Synthetic Studies on Mesoionic Compounds. The Mesoionic 1,3-Diazol-4-one System (1)

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The synthesis of the mesoionic 1,3-diazol-4-one system is discussed. The intermediate to this system and the attempted cyclizations are described in detail. Further comments on the stability of these mesoionic compounds are also made.

For several years, mesoionic compounds have been of interest to us as a possible source of pharmacologically active agents. A number of these heterocyclic systems have been synthesized and studied for unique physiological actions (3). These small, planar molecules exhibit a high degree of charge separation between the ring and the exocyclic substituent as well as substantial variations in electron density among the ring elements. Since these characteristics are uncomplicated by stereochemical problems, mesoionic molecules possessing a definitive pharmacological action should be excellent candidates for the study of drug receptor interactions.

In the search for compounds meeting these criteria, we have studied the synthesis of several derivatives of the mesoionic 1,3-diazol-4-one system (I, Scheme I). Although this is not a new mesoionic system, the literature reveals very limited chemical studies and no pharmacology.

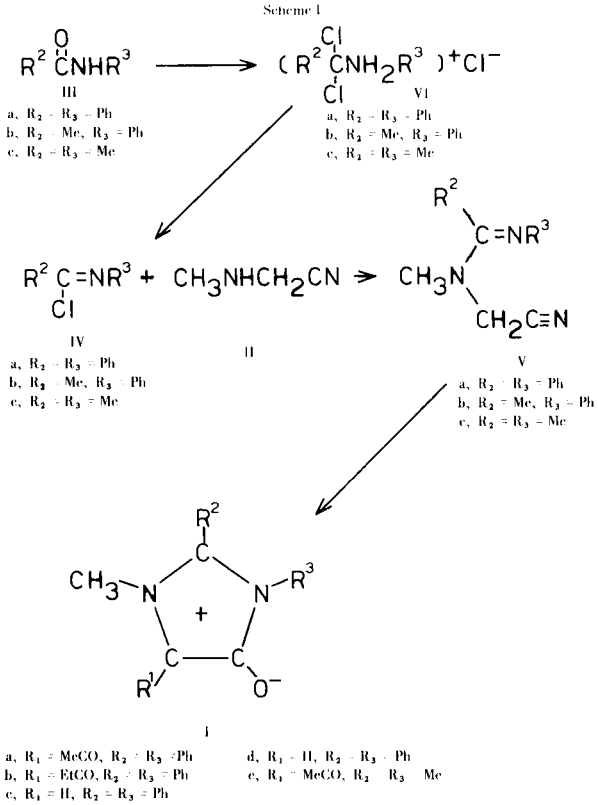
Two fused ring systems containing this nucleus and formulated as mesoionic were reported by Besthorn (4) and Krollpfeiffer and Schneider (5). Fused diazolone imines have been synthesized by Bristow, *et al.* (6).

Lawson and Miles have reported the only nonfused mesoionic 1,3-diazol-4-ones as structures Ia and Ib (Scheme I) (7). In an attempt to repeat the work of these authors, it was found that some of the reactions were not reproducible although the overall synthetic scheme is valid. The present report provides a reproducible route to these systems and some indications concerning the limitations on ring substituents.

The synthetic routes employed in this study are represented in Schemes I and II. *N*-Methylaminoacetonitrile (II, Scheme I) was prepared by the method of Cook and Cox (8). However it should be noted that the method of Blitz and Slotta (9), which produces a bisadduct, would probably be acceptable for this synthesis if hydrolysis of the nitrile is the next step contemplated, since the bisadduct produced is destroyed under such conditions (10).

The chemistry of imino chlorides, (IV, Scheme I) can, in many respects, be predicted from that of acyl chlorides.

