N-[2(1H)-PERIMIDINYLMETHYL]AZINIUM SALTS. THEIR SYNTHESIS AND REACTION WITH ELECTROPHILES

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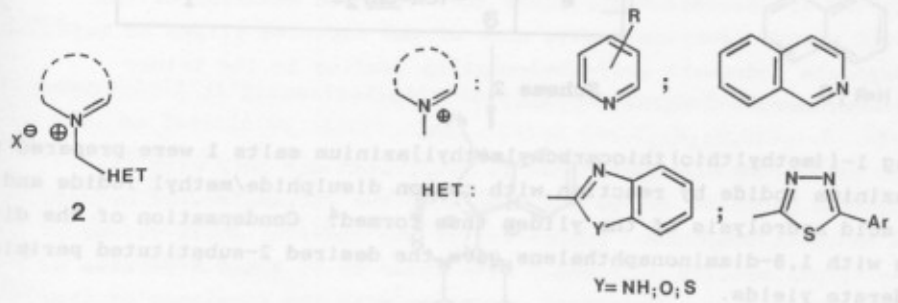
Abstract - A synthesis of new 2-substituted 1H-perimidines by the reaction of 1-[(methylthio)thiocarbonylmethyl]azinium salts and 1,8-diaminonaphthalene is described. Reaction of these perimidine derivatives with several electrophiles is also reported

Reactions of 1-[(methylthio)thiocarbonylmethyl]azinium salts 1 with 1,2-dinucleophilic reagents have allowed convenient preparation of a series of N-(five-membered heteroarylmethyl)azinium 2.[1-5] The interesting activity as antibacterials that we found in some of these compounds stimulated us to try the synthesis of new series of unknown N-(heteroarylmethyl)azinium salts for biological screening.

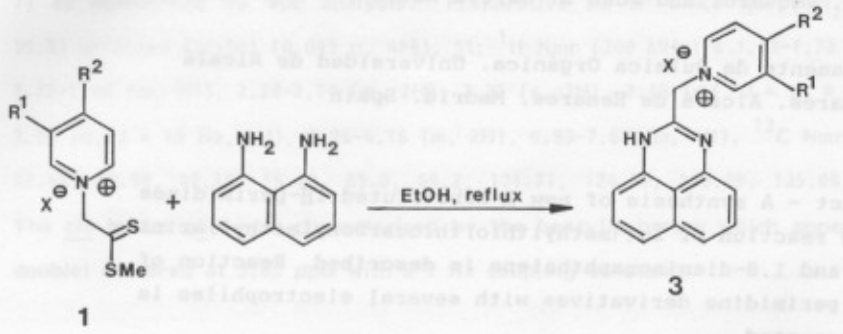


Scheme 1

In this respect we focused our attention on the condensed heterocycle perimidine, one of the few azines that exhibits simultaneously the characteristics of both Π-deficient and Π-excessive heteroaromatic systems[6,7] together with a variety of practical applications of some of its derivatives as dyes,[6-8] analytical reagents,[9,10] antiulcer[11] and antitumor agents,[12] depressants and stimulants of the central nervous system,[13] antihelminthics[14] and antifungals.[15]

The majority of the perimidines reported since 1909, when the first synthesis was described by Sachs,[16] has been prepared by the reaction of 1,8-diaminonaphthalene and various dielectrophilic reagents mainly containing a carbonyl group.[8]

To our knowledge dithio esters have not been previously tested as 1,1-dielectrophilic reagents in perimidine synthesis probably because of the relative difficulties associated with their preparation. In this paper we report the simple synthesis of 2-substituted perimidines 3 using dithio esters as dielectrophilic reagents towards 1,8-diaminonaphthalene.

