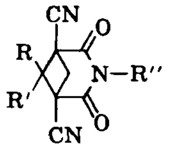
Chemistry of Guareschi Imides II. Enolic Character of β-Aryl Guareschi Imides

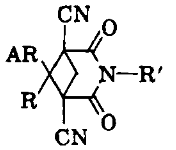
By ARNOLD A. LIEBMAN† and FRANK E. DIGANGI

The bicyclization and methylation reactions of β-aryl Guareschi-like imides were studied and the results indicate a favoring enolic structure that hindered these reactions in alkaline media.

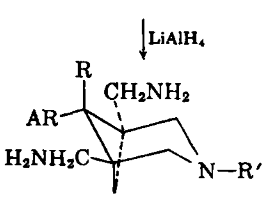
With the successful lithium aluminum hydride reduction of β,β-dialkyl-bicyclo Guareschi imides I (1), it appeared that a series of β-alkyl-β-aryl-bicyclo Guareschi-like imides II might also be prepared which upon reduction would yield compounds having a potential analgesic structure III.



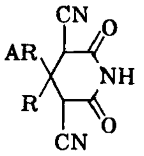
I R, R'-alkyl
R''-H, -CH$_3$



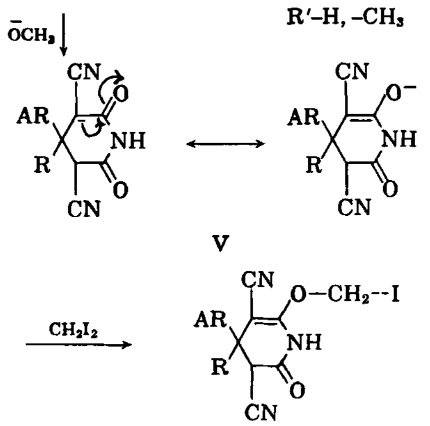
II AR-C$_6$H$_5$ R-alkyl
R'-H, -CH$_3$



III AR-C$_6$H$_5$ R-alkyl
R'-H, -CH$_3$



IV



V

VI

Since the Guareschi reaction is limited to ketones having two methyl or methylene groups adjacent to the carbonyl, starting materials were prepared *via* the two step synthesis developed by Cope (2) for the preparation of ethyl-(1-arylalkylidene)-cyanoacetates followed by the Michael addition of sodium cyanoacetamide using McElvain's (3) procedure.

Treating the β-aryl Guareschi-like imides with sodium methoxide and methylene iodide in the same manner as the β,β-dialkyl Guareschi imides (1) resulted in the recovery of starting material only. Similar results were encountered when α,α'-dicyano-β-methyl-β-phenylglutarimide was converted into its sodio derivative and treated with 1,2-dibromoethane and 1,3-diiodopropane, respectively. The β-ethyl analog also failed to form a bicyclo product with methylene iodide in sodium methoxide solution.

Failure of these β-alkyl-β-aryl Guareschi-like imides IV to form bicyclo heptanes in a manner similar to the β,β-dialkyl Guareschi imides may be attributed to either steric hindrance or an enolic structure inhibiting the reaction. The former may be eliminated since, α,α'-dicyano-β-isobutyl-β-methylglutarimide has been synthesized and it readily underwent the expected bicyclization with methylene iodide (1). On the other hand, dissolving a β-aryl Guareschi-like imide IV in alkoxide solution could result in formation of the enolate anion V which could react with methylene iodide yielding the enol ether system VI. This would decompose to starting material when treated with aqueous acid.

Methylation of α,α'-dicyano-β-methyl-β-penylglutarimide indicated the enolic nature of this compound. When this imide was converted into its mono sodium salt and treated with one molecular equivalent of methyl iodide, reaction appeared to occur since the solution quickly became neutral to moist litmus paper. However, only starting material was isolated from the reaction mixture. When two equivalents of sodium ethoxide and two of methyl iodide were used, a monomethyl product resulted. The entering methyl group attached itself to the imide nitrogen as evidenced by the absence of N—H stretching bands in the infrared spectrum of this compound. A dimethyl compound was obtained when this imide was treated with three equivalents of sodium ethoxide and of methyl iodide. The dimethyl compound was also obtained when six equivalents of sodium ethoxide and of methyl iodide

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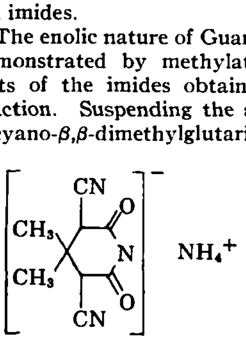
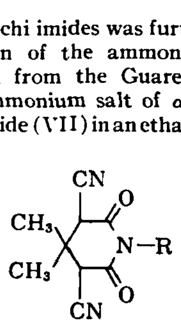
were used. These results are for the most part consistent with those of Kon and Thorpe (4) obtained in methylation studies of β,β-dialkyl Guareschi imides.