Scheme I

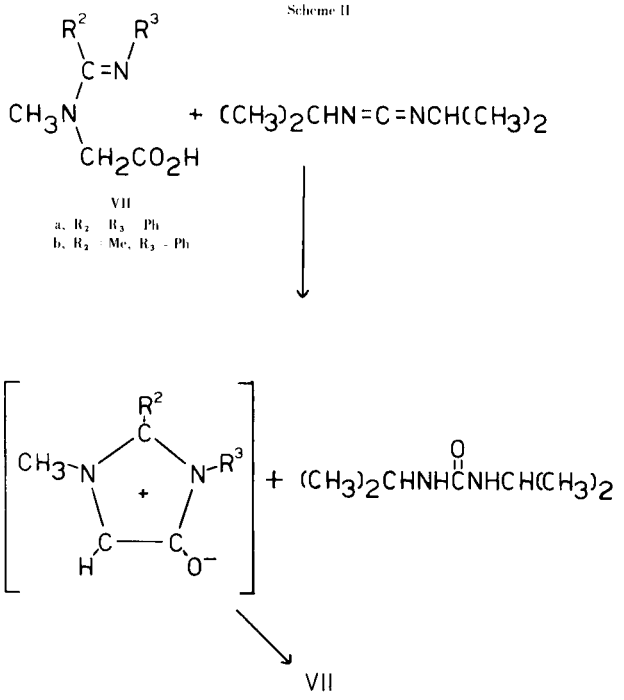


However, the basicity of the imino nitrogen complicates the reactivities of these derivatives. For example, the diphenyl compound (IVa, Scheme I) does not show the presence of a hydrochloride at all; the hydrochloride of the phenyl methyl compound (IVb, Scheme I) is readily decomposable and that of the dimethyl compound (IVc, Scheme I) was decomposed *in situ*, probably to the imino chloride. It is possible to write a mechanism for the synthesis of the amidine (Vc, Scheme I) derived from the dimethyl compound, which does not require the existence of the imino chloride (IVc, Scheme I) at all, as in Scheme III. The nmr spectrum of *N*-phenylacetimidoyl chloride (Table I) illustrates the presence of *syn-anti* equilibria in

these compounds.

The nmr spectrum of the diphenylmethylamidinonitrile (Va, Scheme I) is straightforward, but that of the dimethylphenyl (Vb, Scheme I) is not, since a peak assignable to the methylene protons is apparently missing (Table II). Conceivably, the absorption for these hydrogens is concealed in the aromatic portion of the spectrum. Models show that it would be possible, even likely, for these protons in the diphenylmethyl compound (Va, Scheme I) to be in the shielding cone of the phenyl ring attached to the imino carbon causing them to appear upfield. In the dimethylphenyl compound (Vb, Scheme I) the absence of the shielding effect of the phenyl ring allows the absorption to occur downfield in the aromatic region. Also, in

Scheme II



Scheme III

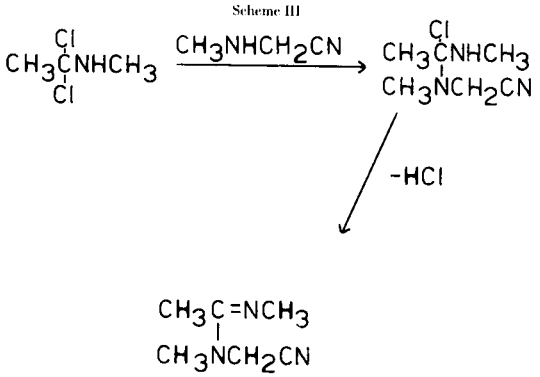


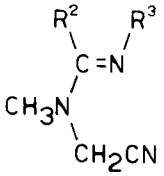
TABLE I

Nuclear Magnetic Resonance Spectrum of *N*-Phenylacetimidoyl Chloride (IVb, Scheme I)

Shift Position	Multiplicity	Integration
429 Hz.	multiplet	5H
152	singlet	3H

TABLE II

Nuclear Magnetic Resonance Spectra of Amidinonitriles (V, Scheme II)



	Shift Position			
	CH_2	CH_3	R_2	R_3
Va, $R_2 = R_3 =$ Ph	258 Hz.	172 Hz.	410 Hz.	410 Hz.
Vb, R_2 = Me, R_3 = Ph	415	313	110	415
Vc, $R_2 = R_3$ = Me (a)	400	223	151	215

(a) This compound was examined as the hydrochloride.

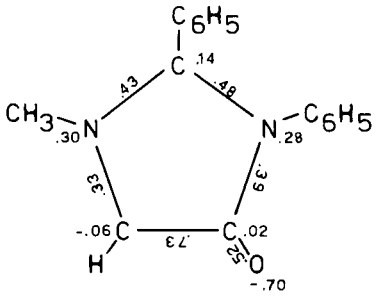


Figure 1. π Charge Densities and Bond Orders of 1-Methyl-2,3-diphenyl-1,3-diazol-4-one.