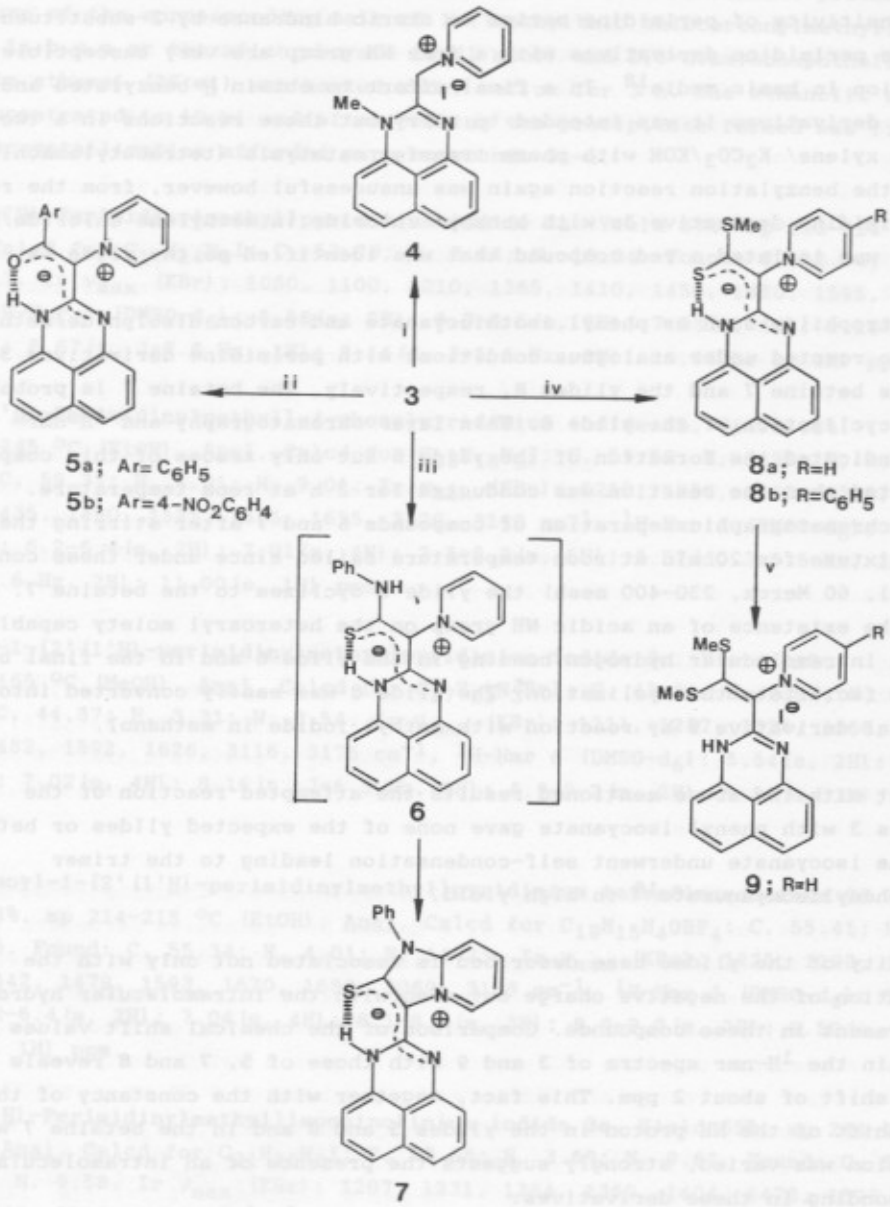


	R^1	R^2	X
a	H	H	I
b	H	C_6H_5	I
c	Br	H	I
d	$CONH_2$	H	BF_4
e	$-(CH{=}CH)_2-$		I

Scheme 2

The starting 1-[(methylthio)thiocarbonylmethyl]azinium salts 1 were prepared from 1-phenacylazinium iodide by reaction with carbon disulphide/methyl iodide and subsequent acid hydrolysis of the ylides thus formed[4]. Condensation of the dithio esters 1a-e with 1,8-diaminonaphthalene gave the desired 2-substituted perimidines 3a-e in moderate yields.

