Chemistry of Heterocyclic Compounds, Vol. 40, No. 1, 2004

PYRROLE OXIMES: SYNTHESIS, REACTIONS, AND BIOLOGICAL ACTIVITY. (REVIEW)

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Data on the production methods and reactions of pyrrole aldoximes and ketoximes and their derivatives are reviewed. The synthesis of new heterocycles from the pyrrole oximes is examined separately. The principal results from investigation of the biological activity of pyrrole oximes are described.

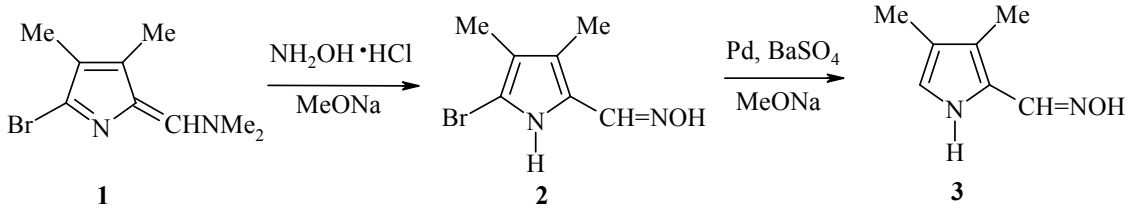
Keywords: oximes, pyrrole, biological activity.

Pyrrole oximes are widely used as intermediates in fine organic synthesis. In the present work the methods for the production and the reactions of pyrrole oximes are reviewed. Methods for the synthesis of new heterocycles from derivatives of these oximes are dealt with in a separate section. The principal methods for investigation of the structure of pyrrole oximes with regard to isomerism are also briefly examined. The main paths for the selective production of the *E*- and *Z*-isomers of the oximes and their O-ethers are described. The last section of the paper gives the results from research into the biological activity of derivatives of pyrrole oximes.

1. SYNTHESIS AND STRUCTURE OF PYRROLE OXIMES

1.1. Synthesis of Pyrrole Oximes

The classical method for the synthesis of pyrrole oximes is based on the reaction of an aldehyde or ketone with hydroxylamine hydrochloride in pyridine–ethanol [1, 2], sodium acetate–methanol or ethanol [3-6], sodium carbonate–ethanol–water [7], or potassium hydroxide–ethanol [8] systems. By modifying these methods it is possible to obtain the pyrrole oxime **2** from 5-bromo-2-dimethylmethylene-3,4-dimethyl-2H-pyrrole (**1**). Debromination of the oxime **2** in the system containing palladium on barium sulfate–sodium methoxide–sodium hydroxide leads to 3,4-dimethylpyrrolecarbaldehyde oxime (**3**) [9].



1 **2** **3**

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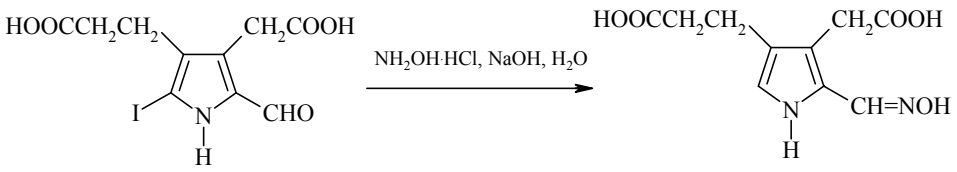
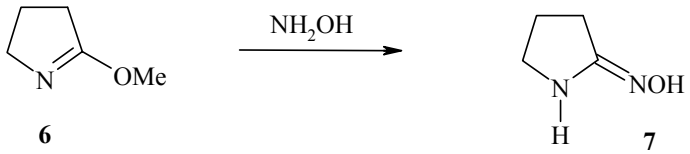
Unexpected deiodination during the synthesis of pyrrole oxime was described in [10]. Thus, the reaction of the aldehyde **4** with hydroxylamine hydrochloride in the presence of 10% aqueous sodium hydroxide gives the oxime **5** with a yield of 81% [10].



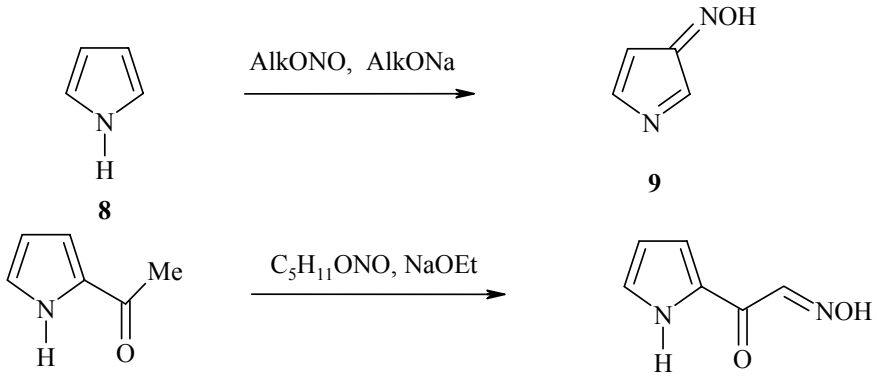
4 **5**

2-Methoxy-1-pyrroline (**6**) and hydroxylamine in alcohol give 2-pyrrolidone oxime (**7**) [11].



6 **7**

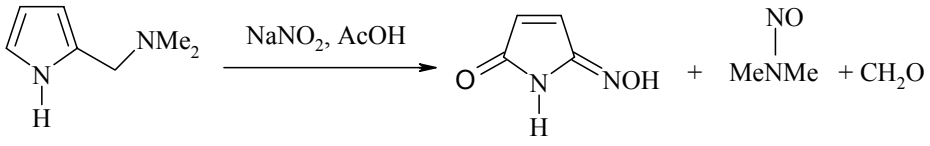
A series of methods for the synthesis of pyrrole oximes were based on the nitrosation of indole derivatives [12-15]. For example, pyrrole (**8**) and alkyl nitrites in the presence of sodium alcoholates give a salt of the oxime **9** [16]. The ketoxime **11** is formed as the only product during the nitrosation of 2-acetylpyrrole (**10**) with amyl nitrite [17]



8 **9**

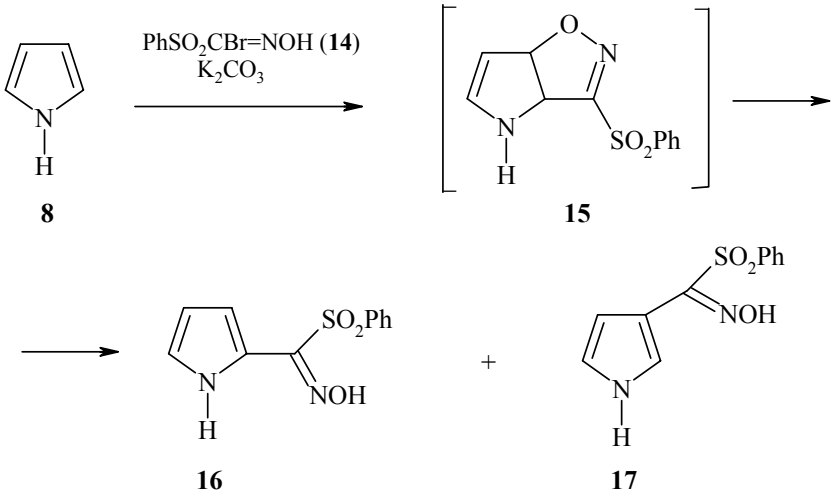
10 **11**

The nitrosation of 2-(dimethylaminomethyl)pyrrole (**12**) with sodium nitrite in acetic acid gives a mixture of the oxime **13**, N-nitrosodimethylamine, and formaldehyde [18].

