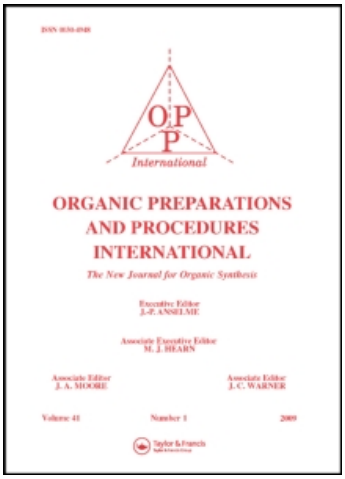

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SYNTHETIC AND ANALYTICAL ASPECTS OF THE CHEMISTRY OF PIRACETAM-TYPE SUBSTITUTED PYRROLIDINES. A REVIEW

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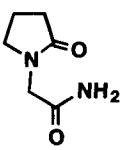
INTRODUCTION

A nootropic drug is characterized by its enhancement of learning and memory, its facilitation of the flow of information between the cerebral hemispheres, its enhancement of the general resistance of the brain function to physical and chemical insults, and by its lack of psychological and general cardiovascular pharmacological activities.[67]

The original impetus for the synthesis of the early racetams 2-oxo-(1-pyrrolidineacetic acid derivatives) was a search for antiemetics based on an alleged GABAergic mechanism. Then, the discovery in 1971 of the nootropic properties of piracetam (2-oxo-1-pyrrolidineacetamide, **1**)[226] aroused considerable independent chemical and pharmacological interest in **1** and the analogous racetams, which so far has led to the synthesis and characterization of hundreds of derivatives. So far, piracetam and oxiracetam (4-hydroxy-2-oxo-1-pyrrolidineacetamide) as well as the closely related aniracetam [*N*-(4'-methoxybenzoyl)-2-oxopyrrolidine] and tenilsetam [2-oxo-3-(2'-thienyl)piperazine] have been marketed as nootropic drugs while other racetams, *i. e.* DM-9384 [*N*-(2',6'-dimethylphenyl)-2-oxo-1-pyrrolidineacetamide], dupracetam [*N,N'-bis*(2-oxo-1-pyrrolidineacetyl)hydrazine], etiracetam (α-ethyl-2-oxo-1-pyrrolidineacetamide), and pramiracetam [*N*-[2'-(diisopropylamino)ethyl]-2-oxopyrrolidineacetamide], are undergoing clinical testing (Fig. 1).



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This survey summarizes chemical data concerning racetams (piracetam-analogous potential nootropics) retrieved by a CAS Online search while a parallel review published elsewhere[67] presents the corresponding pharmacological data. The present review is devoted to 2-oxo-1-pyrrolidineacetic acid derivatives which have been prepared as potential nootropics. We present their syntheses as well

as typical reactions and also summarize analytical work carried out with a number of candidate drugs. As summary observation, however, it would only be fair to say that much work remains to be done to put the synthesis of many of these interesting materials on a general and systematized basis, notwithstanding the good work of literally hundreds of researchers. Because of their significant pharmacological promise, an orderly exploration of synthetic details has lagged behind the rapid search for efficacious samples. For example, in some cases yields have not been optimized. In other cases, compounds which share similar structural features have been prepared by different researchers using very different methods without comparison of the benefits or deficiencies of one over the other. Our survey focuses on the literature surrounding 661 racetams selected from a CAS Online substructure search with 1666 hits. As a service to the chemically community, the authors can provide on request extensive tables listing compound structures and CAS Registry Numbers keyed to the References Section of this review; space limitations prohibit their printing here.

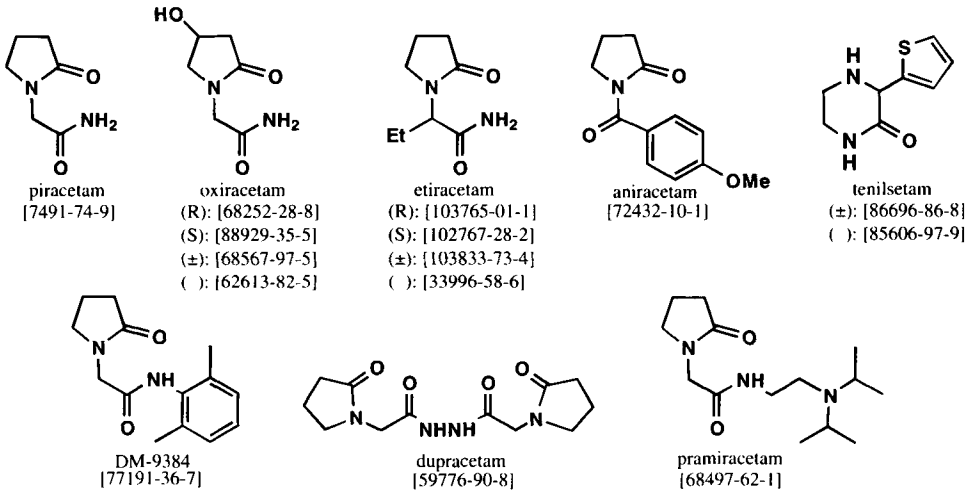
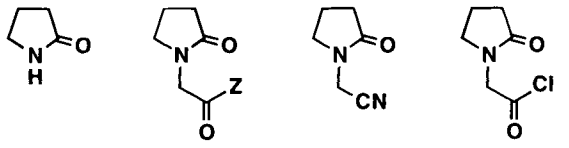