In general, the perimidine derivatives obtained were rather hard to deal with. Thus attempted N-acylation with benzoyl chloride in acetonitrile/pyridine resulted in partial recovery of starting material under several conditions. N-Alkylation with methyl iodide also failed to give the desired derivative when bases such as KOH in toluene-chlorobenzene, and NaH in dimethylformamide or dimethoxyethane were used under nitrogen, and an extensive decomposition of the starting material was observed. When Na_2CO_3 was employed in acetone, decomposition also occurred but an appreciable amount (12%) of the 1-methylperimidine derivative 4 was isolated. A better yield (55%) was obtained when the reaction was carried out in degasified dimethyl sulfoxide. However, when these conditions were used for alkylation with benzyl chloride no detectable amount of the alkylated derivative was obtained even after 24 h at 80 °C, and no starting material was recovered.



Scheme 3. i, CH_3I/Na_2CO_3/DMSO, room temp.; ii, $ArCOCl/K_2CO_3$(aq., 50%)/CH_2Cl_2, room temp.; iii, $PhN{=}C{=}S/K_2CO_3$(aq., 50%)/CH_2Cl_2, room temp.; iv, $CS_2/CH_3I/K_2CO_3$ (aq.,50%) room temp.; v, CH_3I/CH_3OH, room temp.

One possible reason for the failure of these N-substitution reactions may be the extreme sensitivity of perimidine series to steric hindrance by 2-substituents.[8] Furthermore perimidine derivatives with a free NH group are very susceptible to autooxidation in basic media.[18] In a final effort to obtain N-benzylated and N-acylated derivatives it was intended to carry out these reactions in a two-phase system. In xylene/ K_2CO_3/KOH with phase transfer catalysis (tetrabutylammonium sulphate) the benzylation reaction again was unsucessful however, from the reaction of the perimidine derivative 3a with benzoyl chloride in methylene chloride/K_2CO_3 (aq., 50%) was isolated a red compound that was identified as the ylide 5a.

Other electrophiles such as phenyl isothiocyanate and carbon disulphide/methyl iodide also reacted under analogous conditions with perimidine derivatives 3 to give the betaine 7 and the ylides 8, respectively. The betaine 7 is probably formed by cyclization of the ylide 6. Thin layer chromatography and ^{1}H-nmr analysis indicated the formation of the ylide 6 but only traces of this compound were detected when the reaction was conducted for 3 h at room temperature. Attempted chromatographic separation of compounds 6 and 7 after stirring the reaction mixture for 20 min at room temperature failed since under these conditions (silica gel, 60 Merck, 230-400 mesh) the ylide 6 cyclizes to the betaine 7. In this respect, the existence of an acidic NH group on the heteroaryl moiety capable of forming an intramolecular hydrogen bonding in the ylide 6 and in the final betaine 7 seems to facilitate the cyclization.[5] The ylide 8 was easily converted into ketene dithioacetal derivative 9 by reaction with methyl iodide in methanol.

In contrast with the above mentioned results the attempted reaction of the perimidines 3 with phenyl isocyanate gave none of the expected ylides or betaines. Instead the isocyanate underwent self-condensation leading to the trimer N,N,N-triphenylisocyanurate[18] in high yield.

The stability of the ylides here described is associated not only with the delocalization of the negative charge but also with the intramolecular hydrogen bonding present in these compounds. Comparison of the chemical shift values of the NH proton in the ^{1}H-nmr spectra of 3 and 9 with those of 5, 7 and 8 reveals a downfield shift of about 2 ppm. This fact, together with the constancy of the chemical shift of the NH proton in the ylides 5 and 8 and in the betaine 7 when the concentration was varied, strongly suggests the presence of an intramolecular hydrogen bonding in these derivatives.

EXPERIMENTAL

Melting points were determined on a Buchi SMP-20 and are uncorrected. Ir spectra were recorded on Perkin Elmer 700 or 1310 Spectrophotometers. ^{1}H-Nmr spectra were obtained on Bruker WP 60 and Varian FT-80A instruments using TMS as internal reference.