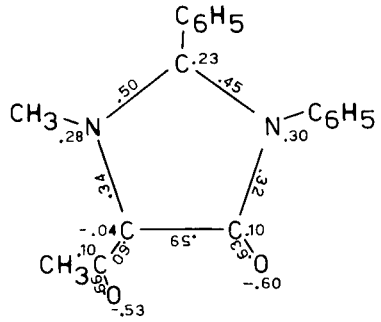


Figure 2. π Charge Densities and Bond Orders of 1-Methyl-2,3-diphenyl-5-acetyl-1,3-diazol-4-one.

the trimethyl derivative (Vc, Scheme I), as the hydrochloride, the phenyl ring is not present and the methylene peak is at 400 Hz. Although the compound is protonated, a downfield shift of 150 Hz. is more than would be expected from the electronegativity of the nitrogen. Additionally, integration of the spectrum of the dimethylphenyl compound (Vb, Scheme I) supports this view.

The original intent of this study was the synthesis of several derivatives of the basic ring system, particularly less substituted ones. It was especially hoped that the acyl moiety could be eliminated. It soon became apparent that the cyclization procedure reported by Lawson and Miles was not suitable, since the ring was almost certain to be acylated by this method (7). Further attempts were made to use the carboxylic anhydride reagent, with modification, to close the ring without acylation. An equivalent of acetic anhydride was added to a dilute solution of the sodium salt of the amidino acid (VIIb, Scheme II) in dimethylformamide, with no positive results. Addition of an equal volume of triethylamine to the compound in acetic anhydride as reported by Hashimoto and Ohta (11) resulted in the isolation of sarcosine and sodium acetate, which indicates that the amidino acid (VIIb, Scheme II) starting material was not stable under these conditions, or, alternately, the product cyclized and subsequently underwent solvolysis. A mixture of acetic anhydride and pyridine, however, when added to the amidino acid, produced cyclized product, which was found to be acylated.

Another approach to cyclization was attempted using carbodiimide reagents, since such a procedure would eliminate the possibility of acylation. The reaction was attempted with diisopropylcarbodiimide in a benzene solution of the sodium salt of the amidino acid (VIIa, Scheme II). Several changes were noted during the reaction, including the appearance of long wavelength absorption in the ultraviolet spectrum. On evaporation of the solvent, diisopropyl urea crystallized providing confirmation that a reaction had, indeed, occurred. A red oil was isolated which absorbed electromagnetic energy at about 350 mμ and which was suspected of being the unacylated mesoionic 1,3-diazol-4-one (Ic, Scheme I). Attempts to crystallize this oil however, led to isolation of the starting amidino acid, (VIIa, Scheme II) in a very pure state as the only product.

In this work, the successful synthesis and characterizations of three new amidines as intermediates to the preparation of the corresponding mesoionic diazolones is reported. Further studies on the cyclization of these intermediate amidines provided the mesoionic compounds Ia and Ie (Scheme I). Attempts to prepare the other derivatives, Ic and Id (Scheme I) were not successful.

Preliminary molecular orbital calculations, using the Hückel Omega technique (16), indicated that, in those diazolones where the ring is not substituted with an acyl function, the exocyclic oxygen atom bears almost a unit negative charge. Charge densities of this magnitude are unusual in mesoionic systems and might tend to decrease their stability (3). A comparison of Figures 1 and 2 readily demonstrates the contribution of the substituent carbonyl functionality to the mesomeric delocalization. Preliminary data in our laboratory of an alternate synthetic route for this system supports our contention that, unless the diazolone ring is acylated, a large amount of unsaturation in the other substituents is necessary to delocalize the electron density (12).

EXPERIMENTAL (15)

N-Methylaminoacetonitrile (II, Scheme I).

A solution of 2 moles of methylamine in methanol was added to a solution of 0.75 mole of glycolonitrile in methanol at 0° by the procedure of Cook and Cox (8). The fraction (46 g., 0.65 mole, 87%) distilling at 68° (20 mm.) gave a hydrochloride melting at 106° which agrees with a literature value (8). Its spectral characteristics were; nmr: singlet, 203 Hz. (2H), singlet 133 Hz., (3H), (neat); ir: 3680, 3360, 3000-2800, 2225, k. (carbon tetrachloride).

