REACTIONS OF AN o-QUINONE MONOIMIDE WITH PYRROLES*

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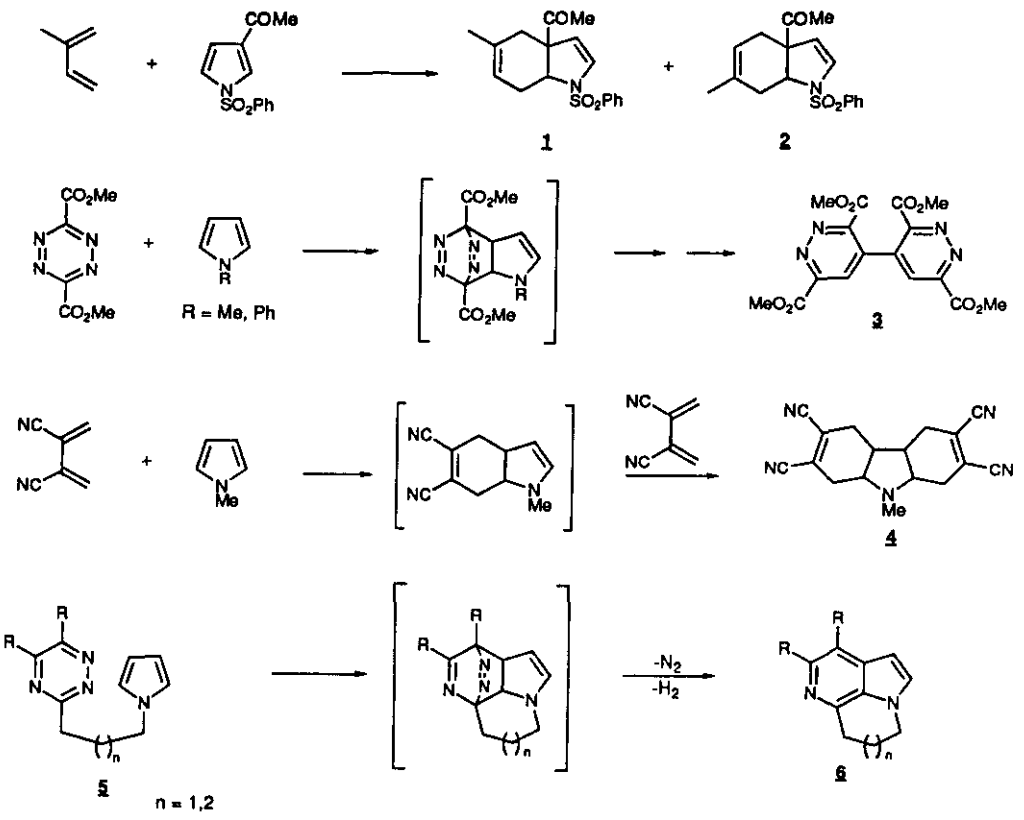
Abstract - The o-quinone monoimide (**7**) undergoes inverse electron demand Diels-Alder reactions with 1-benzenesulfonyl- and 1-carbomethoxypyrroles. The initial adduct (**9**), formed when **7** interacts with 1-carbomethoxypyrrole, underwent a further cycloaddition with **7** yielding a 2:1 adduct (**10**). Similar 2:1 adducts result when **7** reacts with 1-methyl-2-acetyl- and 1-methyl-2-carbomethoxypyrroles. Compound (**7**) reacts formally as an electrophile when it is admixed with 1-methyl- and 1-methyl-3-acetylpyrroles to give substituted pyrroles.

Pyrroles usually react as dienes in Diels-Alder reactions.[1a-q] Exceptions to this behavior occur when the pyrrole bears two electron-withdrawing groups. In these instances the pyrrole displays dienophilic properties. For example, 3-acetyl-1-phenylsulfonylpyrrole adds to isoprene to give a mixture of **1** and **2** (Scheme 1)[2]. Pyrroles also have been shown to be dienophiles in inverse electron demand Diels-Alder reactions although in the studies heretofore reported the Diels-Alder adducts presumed to be formed initially are unstable and undergo further transformations. Examples include the reactions of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with 1-methyl- and 1-phenylpyrroles to give compound (**3**)[3] (Scheme 1), the cycloaddition of 1-methylpyrrole to 1,3-buta-

*Dedicated to Professor Rolf Huisgen on the occasion of his 75th Birthday.

diene-2,3-dicarbonitrile to form 4[4] and the conversion of 1,2,4-triazinyl-tethered pyrroles such as 5 into 6[5]. Compounds (3) and (4) were obtained in low yields but 6's were isolated in yields of 75-80%.