Preparation of N-[2(1H)-perimidinylmethyl]azinium salts 3; General procedure: A mixture of the corresponding salt of 1-[(methylthio)thiocarbonylmethyl]azinium iodide **1a,b,c,e** or tetrafluoroborate **1d** (1 mmol) and 1,8-diaminonaphthalene (1.5 mmol) in ethanol (25 ml) was heated under reflux for 3 h. The ethanolic solution was concentrated to 10 ml and after cooling the precipitate formed was filtered off. Recrystallization afforded pure compounds **3a-e**.

1-[2'(1'H)-Perimidinylmethyl]pyridinium iodide 3a. Yield 57%. mp 213-214 °C (MeOH). Anal. Calcd for $C_{17}H_{14}N_3I$: C, 52.73; H, 3.64; N, 10.84. Found: C, 52.84; H, 3.77; N, 11.17. Ir ν_{max} (KBr): 1050, 1100, 1210, 1365, 1410, 1450, 1480, 1595, 1620, 3200 cm^{-1}. ^{1}H-Nmr δ (DMSO-d_6): 5.58(s, 2H); 6.0-6.6(m, 2H); 7.03(s, 4H); 8.10(t, J=6.5 Hz, 2H); 8.67(t, J=7.6 Hz, 1H); 9.14(d, J=5.6 Hz, 2H); 11.06(br s, 1H) ppm.

1-[2'(1'H)-Perimidinylmethyl]-4-phenylpyridinium iodide 3b. Yield 86%. mp 244-245 °C (EtOH). Anal. Calcd for $C_{23}H_{18}N_3I$: C, 59.62; H, 3.92; N, 9.07. Found: C, 59,37; H, 4.01; N, 9.01. Ir ν_{max} (KBr): 1210, 1230, 1290, 1370, 1410, 1435, 1480, 1525, 1595, 1625, 3120, 3180 cm^{-1}. ^{1}H-Nmr δ (DMSO-d_6): 5.54 (s, 2H); 6.2-6.4(m, 2H); 7.01(s, 4H); 7.6-8.2(m, 5H); 8.57(d, J=6.6 Hz, 2H); 9.07 (d, J=6.6 Hz, 2H); 11.00(s, 1H) ppm.

3-Bromo-1-[2'(1'H)-perimidinylmethyl]pyridinium iodide 3c. Yield 52%. mp 164-165 °C (MeOH). Anal. Calcd for $C_{17}H_{13}N_3BrI$: C, 43.81; H, 2.81; N, 9.01. Found: C, 44.37; H, 3.31; N, 8.54. Ir ν_{max} (KBr): 1211, 1287, 1334, 1366, 1411, 1450, 1482, 1592, 1626, 3116, 3176 cm^{-1}. ^{1}H-Nmr δ (DMSO-d_6): 5.54(s, 2H); 6.2-6.4 (m, 2H); 7.02(s, 4H); 8.16(t, J=6.3 Hz, 1H); 8.9-9.2(m, 2H); 9.50(s, 1H); 10.99(s, 1H) ppm.

3-Carbamoyl-1-[2'(1'H)-perimidinylmethyl]pyridinium tetrafluoroborate 3d. Yield 64%. mp 214-215 °C (EtOH). Anal. Calcd for $C_{18}H_{15}N_4OBF_4$: C, 55.41; H, 3.87; N, 14.36. Found: C, 55.34; H, 4.01; N, 14.23. Ir ν_{max} (KBr): 1225, 1290, 1369, 1410, 1442, 1479, 1593, 1620, 1683, 3069, 3153 cm^{-1}. ^{1}H-Nmr δ (DMSO-d_6): 5.62(s, 2H); 6.2-6.4(m, 2H); 7.04(s, 4H); 8.1-8.6(m, 3H); 8.9-9.2(m, 2H); 9.52(s, 1H); 11.02(s, 1H) ppm.

