Use of an even bulkier basic solvent such as dicyclohexyl-methylamine brought about no appreciable change.

In respect of obtaining the cis compounds, these experiments suggest as the most favourable pathway decarboxylation of the cis half esters without solvent. The cis compounds are then obtained without interfering solvents and can be separated from the trans proportion directly and in the optimum way by column chromatography on Sephadex LH 20.

We are now in a position to prepare respectively enough pure cis-and trans-3-aryl-carboxy-pyrrolidones and their esters **10b** and **10a** and, by 12-hour hydrolysis with hydrochloic acid, to convert them into the corresponding threo-and erythro-3-aryl-glutamic acids.[19] Under these conditions a configuration reversal on the C-2 atom is avoided. Subsequently, the free threo-and erythro-aryl-glutamic acids were obtained in the pure form via an anion exchanger and were tested biologically.

The result was disappointing: Neither viruses nor cancer cells nor normal cells were influenced noticeably by these compounds, which so far



Ar	% 15b	% 15a
-C6H4-OH	25	20
-C6H4-OCH3	60	54
-C6H4-CH3	79	40
-C6H5	94	63
-C5H4N	86	67
-C5H4N	66	60
-C5H4N	56	79
-C6H4-NO2	74	56

Pachaly 1972

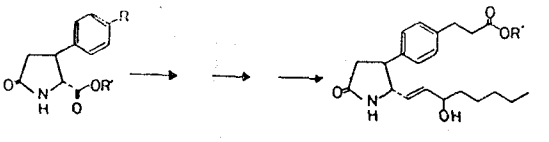
Scheme 24 and Table XII.

have been tested at the Bonn Microbiological Institute and at the National Cancer Institute.

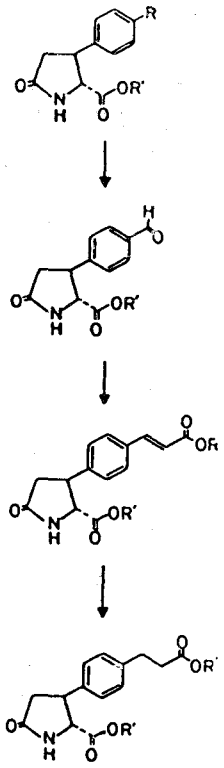
We suggest that tripeptides of the aryl-glutamic acids would give an other result because active oligopeptide-transport-systems are able to transport these tripeptides in the cell.

Since some years aza-analogous prostanoids are interesting objects which are synthesized to improve the natural prostaglandines. Likewise 11-aza-prostanoids are very interesting derivatives which should be synthesized from trans-3-aryl-5-oxo-pyrrolidines.

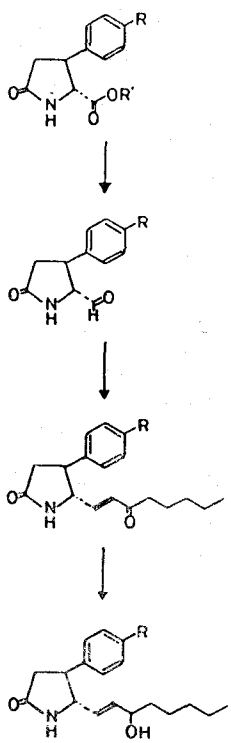
Here the aromat as part of the first side chain only should be lengthened with 3 C-atoms,



Scheme 25.



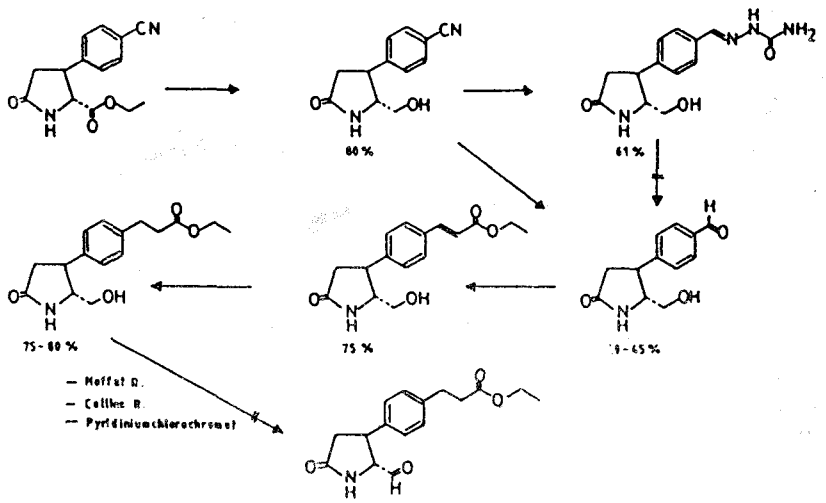
Scheme 26.