Scheme 1



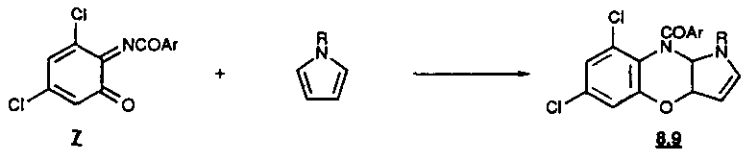
Previously we have described the reactions of o-quinone monoimides with furans and benzofurans,[6-8] thiophenes[9] and indoles.[8,10] In this paper we report the reactions of the o-quinone monoimide (7) with some pyrroles. Depending upon the substituent groups attached to the pyrrole nucleus there are produced either isolable inverse electron demand Diels-Alder adducts in good yields or adducts that are formally the result of an electrophilic attack by 7 on the pyrrole nucleus.

PRESENTATION OF RESULTS

Admixing of 7 with 1-benzenesulfonylpyrrole and with 1-carbomethoxypyrrole in methylene

chloride at ambient temperature gave **8** and **9** respectively in yields over 80% (Scheme 2). The structure of **8** was proved by X-ray crystallography. The thermal ellipsoid diagram of **8** is depicted in Figure 1.

Scheme 2



7

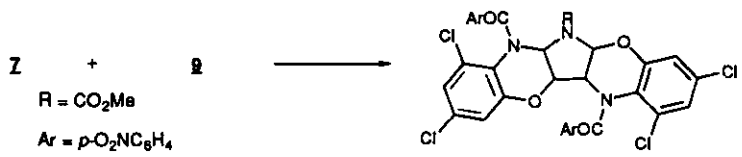
Ar = *p*-$O_2NC_6H_4$

8: R = $PhSO_2$; **9** R = CO_2Me

Compounds (**8**) and (**9**) were also characterized by ^1H nmr, ^{13}C nmr, infrared and mass spectroscopies and elemental analyses. The ^{13}C nmr spectrum of **8** exhibited resonances at 70.2 ppm and 86.7 ppm and that of **9** at 69.8 ppm and 86.1 ppm. These values are typical for sp^3 carbons bonded to two nitrogen atoms (~70 ppm) and for sp^3 carbons linked to an oxygen atom and to an allylic carbon (~86 ppm). The resonances compare favorably with those of the indole analogs of **8** and **9**.[10]

Compound (**7**) combines with **9** to produce the 2:1 adduct (**10**) (Scheme 3). The same adduct can be obtained directly by mixing two equivalents of **7** with one of 1-carbomethoxypyrrole. Analogous 2:1 adducts (**11** and **12**) are also formed when **7** is interacted with 1-methyl-2-acetyl- and 1-methyl-2-carbomethoxypyrroles (Scheme 3). In the case of