2-[2'(1'H)-Perimidinylmethyl]isoquinolinium iodide 3e. Yield 69%. mp 244-245 °C (MeOH). Anal. Calcd for $C_{21}H_{16}N_3I$: C, 57.68; H, 3.69; N, 9.61. Found: C, 57.42; H, 3.84; N, 9.58. Ir ν_{max} (KBr): 1207, 1231, 1284, 1369, 1404, 1478, 1593, 1624, 3003, 3043, 3118, 3177 cm^{-1}. ^{1}H-Nmr δ (DMSO-d_6): 5.66(s, 2H); 6.2-6.4(m, 2H); 7.02(s, 4H); 8.3-8.7(m, 6H); 10.16(s, 1H); 11.03(s, 1H) ppm.

1-[2'(1'-Methylperimidinyl)methyl]pyridinium iodide 4. A suspension of the perimidine derivative **3a** (0.39 g, 1 mmol), anhydrous sodium carbonate (0.16 g, 1.5 mmol) and methyl iodide (0.21 g, 1.5 mol) in degasified DMSO (5 ml) was stirred at room temperature for 4 h. The precipitate formed was filtered off, washed with water (3x5 ml) and recrystallized from ethanol to give the title compound (0.22 g, 55%). mp 246-247°C. Anal. Calcd for $C_{18}H_{16}N_3I$: C, 53.88; H, 4.02; N, 10.47. Found: C, 53.96; H, 4.25; N, 10.64. Ir ν_{max} (KBr): 1326,

1380, 1405, 1484, 1590, 1623, 1631, 3038 cm^{-1}. ^{1}H-Nmr δ (DMSO-d_6): 3.26(s,3H); 5.98(s, 2H); 6.2-6.5(m, 2H); 7.16 (s, 4H); 8.22(t, J=6.5 Hz, 2H); 8.71(t, J=7.6 Hz, 1H); 8.98(d, J=5.5 Hz, 2H) ppm.

Preparation of the ylides 5a,b. General procedure: To a mixture of the perimidine derivative **3a** (2 mmol), a solution of 50% potassium carbonate (20 ml) and methylene chloride (20 ml) was added dropwise the corresponding acyl chloride (2.4 mmol) and the mixture was stirred at room temperature for 20 min. The reaction mixture was extracted with methylene chloride (5x20 ml) and the organic phase was dried over magnessium sulphate and evaporated to give a solid residue that was purified by chromatography on silica gel (60 Merck, 230-400 mesh) using methylene chloride as eluent. Recrystallization gave analytical samples of **5a,b**.

1-(Benzoyl)-1-[2'(1'H)-perimidinyl]]pyridinium methylide 5a. Yield 30%. mp 254-256 °C (Acetone). Anal. Calcd for $C_{24}H_{17}N_3O$: C, 79.32; H, 4.71; N, 11.56; Found: C, 78.99; H, 4.71; N, 11.56. Ir ν_{max} (KBr): 1265, 1330, 1365, 1403, 1439, 1472, 1515, 1568, 1621, 3046, 3112 cm^{-1}. ^{1}H-Nmr δ (DMSO-d_6): 6.0-6.3(m, 2H); 6.92(s, 4H); 7.15 (s, 5H); 7.87(t, J=6.4 Hz, 2H); 8.40(t, J=7.0 Hz, 1H); 8.89(d, J=5.3 Hz, 2H); 13.08 (s, 1H) ppm.

1-(4'-Nitrobenzoyl)-1-[2'(1'H)-perimidinyl]pyridinium methylide 5b. Yield 28%. mp 263-265 °C (Acetone). Anal. Calcd for $C_{24}H_{16}N_4O_3$: C, 70.58; H, 3.95; N, 13.72. Found: C, 70.52; H, 4.20; N, 14.02. Ir ν_{max} (KBr): 1266, 1341, 1368, 1412, 1478, 1521, 1568, 1624, 3049, 3119 cm^{-1}. ^{1}H-Nmr δ (DMSO-d_6): 6.0-6.3(m, 2H); 6.88 (s, 4H); 7.36(d, J=8.5 Hz, 2H); 7.7-8.0(m, 4H); 8.38(t, J=7.4 Hz, 1H); 8.89(d, J=5.5 Hz, 2H); 12.74(s, 1H) ppm.