N-Phenylbenzimidoyl Chloride (IVa, Scheme I).

Benzanilide (20 g., 0.1 mole) (IIIa, Scheme I) was dissolved in 30 ml. of thionyl chloride and refluxed. The imino chloride IVa (21 g., 0.097 mole, 97%) (Scheme I) was isolated by the method of Lawson and Miles (7), m.p. 40°; ir: 3050, 3000-2800, 1670, 1600, 1580, k. (Nujol).

N-Phenylacetimidoyl Chloride (IVb, Scheme I).

Fourteen grams (0.1 mole) of acetanilide (IIIb, Scheme I) were dissolved in chloroform and 20 g. (0.1 mole) of phosphorus pentachloride were added, which caused the mixture to warm and effervesce. The solution was then refluxed for one-half hour, at which time the solvent was removed *in vacuo* at 50°. An oil was obtained which was heated with benzene. Hydrogen chloride was evolved and the oil dissolved in the benzene (13). This solution was again evaporated *in vacuo*, and a glassy residue (IVb, Scheme I) was obtained. Its nmr spectrum showed a multiplet, 429 Hz. (5H), singlet, 152 Hz. (3H), (deuteriochloroform).

1,1-Dichloro-1-methylaminoethane Hydrochloride (VIc, Scheme I).

N-Methylacetamide (7.3 g., 0.1 mole) (IIIc, Scheme I) and 21 g. (0.1 mole) of phosphorus pentachloride were dissolved in chloroform and refluxed for one-half hour (13). The solvent was removed under vacuum at 50° to yield an oil (VIc, Scheme I). The spectral data were; nmr: multiplet 360 Hz. (2H), singlet 200 Hz. (3H), singlet 160 Hz. (3H), (neat); ir: 1650, k. (chloroform).

N-Methyl-*N*-cyanomethyl-*N'*-phenylbenzamidine (Va, Scheme I).

The method of synthesis follows that of Allais (14), however changes in workup were necessary. Two equivalents of *N*-methylaminoacetonitrile (II, Scheme I) in toluene were added to one equivalent of imino chloride IVa (Scheme I) in toluene while the temperature was kept below 10°. On evaporation of the solvent an oil was obtained to which was added ether and 2*N* potassium hydroxide. The phases were separated and extraction of the aqueous phase was continued until the ether extracts were color-

less. The ethereal extracts were dried with sodium sulfate, and evaporated under reduced pressure. Crystals of the amidine Va (Scheme I) were obtained from ether-petroleum ether (7 g., 0.03 mole, 85%) m.p. 104-106°. The spectral data were; nmr: 410 Hz. (10H), multiplet, 258 Hz. (2H) singlet, 172 Hz. (3H) singlet, (deuteriochloroform); ir: 3675, 3600-2800, 2250, 1600, k. (chloroform).

N-Methyl-*N*-cyanomethyl-*N'*-phenylacetamidine (Vb, Scheme I).

A solution of 14 g. (0.2 mole) of *N*-methylaminoacetonitrile (II, Scheme I) in chloroform was added to a chloroform solution of 15.4 g. (0.1 mole) of *N*-phenylacetimidoyl chloride (IVb, Scheme I) at a temperature below 10°. A white precipitate developed. The solvent was removed under reduced pressure. Ether followed by 2*N* potassium hydroxide was added to the residue. After shaking, the phases were separated. The resulting aqueous phase was extracted with ether, and the combined ethereal extracts were dried with sodium sulfate and evaporated. Seven grams (0.04 mole) of crystalline Vb (Scheme I) were isolated, m.p. 116-117°. The spectral data were; nmr: multiplet 415 Hz. (7H), doublet 316 Hz. (1.5H), doublet 311 Hz. (1.5 H), singlet 110 Hz. (3H), (deuteriochloroform); ir: 2410, 1660, 1610, k. (chloroform).

N-Methyl-*N*-cyanomethyl-*N'*-methylacetamidine Hydrochloride. (Vc, Scheme I).