Fig. 1. Representative Racetams

I. SYNTHETIC ASPECTS

1. Syntheses Based on Preformed Pyrrolidine-derived Precursors

The most widely used method of synthesis of racetams is based upon the side-chain modification of preformed 2-pyrrolidinones. Key intermediates for such reactions are 2-pyrrolidinone (**2**) as



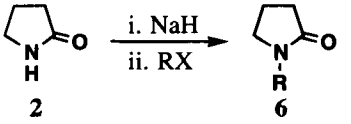
2 **3** **4** **5**

a, Z = OH
b, Z = OMe
c, Z = OEt

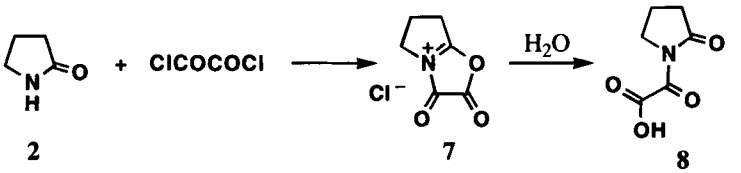
well as 2-oxopyrrolidine-1-acetic acid (**3a**), its methyl and ethyl ester (**3b** and **3c**) respectively, 2-oxopyrrolidine-1-acetonitrile (**4**), and 2-oxopyrrolidine-1-acetyl chloride (**5**).

a) 2-Pyrrolidinones

Thus, **2** has been condensed (after deprotonation with strong bases such as sodium or potassium hydride) with alkyl halides such as haloacetamides,[77,157,189,203,211-213] haloacetic acid esters,[87] haloacetaldehyde derivatives,[48] and 3-bromodihydro-2(3*H*)-furanone[183] to give racetams **6** in 76-86% yield (Eq. 1). Cyclization of 2-pyrrolidinone with oxalyl chloride to the bicyclic salt **7** and subsequent *in situ* hydrolysis yields **8**[195] in 42% crude yield (Eq. 2). Correspondingly, the acid-

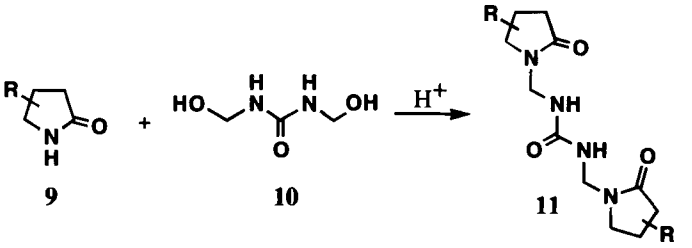


2 **6** (1)

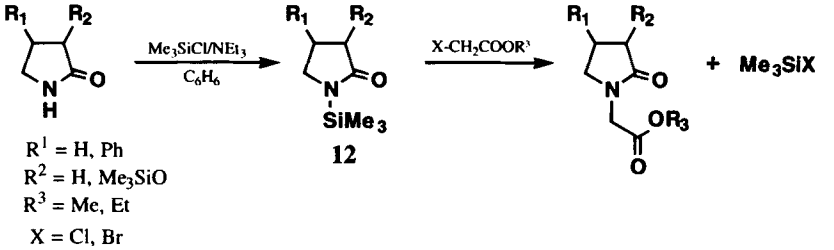


2 **7** **8** (2)

catalyzed condensation of ring substituted 2-pyrrolidinones **9** with *N,N'-bis*(hydroxymethyl)urea **10** yields *bis*-Mannich bases **11** with racetam-inverse amide functionalities (Eq. 3).[35] Being convenient



9 **10** **11** (3)

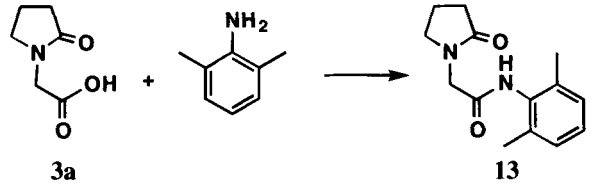


12 (4)

2-oxopyrrolidinide anion synthons, 1-(trimethylsilyl)-2-pyrrolidinones **12** have also been *N*-alkylated with haloacetic acid esters[102] (Eq. 4). The neutral reaction conditions in this system (for instance $BrCH_2COOMe$, 150-160°, 30 min, 73% yield) supplement the typical methods requiring bases employed elsewhere.

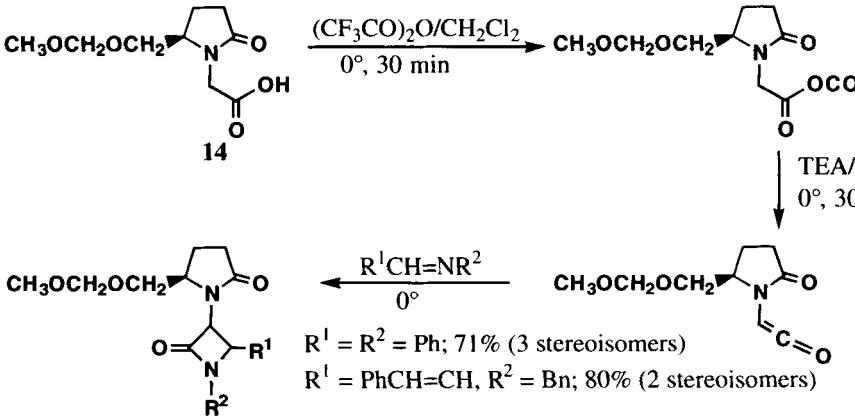
b) 2-Oxopyrrolidine-1-acetic Acid

2-Oxopyrrolidine-1-acetic acid (**3a**) has been converted to racetams by dehydration of its ammonium salts[203,213] and by amidation with 2,6-dimethylaniline/DCC[14,15] to yield the experimental nootropic drug DM-9384 **13** (Eq. 5). Corresponding amidations have been carried out with **3a** and



