HETEROCYCLES, Vol. 14, No. 7, 1980

Reissert Compounds Derived From Diazaaromatic Systems

Frank D. Popp

Department of Chemistry, University of Missouri-Kansas City,
Kansas City, Missouri 64110, U.S.A.

The preparation and reactions of Reissert compounds from phthalazine, naphthyridines, phenanthrolines, and ellipticine are discussed in detail. Attempts to extend Reissert compound formation to other diaza systems are also discussed.

INTRODUCTION:

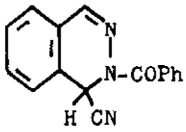
The chemistry of Reissert compounds has been the subject of several reviews.[1-4] Initial activity in this field was restricted to N-acyldihydroquinaldonitriles and N-acyldihydroisoquinaldonitriles. In more recent years this interest has been expanded to attempts to prepare Reissert compounds from diazaaromatic systems. This review presents a survey of the work carried out in this latter area.

TWO NITROGENS IN ONE RING:

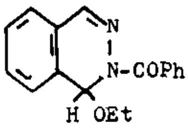
Phthalazine:

A Reissert compound (1) was prepared by the reaction of phthalazine, benzoyl chloride, and potassium cyanide using the methylene chloride-water solvent system.[5,6] Subsequently it was found that this system gave inconsistent yields of the Reissert compound (1) with contamination by significant quantities of the pseudo base (2) (obtained after recrystallization from ethanol).[7] Use of a phase transfer catalyst eliminated the formation of 2 and gave good yields of 1.[7] Even higher yields of 1 were obtained by reaction of phthalazine, benzoyl chloride, and trimethylsilyl cyanide in methylene chloride containing a catalytic amount of aluminum chloride.[8] Under no conditions could a di-Reissert compound be obtained by reaction at the second nitrogen.[6,9]

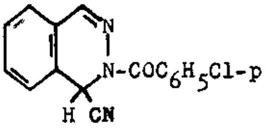
Reissert compounds have also been prepared from phthalazine and p-anisoyl chloride,[10,11] p-chlorobenzoyl chloride,[12] p-tolyl chloride,[12] and acetyl chloride.[12] The phase transfer catalyst method was used in the last three cases.[12] Attempts to use the methylene chloride-water method to prepare 3 gave mainly 4.[12] This result was reversed by the addition of a phase transfer catalyst. The Reissert compound (5) has been prepared[8] by both the phase transfer and trimethylsilyl cyanide methods.



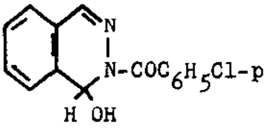
1



2



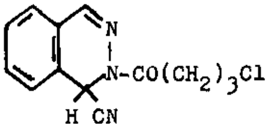
3



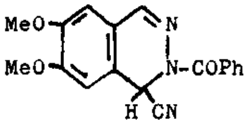
4

Several substituted phthalazines have also been converted to Reissert compounds. Thus benzoyl chloride has been reacted, by the trimethylsilyl cyanide method, with 6,7-dimethoxyphthalazine to give 6[13] and with 1-methyl- and 1-(3,4-dimethoxybenzyl)phthalazine to give compounds of the type 7.[8]

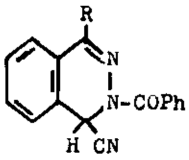
Using the methylene chloride-water solvent system phthalazine and potassium cyanide have been reacted with diphenylcarbamoyl chloride, diethylcarbamoyl chloride, benzenesulfonyl chloride, ethyl chloroformate, and diethyl chlorothiophosphate to give a series of Reissert analogs.[6] The analog 8 was also prepared by both the phase transfer catalyst and trimethylsilyl cyanide methods.[8]



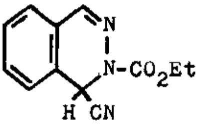
5



6



7

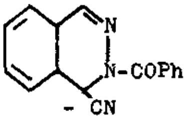


8

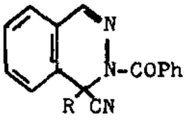
The anion (9) derived from 1, most generally by treatment with sodium hydride in dimethylformamide, behaves very similarly to the corresponding anion in the isoquinoline series. Thus alkylation with methyl iodide[5,6] and a variety of benzyl halides[8] gave rise to 10 which has been hydrolyzed with base to 1-substituted phthalazines (11). Use of this sequence with 6 and 3,4-dimethoxybenzyl chloride led to a convenient synthesis of 3-azapapaverine (12).[13] Alkylation of 1, via 9, has also been carried out with oxydibenzyl bromides to give phthalazine analogs of bis-benzylisoquinolines.[8] Reissert compounds of the type 7 have been used to prepare 1,4-disubstituted phthalzines.[8]