Scheme 3

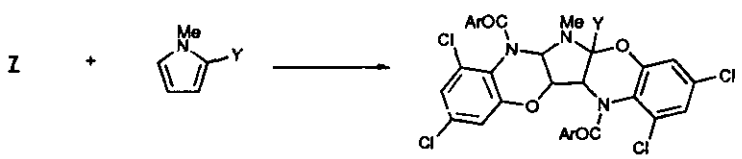


7 + **9**

R = CO_2Me

Ar = *p*-$O_2NC_6H_4$

10



7 +

11: Y = COMe; **12**: Y = CO_2Me

11,12

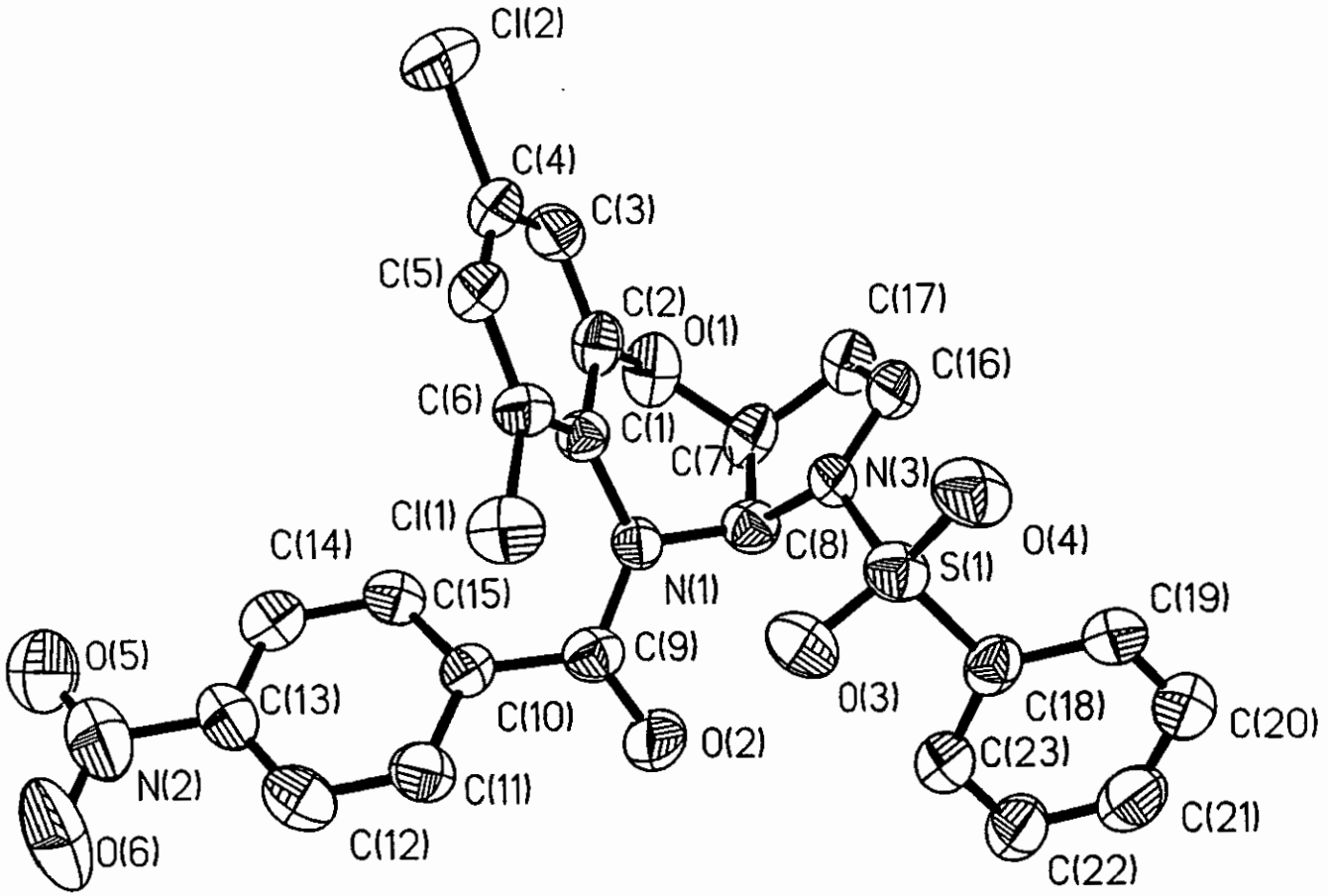
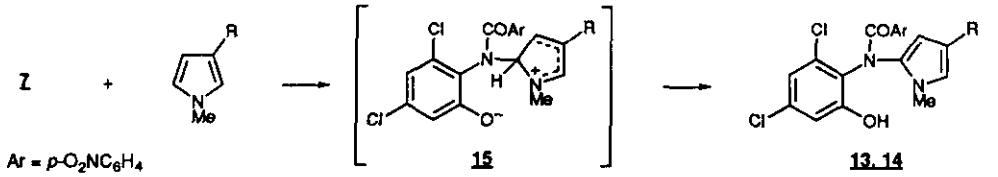


Figure 1. Thermal ellipsoid (50% probability) plot of compound (**8**). Hydrogen atoms have been omitted for clarity.

the latter two pyrroles it was not possible to isolate 1:1 adducts. The ^{13}C nmr chemical shifts for the four sp^3 carbons of **10-12** are consistent with the anticipated values and are shown in the Experimental Section.