3a **13** (5)

ethyl glycinate,[182] with glycyl piperidides,[148] 4-(glycylamino)pyridine/DCC,[149] glycylglycinamide hydrochloride,[11] glycylalaninamide hydrochloride,[12] L-glutamic esters/DCC and L-glutamide esters/DCC[165] under typically mild peptide bond forming conditions (*inter alia*, *via* activated esters of **3a** such as pentachlorophenyl esters and *via* mixed anhydrides formed from **3a** and isobutyl chloroformate) to yield peptidic racetams. Analogous amidations have been carried out with 4-aryl-2-oxopyrrolidine-1-acetic acids, amines, and triphenyl phosphite at 180°.[29] *(S)*-5-(Methoxymethoxymethyl)-2-oxopyrrolidine-1-acetic acid (**14**) has been converted (*via* the mixed anhydride with trifluoroacetic acid) to the corresponding ketene which forms the corresponding 2-azetidinones **15** with Schiff bases (Eq. 6).[89]



14 (6)

c) 2-Oxopyrrolidine-1-acetic Acid Esters

Most commonly, 2-oxopyrrolidine-1-acetic acid esters (mostly the methyl **3b** or ethyl ester **3c**; for the preparation of **3c** see ref. 214) have been employed in racetam forming amidations with primary and secondary amines,[59,92,105,106,118,121,203,213] including ethylenediamine,[17] dialkylaminoalkylamines,[20,115,116] and 1-substituted piperazines[215] to yield close analogs of the nootropic pramiracetam (see Fig. 1), and with 2-arylethylamines,[221] tetrahydroacridines,[108,109,140] monosubsti-

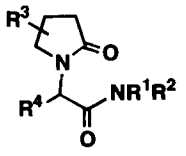
tuted guanidines,[119] and *(S)*-1-(2-aminoethyl)-2-(hydroxymethyl)pyrrolidine.[191] With hydrazine,[110] 2-oxopyrrolidine-1-acetic acid hydrazide,[156] and 5-methyl-2-oxopyrrolidine-1-acetic acid hydrazide[155] analogs of the nootropic dupracetam (see Fig. 1) are formed. Analogous reactions have been carried out with ring substituted 2-oxopyrrolidine-1-acetic acid esters.[13,110,121,234] Yields in the range of 42-91% have been reported.

d) 2-Oxopyrrolidine-1-acetyl Halides

2-Oxopyrrolidine-1-acetyl halides (for the preparation of the chloride **5** see ref. 81) have been amidated with amines (in methanol at 0°) to give racetams **16**.[203,213]

e) Ring Substituted 2-Oxopyrrolidine-1-acetonitriles

Ring substituted 2-oxopyrrolidine-1-acetonitriles **17** upon treatment with hydroxylamine hydrochloride form the corresponding amidoximes **18** which in turn can be *O*-acylated.[64] Compounds **18** and their derivatives appear to possess significant biological activity.



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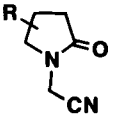

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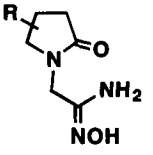

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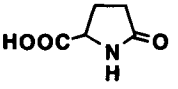


19

f) Other 2-Pyrrolidinones

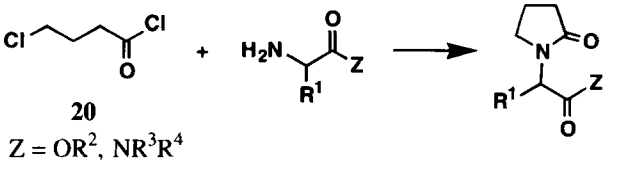
Pyroglutamic acid derivatives **19** have similarly been condensed with chloroacetic acid esters[86] and amides.[43] Other ring substituted 2-pyrrolidinones **9** such as 3-amino-,[208] *(R)/(S)*-3-hydroxy- (*via* intermediate *N*-silylation),[3] 4-phenyl-,[63,100,101] and *(R)*-4-hydroxy-2-pyrrolidinone,[153] as well as the *O*-protected *(S)*-5-hydroxymethyl,[90] and 5-methyl[88] derivatives have been similarly derivatized.