3-[2'(1'H)-Perimidinyl]-1-phenylimidazo[1,2-a]pyridinium-2-thiolate 7: To a mixture of the perimidine derivative **3a** (0.78 g, 2 mmol), 50% potassium carbonate (20 ml) and methylene chloride (20 ml), phenyl isothiocyanate (0.32 g, 2.4 mmol) was added and the mixture was stirred 3 h at room temperature. The reaction mixture was extracted with methylene chloride (5x20 ml) and the combined organic extracts were dried over magnessium sulphate and evaporated to give a solid residue that was washed with ether and recrystallized to give pure betaine **7** (0.52 g, 66%). mp 314-315 °C (ethyl acetate-methylene chloride). Anal. Calcd for $C_{24}H_{16}N_4S$: C, 73.45; H, 4.11; N, 14.27. Found: C, 73.56; H, 4.23; N, 13.97; Ir ν_{max} (KBr): 1303, 1361, 1433, 1505, 1586, 1629, 3041, 3105 cm^{-1}. ^{1}H-Nmr δ (DMSO-d_6): 6.2-7.7(m, 14H); 10.58 (d, J=6.7 Hz, 1H); 13.03(s, 1H) ppm.

Preparation of the ylides 8a,b. General procedure: To a suspension of the corresponding perimidine derivative **3a,b** (2 mmol) in carbon disulphide (20 ml) and a solution of 50% potassium carbonate (20 ml), methyl iodide (0.57 g, 4 mmol) was added and the mixture was stirred at room temperature (3 h for **8a** and 48 h for **8b**). The precipitate obtained was filtered off, washed with water until neutral and recrystallized to give pure ylides **8a,b**.

1-[[(Methylthio)thiocarbonylmethyl][2'(1'H)-perimidinyl]]pyridinium methylide 8a. Yield: 50%. mp 214-215 °C (EtOH). Anal. Calcd for $C_{19}H_{15}N_3S_2$: C, 65.30; H, 4.33; N, 12.02. Found: C, 65.33; H, 4.55; N, 12.38. Ir ν_{max} (KBr): 1195, 1276, 1331, 1365, 1406, 1449, 1467, 1588, 1624, 3040, 3110 cm^{-1}. ^{1}H-Nmr δ (DMSO-d_6): 2.35 (s, 3H); 5.9-6.3 (m, 2H); 6.96 (s, 4H); 8.15 (t, J=6.6 Hz, 2H); 8.70 (t, J=7.7 Hz, 1H); 8.97 (d, J=5.4 Hz, 2H); 13.83 (s, 1H) ppm.

1-[[(Methylthio)thiocarbonylmethyl][2'(1'H)-perimidinyl]]-4-phenylpyridinium methylide 8b. Yield 48%. mp 260-261 °C (Acetone). Anal. Calcd for $C_{25}H_{19}N_3S_2$: C, 70.56; H, 4.50; N, 9.87; Found: C, 70.67; H, 4.23; N, 10.15. Ir ν_{max} (KBr): 1074, 1193, 1267, 1328, 1366, 1416, 1554, 1587, 1624, 3040, 3110 cm^{-1}. ^{1}H-Nmr δ (DMSO-d_6): 2.38 (s, 3H); 6.1-6.3 (m, 2H); 6.92 (s, 4H); 7.5-7.7 (m, 3H); 8.0-8.2 (m, 2H); 8.49 (d, J=6.4 Hz, 2H); 8.95 (d, J=6.4 Hz, 2H); 13.53 (s, 1H) ppm.