Treatment of 5 with sodium hydride in dimethylformamide led to intramolecular alkylation, as in the isoquinoline series, to give 13.[8] Condensation of 1 with ethyl cinnamate and ethyl acrylate in the presence of phenyl lithium in dioxane gave rise to the Michael addition products 14 (R = Ph and H respectively).[8]

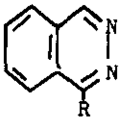
Reaction of 15 with acrylonitrile in the presence of potassium t-butoxide in dimethylsulfoxide gave a series of pyrrolo[2,1-*a*]phthalazines (16).[14] Formation of both 14 and 16 probably proceeds through the common intermediate 17.



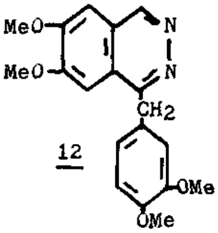
9



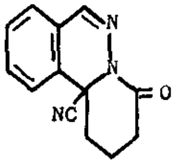
10



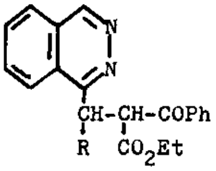
11



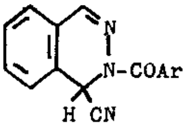
12



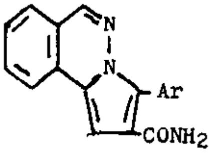
13



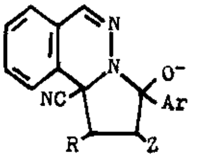
14



15

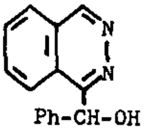


16

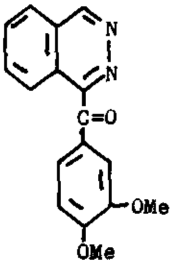


17

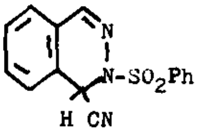
Treatment of the phthalazine Reissert anion with aldehydes also proceeds as in the isoquinoline series. Thus 9 reacts with benzaldehyde to give, after hydrolysis, the alcohol 18.[6] Reaction of 9 with 3,4-dimethoxybenzaldehyde gave, after hydrolysis and oxidation the ketone 19.[8] The same product (19) is also obtained by similar treatment of 8.[8] Treatment of the Reissert analog 20[6] with base gave rise to a good yield of 1-cyanophthalazine.[8]



18

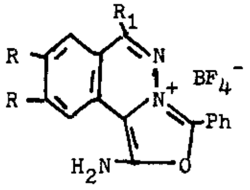


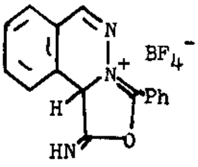
19

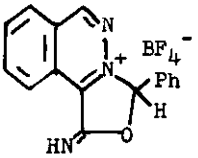


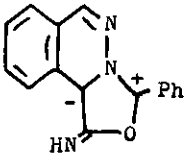
20

Treatment of Reissert compounds with fluoroboric acid in acetic acid is known to give the hydrofluoroborate salt of the Reissert compound. The Reissert compounds of phthalazine,[10,11,15] 1-methylphthalazine,[15] and 6,7-dimethoxyphthalazine[15] have thus been converted to hydrofluoroborate salts of the type 21. That the tautomer 21 predominates in an equilibrium[10] involving 21-24 and fluoroboric acid has been shown[11] in the case of the hydrofluoroborate salt derived from the phthalazine Reissert compound. Treatment of 21 ($R = R_1 = H$) with sodium bicarbonate solution gave the original Reissert compound (1),[10,11] while use of a deuterium oxide solution of sodium bicarbonate gave 1 deuterated in the 1-position.[11] Treatment of 21 with aqueous acid gave benzaldehyde.[10]