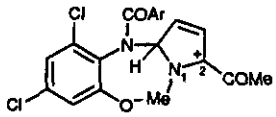
In contrast to the above pyrroles, 1-methyl- and 1-methyl-3-acetylpyrroles react with **7** to give not cycloaddition products but instead the adducts (**13**) and (**14**) (Scheme 4). The ^1H nmr, ^{13}C nmr and infrared spectra indicated the presence of a phenolic group. The site of substitution on the pyrrole ring was determined from the ^{13}C and

Scheme 4



^1H chemical shifts, and NOE experiments on 3-acetyl-1-methylpyrrole and **14**. The formation of **13**, **14** can be rationalized by *assuming that the interaction* of **7** with the pyrroles produces the zwitterion (**15**) (or an unstable Diels-Alder adduct which is transformed into **15**) in which the positive charge is effectively delocalized over the pyrrole ring. In the reactions of **7** with 1-phenylsulfonyl- and 1-carbomethoxypyrroles the electron withdrawing groups render the pyrrole ring less likely to sustain a positive charge thereby negating the formation of *a zwitterion. As a result a concerted* [4+2] cycloaddition occurs.

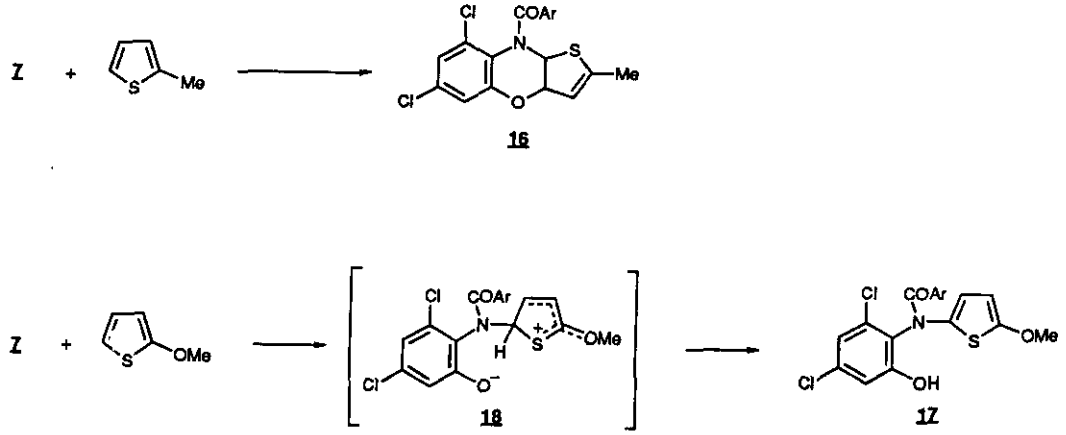
It is of interest to note that **7** with 2-acetyl-1-methylpyrrole forms the Diels-Alder adduct (**11**) rather than a product of electrophilic substitution such as occurs when **7** reacts with 1-methyl-3-acetylpyrrole. With the former pyrrole zwitterion formation is less favored due to the repulsive interactions generated between the positive charge on C-2 and the partially positive charge on the carbonyl carbon as exemplified by resonance structure (A). Accordingly, in this instance, a concerted inverse electron demand *Diels-Alder reaction occurs leading to* **11**.



(A)

Thiophenes,[9] furans[6-8] and indoles[8,10] also react with **7** to give either inverse electron demand Diels-Alder adducts or electrophilic substitution products. Once again the products formed are dependent upon the nature of the substituent groups bonded to the heterocycle. For example, 2-methylthiophene and **7** produces the cycloadduct **16** whilst 2-methoxythiophene and **7** yields **17**. The intermediacy of a zwitterion (**18**) is a most likely precursor of **17** (Scheme 5).