1-[2',2'-Bis(methylthio)-1'-[2''-(1''H)-perimidinyl]]ethenylpyridinium iodide 9: To a mixture of the ylide **7a** (0.69 g, 2 mmol) in methanol (20 ml), methyl iodide (1.13 g, 8 mmol) was added and the mixture was stirred at room temperature for 7 h. The solvent and the excess of methyl iodide were eliminated under reduced pressure and the oily residue obtained was triturated with ethyl acetate giving a red solid which was purified by recrystallization from ethyl acetate to give the title compound (0.67 g, 68%). mp 197-198 °C (ethyl acetate). Anal. Calcd for $C_{20}H_{18}N_3IS_2$: C, 48.88; H, 3.69; N, 8.55. Found: C, 48.91; H, 3.91; N, 8.49. Ir ν_{max} (KBr): 1158, 1195, 1274, 1369, 1406, 1423, 1467, 1525, 1592, 1626, 3041, 3100, 3170 cm^{-1}. ^{1}H-Nmr δ (DMSO-d_6): 2.40 (s, 3H); 2.61 (s, 3H); 6.3-6.5 (m, 2H); 7.04 (s, 4H); 8.32 (t, J=6.6 Hz, 2H); 8.81 (t, J=7.8 Hz, 1H); 9.23 (d, J=5.6 Hz, 2H); 10.90 (s, 1H) ppm.

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REFERENCES

1. J. Alvarez-Builla, F. Sanchez-Trillo, and G. Quintanilla, J. Chem. Soc., Perkin Trans I, 1984, 2693.

2. J. Alvarez-Builla, E. Galvez, A. M. Cuadro, F. Florencio, and S. Garcia-Blanco, J. Heterocycl. Chem., 1987, 24, 917.

3. A. M. Cuadro, J. Alvarez-Builla, and J. J. Vaquero, Heterocycles, 1988, 27, 1233.

4. A. M. Cuadro, J. Alvarez-Builla, and J. J. Vaquero, Heterocycles, 1989, 29, 57.

5. R. Carceller, J. L. Garcia-Navio, M. L. Izquierdo, J. Alvarez-Builla, J. Sanz-Aparicio, and F. Florencio, Heterocycles, 1989, 29, 1877.

6. J. H. Richmond, "Six-membered Heterocyclic Nitrogen Compounds with Three Condensed Rings", Academic Press, New York, 1958, p. 518.

7. A. F. Pozharskii and V. V. Dal'nikovskaya, Russiam Chemical Reviews, 1981, 50, 816.

8. F. Urseanu, I. D. Popescu, V. Moise, and I. Ulad, Ind. Usoara. Text., Tricotaje, Confectii Text., 1983, 34, 542 (Chem. Abstr., 1984, 101, 92764g).

9. W. L. Stephen, Anal. Chim. Acta, 1970, 50, 413.

10. N. Ishikawa and T. Muramatsu, Nippon Kagaku Kaishi, 1973, 3, 563 (Chem. Abstr., 1973, 78, 147873).

11. U. Burkhardt and S. Johne, Ger.(East) DD, 1984, 232,917 (Chem. Abstr., 1986, 105, 226625f).

12. J. M. Herbert, P. D. Woodgate, and W. A. Denny, J. Med. Chem., 1987, 30, 2081.

13. V. V. Dal'nikovskaya, I. V. Komissarov, A. F. Pozharskii, and I. T. Filippov, Khim.-Farm. Zh., 1978, 12, 85 (Chem. Abstr., 1979, 90, 87380d).

14. A. F. Bekhli, S. K. Drusuyatskaya, B. V. Lopatin, A. S. Naidenova, and O. P. Zelya, Khim.-Farma. Zh., 1979, 13, 54 (Chem. Abstr., 1979,90, 168544n).

15. G. Kempter, "Advances in Pesticide Chemistry", Pergamon Press, Oxford, 1979, part II, p.75.

16. F. Sachs, Annalen, 1909, 365, 53.

17. V. Paragamian, M. B. Baker, B. M. Puma, and J. Reale, J. Heterocycl. Chem., 1968, 591.

18. H. Ulrich, "Cycloaddition Reactions of Heterocumulenes", Academic Press, New York, 1967, p. 128.

19. H. Ulrich and R. Richter, "Neuere Methoden der Präparativen Chemie", Verlag Chemie, Weinheim, Vol. VI, 1970, p. 267.

20. W. Broda, E. V. Dehmlow, and H. J. Schulz, Isr. J. Chem., 1985, 26, 222.

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