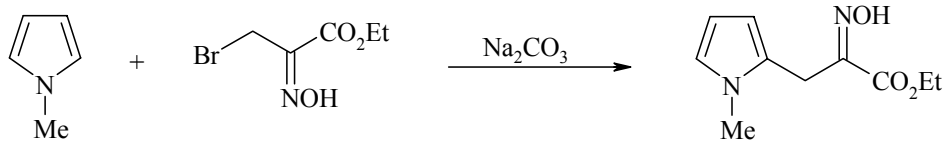


12 **13**

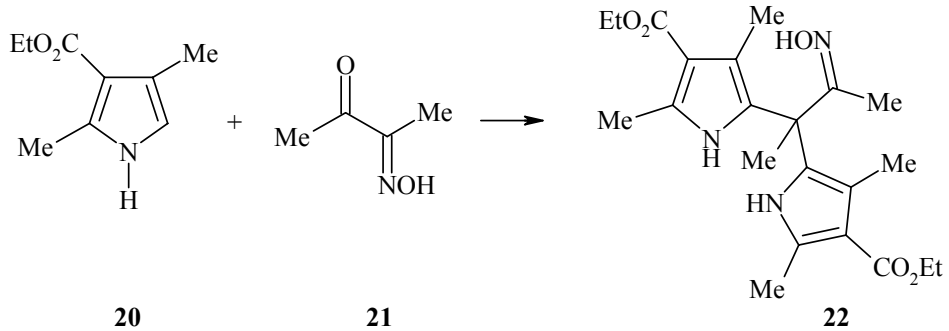
The pyrrole oximes **16** and **17** (ratio 90:10, overall yield 74%) were obtained successfully by the reaction of pyrrole with the bromo oxime **14** in the presence of sodium carbonate. The products are formed through the cycloadduct **15** as intermediate [19].



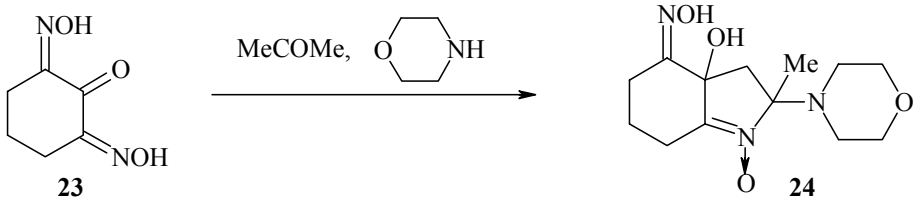
1-Methylpyrrole (**18**) reacts readily with the oxime of ethyl bromopyruvate in a basic medium and forms the oxime **19** with a 67% yield [20].



The condensation of 3-ethoxycarbonyl-2,4-dimethylpyrrole (**20**) with the α-diketone monoxime **21** gives the *gem*-dipyrrolyl derivative **22** [21].



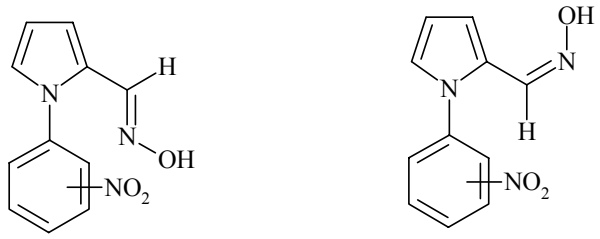
The reaction of the dioxime **23** with acetone and morpholine leads to the formation of 3α-hydroxy-2-methyl-2-morpholino-4-hydroxyimino-2,3,4,5,6,7-hexahydro-3αH-indole 1-oxide (**24**) with a yield of 80% [22].



23 **24**

1.2. The Structure of Pyrrole Oximes

One of the most reliable methods for the determination of the structure of isomeric pyrrole oximes is NMR spectroscopy. In [23] the stereochemistry of the oximes of 2-carbonyl derivatives of 1-nitrophenylpyrroles was studied in detail. 2-Formyl-1-nitropyrroles readily give oximes in reaction with hydroxylamine and always as a mixture of two isomers, *s-trans-syn* (**25**) and *s-trans-anti* (**26**), which can be separated by chromatography. The ratio of the isomers amounts to 2:1 in the case of 1-(4-nitrophenyl)-2-formylpyrrole oxime and 4:1 for the 3-isomer. This means that conjugation of the nitro group with the pyrrole ring stabilizes the *s-trans-syn* isomer.

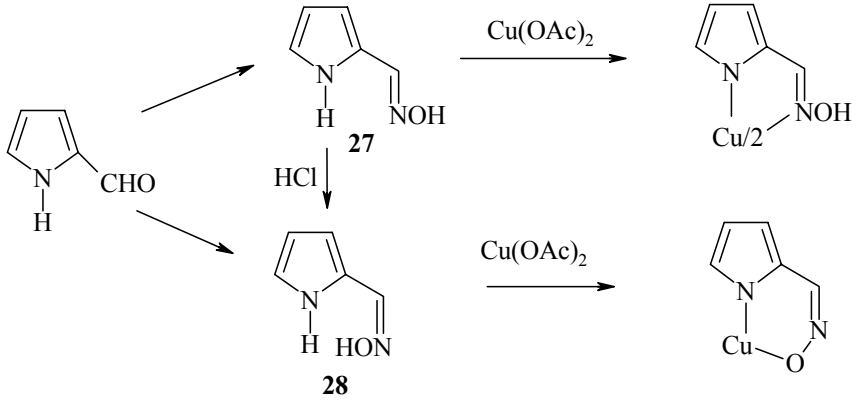


25 **26**

The difference between the chemical shifts of α-H and OH amounts to 2.91-2.92 for the *syn* isomer and 4.30 ppm for the *anti* isomer.

The $^{15}N–^{1}H$ spin–spin coupling constant (12.5 Hz) was determined for the *anti* isomer of pyrrole 2-aldoxime in acetone [24].

Several papers have been devoted to the synthesis, structure, and transformations of pyrrole aldoximes and ketoximes [25-27]. Thus, the two isomeric *anti* (**27**) (mp 164.5°C) and *syn* (**28**) (mp 70-71°C) products are formed in the synthesis of 2-pyrrolecarbaldehyde oxime. The *syn* isomer of the oxime is less stable and is readily transformed into the *anti* isomer on heating, during storage, during irradiation, or in the presence of HCl. In reaction with copper acetate the *anti* isomer **27** forms a 1:1 complex, while the *syn* isomer **28** forms a 1:2 complex. It was also shown that the *syn* isomer of 2-acetylpyrrole oxime is converted into the *anti* isomer in the presence of HCl.