21

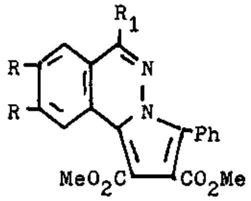

22

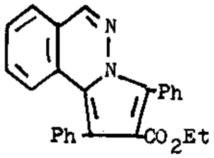

23

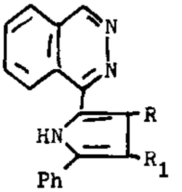

24

Reaction of the salt 21 with dimethyl acetylenedicarboxylate gave the pyrrolo[2,1-a]phthalazine (25).[15] A similar reaction of 21 ($R = R_1 = H$) with ethyl phenylpropiolate gave 26.[15] These reactions of 21 with alkynes probably proceed through a 1,3-dipolar cycloaddition followed by loss of isocyanic acid from the intermediate adduct.

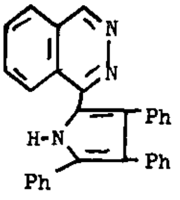
Reaction of 21 ($R = R_1 = H$) with alkenes, such as styrene and diethyl maleate, gave the 2-(1-phthalazyl)pyrroles 27 and 28 respectively.[15] These reactions of 21 with alkenes undoubtedly proceed through initial Diels-Alder reaction followed by complex condensation-rearrangement reactions.

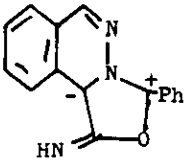

25

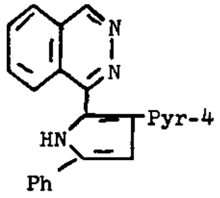

26

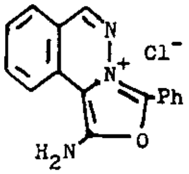

27 $R = Ph$, $R_1 = H$

28 $R = R_1 = CO_2Et$


29


30

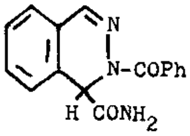

31


32

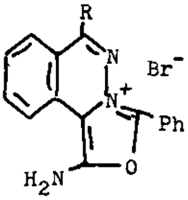
Reaction of the phthalazine Reissert compound (1) with 1,1-diphenylethylene in the presence of concentrated sulfuric acid in anhydrous dioxane gave a mixture of 29 and 30 (only one of several resonance forms shown). Reaction of 1 with 4-vinylpyridine in the presence of concentrated hydrochloric acid in dioxane gave a similar result in that 31 and 30 were isolated.[15] The mesoionic compound (30) reacted with dimethyl acetylenedicarboxylate to give 25 ($R = R_1 = H$). Reaction of 1 with cinnamonitrile in the presence of concentrated hydrochloric acid in dioxane gave only the chloride 32.[15] The same chloride (32) was also obtained when 1 was reacted with concentrated hydrochloric acid in dioxane at room temperature in the absence of cinnamonitrile. Reaction of the phthalazine Reissert compound (1) with acrylonitrile in the presence of hydrochloric acid gave 30, 33, and an unidentified product.[15] The compound 33 was also obtained by the reaction of 1 with 30% hydrogen peroxide in acetone.[15]

Acid-catalyzed hydrolysis of 1 in the presence of 2,4-dinitrophenylhydrazine gave benzaldehyde-2,4-dinitrophenylhydrazone, while hydrolysis with hydrobromic acid in acetic acid was reported to give phthalazine-1-carboxylic acid hydrobromide.[5,6] A reinvestigation of this latter reaction showed that an intermediate of the type 34 could be isolated from the acid-catalyzed hydrolysis of both 1 and 7 ($R = CH_3$).[15] The compound 34 reacted with dimethyl acetylenedicarboxylate to give 25 and with base to give the parent Reissert compound. The intermediate obtained by treatment of the phthalazine Reissert compound with acid appears to be more stable than the corresponding intermediates derived from quinoline and isoquinoline.

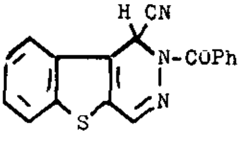
The mass spectra[11,15,16] and the ^1H nmr spectra[11,15] of a number of the compounds in the phthalazine series have been reported.