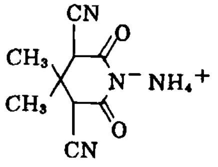
The enolic nature of Guareschi imides was further demonstrated by methylation of the ammonium salts of the imides obtained from the Guareschi reaction. Suspending the ammonium salt of α,α'-dicyano-β,β-dimethylglutarimide (VII) in an ethanol-benzene mixture and adding a slight excess of dimethyl sulfate resulted in a clear solution which was subsequently diluted with water. Upon standing, the solution precipitated a mixture of products, apparently the free imide VIII and the N-methylimide IX. Significantly, the precipitated material consisted entirely of neither VIII nor of IX, indicating a starting mixture of amonium salts X, XI. Similar results were encountered when the ammonium salt of α,α'-dicyano-β,β-pentamethyleneglutarimide was treated with dimethyl sulfate.



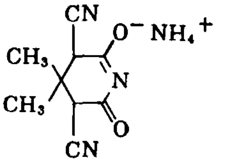
VII



VIII R-H
IX R-CH$_3$



X



XI

EXPERIMENTAL[1]

Ethyl-(1-phenylethylidene)-cyanoacetate.—In a 1-L., three necked, round-bottom flask equipped with a stirrer and Dean-Stark water separator were placed 120 Gm. (1 mole) of acetophenone, 113 Gm. (1 mole) of ethyl cyanoacetate, 48 Gm. (0.8 mole) of glacial acetic acid, 15.4 Gm. (0.2 mole) of ammonium acetate, and 200 ml. of anhydrous benzene. The mixture was treated according to the procedure of Cope (2) and McElvain (3) and upon distillation yielded 117 Gm. (54%) of product boiling between 145–160°/0.7 mm. Reported (3) boiling range is 135–160°/0.35 mm.

α,α' - Dicyano - β - methyl - β - phenylglutarimide.—According to the procedure of McElvain and Clemens (5), 0.5 mole of sodium cyanoacetamide was treated with 0.5 mole of ethyl-(1-phenylethylidene)-cyanoacetate. The dried product weighed 114.4 Gm. (90%) and melted at 272–278° (decompn). Reported (5) melting point is 274–278° (decompn).

Attempted Preparation of β-Alkyl-β-aryl-bicyclo Guareschi Imides.—In a 1-L., round-bottom flask fitted with a reflux condenser were placed 275 ml. of absolute methanol and 17.2 Gm. (0.75 Gm. atom) of sodium, added in small portions. When the sodium had dissolved, 63.3 Gm. (0.25 mole) of α,α'-dicyano-β-methyl-β-phenylglutarimide was added and the mixture heated under reflux for 1/2 hour during which time the imide dissolved. To the solution, 101.0 Gm. (0.38 mole) of methylene iodide was added and reflux continued for 3 hours during which time the methylene iodide dissolved. The solution was cooled and poured with stirring into 325 ml. of water containing 72 ml. of concentrated hydrochloric acid. When precipitation was complete, the solid was removed and washed repeatedly with ether. Recrystallization of this material from methanol and acetone yielded 39.1 Gm. of starting material. This experiment was repeated under extremely anhydrous conditions, using highly purified starting material and reagents. The solid that was obtained was recrystallized from absolute ethanol and melted at 282°. A mixed melting point with starting material caused no depression and the infrared spectrum was identical with that of starting material. Similar results were obtained when these β-aryl Guareschi-like imides were treated with 1,2-dibromoethane and 1,3-diiodopropane. In the latter instance, the above conditions were observed and in addition, the reaction was attempted in tetrahydrofuran using sodium hydride as the base.

Reaction of α,α'-Dicyano-β-methyl-β-phenylglutarimide with One Molecular Equivalent of Methyl Iodide.—A solution of sodium ethoxide was prepared by adding 0.92 Gm. (0.04 Gm. atom) of sodium to 50 ml. of absolute ethanol. To the solution, 20.1 Gm. (0.04 mole) of α,α'-dicyano-β-methyl-β-phenylglutarimide suspended in 200 ml. of absolute ethanol was added with stirring. The reaction mixture quickly became homogeneous and 6.0 Gm. (0.044 mole) of methyl iodide was added with stirring over a period of 10 minutes. The mixture was stirred and heated under reflux for 15 minutes when a sample was neutral to moist litmus paper. Reflux was continued for 1 hour after which time 150 ml. of ethanol was removed by distillation under reduced pressure. The remaining solution was cooled and poured into 300 ml. of water containing 25 ml. of concentrated hydrochloric acid. The precipitated material was collected, washed with ether and recrystallized from ethanol, melting at 282–285° (decompn). A mixed melting point with starting material gave no depression in the melting point. The infrared spectrum of this material was identical to that of starting material.

α,α' - Dicyano - β - methyl - β - phenyl - N - methylglutarimide.—The conditions in the preceding experiment were followed using 12.7 Gm. (0.05 mole) of the imide, 2.3 Gm. (0.1 Gm. atom) of sodium and 15.6 Gm. (0.11 mole) of methyl iodide. The reaction mixture was neutral to moist litmus paper when the methyl iodide had all been added. The neutral solution was refluxed for an additional hour when it was evaporated under reduced pressure to a volume of 100 ml. and diluted with 300 ml. of water followed by 25 ml. of concentrated hydrochloric acid. An oil separated which was solidified with stirring and recrystallized from ethanol yielding 6.6 Gm. (49%) of the monomethyl product melting between 172–181°. The infrared spectrum of this compound differed with that of starting material in that no N—H bands were present.