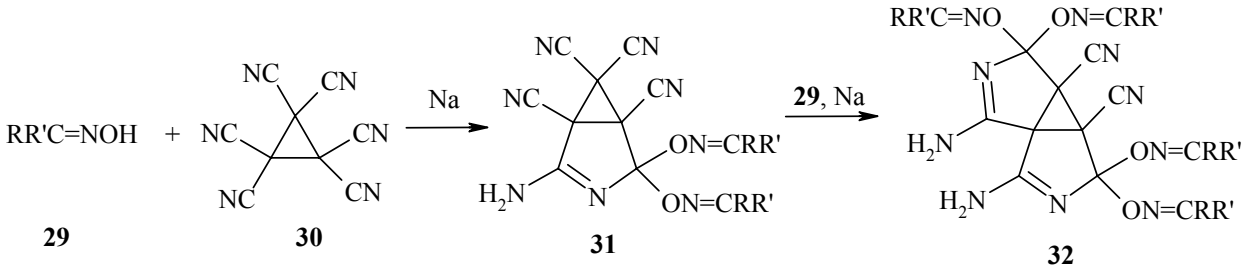
The structure of pyrrole oximes has also been investigated by UV spectroscopy [28, 29], polarography [30], spectrophotometry [30, 31], and potentiometry [31].

2. REACTIONS OF PYRROLE OXIMES

2.1. Synthesis of the Ethers of Pyrrole Oximes

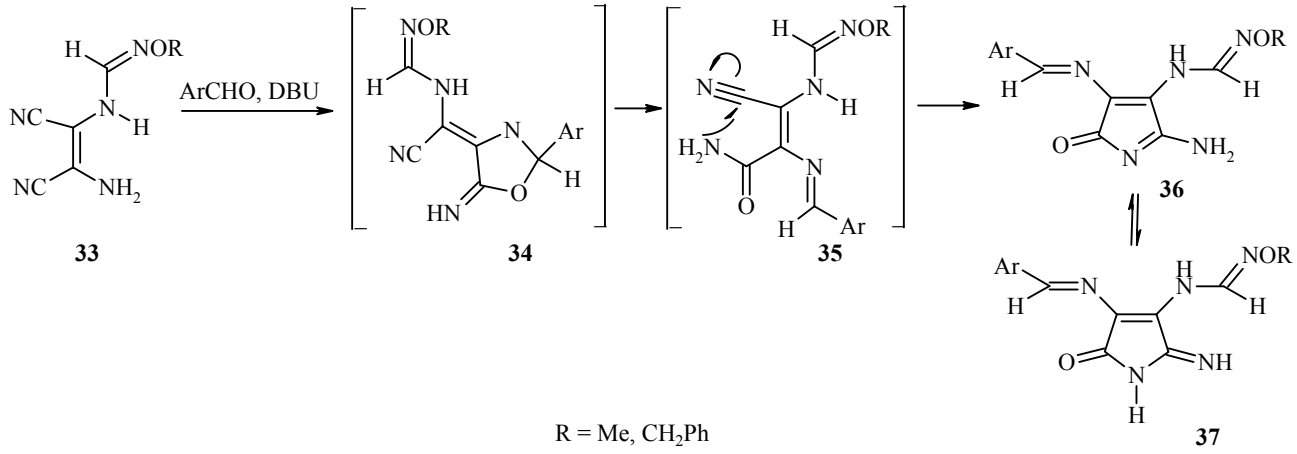
The chief method for the synthesis of the O-ethers of pyrrole oximes is based on the reaction of O-alkyl derivatives of hydroxylamine with carbonyl derivatives in the presence of sodium acetate in aqueous ethanol [6]. Another method for the synthesis of the O-ethers of pyrrole aldoximes is based on the reaction of the salts of the oximes with alkyl halides. It should be noted that only the *E*-isomers of pyrrole aldoximes give O-alkyl derivatives. *Z*-Aldoximes give mainly the N-alkylated products – nitrones [32]. Phase-transfer catalysis systems alkyl bromide (RBr)–10% aq. NaOH–$Oct_4N^+Br^-$–PhH or RBr–solid K_2CO_3–18-crown-6–PhH were used successfully by the authors for the O-alkylation of pyrrole oximes.

The ketone oximes **29** react with hexacyanocyclopropane (**30**) in the presence of metallic sodium and give 2-amino-4,4-di(alkylideneaminooxy)-1,5,6,6-tetracyano-3-azabicyclo[3.1.0]hex-2-enes **31** with yields of up to 74%. The further reaction of compound **31** with the oxime (RR'C=NOH) and sodium leads to the tricyclic derivatives of oximes **32** [33].



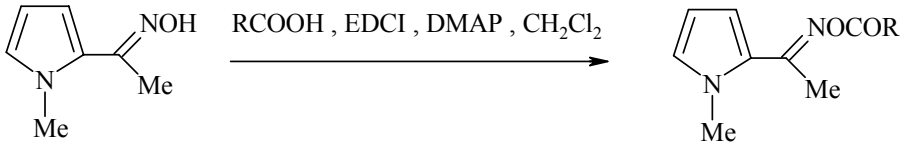
R, R' = Alk

The formamidoximes **33** react with aldehydes in the presence of DBU and give the tautomeric oximes **36** and **37** with yields of 29-68%. The products are formed through the intermediates **34** and **35** [34].



R = Me, CH_2Ph

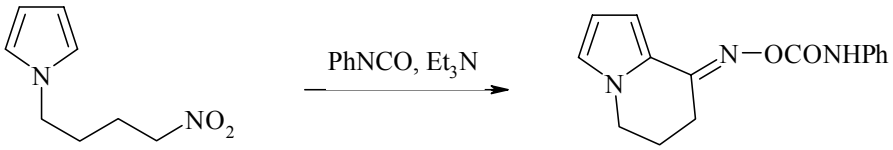
2-Acetylpyrrole O-acetyloxime was obtained by acylation of the oxime in the acetyl chloride–triethylamine system [35]. The pyrrole ketoxime **38** was also acylated by acids (RCOOH) in the 4-dimethylaminopyridine (DMAP)–3-(dimethylaminopropyl)-1-ethylcarbodiimide (EDCI)–methylene chloride system and gave the acyl derivatives **39** with yields of up to 78% [36].



38 **39**

R = Alk, Py

The pyrrole oxime carbamate (**41**) was obtained with a yield of 67% from N-(4-nitrobutyl)pyrrole (**40**) in the presence of phenyl isocyanate and triethylamine [37].