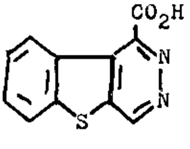
33



34



35



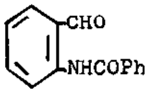
36

[1]Benzothieno[2,3-d]pyridazine:

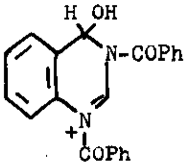
The Reissert compound 35, which can be considered analogous to the phthalazine Reissert compound has been prepared using the methylene chloride-water solvent system.[17] Hydrolysis of 35 with hydrobromic acid in acetic acid gave the carboxylic acid 36.[17]

Quinazoline:

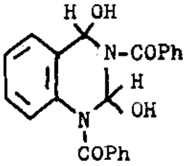
Reaction of quinazoline with potassium cyanide and benzoyl chloride using the methylene chloride-water system gave 2-formylbenzanilide (37).[18] This same product is formed in the absence of cyanide and it is assumed[18] that the ring opening proceeds via 38, 39, and 40.



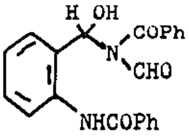
37



38

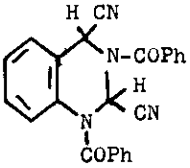


39

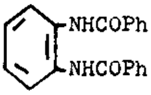


40

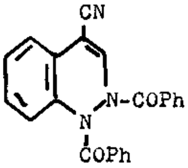
When quinazoline is reacted with benzoyl chloride and trimethylsilyl cyanide in methylene chloride, with or without the presence of anhydrous aluminum chloride, a Reissert type compound believed to have structure 41 is obtained.[19] It should be noted that 41 is analogous to the proposed intermediate 39. In the presence of aluminum chloride a low yield of a compound in which one of the nitrile groups of 41 had been converted to an amide is obtained, while in the absence of aluminum chloride a low yield of 4-cyano-3,4-dihydroquinazoline is obtained.[19] Alkylation of 41 with methyl iodide and sodium hydride in dimethylformamide gives rise to a monomethyl adduct.



41



42



43

Quinoxaline:

Reaction of quinoxaline with potassium cyanide and benzoyl chloride using the methylene chloride-water solvent system gave the ring-opened product 42.[20] Under these same conditions benzimidazole and 2-methylquinoxaline also gave 42.[19] The same product (42) has also been obtained from benzimidazole on treatment with benzoyl chloride and aqueous alkali at 0°.[21]

Cinnoline:

Reaction of cinnoline with benzoyl chloride and trimethylsilyl cyanide in anhydrous methylene chloride gives a product that appears to have structure 43.[19] Treatment of 43 with base gave 4,4′-bicinnolyl.

NITROGENS IN SEPARATE RINGS:

Naphthyridines:

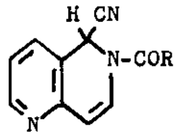
The formation of Reissert compounds has been studied with 1,6-; 1,7-; and

1,8-naphthyridines.

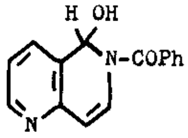
Reaction of 1,6-naphthyridine with benzoyl chloride and silver cyanide in chloroform afforded the Reissert compound 44 whose structure was proven by spectral methods.[22] Use of potassium cyanide in place of silver cyanide in this reaction was reported[22] to give a complicated mixture in low yield. Later work, however, indicated that benzoyl chloride and potassium cyanide in methylene chloride-water or in water gave the pseudo base 45.[23] Reissert compounds 46-48 were formed, although in low yield, using acetyl, propionyl, and butyryl chlorides in these latter two solvent systems.[23] The ^{1}H nmr and ultraviolet spectra of these compounds have been studied and are consistent with reaction at C-5 and N-6.