2. Syntheses Based on Acyclic Precursors

A large number of syntheses of racetams (including chiral compounds) employ ring closure of a suitable precursor as one of the last steps. A rather varied selection of starting materials has been employed. The main motive for the synthetic variations developed is no doubt a desire to find patentable new routes to known and new racetams.

a) 4-Halobutanoyl Halides

Typical starting materials for syntheses of this type yielding esters or amides are 4-chlorobutanoyl chloride **20** [and (sometimes silylated) amino acids (especially glycine), dipeptides, etc.], as illustrated in Eq. 7.[31,38,39,66,154,170,173,192]



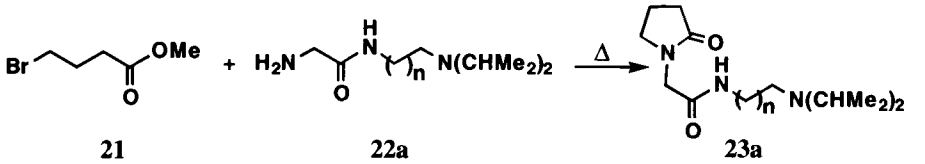
(7)

20

$Z = OR^2, NR^3R^4$

b) 4-Halobutanoic Acid Esters

Methyl 4-bromobutanoate **21** alkylates *N*-(alkylaminoalkyl)glycinamides **22a** (Eq. 8); the intermediates thus obtained can be cyclized to racetams **23a** by heating.[113]

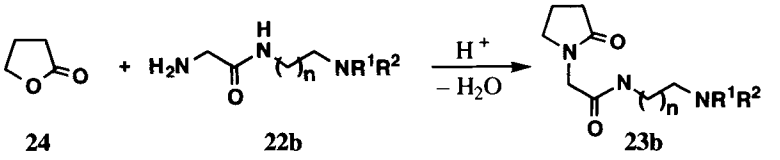


(8)

21 **22a** **23a**

c) γ-Butyrolactone

Under acidic conditions γ-butyrolactone **24** will alkylate *N*-(alkylaminoalkyl)glycinamides **22b**; the intermediates thus obtained can be cyclized to racetams **23b** by treatment with sulfuric acid (Eq. 9).[120]

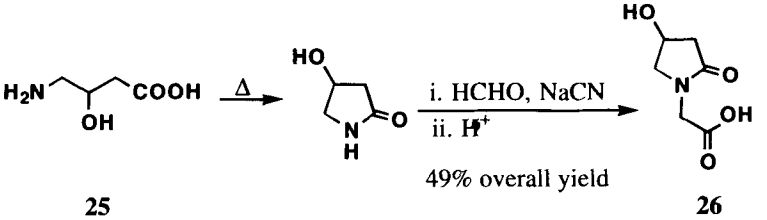


(9)

24 **22b** **23b**

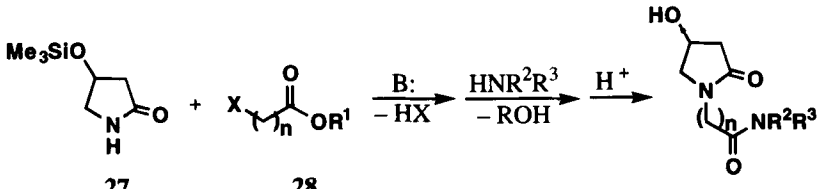
d) 4-Aminobutanoic Acid Derivatives

γ-Amino-β-hydroxybutyric acid (GABOB) **25** can be cyclized, then treated with formaldehyde and sodium cyanide and finally hydrolyzed to form 4-hydroxy-2-oxo-1-pyrrolidineacetic acid **26** (Eq. 10), in 49% yield .[130] *O*-Silylated β-hydroxy-γ-butyrolactam **27** upon treatment with alkyl ω-haloalkanoates **28** forms esters which can be further amidated to oxiracetam derivatives **29** (Eq. 11).[138,164] Similar synthetic sequences have been carried out with 4-amino-3-phenylbutanoic acid hydrochloride **30** to yield 4-phenyl substituted piracetam derivatives such as **31** (Eq. 12).[100,101]

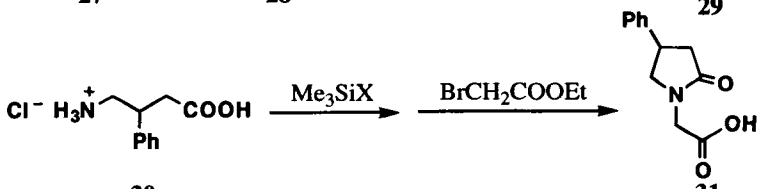


(10)

25 **26**



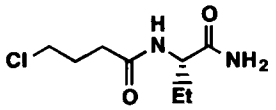
27 28 29 (11)



30 31 (12)

e) (4-Halobutanoyl)glycinamides

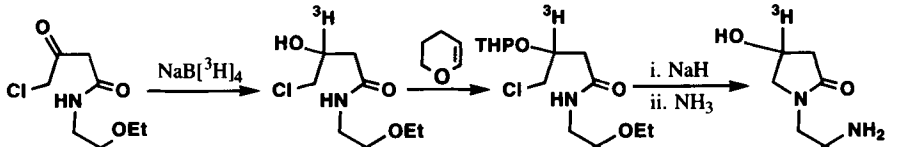
Other starting materials for cyclization procedures are (4-chlorobutanoyl)glycinamides.[214] Thus, under basic conditions *(S)-N*-[1-(carbamoyl)propyl]-4-chlorobutanamide **32** has been cyclized to *(S)*-etiracetam.[65]