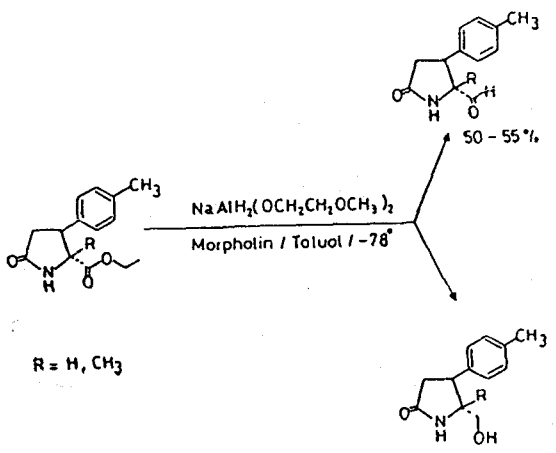
Scheme 27.

while the second chain only is signified with the C-13. For the necessary lengthening of the side chains exist some simple appearing possibilities:

At the aromat R should be changed into an aldehyde group, then the Knoevenagel reaction allowed the introduction of the necessary two C-atoms which followed by a Reduction completed side chain No 1. The natural 5, 6-cis-double bond here is replaced by the aromatic ring. For the building of the second side chain the literature shows some possibilities, which started with corresponding carboxyl-derivatives. The carboxyl group has been changed into the aldehyde function, which react in a Wittig reaction with dimethyl-2-oxo-heptyl-phosphonate. At last the C-15-carbonyl group is to be reduced with sodium-borohydride. But this series of reactions by no means were simple to realize. We started with the 4-cyano-aryl-compound which was selectively reduced with sodium borohydride.[20] Without any problems we got the desired semicarbazone by hydrogenating the cyano group in the presence of semicarbazide; but by no means it was possible to release the desired aldehyde group, Therefore we changed the cyano function directly with lithium-aluminohydride and tetrahydrofurane as solvent at $-70°$ into the aldehyde. The following Knoevenagel reaction yielded the desired cinnamic acid ester, which was hydrogenated with palladium/charcoal without any problems. With that the first



Scheme 28.



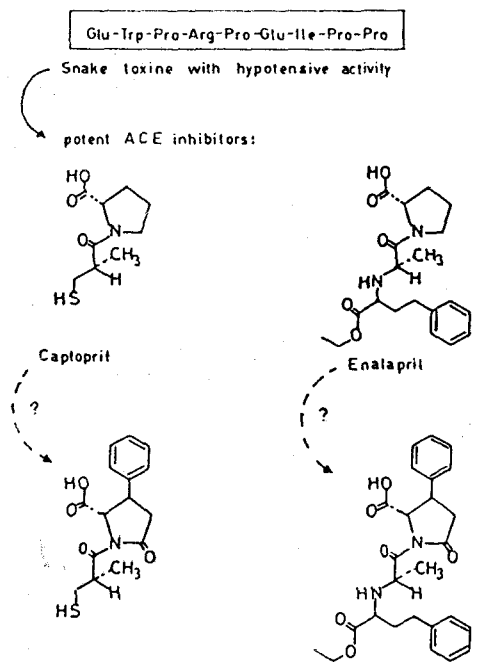
Scheme 29.

side chain was completed. But the following oxidation of the alcohol group in the formyl-function by Moffat reaction or Collins reaction or oxidation with pyridinium-chloro-chromate was totally unsuccessful. We got only unchanged starting material. Therefore we tried to get the desired formyl compound by selection starting with the ethoxycarbonyl compound.

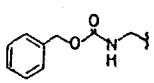
But a lot of typical reduction methods were unsuccessful up to the reduction with sodium bismethoxy-dihydrido-aluminate which yielded the desired aldehyde as dinitrophenylhydrazone.[20] For the following Wittig reaction we don't await special difficulties but this shall be the work of another coworker in the future.

I is well known that a snake toxin with hypotensive activity leads to important angiotensin converting enzyme inhibitors as Captopril or Enalapril.

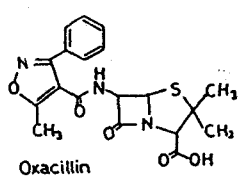
Aryl-pyrrolidonyl-carboxylates as well are potentially good starting materials for the synthesis of ACE inhibitors which is just under progress. One should get corresponding derivatives to Captopril resp. Enalapril. The first results of the acylation reaction which we have

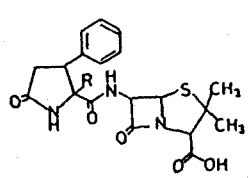


Scheme 30.