When 1,6-naphthyridine was reacted with the above aliphatic chlorides in the presence of a phase transfer catalyst the Reissert compounds 46-48 were obtained together with 2-(2-acylaminovinyl)-α-acyl-3-pyridineacetonitriles.[24] Use of benzoyl chloride under these conditions gave the Reissert compound 44.[24] Alkaline hydrolysis of the pseudo base 45 gave 1,6-naphthyridine, while 45 under conditions of the Reissert reaction for an extended period of time gave 2-(2-benzoylaminovinyl)-α-benzoyl-3-pyridineacetonitrile.[24]

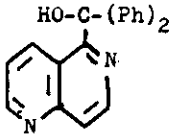
Acid hydrolysis of the Reissert compound 44 gave 1,6-naphthyridine-5-carboxamide, 1,6-naphthyridine-5-carboxylic acid, and benzaldehyde.[25] Reaction of 44 with methyl magnesium bromide gave 1,6-naphthyridine-5-carbonitrile, while reaction with phenyl magnesium bromide afforded 49. Alkylation of 44 took place in the expected position to give after hydrolysis 5-substituted-1,6-naphthyridines.[25]



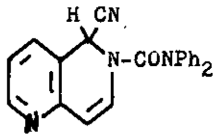
44 R = Ph
46 R = Me
47 R = Et
48 R = n-Pr



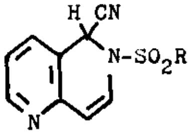
45



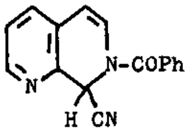
49



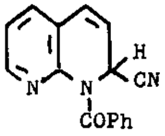
50



51



52



53

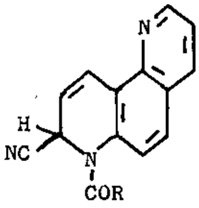
Reaction of 1,6-naphthyridine with potassium cyanide and N,N-diphenylcarbamoyl chloride in methylene chloride-water gave the Reissert analog 50, while use of methane- or benzenesulfonyl chloride in either methylene chloride-water or water gave 1,6-naphthyridine-5-carbonitrile, apparently via an unstable intermediate of the type 51.[23]

Reaction of 1,7-naphthyridine with benzoyl chloride and potassium cyanide in water gave the Reissert compound 52.[26]

Reaction of 1,8-naphthyridine with benzoyl chloride and potassium cyanide in methylene chloride-water in the presence of a phase transfer catalyst gave the Reissert compound 53.[19]

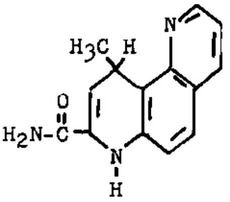
Phenanthrolines:

Attempts to form Reissert compounds have been studied with 1,7-; 1,10-; 4,6-; and 4,7-phenanthrolines. 1,10-Phenanthroline, benzoyl chloride, and potassium cyanide fail to give a Reissert compound in water,[27] and in methylene chloride-water.[28] The trimethylsilyl cyanide method also fails with 1,10-phenanthroline and benzoyl chloride.[29]



54 R = Ph

56 R = OEt

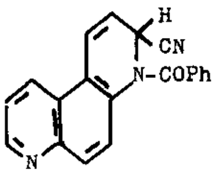


55

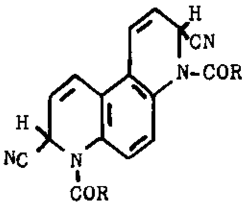
1,7-Phenanthroline reacts with benzoyl chloride and potassium cyanide in methylene chloride-water[28,29] to give 54. This same Reissert compound can also be prepared by means of the trimethylsilyl cyanide method.[29] Acid-hydrolysis of 54 in the presence of 2,4-dinitrophenylhydrazine gave benzaldehyde-2,4-dinitrophenylhydrazone. Alkylation of 54 with methyl iodide in the presence of sodium hydride gave a 10-methyl-7,10-dihydro adduct which on hydrolysis with base gave a product believed to be 55.[29] Reaction of 1,7-phenanthroline with ethyl chloroformate and trimethylsilyl cyanide gave the Reissert analog 56, while reaction with potassium cyanide and benzenesulfonyl chloride led directly to 8-cyano-1,7-phenanthroline.[29]

4,7-Phenanthroline with benzoyl chloride and potassium cyanide in methylene chloride-water in the presence of a phase transfer catalyst gave the mono-Reissert compound 57,[24,29] while reaction with benzoyl chloride and trimethylsilyl cyanide gave the bis-Reissert compound 58.[29] Acid hydrolysis of both 57 and 58 in the presence of 2,4-dinitrophenylhydrazine gave benzaldehyde-2,4-dinitrophenylhydrazone, while hydrolysis of 58 with hydrobromic acid in acetic acid gave 59.[29]