40 **41**

2.2. Reactions of Pyrrole Oxime Groups and Rings

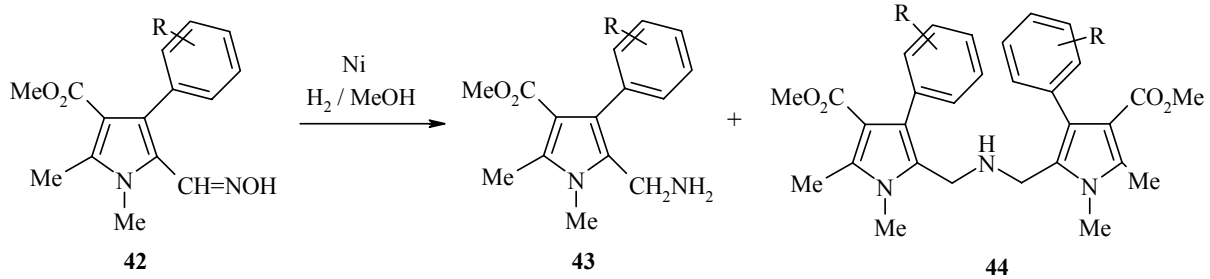
Recent advances in the chemistry of oxime derivatives were reviewed in [38]. In this section the chemistry of pyrrole oximes will mainly be discussed.

The dehydration of the oximes was described extensively in the review [39]. In addition, pyrrole oximes are easily transformed into the corresponding nitriles in the presence of acetic anhydride [5, 40-45], acetic anhydride–sodium acetate [46], *p*-toluenesulfonic acid–DMF [47], or epichlorohydrin–sodium methoxide [48].

Pyrrole aldoximes and ketoximes were hydrogenated to the corresponding derivatives of primary pyridine amines in the presence of Raney nickel in dioxane or ethanol [49], rhodium–aluminum oxide or Raney nickel in methanol [50], or platinum dioxide–acetic acid [51]. During hydrogenation with Raney nickel 4-aryl-5-formyl-3-methoxycarbonyl-1,2-dimethylpyrrole oximes (**42**) give a mixture of primary amines **43** (yields 32-40%) and dimeric products **44** (yields 30-35%) [52].

Pyrrole aldoximes were also reduced to primary amines in the presence of sodium amalgam [53].

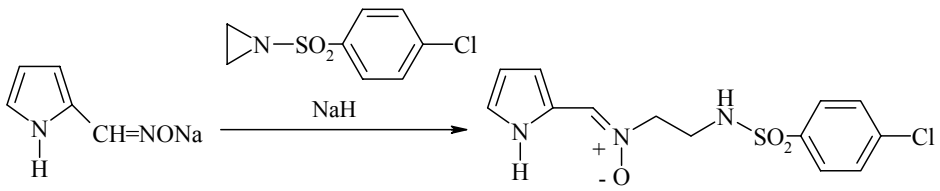
The transformation of 2-pyrrolecarbaldehyde oxime to the corresponding aldehyde (yield 88%) takes place readily in the presence of cetyltrimethylammonium permanganate [54].



42 **43** **44**

R = H, OAlk

It should also be noted that C-(2-pyrrolyl) N-[2-(4'-chlorophenylsulfonamido)ethyl] nitrone (**46**) can be generated by the reaction of the salt of the pyrrole oxime **45** with N-(4-chlorophenylsulfonyl)aziridine in the presence of sodium hydride [55].

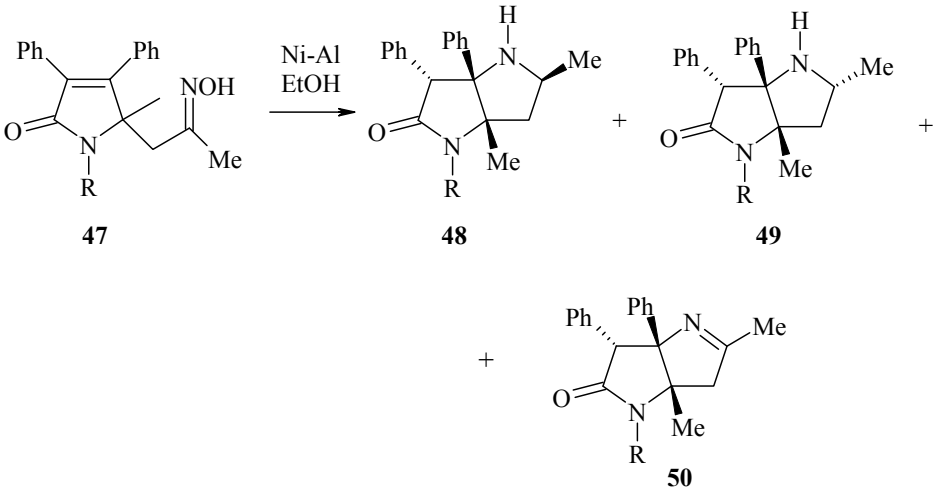


45 **46**

2.3. The Synthesis of New Heterocycles from Pyrrole Oximes

Advances in the synthesis of heterocyclic systems from oximes were reviewed in [56], and in this section we will dwell on the specific reactions of pyrrole oximes.

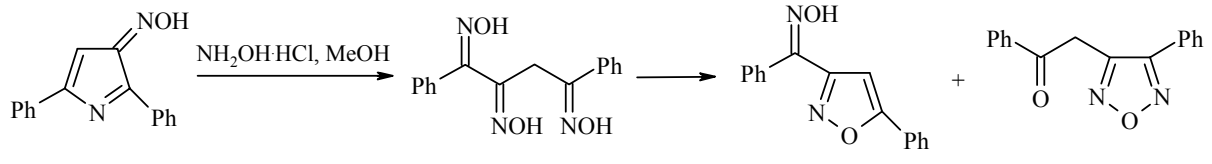
In the presence of Raney nickel, generated *in situ*, the oximes **47** give a mixture of several pyrrolo-[2,3-*b*]pyrrolones **48** and **49** (overall yield 16-41%) and **50** (yield 4-48%) [57].



47 **48** **49** **50**

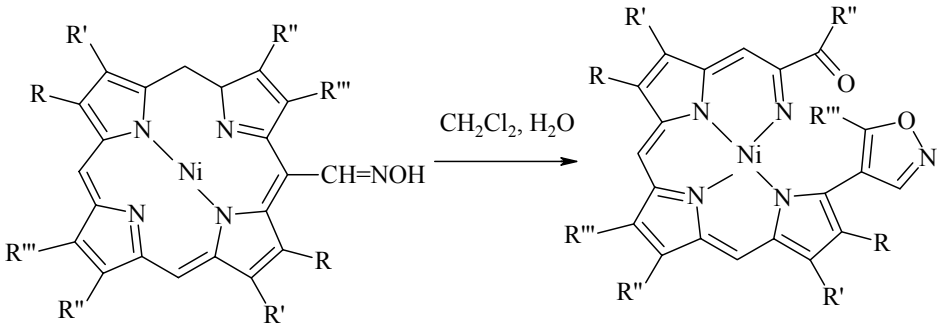
R = H, Alk

Several papers have been devoted to synthesis of the isoxazole derivatives of pyrrole oximes. The reaction of 3-hydroxyimino-2,5-diphenylpyrrole (**51**) with $NH_2OH \cdot HCl$ in methanol leads to the trioxime **52** and then to a mixture of 3-benzoyl-5-phenylisoxazole oxime (**53**) and 3-phenyl-4-phenylacetyl-1,2,5-oxadiazole (**54**). Under similar conditions 3-hydroxyimino-2-methyl-5-phenylpyrrole only gives 3-acetyl-5-phenylpyrrole oxime [58].