Scheme 5

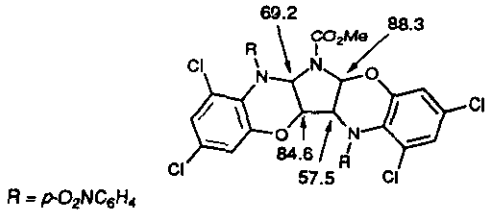


EXPERIMENTAL

1-Phenylsulfonyl-6,8-dichloro-3a,9a-dihydro-9-(4-nitrobenzoyl)-9*H*-pyrrolo[3,2-*b*][1,4]-benzoxazine (**8**). Compound (**7**)[6] (187 mg, 0.575 mmol) was added to a solution of 120 mg (0.580 mmol) of 1-benzenesulfonylpyrrole in 1.4 ml of CH_2Cl_2. After two days the reaction mixture was filtered to give 232 mg of **8**. The filtrate was evaporated and the gummy residue triturated with MeOH to provide an additional 38 mg of **8** (total yield 88%). Two recrystallizations from MeOH gave **8** (mp 215-216 °C). Anal. Calcd for $C_{23}H_{15}N_3O_6Cl_2S$: C, 51.89; H, 2.84; N, 7.89. Found: C, 51.71; H, 3.17; N, 7.77.

1-Carbomethoxy-6,8-dichloro-3a,9a-dihydro-9-(4-nitrobenzoyl)-9*H*-pyrrolo[3,2-*b*][1,4]benzoxazine (**9**). To a solution of 66.6 mg (0.53 mmol) of 1-carbomethoxypyrrole in 2.5 ml of CH_2Cl_2 was added 173 mg (0.532 mmol) of **7**. After 17 h the solvent was evaporated, the gummy residue triturated with MeOH and the MeOH evaporated. After several triturations the suspension was filtered to give **9** (200 mg, 83%). Two recrystallizations of **9** from hexane followed by two recrystallizations from MeOH gave an analytical sample of **9** (mp 204-206 °C; ms m/z 449). Anal. Calcd for $C_{19}H_{13}N_3O_6Cl_2$: C, 50.69; H, 2.91; N, 9.33. Found: C, 50.83; H, 3.36; N, 8.99.

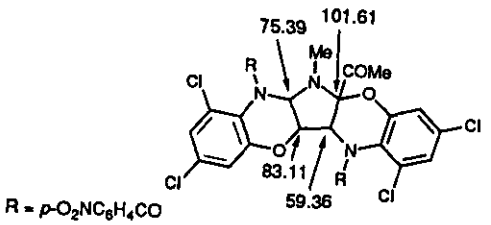
Methyl-1,3,8,10-tetrachloro-6a,12a,12b,13-tetrahydro-7,13-bis(4-nitrobenzoyl)-7*H*-pyrrolo-[2,3-*b*:4,5-*b*]bis[1,4]benzoxazine-6(5a*H*)-carboxylate (**10**). Method A. To a solution of 90 mg (0.20 mmol) of **9** in 1.5 ml of CH_2Cl_2 was added 73.2 mg (0.22 mmol) of **7**. After 3 days the solvent was evaporated, the gummy residue triturated with MeOH and the MeOH evaporated. This procedure was repeated several times to give 145 mg (93.5%) of crude **10**. Three recrystallizations from toluene gave **10** (mp 270-272 °C; ms m/z 775). Anal. Calcd for $C_{32}H_{19}N_5O_{10}Cl_4$: C, 49.56; H, 2.47; N, 9.03. Found: C, 49.41; H, 2.74; N, 8.86. The natural abundance ^{13}C nmr spectrum of **10** ($CDCl_3$) is summarized in the following structure:



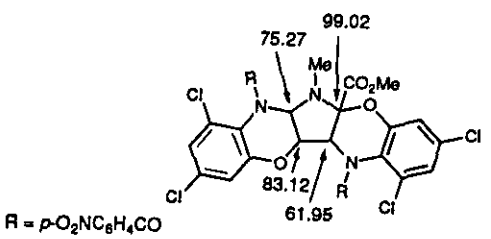
Method B. Compound (**7**) (335 mg, 1.03 mmol) was added to a solution of 64.3 mg of *N*-carboethoxypyrrole (0.51 mmol) in 2.90 ml of CH_2Cl_2. Crude **10** (327 mg, 83%) was isolated by the same procedure utilized in Method A.