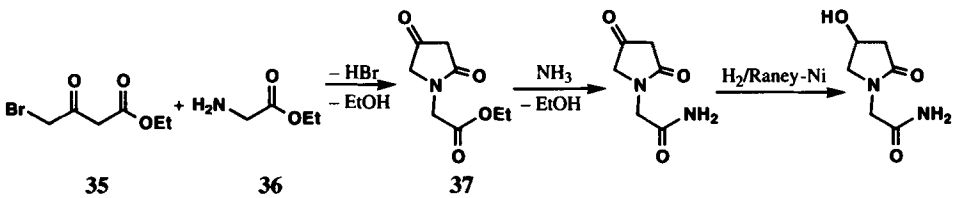
32

f) Acetoacetic and Pyruvic Acid Derivatives

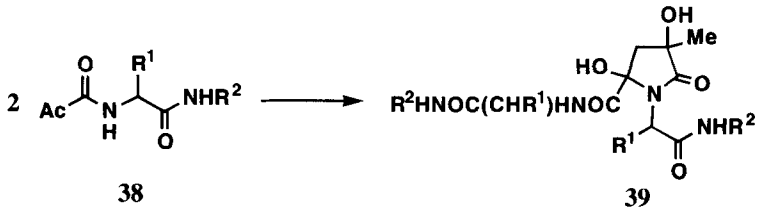
Treatment of $ClCH_2COCH_2CONHCH_2COOEt$ with $NaB[^3H]_4$, protection of the reduction product **33** with 2,3-dihydropyran, cyclization with sodium hydride, deprotection, and amidation furnished [4-^{3}H]-labelled oxiracetam **34**, required for metabolic studies (Eq. 13).[32] Ethyl γ-bromoacetoacetate **35** condenses with ethyl glycinate **36** to an ester[46] **37** which can be amidated[32] and subsequently reduced with sodium borohydride[32] or by Raney nickel catalyzed hydrogenation[97] to form oxiracetam (Eq. 14). Aldol cyclocondensations of *N*-(pyruvoyl)glycinamides **38** also lead to racetams **39** (Eq. 15).[73] These procedures potentially allow considerable variation of both ring and side-chain substitution in racetams.



33 **34** (13)



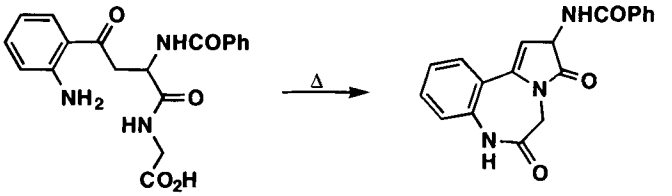
35 **36** **37** (14)



38 39 (15)

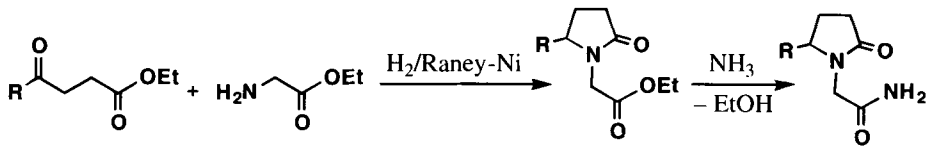
g) 4-Oxoalkanoic Acid Derivatives

4-Oxoalkanoic acid derivatives such as *N*-benzoyl-DL-2-phenacylglycylglycine **40** have been cyclized to the corresponding 2-pyrrolinones **41** (Eq. 16),[181] thus providing 3,5-disubstitution of



40 41 (16)

the pyrroline ring system. Reductive cyclization of ethyl γ-keto alkanoates **42** with ethyl glycinate **36**, followed by amidation, also leads to racetams **43** (Eq. 17).[193]



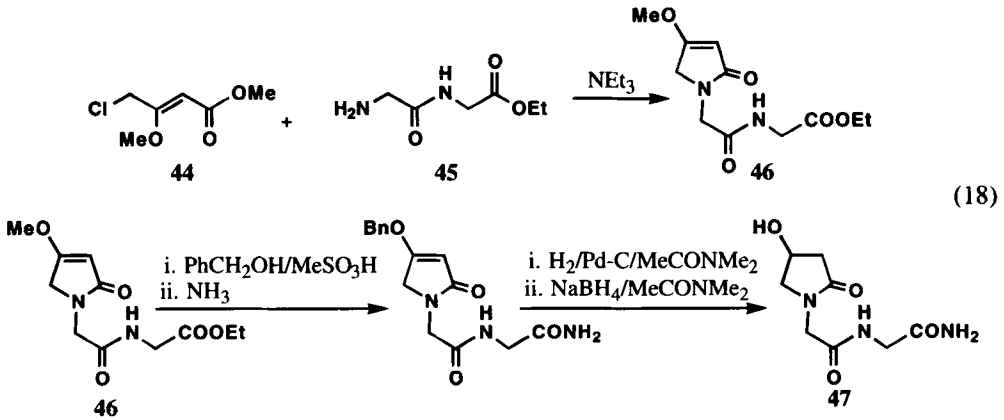
42 36 43 (17)

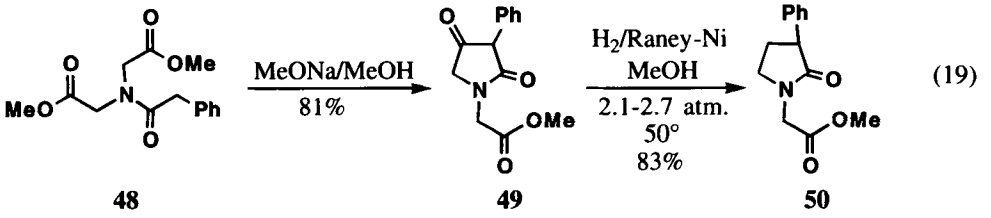
h) 4-Halo-3-alkoxy-2-butenoic Acid Esters