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[1] Melting points are uncorrected and were taken with a Thomas Hoover capillary tube melting point apparatus. Microanalyses were performed by the Microanalytical Laboratory of the University of Minnesota.

Anal.—Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90. Found: C, 67.47; H, 5.04.

α,α' - Dicyano - α' - β - dimethyl - β - phenyl - N-methylglutarimide.—Using the above procedure, but using 0.15 Gm. atom of sodium and 0.165 mole of methyl iodide to 0.05 mole of the imide, yielded 10 Gm. (71%) of the product, m.p. 190–192°.

Anal.—Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.32; H, 5.38. Found: C, 68.29; H, 5.37.

Similar results were obtained with a 2:1 ratio of methyl iodide to each active hydrogen and the solution refluxed for 21 hours. Assignment of the second entering methyl group to the α'-position rather than the α is an arbitrary one.

Reaction of the Ammonium Salt of α,α'-Dicyano-β,β-dimethylglutarimide with Dimethyl Sulfate.—The ammonium salt of α,α'-dicyano-β,β-dimethylglutarimide, 52.0 Gm. (0.25 mole), was suspended in a mixture of 100 ml. of anhydrous benzene and 100 ml. of absolute ethanol contained in a 500 ml., three necked, round-bottom flask equipped with a stirrer, dropping funnel, and reflux condenser. The mixture was stirred and heated under reflux for 1 hour after which time 37.8 Gm. (0.3 mole) of dimethyl sulfate was added with stirring. After the addition was completed, the mixture was stirred and heated under reflux for 2 hours. Within the first 15 minutes of this reflux period, the solid had all dissolved. The solution was cooled, diluted with an equal volume of water and refrigerated overnight. The solid that had separated (31.8 Gm.), was collected, and recrystallized from 60% ethanol. This material melted between 139–155°. A mixed melting point of α,α'-dicyano-β,β-dimethylglutarimide and α,α'-dicyano-β,β-dimethyl-N-methylglutarimide melted at 144–155°.

SUMMARY

1. β-Aryl Guareschi-like imides failed to undergo bicyclization with α,Ω-dihalides.
2. The failure of β-aryl Guareschi-like imides to undergo bicyclization is attributed to a favored enolic system in the presence of alkali which in turn resists the expected reaction.

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Mercury(II) Complex of *d*-Cycloserine

By NICHOLAS G. LORDI

The apparent formation constant of the 2:1 complex of *d*-cycloserine and mercury (II) has been measured and found to be $10^{17.5}$ at 25° in solutions of ionic strength of ~0.4. Evidence is presented to substantiate the conclusion that chelation contributes little to the structure of the complex.

As part of a study dealing with the influence of metal ions on the mode of degradation of the antibiotic *d*-cycloserine (*d*-4-amino-3-isoxazolidone) in aqueous solution, the apparent formation constant of the mercury(II) complex of cycloserine was measured. Neilands (1) and Neuzil and Breton (2) have indicated that cycloserine formed 1:1 and 2:1 complexes with copper(II), zinc(II), cadmium(II), cobalt(II), and nickel(II). No significant complex formation was observed with beryllium(II), magnesium(II), manganese(II), iron(II), and iron(III). It was of interest to compare the stability of the cycloserine–mercury(II) complex with the stabilities reported for similar complexes with other metal ions, as well as with several of the metal ion complexes of other ligands.

EXPERIMENTAL

A potentiometric technique was employed (3, 4). The potential of a mercury electrode in equilibrium with a solution of the mercury(II)–cycloserine complex in the presence of excess cycloserine was measured as a function of pH. Solutions were prepared containing from 0.01 to 0.05 *M* cycloserine, equimolar amounts of sodium hydroxide, from 0.0004 to 0.001 *M* mercuric acetate,[1] and sufficient potassium nitrate to adjust their ionic strength to 0.4. The potential of the mercury electrode (Sargent No. S-30438) *vs.* a saturated calomel electrode (S.C.E.) isolated from the solution through a 1.5 *M* potassium nitrate agar salt bridge was measured using a Fisher student potentiometer. The pH of the solution was varied by titration under nitrogen with 1 *M* perchloric acid. The resulting volume changes amounted to less than 8 per cent of the initial volume at the end of the titration. Corrections were made for concentration changes owing to dilution when significant. A Beckman model G pH meter was employed, using an external glass electrode (type 1190-80) to measure the pH. Since the complex was observed to precipitate at pH values greater than 8, the potential measurements were restricted to the pH range 2–8. The temperature of the solution and calomel electrode was maintained at 25 ± 0.5°.

The apparent dissociation constants of the cycloserine were also measured in 0.4 *M* potassium

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[1] The acetate and nitrate ions present in the system would have a negligible effect (other than that due to alteration in ionic strength) on the measured potential, owing to the much greater concentration of cycloserine than acetate and the very weak tendency of mercury(II) to complex nitrate.