5a-Acetyl-1,3,8,10-tetrachloro-5*a*,6,6*a*,12*a*,12b,13-hexahydro-6-methyl-7,13-bis(4-nitrobenzoyl)-7*H*-pyrrolo[2,3-*b*:4,5-*b*]bis[1,4]benzoxazine (**11**). To a solution of 37.8 mg (0.31 mmol) of 2-acetyl-1-methylpyrrole in 2.3 ml of CH_2Cl_2 was added 207.4 mg (0.638 mmol) of **7**. The solvent was evaporated after 4 d and the residue triturated with MeOH

several times. The crude **11** (198 mg, 83%) was recrystallized twice from MeOH to give an analytical sample (mp 206-210 °C; ms m/z 774). Anal. Calcd for $C_{33}H_{21}N_5O_9Cl_4$: C, 51.24; H, 2.73; N, 9.05. Found: C, 51.03; H, 2.80; N, 8.84. The natural abundance ^{13}C nmr spectrum of **11** ($CDCl_3$) is summarized in the following structure:

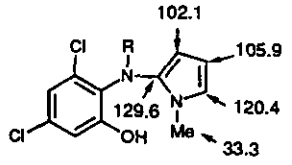


5a-Carbomethoxy-1,3,8,10-tetrachloro-5a,6,6a,12a,12b,13-hexahydro-6-methyl-7,13-bis(4-nitrobenzoyl)-7*H*-pyrrolo[2,3-*b*:4,5-*b*]bis[1,4]benzoxazine (**12**). Compound (**7**) (94 mg, 0.29 mmol) was added to a solution of 21 mg (0.15 mmol) of 1-methyl-carbomethoxypyrrole in 1.0 ml of $CHCl_3$. After 3 d the solvent was evaporated and the residue triturated with MeOH to give 103 mg (90%) of crude **12**. Recrystallization 3 times from EtOH gave **12** (mp 205-207 °C; ms m/z 789). Anal. Calcd for $C_{33}H_{21}N_5O_{10}Cl_4$: C, 50.21; H, 2.68; N, 8.87. Found: C, 50.04; H, 2.25; N, 8.83. The natural abundance ^{13}C nmr spectrum of **12** ($CDCl_3$) is summarized in the following structure:



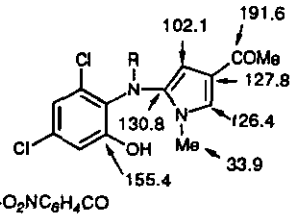
N-(2,4-Dichloro-6-hydroxyphenyl)-*N*-(1-methylpyrrol-2-yl)-4-nitrobenzamide (**13**). To a solution of 42 mg (0.52 mmol) of 1-methylpyrrole in 0.60 ml of CH_2Cl_2 was added 162 mg (0.50 mmol) of **7**. After 1 d the reaction mixture was filtered to give 62 mg of **13**. The filtrate was evaporated, the gummy residue triturated with MeOH and the MeOH evaporated. This procedure was repeated several times resulting in the isolation of an additional 127 mg of **13** (total yield 92%). An analytical sample of compound (**13**) was prepared by dissolving in a minimal amount of hot MeCN and adding water until the

solution became turbid. The precipitate was filtered and the above purification method repeated forming **13** (mp 204-206 °C, ms m/z 405). Anal. Calcd for $C_{18}H_{13}N_3O_4Cl_2$: C, 53.22; H, 3.23; N, 10.34. Found: C, 53.27; H, 3.55; N, 10.28. The natural abundance ^{13}C nmr spectrum of **12** ($CDCl_3$) is summarized in the following structure:



R = *p*-$O_2NC_6H_4$

N-(2,4-Dichloro-6-hydroxyphenyl)-*N*-(1-methyl-4-acetylpyrrol-2-yl)-4-nitrobenzamide (**14**). To a solution of 116 mg (0.94 mmol) of 1-methyl-3-acetylpyrrole in 3.5 ml of CH_2Cl_2 was added 266 mg (0.818 mmol) of **7**. The reaction mixture was filtered after 1 d to give 210 mg of **14**. The filtrate was evaporated and the residue triturated with MeOH which afforded an additional 116 mg of **14**. The total yield of **14** was (326 mg) 88.9%. Three recrystallizations from MeOH gave **14**, mp 262-265 °C; ms m/z 447. Anal. Calcd for $C_{20}H_{15}N_3O_5Cl_2$. C, 53.59; H, 3.37; N, 9.37. Found: C, 53.37; H, 3.77; N, 9.28. The natural abundance ^{13}C nmr spectrum of **14** is summarized in the following structure:



R = *p*-$O_2NC_6H_4CO$

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REFERENCES

1. a) G. Wittig, Angew. Chem., 1957, 69, 245. b) L. Mandell and W. A. Blanchard, J. Am. Chem. Soc., 1957, 79, 6198. c) R. M. Acheson and J. M. Vernon, J. Chem. Soc., 1961, 457. d) N. W. Gabel, J. Org. Chem., 1962, 27, 301. e) R. M. Acheson and J. M. Vernon, J. Chem. Soc., 1962, 1148. f) L. Mandell, J. U. Piper, and C. E. Pesterfield, J. Org. Chem., 1963, 28, 574. g) R. M. Acheson and J. M. Vernon, J. Chem. Soc., 1963, 1008. h) D. D. Callander, P. L. Coe, J. C. Tatlow, and A. J. Uff, Tetrahedron, 1969, 25, 215. i) G. W. Gribble, N. R. Easton, and J. T. Eaton, Tetrahedron Lett., 1970, 1075. j) J. Bornstein, D. E. Remy, and J. E. Shields, Tetrahedron Lett., 1974, 4247. k) M. Ahmed and J. M. Vernon, J. Chem. Soc., Chem. Comm., 1976, 462. l) P. S. Anderson, M. E. Christy, E. L. Engelhardt, G. F. Lundell, and G. S. Ponticello, J. Heterocycl. Chem., 1977, 14, 213. m) G. W. Gribble, R. W. Allen, C. S. LeHoullier, J. T. Eaton, N. R. Easton, R. I. Slayton, and M. P. Sibi, J. Org. Chem., 1981, 46, 1025. n) H. Kotsuki, Y. Mori, and H. Nishizawa, Heterocycles, 1982, 19, 1915. o) G. W. Gribble, M. P. Sisi, S. Kumar, and W. J. Kelly, Synthesis, 1983, 502. p) C. S. LeHoullier and G. W. Gribble, J. Org. Chem., 1983, 48, 2364. q) M. G. B. Drew, A. V. George, N. S. Isaacs, and H. S. Rzepa, J. Chem. Soc., Perkin Trans. I, 1985, 1277.

2. E. Wenkert, P.D.R. Moeller, and S. R. Piettre, J. Am. Chem. Soc., 1988, 110, 7188.

3. G. Seitz and T. Kämpchen, Arch. Pharm., 1978, 311, 728.

4. R. L. Cobb, V. C. Vives, and J. E. Mahan, J. Org. Chem., 1978, 43, 931.

5. J. H. Li and J. K. Snyder, J. Org. Chem., 1993, 58, 516.

6. H. W. Heine, B. J. Barchiesi, and E. A. Williams, J. Org. Chem., 1984, 49, 2560.

7. H. W. Heine and E. A. Williams, Trav. Chim. Pays-Bas, 1986, 105, 403.

8. H. W. Heine, C. Olsson, J. D. Bergin, J. B. Foresman, and E. A. Williams, J. Org. Chem., 1987, 52, 97.

9. H. W. Heine, D. K. Williams, J. L. Rutherford, J. Ramphal, and E. A. Williams, Heterocycles, 1993, 35, 1125.

10. D.St. C. Black, D. C. Craig, H. W. Heine, N. Kumar, and E. A. Williams, Tetrahedron Lett., 1987, 28, 6691.

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