The Reissert analog 60 has also been prepared. Alkylation of 58 with methyl iodide in the presence of sodium hydride leads to a dialkylated product.[29]

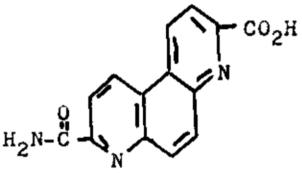


57



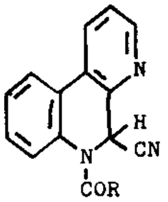
58 R = Ph

60 R = OEt

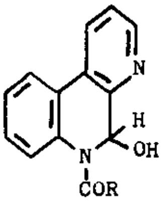


59

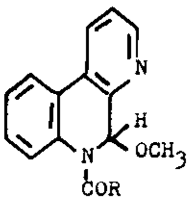
4,6-Phenanthroline gave a rather confusing set of results.[30] Reaction of this phenanthroline with potassium cyanide and acetyl, propionyl, and butyryl chlorides in methylene chloride-water gave mixtures of 61, 62, and 63 with the Reissert compounds (61) formed only in very low yield.[30] Use of benzoyl chloride in this procedure gave only the pseudo base 62.[30,31] Use of silver cyanide and benzoyl chloride with 4,6-phenanthroline in methylene chloride gave 62 (R = Ph) and 64;[30] these same reagents in chloroform gave 64;[31] while use of absolute chloroform gave a 3% yield of 65.[30] The pseudo base 62 (R = Ph) can be reconverted to 4,6-phenanthroline on treatment with base.[29] A Reissert compound (61, R = Ph) has been prepared from 4,6-phenanthroline and benzoyl chloride using the trimethylsilyl cyanide method.[29]



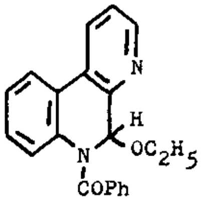
61



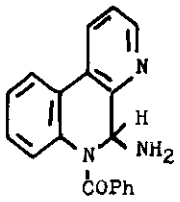
62



63



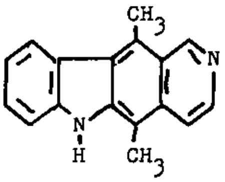
64



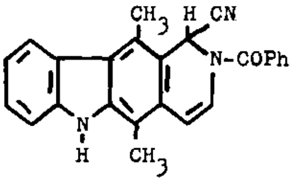
65

Ellipticine:

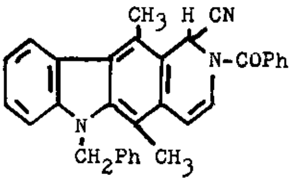
The antineoplastic alkaloid ellipticine (66) has been reacted with benzoyl chloride and potassium cyanide in methylene chloride-water, or better with benzoyl chloride and trimethylsilyl cyanide in methylene chloride, to give the Reissert compound 67.[32] In a similar manner 9-methoxyellipticine and a number of 6-substituted ellipticines have also been converted to Reissert compounds.[32,33] 1-Cyanoellipticines have been prepared through reaction with benzenesulfonyl chloride and trimethylsilyl cyanide.



66

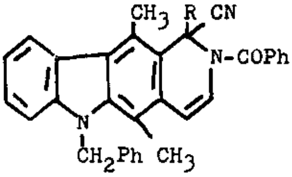


67

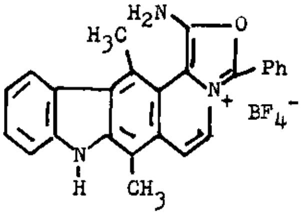


68

Reaction of the Reissert compound 68 with alkyl halides in dimethylformamide in the presence of sodium hydride gave the alkylation products 69 which could be hydrolyzed to 1-alkyl-6-benzylellipticines.[32,33] The ellipticine Reissert compound (67) has also been converted to its fluoroborate salt 70 by treatment with fluoroboric acid in glacial acetic acid.[32]