51 **52** **53** **54**

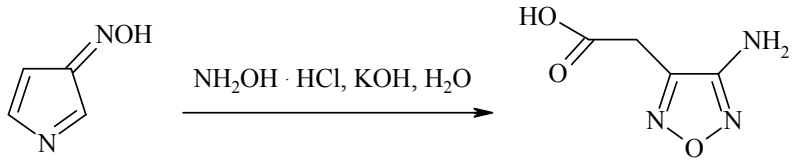
In the presence of methylene chloride and water the *meso*-formylporphyrin oximes **55** give the isoxazoles **56** with a yield of ~50% [59].



55 **56**

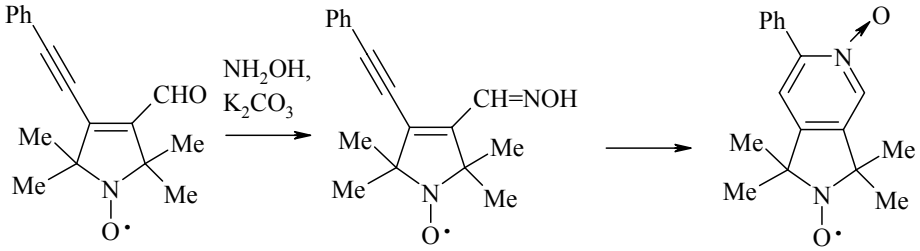
R, R', R", R"' = Alk

The sodium salt of the oxime **9** in the hydroxylamine hydrochloride–potassium hydroxide–water system gives the oxadiazole **57** with a yield of 78% [16].



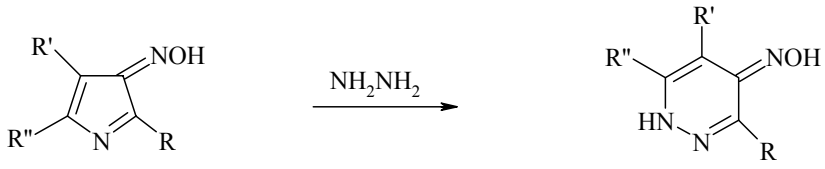
9 **57**

The nitroxyl radical of 2,2,3,3-tetramethyl-4-phenylethynyl-2,5-dihydro-1H-pyrrole-3-carbaldehyde (**58**) reacts in the hydroxylamine hydrochloride–potassium carbonate–ethanol–water system with the formation of the pyrrolo[3,4-*c*]pyridine radical **60** with a yield of 82%. The product **60** is formed through the oxime **59** as intermediate [60].



58 **59** **60**

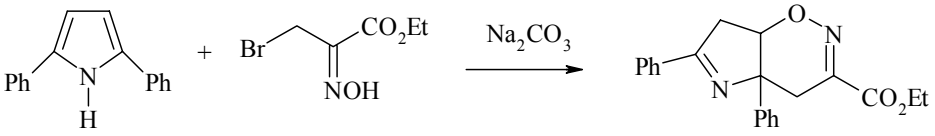
The hydroxyiminopyrroles **61** react with hydrazine with cleavage of the ring and form dihydropyridazine oximes **62** as the only product [61].



61 **62**

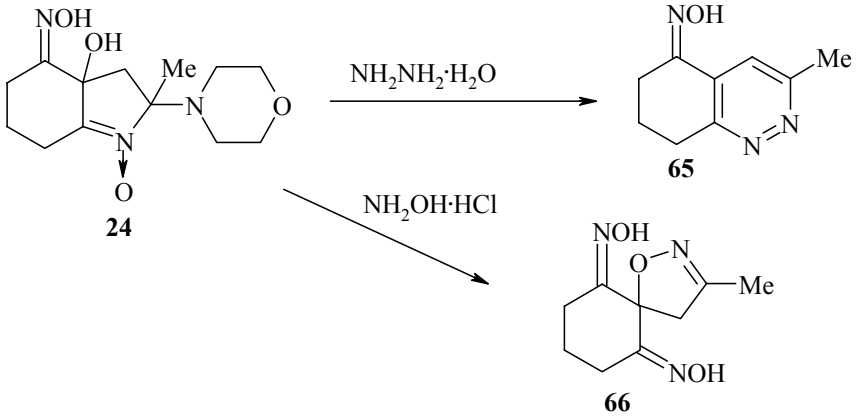
R, R', R" = H, Alk

Cyclization of 2,5-diphenylpyrrole (**63**) with the oxime of ethyl bromopyruvate in the sodium carbonate–methylene chloride system leads to ethyl 4a,6-diphenyl-4,4a,7,7a-tetrahydropyrrolo[2,3-*e*]-1,2-oxazine-3-carboxylate (**64**) with a yield of 36% [20].



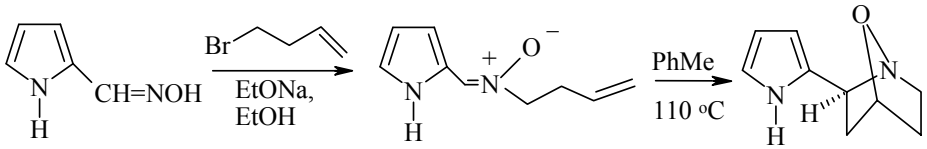
63 **64**

The reaction of compound **24** with hydrazine hydrate in acetic acid leads to tetrahydrocinnoline oxime **65** with a 32% yield. The reaction of compound **24** with hydroxylamine hydrochloride gives the spiro derivative of isoxazoline **66** (yield 75%) [22].



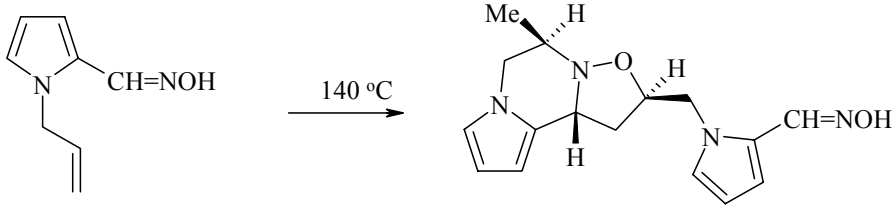
24 **65** **66**

The reaction of the *Z*-isomer of 2-pyrrolecarbaldehyde oxime **28** with 4-bromo-1-butene leads to C-2-pyrrolyl N-3-butenyl nitrone **67** with a yield of 43%. Intramolecular thermocycloaddition of **67** leads to *exo*-C-2-pyrrolyl-1-aza-7-oxabicyclo[2.1.1]heptane (**68**) with a yield of 49% [62].