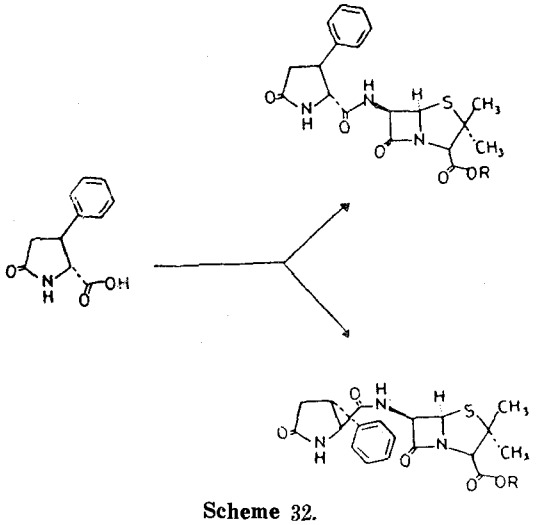
R	R'	R''	yield (%)
H_3C-	H	H	63
H_3C-	CH_3	H	55
	H		55
	H	H	61

Scheme 31 and Table XIII.





Structure 3.

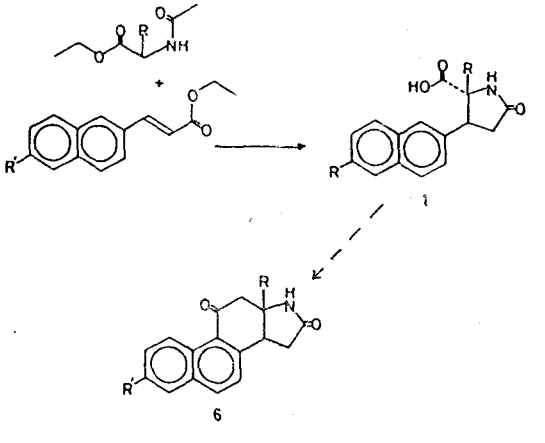


Scheme 32.

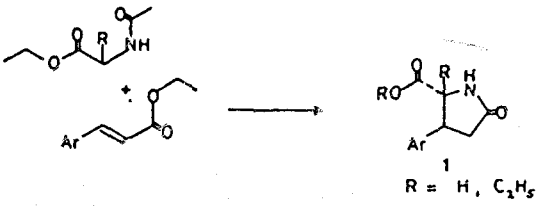
while the second chain only is signified with the C-13. For the necessary lengthening of the side chains exist some simple appearing possi- esters.

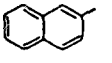
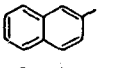
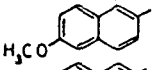
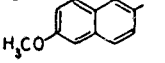
Another coworker just started to synthesize some oxacillin-like β-lactam antibiotics. If the reaction was done with d, l-trans aryl-pyrrolidones one gets two diastereomeric derivatives which can be separated chromatographically:

Scheme 32 shows the first results with 6-amino-penicillamic acid ester. Until now my co-worker has some difficulties in splitting off the ester group R which is presented by a benzhydryl group.[22]



Scheme 33.



	Ar	R	% Ausbeute
1a		H	46,5
1b		CH_3	50,8
1c		H	48,5
1d		CH_3	56,3
1e		H	51,8
1f		CH_3	50,3

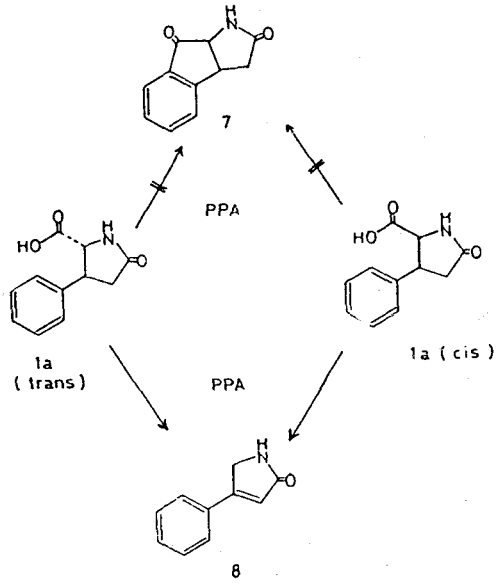
Scheme 34 and Table XIV.

Azasteroids are very interesting analogs of natural products which have bactericid, antiphlogistic, androgene anabolic and CNS-stimulating activities as well as antimycotic properties. There are a lot of circumstantial synthesis which allowed to insert nitrogen at several places of the steroids. 3-aryl-2-cis-methyl-2-trans-carboxy-pyrrolidones are as well promising starting materials for a synthesis of 17-aza-steroids.