Sixty-six grams (0.4 mole) of 1,1-dichloro-1-methylaminoethane hydrochloride (VIc, Scheme I) were dissolved in chloroform and cooled to 0°. To this mixture was added a solution of 112 g. (1.6 moles) of *N*-methylaminoacetonitrile (II, Scheme I) in chloroform. The solution was refluxed for one-half hour. The solvent was removed *in vacuo*, and crystals separated from the remaining oil on cooling. They were collected by filtration and recrystallized from alcohol-ether, m.p. 238-240°. The spectral data were; nmr: singlet 400 Hz., singlet 223 Hz., singlet 215 Hz., singlet 151 Hz., (deuterium oxide); ir: 2333, 1639, 1575 k. (potassium bromide).

No integration is included because the dioxane standard interfered with it.

N-Methyl-*N*-(*N'*-phenylacetimidoyl)aminoacetic Acid. (VIIb, Scheme II).

Seven grams (0.04 mole) of the amidine, *N*-methyl-*N*-cyanomethyl-*N'*-phenylacetamidine (Vb, Scheme I), were refluxed in 50 ml. of 10% hydrochloric acid for one hour. The solvent was removed under vacuum and the remaining solid was treated with saturated sodium bicarbonate solution until the *p*H was above seven. The undissolved material was removed by filtration and the solution was evaporated to dryness. This solid was extracted with hot dimethylformamide. On cooling, a small amount of crystalline VIIb (Scheme II) precipitated. The spectral data were; nmr: multiplet 377 Hz. (5H), singlet 185 Hz. (3H), singlet 100 Hz. (2H), singlet 66 Hz. (3H); (deuterium oxide plus anhydrous hydrogen chloride).

Attempts to Synthesize Mesoionic 1-Methyl-2,3-diphenyl-1,2-diazol-4-one (Ic, Scheme I).

(A)

To 62 g. (0.25 mole) of *N*-methyl-*N*-cyanomethyl-*N'*-phenylbenzamidine (Va, Scheme I), 500 ml. of 10% hydrochloric acid was added. The solution was refluxed for one-half hour. Solvent was removed *in vacuo* and the solid remaining was extracted with alcohol. This solution was cooled and ammonium chloride was removed by filtration. The solution was evaporated to dryness. The solid residue (55 g., 0.18 mole) of *N*-methyl-*N*-(*N'*-phenylbenzimidoyl)aminoacetic acid (VIIa, SchemeII) was dispersed in benzene. A benzene solution containing 25 g. (0.2 mole) of diisopropylcarbodiimide was added. The mixture became warm and the solid dissolved. A white precipitate formed which redissolved. This mixture was allowed to stand at room temperature for 24 hours. The solvent was partially evaporated *in vacuo* and diisopropylurea precipitated. On further concentration, a brown oil was obtained. This oil was crystallized from acetone/water to provide the starting amidino acid VIIa (Scheme II) m.p. 166-167°. The spectral data were; nmr: multiplet, 437 Hz. (10H), singlet 248 Hz. (1H), singlet 180 Hz. (3H) (deuterioacetone); ir: 3289, 3125, 3077, 2915, 1672, 1634, (potassium bromide).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.6; H, 5.97; N, 10.4. Found: C, 71.4; H, 5.92; N, 10.4.

After removal of *N*-Methyl-*N*-(*N'*-phenylbenzimidoyl)aminoacetic acid (VIIa, Scheme II) from the previous mixture, a red oil was left. It absorbed electromagnetic energy at 350 mμ, but only amino acid VIIa, (Scheme II) could be isolated from the oil. When the red oil was dissolved in benzene and allowed to stand for one hour, the amidino acid (VIIa, Scheme II) precipitated and the red color disappeared.

(B)

Also, 1.65 g. (0.006 mole) of amidino acid VIIa (Scheme II) were dispersed in benzene and 0.882 g. (0.007 mole) of diisopropylcarbodiimide were added. The mixture stood at room temperature for twelve hours. It was then refluxed for twelve hours. No change in the ultraviolet spectrum was noted. A solid was isolated, which boiled at about 90°, then solidified and remelted at 166-167°.

(C)

This residue was then dissolved in chloroform and 0.882 g. (0.007 mole) of diisopropylcarbodiimide were added. This was allowed to stand for twelve hours at room temperature, then refluxed for twelve hours. No change in the ultraviolet spectrum of the reaction mixture was noted during this time. Upon evaporation of the solvent *in vacuo* a solid was obtained which melted at 166-167°

Attempted Synthesis of 1,2-Dimethyl-3-phenyl-1,3-diazol-4-one (Id, Scheme I).