28 **67** **68**

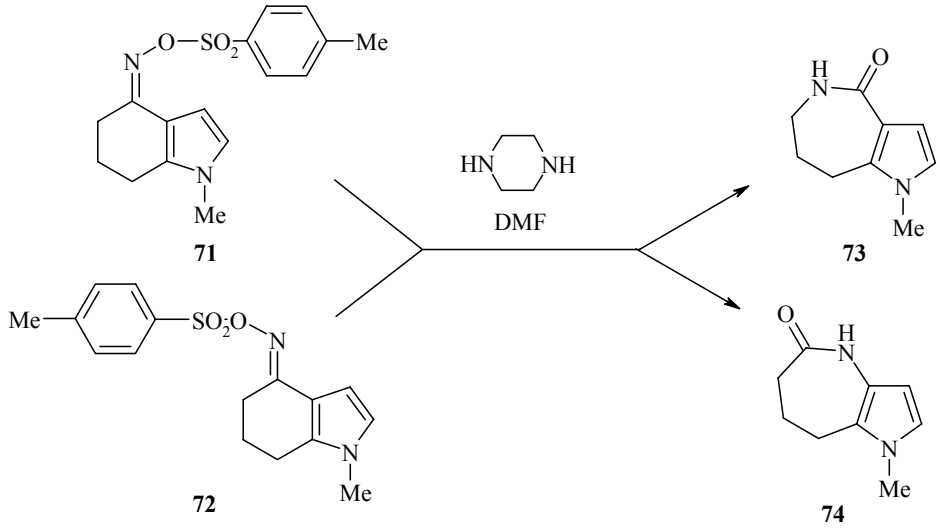
The thermal cyclization of 1-allyl-2-pyrrolecarbaldehyde (**69**) was described in [63]. In this case in boiling xylene the oxime **69** gives the dimer **70** with a yield of 52%.



69 **70**

2.4. The Beckmann Rearrangement of Pyrrole Oximes

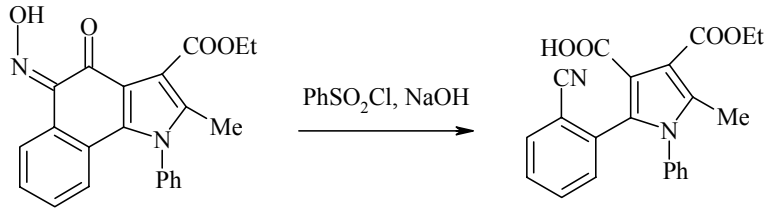
The Beckmann rearrangement is one of the most characteristic reactions of oximes. In the presence of phosphorus pentachloride [27] or hydrochloric acid [7] the *E*- and *Z*-isomers of pyrrole ketoximes give acylaminopyrroles. A simple method was also developed for the synthesis of the isomeric derivatives of pyrroloazepines **73** and **74** by the rearrangement of *syn*- and *anti*-4-tosyloxyimino-4,5,6,7-tetrahydroindoles **72** [64].



71 **72** **73** **74**

Reaction 1,3-dimethyl-1,5,6,7-tetrahydro-4H-indol-4-one oxime in polyphosphoric acid leads to 1,3-dimethyl-5,6,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4(1H)-one [65].

During the treatment of 3-ethoxycarbonyl-2-methyl-4,5-dioxobenzo[*g*]indole 5-monoxime (**75**) in an alkaline medium 5-(2-cyanophenyl)-3-ethoxycarbonyl-2-methyl-1-phenyl-4-pyrrolecarboxylic acid (**76**) was formed with a yield of 87% as a result of a Beckmann rearrangement [66].

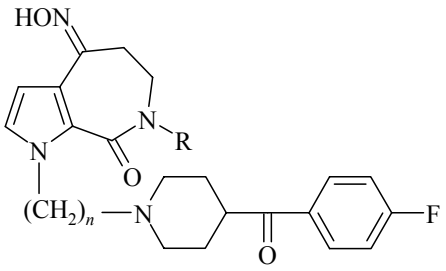


75 **76**

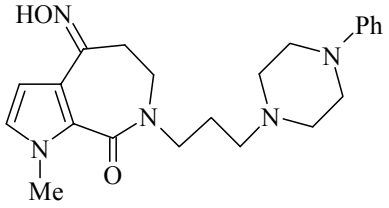
3. THE BIOLOGICAL ACTIVITY OF DERIVATIVES OF PYRROLE OXIMES

3.1. Action on the Cardiovascular System

The pyrrole oximes **77**, which exhibited anti-serotonin 5-HT_2-receptor activity, were proposed as antihypertensive and anticoagulation drugs [67, 68].



77

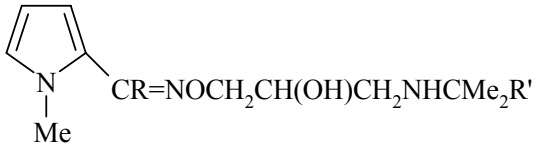


78

R = H, Alk; n = 3–5

The oxime derivatives of pyrroloazepines also exhibited vasodilating activity. Among these compounds the oxime **78** was mentioned as one of the most active [69, 70].

The blocking action of pyrrole O-(2-alkylamino-2-hydroxypropyl)oximes **79** on β-adrenoceptors has also been investigated [71].

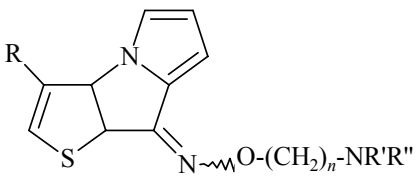


79

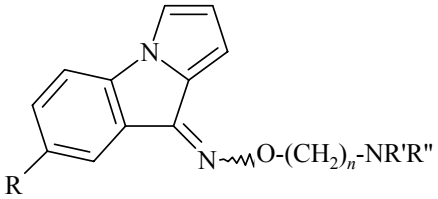
R = H, Alk, Ar; R' = H, Me

3.2. Antidepressant Activity

The tricyclic derivatives of the pyrrole oximes **80** and **81** exhibited high antidepressant activity [72, 73].



80

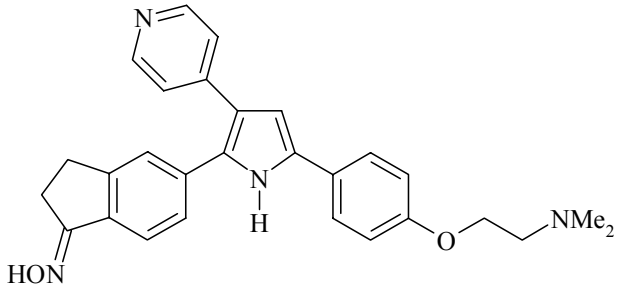


81

R,R',R'' = H, Alk; n = 2, 3

3.3. Analgesic and Anti-inflammatory Activity

Oxime derivatives containing pyrrole and pyridine fragments were studied as inhibitors of Raf kinase [74]. All these compounds can be used as analgesics and agents against migraine, and the oxime **82** is one of the most active.

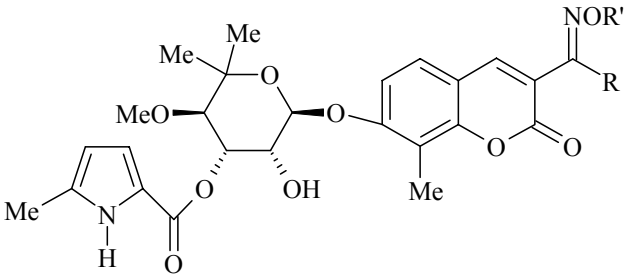


82

The O-lauroyl- and O-nicotinoyloximes of 1-methyl-2-acetylpyrrole possess anti-inflammatory activity [36].