Methyl 4-chloro-3-methoxy-2-butenoate (**44**) reacts with ethyl glycylglycinate (**45**) to give an intermediate **46** which, after methyl/benzyl exchange with $C_6H_5CH_2OH/CH_3SO_3H$, hydrogenolytic debenzylation, amidation, and $NaBH_4$ reduction, yields the *N'*-substituted oxiracetam **47** (Eq. 18).[125]

i) Iminodiacetic Acid Derivatives

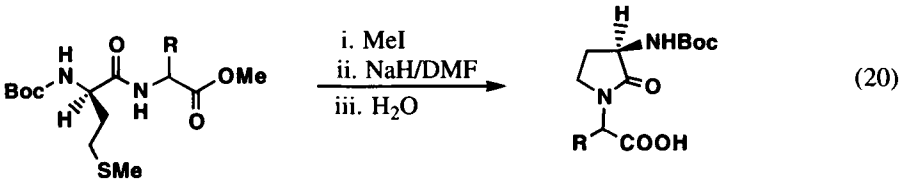
Dimethyl *N*-phenacetyliminodiacetate (**48**) can be cyclized with sodium methoxide to yield 3-phenyl-2,4-pyrrolidinedione **49** which upon Raney nickel catalyzed hydrogenation, is converted to the corresponding 2-pyrrolidinone derivative **50** (Eq. 19).[97] The importance of the phenyl substituent for the success of the reaction sequence has not been determined.





j) α-Amino Acid Derivatives

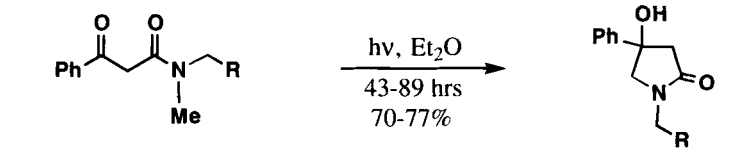
Chiral amino acid derivatives such as [(5*S*)-5-amino-5-carboxypentanoyl]-L-homocysteinyl-D-valine[6] and -L-cysteine[5] can be cyclized to racetams subject to catalysis by isopenicillin N synthase. Appropriate protected methionine derivatives **51** can be cyclized by *S*-methylation and subsequent treatment with base (Eq. 20).[51] Photolysis of *N*-methyl-*N*-(3-phenyl-3-oxopropanoyl)-



glycine derivatives **52** in ambient light leads to the corresponding 4-hydroxy-4-phenyl-2-oxopyrrolidine-1-acetic acid **53** derivatives (Eq. 21).[84]

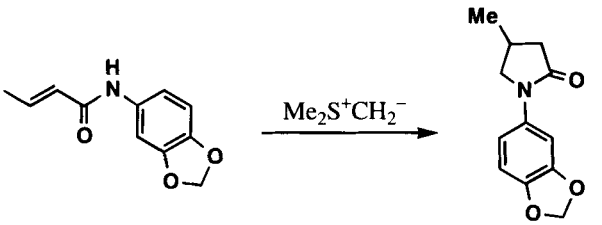
k) Crotonic Acid 3,4-Methylenedioxyanilide

Treatment of crotonic acid 3,4-methylenedioxyanilide **54** with dimethylsulfonium methylide gives the corresponding 1-aryl-2-pyrrolidinone **55** (Eq. 22), strictly speaking a non-racetam,[224] but ofpharmacological interest as antiinflammatory and weak analgesic. This ring closure procedure could probably also be applied to the preparation of racetams.



R = CO_2Et, $CONH_2$, CN

52 **53** (21)

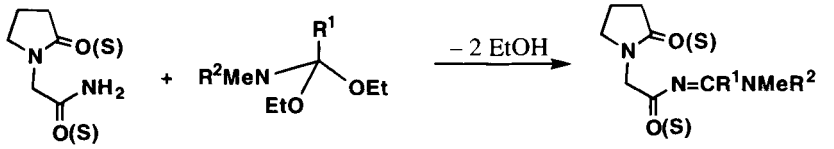


54 **55** (22)

3. Functional Modification of Racetams

a) Formation of Side-chain Amidine Derivatives

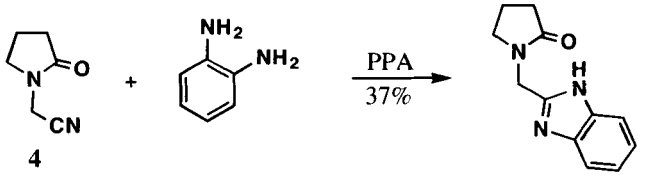
Apart from standard protection/deprotection procedures modifications of racetams include condensation with *N,O,O*-orthoformates to give formamidines **56** (Eq. 23).[93,200] 2-Oxopyrrolidine-1-



R^1, R^2 = $CH_2CH_2CH_2$
H, Me

56 (23)

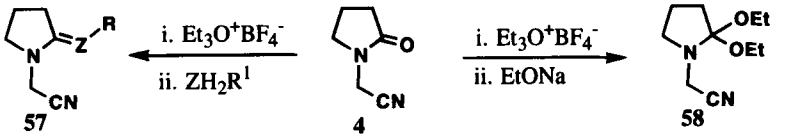
acetonitrile **4** reacts with *o*-phenylenediamine or 3,4-diaminopyridine to form the corresponding cyclic amidines (Eq. 24).[222]