The amino acid, *N*-methyl-*N*-(*N'*-phenylacetimidoyl)aminoacetic acid (VIIb, Scheme II) prepared previously, was divided in two portions. The first portion was dissolved in dimethylformamide to which was added 4.1 g. (0.04 mole) of acetic anhydride. This was heated on a steam bath for one hour, and then stored at room temperature in the dark for two weeks. No significant ultraviolet absorption ever developed in this solution, although sodium acetate did precipitate. The second portion was dissolved in a mixture of 25 ml. of acetic anhydride and 25 ml. of triethylamine, heated on the steam bath for one and one-half hours and stored for two weeks in the dark (11). Triethylamine hydrochloride and sodium *N*-methylaminoacetate were isolated from this mixture.

Mesoionic 1-Methyl-2,3-diphenyl-5-acetyl-1,3-diazol-4-one (Ia, Scheme I).

A solution of 5.0 g. (0.02 mole) of the amidine Va (Scheme I) in 50 ml. of 20% hydrochloric acid was refluxed for three-fourths of an hour. Solvent was removed under vacuum and saturated sodium bicarbonate solution was added until the *p*H was above seven. A small amount of residue was removed by filtration, and the solvent was again evaporated *in vacuo*. Twenty-five milliliters of acetic anhydride was added, and the mixture was heated on a

steam bath for one and one-half hours. Sodium acetate and sodium carbonate were filtered from the cooled solution. The acetic anhydride was evaporated under vacuum and an oil was obtained. To this oil, an indeterminate amount of xylene was added and evaporated. This was repeated till the oil solidified. The solid was then extracted with benzene and the solution so obtained was concentrated, and refrigerated. The mesoionic 1-methyl-2,3-diphenyl-5-acetyl-1,3-diazol-4-one (Ia, Scheme I) precipitated as white crystals (2 g., 33%), m.p. 241-243° (7). The spectral data were; nmr: singlet 430 Hz. (5H), singlet 417 Hz. (5H), singlet 204 Hz. (3H), singlet 114 Hz. (3H) (deuterioacetone); ir: 3049, 2950, 1664, 1600, 1497 k. (potassium bromide); uv: 260, 320, 328 (s) mμ (ethanol).

Mesoionic 1,2,3-Trimethyl-5-acetyl-1,3-diazol-4-one (Ic, Scheme I).

A solution of 14 g. (0.02 mole) of *N*-methylaminoacetonitrile (II, Scheme I) in chloroform was added to 17 g. (0.1 mole) of 1,1-dichloro-1-methylaminoethane hydrochloride (VIc, Scheme I) in chloroform at 7°. White crystals precipitated which were left in the flask. The chloroform was evaporated, 2*N* potassium hydroxide solution was added and the aqueous phase was extracted with ether. The ethereal extracts were dried with sodium sulfate and evaporated to an oil.

After addition of 350 ml. of 10% hydrochloric acid, the solution was heated at reflux for one hour. Solvent was removed *in vacuo* and saturated sodium bicarbonate solution was added till the *p*H was above seven. The solution was filtered and the filtrate was evaporated under reduced pressure to dryness. A solid was obtained to which was added 50 ml. of acetic anhydride. This was heated on the steam bath for one and one-half hours. A white solid which did not melt below 400° was removed by filtration. The filtrate was evaporated to dryness and azeotroped twice with xylene to remove residual acetic anhydride. The brown oil which was left was subjected to vacuum distillation. While acetic acid was removed by distillation, charring was noted. An acetone solution of the residue yielded a small amount of crystals on concentration. These melted at 213 to 215° and absorbed electromagnetic energy at 240, 303 and 308 (s) mμ. Not enough was obtained for further study.

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(16) The Hückel Omega Molecular orbital calculations were performed on an IBM 360/65 computer at the University of Nebraska Computing Center. The heteroatom parameters were those reported by E. B. Roche and L. B. Kier, *Tetrahedron*, **24**, 1673 (1968). A standard program for HMO calculations with the Omega technique was modified by James E. Cox, and is available from the authors.

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