3.4. Bactericidal Activity

Derivatives of 2-pyrrolecarbaldehyde oximes have exhibited high bactericidal activity [75-77]. The pyrrole oxime fragment also enters into the structure of certain penicillin antibiotics [78]. It was recently shown that ethers of pyrrole oximes **83** have high bactericidal activity against resistant strains of bacteria [79].

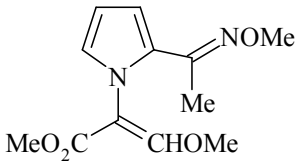


83

R, R' = Alk

3.5. Pyrrole Oximes as Fungicides and Plant Growth Regulators

The ethers of pyrrole oximes exhibit high fungicidal, insecticidal, and acaricidal activity [80]. Among these compounds, in particular, the ether **84** should be mentioned [81].



84

The ethers of pyrrole amidoximes [(pyrrolyl)C(NH_2·HCl)=NOCHR'CO_2R", where R', R" = alkyl] exhibited good herbicidal activity [82].

REFERENCES

1. P. Fournari and J. Tirouflet, *Bull. Soc. Chim. France*, 484 (1963).
2. P. Foumari, *Bull. Soc. Chim. France*, 488 (1963).
3. V. Carelli, M. Cardellini, and F. Morlacchi, *Ann. Chim.*, **57**, 1462 (1967); *Chem. Abstr.*, **69**, 2794 (1968).
4. J. Elguero, R. Jacquier, and B. Shimizu, *Bull. Soc. Chim. France*, 2823 (1969).
5. T. N. Borisova, A. E. Aliev, E. A. Sorokina, A. A. Sinitsina, and A. V. Varlamov, *Khim. Geterotsikl. Soedin.*, 534 (1995).
6. M. Boulouard, P. Dallemagne, and S. Rault, *J. Heterocycl. Chem.*, **34**, 1219 (1997).
7. V. Sprio, P. Madonia, and R. Caronia, *Ann. Chim.*, **49**, 169 (1959); *Chem. Abstr.*, **53**, 16105 (1959).
8. S. Umio, K. Kariyone, and K. Tanaka, Jpn. Patent 6725655; *Chem. Abstr.*, **69**, 51986 (1968).
9. E. Brunner, *Liebigs Ann. Chem.*, 1207 (1981).
10. G. P. Arsenault and S. F. MacDonald, *Can. J. Chem.*, **39**, 2043 (1961).
11. A. Etienne and Y. Correia, *Compt. Rend. Acad. Sci.*, **259**, 2660 (1964).
12. M. A. T. Rogers, US Patent 2382916; *Chem. Abstr.*, **40**, 904 (1946).
13. T. Aiello, *Gazz. Chim. Ital.*, **67**, 55 (1937).
14. T. Aiello and G. C. Vaccaro, *Gazz. Chim. Ital.*, **81**, 288 (1951).
15. J. M. Tedder and B. Vebster, *J. Chem. Soc.*, 1638 (1962).
16. B. Sheremetev, *Mendeleev Commun.*, 135 (1998).
17. T. Aiello and V. Spiro, *Gazz. Chim. Ital.*, **89**, 2526 (1959).
18. R. N. Loeppky, J. R. Outram, W. Tomasik, and J. M. Faulconer, *Tetrahedron Lett.*, **24**, 4271 (1983).
19. P. A. Wade and M. K. Pillay, *Gazz. Chim. Ital.*, **114**, 239 (1984).
20. T. L. Gilchrist and A. Lemos, *J. Chem. Soc. Perkin Trans. I*, 1391 (1993).
21. A. Treibs and F. Reitsam, *Chem. Ber.*, **90**, 777 (1957).
22. V. A. Samsonov, L. B. Volodarskii, I. Yu. Bagryanskaya, and Yu. V. Gatilov, *Khim. Geterotsikl. Soedin.*, 1055 (1996).
23. M. del K. Pina, V. A. Budylin, M. Rodriges, and Yu. G. Bundel', *Khim. Geterotsikl. Soedin.*, 185 (1989).
24. D. Crepaux and J.-M. Lehn, *Org. Magn. Reson.*, **7**, 524 (1975).
25. A. P. Terent'ev and A. N. Makarova, *Vestn. Mosk. Un-ta*, No. 4, 97 (1947); *Chem. Abstr.*, **42**, 1590 (1948).
26. A. P. Terent'ev and A. N. Makarova, *Vestn. Mosk. Un-ta*, No. 4, 101 (1947); *Chem. Abstr.*, **42**, 1590 (1948).
27. A. P. Terent'ev and A. N. Makarova, *Zh. Obshch. Khim.*, **21**, 270 (1951); *Chem. Abstr.*, **45**, 7105 (1951).
28. H. J. Anderson and S. J. Griffiths, *Can. J. Chem.*, **45**, 2227 (1967).
29. T. Marey and M. J. Arriau, *Compt. Rend. Acad. Sci.*, **212**, 850 (1971).
30. P. Foumari, M. Person, G. Watelle-Marion, and M. Delepine, *Comp. Rend. Acad. Sci.*, **253**, 1059 (1961).
31. T. Canals, J. L. Bernal, and V. Cerda, *Quim. Anal. (Barcelona)*, **2**, 131 (1983); *Chem. Abstr.*, **103**, 53609 (1985).
32. Q. Chen, X. Wang, and M. Meng, *Gaodeng Zuexiao Huaxue*, **8**, 911 (1987); *Chem. Abstr.*, **109**, 92369 (1988).
33. O. E. Nasakin, P. M. Lukin, E. V. Vershinin, O. V. Yashkanova, A. N. Lyshikov, Ya. G. Urman, S. V. Linderman, Yu. T. Struchkov, and A. Kh. Bulai, *Zh. Org. Khim.*, **31**, 370 (1995).
34. B. L. Booth, F. A. T. Costa, R. Pritchard, and M. F. Proenca, *Synthesis*, 1269 (2000).
35. G. Anderson, Jr. and M. M. Exner, *J. Org. Chem.*, **42**, 3952 (1977).