(24)

b) Formation of 2-Methylene and 2-Imino Derivatives

2-Methylene derivatives such as **57** (with anticonvulsant and antihypoxic activity) can be prepared *via* *O*-ethylation of racetams such as **4** with triethyloxonium tetrafluoroborate and subsequent condensation with active methylene compounds (Eq. 25).[123] *O*-Ethylation, followed by condensation with arylamines, gives the 2-imino derivatives.[199]

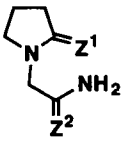


(25)

R, Z = NO_2, CH
$CONH_2$, C-CN
Ph, N
4-$MeOC_6H_4$, N

c) Formation of Thioxo Derivatives

Considerable effort has been spent on the preparation of thioxo analogs of piracetam **59** (which could be expected to exhibit increased lipophilicity and thus improved *in vivo* distribution behavior without loss of biological activity), typically by thionation of piracetam **1** or 2-oxopyrrolidine-1-acetonitrile **4** with phosphorus pentasulfide.[69-71]



Z^1, Z^2 = S, O

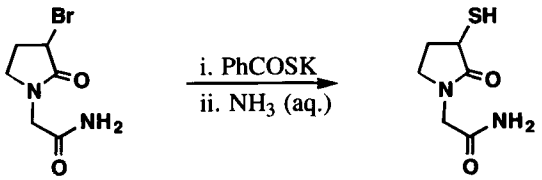
59

d) Formation of Ortho Ester Amides

2-Oxopyrrolidine-1-acetonitrile **4** has been converted to the corresponding ortho ester amide **58** by subsequent treatment with triethyloxonium tetrafluoroborate and ethoxide (Eq. 25).[199]

e) Formation of Thiol Derivatives

The 3-bromo derivative of piracetam **60** has been converted to the corresponding thiol **61** by treatment with potassium thiobenzoate and subsequently with ammonia (Eq. 26).[33]

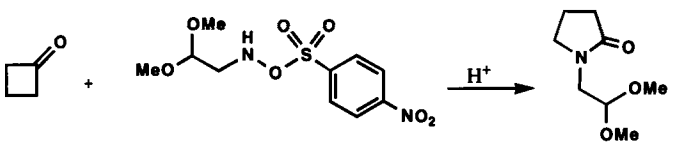


60 **61**

(26)

4. Miscellaneous Reactions

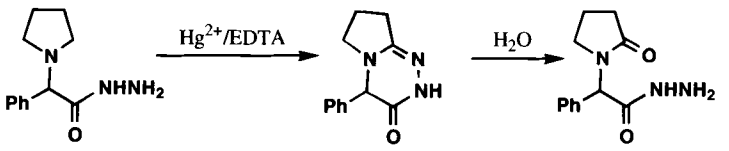
2-Oxopyrrolidine-1-acetaldehyde dimethyl acetal (**64**), a potential piracetam precursor, can be obtained in a sophisticated ring expansion reaction (Eq. 27) from cyclobutanone (**62**) and (4-nitrobenzenesulfonyloxyamino)acetaldehyde dimethyl acetal (**63**, prepared *in situ* from



62 **63** **64**

(27)

bis-4-nitrobenzenesulfonyl peroxide).[85] Further syntheses of racetams involve Michael additions to 3-methylene-2-pyrrolidinone,[96] reduction of 2,5-dioxopyrrolidine derivatives with sodium tetraborohydride[166] or electrochemically,[169] hydrolysis of 1,2,4-triazin-5-ones **65** (Eq. 28),[131] and amidation of



(28)

65

bipyrrolediones.[160] Dupracetam can be hydrogenated to yield piracetam **1**[108] and hydrolyzed to give 2-oxopyrrolidine-1-acetic acid hydrazide.[196]

5. Tables of Compounds

A selection of 661 racetams found by a CAS Online substructure search (highest registry number found: 138258-48-7) has been organized in ten tables which are available from the authors upon request.

II. ANALYTICAL ASPECTS

The analytical methodology shown below is an intrinsic part of the pharmaceutical and pharmacologic work which must be carried out with candidate drugs of the racetam type.

1. Potentiometry

Differential potentiometric titration can be used to determine amide drugs, including piracetam **1**, in binary mixtures.[220] Amides, including piracetam **1**, can be detected by a potentiometric method combined with an ammonia-selective membrane electrode.[37]

2. Colorimetry

Colorimetry of the iron(III) salt of the hydroxamic acid formed from piracetam **1** by nickel(II) catalyzed transamidation of piracetam with hydroxylamine allows a quantitative determination useful for stability evaluation of drug preparations.[162] Analysis of dupracetam has been carried out by hydrolysis and subsequent derivatization with hydroxylamine and colorimetry with Fe(III) ions.[196]

3. Thin Layer Chromatography

A TLC procedure has been elaborated for the determination of 2-pyrrolidinone derivatives, including piracetam **1**.[36]

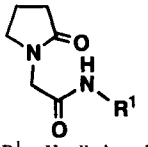
4. High-Pressure Liquid Chromatography

In the context of stability studies the acid and basic hydrolysis of dupracetam has been investigated by HPLC analysis. Piracetam acid hydrazide, 2-oxopyrrolidine-1-acetic acid, and hydrazine were identified.[196,197]

5. Chiral Separation

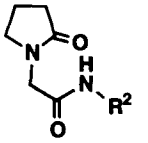
Chiral separation of oxiracetam and its isomers is possible on cellulose based columns.[22,23]

Table 1
N-Substituted 2-Oxopyrrolidine-acetamides; 188 entries.



