

Synthesis of Substituted Dihydroisocarbostyrils from δ -Hydroxyamides Obtained from Dilithio-*N*-substituted *o*-Toluamides

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δ -Hydroxyamides, prepared by condensation of ketones or aldehydes at the 2-methyl group of *N*-substituted *o*-toluamides by means of *n*-butyllithium, were cyclodehydrated with sulfuric acid to form 2,3-disubstituted and 2,3,3-trisubstituted 3,4-dihydroisocarbostyrils. Also, δ -hydroxyamides obtained from condensation of ketones at the 2-benzyl group of *N*-methyl-*o*-benzylbenzamide, were cyclodehydrated to give 2,3,3,4-tetrasubstituted 3,4-dihydroisocarbostyrils. All of the products appeared to be new. This new method, which involves an unusual acid catalyzed cyclodehydration, is convenient and apparently quite general.

Recently, (1) *N*-methyl-*o*-toluamide (Ia) was converted by *n*-butyllithium to dilithioamide (IIa), which was condensed with benzophenone and benzaldehyde to form the δ -hydroxyamides, IIIa and IIIb, respectively (see Scheme I) (2). Also, IIa was condensed with certain cyclic ketones, and the resulting δ -hydroxyamides, as well as IIIa-b, were thermally cyclodeaminated to give the corresponding lactones (1).

In the present investigation this method of synthesis of δ -hydroxyamides was developed and, more significantly, such compounds were found to undergo cyclodehydration with cold, concentrated sulfuric acid to afford corresponding lactams, which are substituted 3,4-dihydroisocarbostyrils. Thus, this method of synthesis of δ -hydroxyamides was extended to IIIc-f and these compounds, as well as IIIa-b, were cyclodehydrated to form 3,4-dihydroisocarbostyrils (IVa-f, respectively) (Scheme I).

SCHEME I

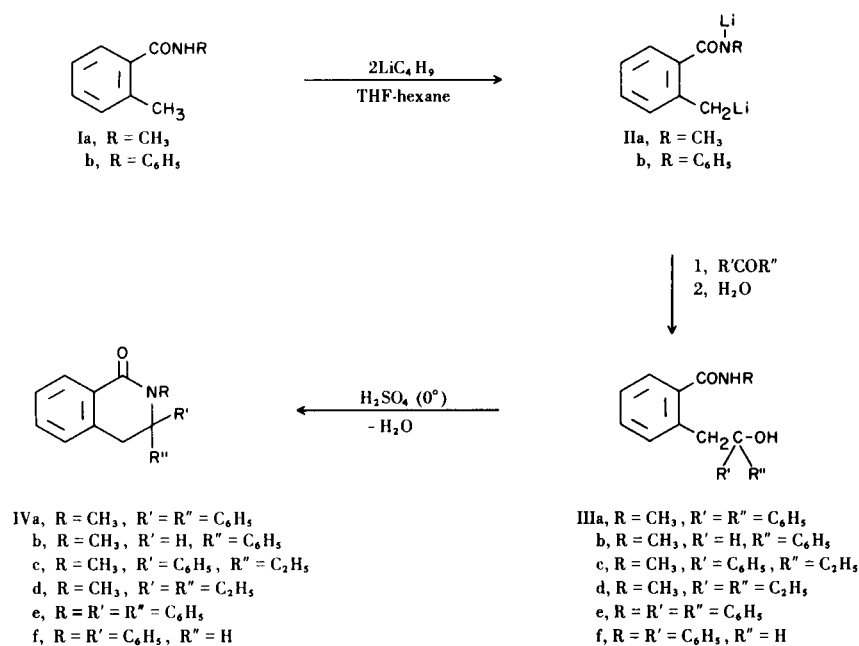


TABLE I

Condensations of Dilithioamides IIa-b and X with Carbonyl Compounds

| Dilithioamide | Carbonyl compound | Reaction temp., °C | Product | Yield % | M.P., °C | Recrystallization solvent |
|---------------|-------------------|--------------------|---------|---------|----------------|---------------------------|
| IIa | Propiophenone | -78 | IIIc | 80 | 127-130 (dec.) | Acetonitrile |
| IIa | Diethyl ketone | -78 | IIIId | 81 | 128-130 (dec.) | Acetonitrile |
| IIb | Benzophenone | 0 | IIIe | 95 | 184-185 | Acetonitrile |
| IIb | Benzaldehyde | 0 | IIIf | 92 | 192-193 | Acetonitrile |
| X | Benzophenone | 0 | XIa | 81 | 216-217 | Acetonitrile |
| X | Diethyl ketone | -78 | XIb | 55 | 134-136 (dec.) | Benzene-hexane |
| X | Cyclohexanone | -78 | XIII | 40 (a) | 136-137 | Aqueous ethanol |

(a) Also some lactone was obtained (detected by ir).