36. T. Katagi, H. Kataoka, K. Takahashi, T. Fujioka, M. Kunimoto, Y. Yamaguchi, M. Fujiwara, and T. Inoi, *Chem. Pharm. Bull.*, **40**, 2419 (1992).
37. W. Dehaen and A. Hassner, *J. Org. Chem.*, **56**, 896 (1991).
38. E. Abele and E. Lukevics, *Org. Prep. Proced. Int.*, **32**, 235 (2000).
39. W. Zhao, *Huaxue Shiji*, **19**, 273 (1997); *Chem. Abstr.*, **127**, 330917 (1997).
40. S. Umio, K. Kariyone, and K. Tanaka, Jpn. Patent 17743 (1967); *Chem. Abstr.*, **68**, 104974 (1968).
41. M. Artico, V. Nacci, G. Filacchioni, and F. Chimenti, *Ann. Chim.*, **58**, 1370 (1968); *Chem. Abstr.*, **70**, 57563 (1969).
42. K. Hattori, M. Hashimoto, and S. Umio, Jpn. Patent 6819939; *Chem. Abstr.*, **70**, 87564 (1969).
43. M. Artico, R. Giuliano, G. C. Porretta, and M. Scalzo, *Farmaco, Ed. Sci.*, **27**, 60 (1972).
44. D. M. Bailey, US Patent 3932458; *Chem. Abstr.*, **84**, 135463 (1976).
45. K. Yoshino, N. Seko, K. Yokota, K. Ito, and G. Tsukamoto, Eur. Patent 159677; *Chem. Abstr.*, **104**, 129898 (1986).
46. P. J. Brignell, E. Bullock, U. Eisner, B. Gregory, A. W. Johnson, and H. Williams, *J. Chem. Soc.*, 4819 (1963).
47. A. Antonowa and S. Hauptmann, *Z. Chem.*, **16**, 17 (1976).
48. M. Alvarez, R. Granados, D. Mauleon, C. Minguillon, and M. Perez, *An. Quim., Ser. C*, **80**, 258 (1984); *Chem. Abstr.*, **103**, 37307 (1985).
49. H. Adkins, I. A. Wolff, A. Pavlic, and E. Hutchinson, *J. Am. Chem. Soc.*, **66**, 1293 (1944).
50. I. Flament, P. Sonnay, and G. Ohloff, *Helv. Chim. Acta*, **60**, 1872 (1977).
51. G. M. Badger and A. D. Ward, *Aust. J. Chem.*, **17**, 649 (1964).
52. Mukherjee, M. Seth, and A. P. Bhaduri, *Indian J. Chem.*, **28B**, 496 (1989); *Chem. Abstr.*, **112**, 76858 (1990).
53. S. N. Prasad and R. Rapers, *Nature*, **175**, 629 (1955).
54. P. Vankar, R. Rathore, and S. Chandrasekaran, *J. Org. Chem.*, **51**, 3063 (1986).
55. H. Ali Dondas, J. E. Cummins, R. Grigg, and M. Thornton-Pett, *Tetrahedron*, **57**, 7951 (2001).
56. E. Abele and E. Lukevics, *Heterocycles*, **53**, 2285 (2000).
57. K. Kascheres and R. A. F. Rodrigues, *Tetrahedron*, **52**, 12919 (1996).
58. T. Ajello and S. Cusmano, *Gazz. Chim. Ital.*, **70**, 127 (1940).
59. G. V. Ponomarev, Yu. V. Morozova, and D. V. Yashunskii, *Khim. Geterotsikl. Soedin.*, 277 (2001).
60. T. Kalai, M. Balog, J. Jeko, W. L. Hubbell, and K. Hideg, *Synthesis*, 2365 (2002).
61. T. Aiello, V. Spiro, and G. Vaccaro, *Gazz. Chim. Ital.*, **89**, 2232 (1959).
62. Q.-H. Chen, X.-Z. Yu, T.-Y. Zhang, and X.-B. Jia, *Acta Chim. Sinica (Engl. Ed.)*, 176 (1989); *Chem. Abstr.*, **112**, 158107 (1990).
63. R. Grigg, J. Markandu, T. Perrior, S. Surendrakumar, and W. J. Warnock, *Tetrahedron Lett.*, **31**, 559 (1990).
64. P. Stoll and F. Troxler, *Helv. Chim. Acta*, **51**, 1864 (1968).
65. V. Bardakos and W. Sucrow, *Chem. Ber.*, **111**, 1780 (1978).
66. A. P. Stankyavichus, L. M. M. Stankyavichene, and P. B. Terent'ev, *Khim. Geterotsikl. Soedin.*, 1462 (1999).
67. A. Mizuno, N. Inomata, M. Miya, T. Kamei, M. Shibata, T. Tatsuoka, M. Yoshida, C. Takiguchi, and T. Miyazaki, *Chem. Pharm. Bull.*, **47**, 246 (1999).
68. A. Mizuno, A. Ogata, T. Kamei, M. Shibata, T. Shimamoto, Y. Hayashi, K. Nakanishi, C. Takiguchi, N. Oka, and N. Inomata, *Chem. Pharm. Bull.*, **48**, 623 (2000).
69. A. Mizuno, H. Cho, M. Hamaguchi, and T. Tatsuoka, Eur. Patent 441349; *Chem. Abstr.*, **115**, 232223 (1991).

70. A. Mizuno, M. Miya, N. Inomata, T. Tatsuoka, and T. Ishihara, PCT Int. Appl. WO Pat. 9303032; *Chem. Abstr.*, **119**, 180819 (1993).
71. R. Granados, D. Mauleon, and M. Perez, *Ann. Quim. Ser. C*, **79**, 275 (1983); *Chem. Abstr.*, **102**, 62011 (1985).
72. S. Rault, M. Robba, J.-C. Lancelot, H. Prunier, P. Renard, B. Pfeiffer, B. Guardiola-Lemaitre, and M.-C. Rettori, Eur. Patent 718299; *Chem. Abstr.*, **125**, 142700 (1996).
73. I. Baglin, C. Daveu, J. C. Lancelot, R. Bureau, F. Dauphin, B. Pfeiffer, P. Renard, P. Delagrange, and S. Rault, *Bioorg. Med. Chem. Lett.*, **11**, 453 (2001).
74. D. K. Dean, A. Naylor, A. K. Takle, and D. M. Wilson, PCT Int. Appl. WO Pat. 0322833; *Chem. Abstr.*, **138**, 255102 (2003).
75. K. Hattori and M. Hashimoto, Jpn. Patent 4662 (1967); *Chem. Abstr.*, **67**, 90663 (1967).
76. D. M. Bailey, US Patent 3883516; *Chem. Abstr.*, **83**, 79072 (1975).
77. M. M. Hania, *Asian J. Chem.*, **14**, 1074 (2002); *Chem. Abstr.*, **137**, 247572 (2002).
78. Glaxo Laboratories Ltd., French Patent 2204404; *Chem. Abstr.*, **81**, 169535 (1974).
79. P. Laurin, D. Ferroud, M. Klich, C. Dupuis-Hamelin, P. Mauvais, P. Lassaigne, A. Bonnefoy, and B. Musicki, *Bioorg. Med. Chem. Lett.*, **9**, 2079 (1999).
80. P. Gerdes, H. Gayer, S. Hillebrand, U. Heinemann, B.-W. Krueger, A. Mauler-Machnik, U. Wachendorff-Neumann, G. Haenssler, K. Stenzel, and P. Loesel, Ger. Patent 19929086; *Chem. Abstr.*, **134**, 56561 (2001).
81. M. Clough, C. R. A. Godfrey, P. J. De Fraine, and B. K. Snell, Eur. Patent 718299; *Chem. Abstr.*, **109**, 190240 (1988).
82. D. Farge, J. Leboul, Y. Le Goff, and G. Poiget, Ger. Patent 2640484; *Chem. Abstr.*, **87**, 39141 (1977).