Some years ago Kwan Seog Sin started his PhD-work in this direction.[23] At first he prepared some new naphthyl-pyrrolidones **1c** to **1f**:

All products were stereochemically the desired compounds which have the carboxyl group trans in relation to the aryl ring.

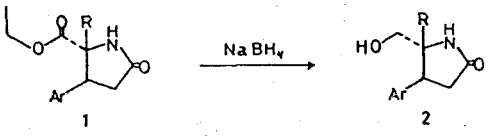
It seems to be possible that these aryl-carboxy-pyrrolidones could cyclisize directly to C-nor-steroid analogs. But the cyclization with polyphosphoric acid always yield nearly 60% 4-phenyl-2-oxo-pyrroline 8 by decarbonylation an elimination of water.[23] These undesired



Scheme 35.

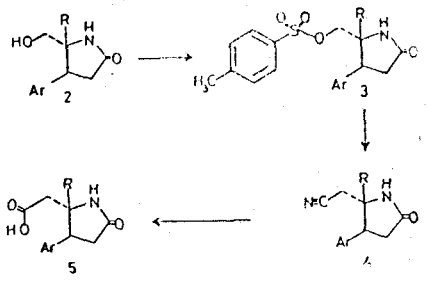
reaction should not take place if a pyrrolidonyl-acetic acid were used as starting material for the cyclization. For the necessary lengthening of the carboxyl-side-chain we reduced at first the ester group with sodium borohydride.

The next step was the tosylation in absolute pyridine followed by the reaction with potassium



Verbdg.	Ar	R	%
2a		H	84,3
2b		CH_3	85,4
2d		CH_3	91,5
2e	H_3CO	H	81,2
2f	H_3CO	CH_3	90,1

Scheme 36 and Table XV.

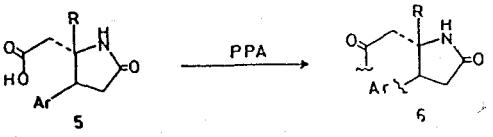


Verbdg.	Ar	R	% 3	% 4	% 5
a		H	68,9	80,6	84,2
b		CH_3	70,8	81,4	80,5
d		CH_3	·		39,8
e	H_3CO	H			42,5
f	H_3CO	CH_3			41,2

Scheme 37 and Table XVI.

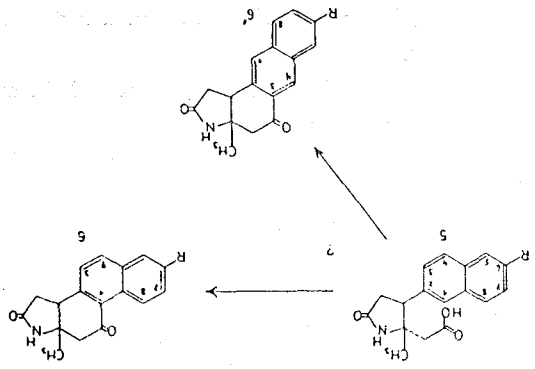
cyanide in dimethyl-formamide and at last by the alkaline hydrolysis which yields the desired pyrrolidonyl-acetic acids 5.

Now the cyclization with a tenfold surplus of polyphosphoric acid at 100 up to 110° Celsius for four hours yielded at least the 17-aza-steroid system. The TLC shows that only compound 6



Verbdg.	Ar	R	%
6a		H	56,0
6b		CH_3	66,5
6d		CH_3	60,4
6f	H_3CO	CH_3	64,5

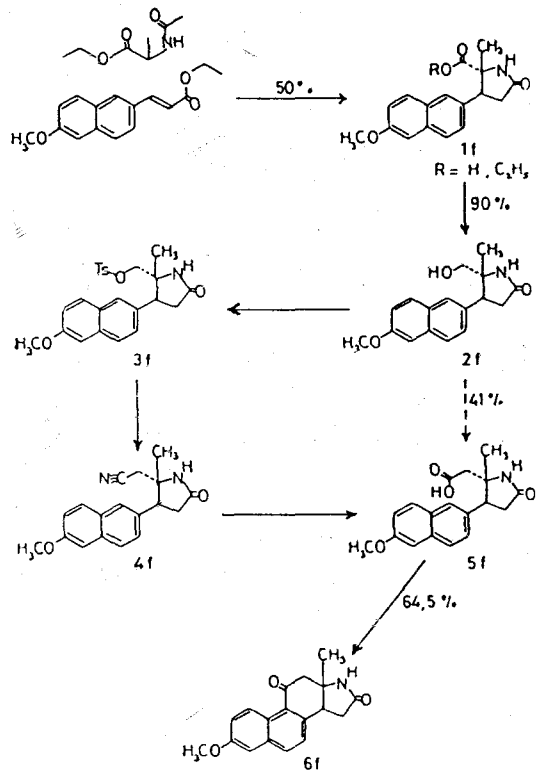
Scheme 38 and Table XVII.