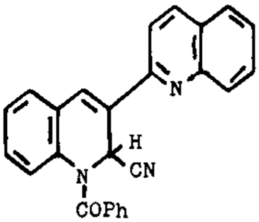
69



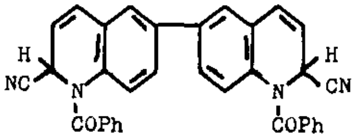
70

Biquinolines:

2,3′-Biquinoline has been converted to the mono-Reissert compound 71 which on acid hydrolysis gave the expected carboxylic acid.[34] 6,6′-Biquinoline gave the di-Reissert compound 72 which on acid hydrolysis gave the expected dicarboxylic acid.[35]



71



72

REFERENCES:

1. W. E. McEwen and R. L. Cobb, Chem. Rev., 1955, 55, 511.
2. F. D. Popp, Adv. Heterocyclic Chem., 1968, 9, 1.
3. F. D. Popp, Heterocycles, 1973, 1, 165.
4. F. D. Popp, Adv. Heterocyclic Chem., 1979, 24, 187.
5. F. D. Popp and J. M. Wefer, Chem. Commun., 1967, 59.

6. F. D. Popp, J. M. Wefer, and C. W. Klinowski, J. Heterocyclic Chem., 1968, 5, 879.
7. D. Bhattacharjee and F. D. Popp, Heterocycles, 1977, 6, 1905.
8. D. Bhattacharjee and F. D. Popp J. Heterocyclic Chem., 1980, 17, in press.
9. D. Bhattacharjee and F. D. Popp, unpublished observations.
10. W. E. McEwen, M. A. Calabro, I. C. Mineo, and I. C. Wang, J. Am. Chem. Soc., 1973, 95, 2392.
11. M. J. Cook, A. R. Katritzky, and A. D. Page, J. Am. Chem. Soc., 1977, 99, 165.
12. B. C. Uff and R. S. Budhram, Heterocycles, 1977, 6, 1789.
13. D. Bhattacharjee and F. D. Popp, J. Pharm. Sci., 1980, 69, 120.
14. B. C. Uff and R. S. Budhram, Synthesis, 1978, 206.
15. D. Bhattacharjee and F. D. Popp, J. Heterocyclic Chem., in press.
16. F. D. Popp, K. T. Potts, and R. Armbruster, Org. Mass Spectro., 1970, 3, 1075.
17. G. Dore, M. Bonhomme, and M. Robba, Tetrahedron, 1972, 28, 2553.
18. B. C. Uff, J. R. Kershaw, and S. R. Chhabra, J. Chem. Soc., Perkin I, 1974, 1146.
19. D. Bhattacharjee and F. D. Popp, J. Heterocyclic Chem., submitted.
20. F. D. Popp and J. M. Wefer, unpublished work quoted in reference 4.
21. E. Bamberger and B. Berle, Annalen, 1892, 273, 342.
22. Y. Kobayashi, I. Kumadaki, and H. Sato, Chem. Pharm. Bull., 1969, 17, 2614.
23. Y. Hamada, I. Takeuchi, and H. Matsuoka, Chem. Pharm. Bull., 1970, 18, 1026.
24. Y. Hamada and K. Shigemura, J. Pharm. Soc. Japan, 1979, 99, 982.
25. Y. Hamada and K. Shigemura, J. Pharm. Soc. Japan, 1979, 99, 1225.
26. I. Takeuchi and Y. Hamada, Chem. Pharm. Bull., 1976, 24, 1813.
27. E. J. Corey, A. L. Borror, and T. Foglia, J. Org. Chem., 1965, 30, 288.
28. F. D. Popp, unpublished work quoted in reference 2.
29. D. Bhattacharjee and F. D. Popp, J. Heterocyclic Chem., submitted.
30. Y. Hamada, K. Morishita, and M. Hirota, Chem. Pharm. Bull., 1978, 26, 350.
31. F. D. Popp and D. Chesney, unpublished results.
32. S. Veeraraghavan and F. D. Popp, Synthesis, 1980, in press.
33. S. Veeraraghavan and F. D. Popp, unpublished results.
34. K. V. Ihnatowicz and St. Niementowski, Chem. Ber., 1919, 52, 186.
35. K. Ueda, J. Pharm. Soc. Japan, 1937, 57, 825.

Received, 8th April, 1980