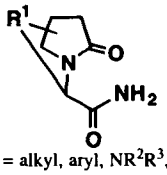
R^1 = H, alkyl, aryl, hetaryl, NR^2R^3, OR^4

Table 2
Miscellaneous *N*-Substituted 2-Oxopyrrolidine-acetamides; 57 entries.



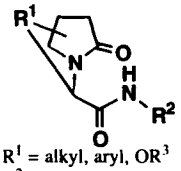
R = voluminous alkyl, aryl, hetaryl

Table 3
Ring or α-Substituted 2-Oxopyrrolidine-acetamides; 76 entries.



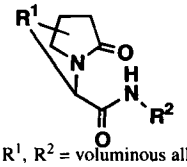
R^1 = alkyl, aryl, NR^2R^3, OR^4

Table 4
(Ring or α-) and *N*-Substituted 2-Oxopyrrolidine-acetamides; 171 entries.



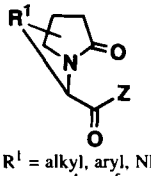
R^1 = alkyl, aryl, OR^3
R^2 = alkyl, aryl, hetaryl, NR^4R^5, OR^6

Table 5
Miscellaneous Ring and *N*-Substituted 2-Oxopyrrolidine-acetamides; 2 entries.



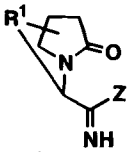
R^1, R^2 = voluminous alkyl or alkoxy

Table 6
2-Oxopyrrolidine-acetic Acid Derivatives; 124 entries.



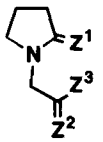
R^1 = alkyl, aryl, NR^2R^3, OR^4, SR^5
Z = OR^6

Table 7
2-Iminopyr-rolidineacetamidine Derivatives; 5 entries.



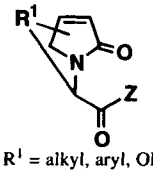
R^1 = Me, Ph
Z = $NHOR^2$

Table 8
2-Oxo, 2-Thioxo, and 2-Iminopyrrolidine-acetic Acids and Derivatives; 23 entries.



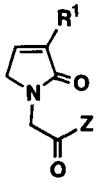
Z^1 = NR^1, O, S
Z^2 = NR^2, O, $(OR^3)_2$, S
Z^3 = H, NR^4R^5, OR^6

Table 9
Ring and α-Substituted 2-Oxo-3-pyrro-lineacetic Acid and Amide Derivatives; 11 entries



R^1 = alkyl, aryl, OR^2
Z = NR^3R^4, OH

Table 10
Miscellaneous 2-Oxopyrroline-acetic Acid and Amide Derivatives; 4 entries.



R = voluminous alkyl
Z = NR^2R^3, OH

The following references in this article refer to table entries.

Table 1: Refs. 1, 2, 9, 11, 12, 14, 15, 17, 18, 36, 20, 21, 25, 26, 36, 38, 39, 42, 44, 45, 49, 54-57, 59, 61, 62, 66, 68, 75, 76, 88, 92, 94, 95, 98, 105-109, 113-122, 134-137, 139, 141-145, 148, 149, 154-156, 159, 161, 162, 165, 170-178, 180, 182, 186, 187, 189, 191, 194, 196-198, 201, 211, 212, 214, 221, 230-233, 235.

Table 2: Refs. 17, 36, 78-81, 92, 122, 140, 150, 157, 158, 167, 221.

Table 3: Refs. 3, 7, 8, 13, 16, 20, 22, 23, 30-32, 35, 37-39, 43, 49, 60, 63, 65, 66, 72, 82, 84, 91, 96, 99-103, 124, 129, 130, 138, 139, 153, 160, 164, 166, 170-173, 179, 182, 183, 188, 190,

193, 202, 203, 213, 215-217, 219, 220, 227-229, 234.

Table 4: Refs. 1, 3, 7-9, 11-16, 18, 20, 21, 23, 25, 26, 30, 34, 37, 42, 44, 45, 49, 54-57, 59, 60, 62, 63, 66, 68, 73, 75-77, 88, 92, 94, 95, 98-102, 105, 106, 110, 113-118, 120, 121, 125, 130, 131, 134-139, 141-145, 148, 149, 151, 153, 155, 156, 161, 168, 175, 176, 178, 182, 183, 186-191, 193, 194, 198, 202, 203, 213-215, 217, 220, 227, 228, 232, 233.

Table 5: Ref. 3.

Table 6: Refs. 3-7, 11, 12, 14, 15, 19, 24, 27-30, 33, 34, 40, 41, 46, 47, 50-53, 59, 65, 66, 74, 82, 83, 86, 87, 89, 90, 96, 97, 102, 103, 112, 127, 130, 132, 133, 148, 149, 151, 152, 160, 163, 182, 183, 185, 192, 199, 203, 205-209, 213, 218, 223-225.

Table 7: Ref. 64.

Table 8: Refs. 48, 58, 64, 69-71, 85, 92, 93, 104, 111, 123, 128, 184, 199, 200.

Table 9: Refs. 10, 17, 36, 124-126, 160, 204.

Table 10: Ref. 160.

III. CONCLUSION

The keen interest in the biological potential of the racetams has stimulated a considerable amount of synthetic and analytical work the results of which amount to a convenient and mature methodology at the disposal of the medicinal chemist.

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