Scheme 39.

is detectable and no trace of any starting material **5**.

An important question still has to be answered: On principle the cyclization could yield the false tetracyclic compound **6** too or as single product. Actual the desired 17-aza-steroid system **6** was the only product which shows in the proton NMR spectrum the typical ortho-split-off



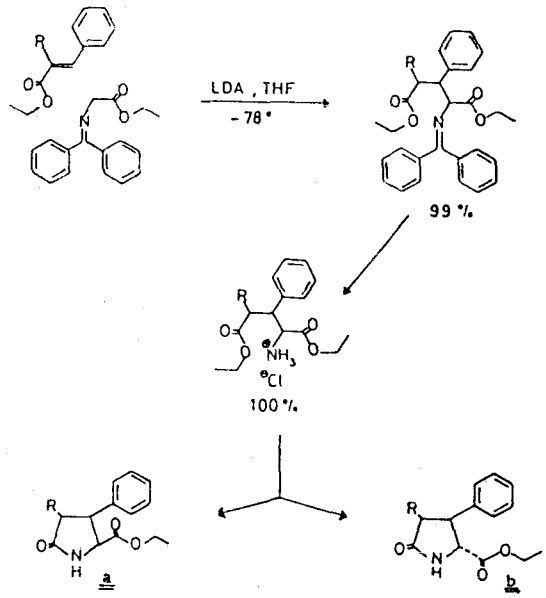
Scheme 40.

from the signal of the aromatic proton 8. All products **6** show the signal of the 18-methyl-group shielded up to high field at 0.83 to 0.88 ppm, which prove the awaited β-position.

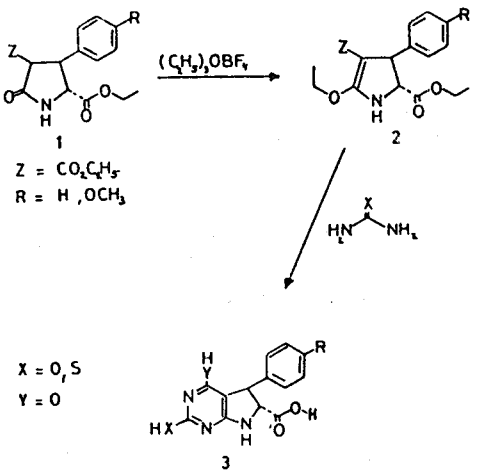
Scheme 40 shows again the whole synthesis for the example of 17-aza-3-methoxy-estra-1, 3, 5, 7, 9-pentaen-11, 16-dione.[23] The total yield about 7 steps was nearly 10%. It seems to be possible now the further derivation of our first examples.

In the synthesis of 7-desaza-purine-like compounds.,[24] we have seen that aryl-pyrrolidones **31a** are principle abtainable with arylidenmalonic acid esters, but these products are very fast changed to the pyrrolizidine-system **32**. For the synthtesis of the desired 7-desaza-purine-system we need the 4-z-3-aryl-pyrrolidone **31a** as starting material therefore we looked at a better possibility to get **31a**.

We have realized a very elegant synthesis which allowed to prepare the desired compounds with excellent yields: Schiff bases of benzophe-



Scheme 41.



Scheme 42.

none with glycine ester react in a Michael addition with the acceptor in the presence of lithium-diisopropylamide (LDA) at −78 degrees Celsius in dimethyl-formamide and yield the Michael addition product with 99%. The N-protection group it splitted off with diluted hydrochloric acid. The hydrochlorides of the 3, 4-disubstituted glutamic acid ester cyclize spontaneously after alkalinizing to the desired pyrrolidones **a** and **b**. Now it has to be proved if this method for preparing pyrrolidones is suitable as well for all other examples.

Scheme 42 shows how we have synthesized the first examples of 7-desaza-purines: The pyrrolidones **1** are quantitavely converted into the lactime ether **2** by triethyl-oxonium-tetrafluoroboride which then react with urea or thiourea to the desaza-purine system **3** with nearly 30%.[24]

I hope that I could demonstrate how manyfold natural product like compounds are available from simple amino acid via Michael reaction.

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