TABLE II

Absorption Spectra and Analyses for δ -Hydroxyamides

| δ -Hydroxy-Amide | Infrared Data (cm^{-1}) | | Empirical Formula | Caled. | | | Found | | |
|-------------------------|------------------------------------|------|---|--------|------|------|-------|------|------|
| | NH and/or OH | C=O | | C | H | N | C | H | N |
| IIIc (a) | 3360, 3250 | 1630 | $\text{C}_{18}\text{H}_{21}\text{NO}_2$ | 76.29 | 7.47 | 4.94 | 76.15 | 7.72 | 4.90 |
| IIIId | 3210, 3100 | 1640 | $\text{C}_{14}\text{H}_{21}\text{NO}_2$ | 71.45 | 8.99 | 5.95 | 71.48 | 9.08 | 5.74 |
| IIIe | 3350, 3220 | 1645 | $\text{C}_{27}\text{H}_{23}\text{NO}_2$ | 82.43 | 5.88 | 3.56 | 82.42 | 5.90 | 3.76 |
| IIIf | 3100 | 1645 | $\text{C}_{21}\text{H}_{19}\text{NO}_2$ | 79.47 | 6.03 | 4.41 | 79.43 | 6.11 | 4.27 |
| XIa (b) | 3440, 3300 | 1640 | $\text{C}_{28}\text{H}_{25}\text{NO}_2$ | 82.52 | 6.42 | 3.44 | 82.53 | 6.24 | 3.45 |
| XIb | 3400, 3290 | 1640 | $\text{C}_{20}\text{H}_{25}\text{NO}_2$ | 77.13 | 8.09 | 4.50 | 77.69 | 8.19 | 4.49 |
| XIII (c) | 3420, 3300 | 1640 | $\text{C}_{21}\text{H}_{25}\text{NO}_2$ | 77.98 | 7.79 | 4.32 | 77.91 | 8.05 | 4.24 |

(a) Nmr δ 7.2 (m, 9, Aromatic), 6.6 (m, 1, OH), 6.15 (broad, 1, NH), 3.1 (d, 2, CH_2 -Ar), 2.75 (d, 3, N- CH_3), 1.9 (q, 2, CH_2 -Me) and 0.72 (t, 3, CH_3) ppm. (b) Nmr δ 7.2 (m, 19, Aromatic), 6.1 (δ , 1, CH-) and 2.65 (d, 3, N- CH_3)-. (c) Nmr δ 8.25 (d, 1, NH) 7.3 (m, 9, aromatic), 5.95 (broad, 1, OH), 4.45 (δ , 2, CH_2 -Ar), 2.8 (d, 3, N- CH_3) and 1.5 (m, 10, $(\text{CH}_2)_5$) ppm.

TABLE III

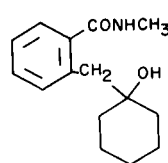
Cyclodehydration of δ -Hydroxyamides with Sulfuric Acid to Form Substituted 3,4-Dihydroisocarbostyrils

| δ -Hydroxy- amide | Product | M.P. or B.P. (mm), °C | Yield % | Recrystallization Solvent |
|-----------------------------|--|--------------------------|-------------|------------------------------|
| IIIa | 2-Methyl-3,3-diphenyl-3,4-dihydroisocarbostyril (IVa) | 196-198 | 54 (85) (a) | Acetonitrile |
| IIIb | 2-Methyl-3-phenyl-3,4-dihydroisocarbostyril (IVb) | 190-192 | 86 | ----- |
| IIIc | 2-Methyl-3-ethyl-3-phenyl-3,4-dihydroisocarbostyril (IVc) | 182 (1.5) (b) | 93 | ----- |
| IIId | 2-Methyl-3,3-diethyl-3,4-dihydroisocarbostyril (IVd) | 134 (2.5) (c) | 70 | ----- |
| IIIe | 2,3,3-Triphenyl-3,4-dihydroisocarbostyril (IVe) | 124-125 | 59 | Ethanol |
| IIIf | 2,3-Diphenyl-3,4-dihydroisocarbostyril (IVf) | 106-107 | 30 (d) | Ethanol |
| V | Spiro[2-methyl-3,4-dihydroisocarbostyril-3,1'-cyclohexane] (VII) | 160 (2.5) | 86 | ----- |
| VI | Spiro[2-methyl-3,4-dihydroisocarbostyril-3,9'-fluorene] (VIII) | 171.5-172.5 | 79 (a) | Acetonitrile |
| XIa | 2-Methyl-3,3,4-triphenyl-3,4-dihydroisocarbostyril (XIIa) | 189-191 | 68 (d) | Aqueous Dimethylformamide |
| XIb | 2-Methyl-3,3-diethyl-4-phenyl-3,4-dihydroisocarbostyril (XIIb) | 190-194 (3) | 85 | ----- |

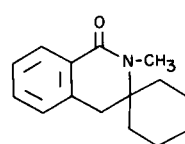
(a) Acetic acid-sulfuric acid was used as cyclization reagent. (b) M.p. 55-57°. (c) M.p. 36-38°. (d) Also some lactone was isolated.

Similarly, the δ -hydroxyamides, V and VI, which are prepared from dilithioamide (IIa) and cyclohexanone and fluorenone (I) were cyclodehydrated to produce the 3,4-dihydroisocarbostyrils (VII and VIII, respectively). Surprisingly, compound VI afforded a water soluble product with sulfuric acid but VIII was obtained with refluxing acetic acid containing sulfuric acid.

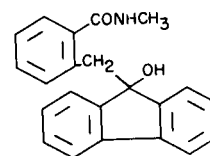
Likewise, *N*-methyl-*o*-benzylbenzamide (IX) was dilithiated and the resulting dilithioamide (X) was condensed with appropriate ketones to form δ -hydroxyamides (IXa-b), which were cyclodehydrated to give the respective 3,4-dihydroisocarbostyrils (XIIa-b) (Scheme II).



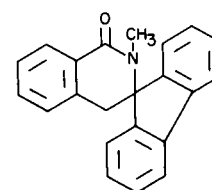
V



VII



VI



VIII

TABLE IV

Infrared Spectra and Analyses for Substituted 3,4-Dihydroisocarbostyrils

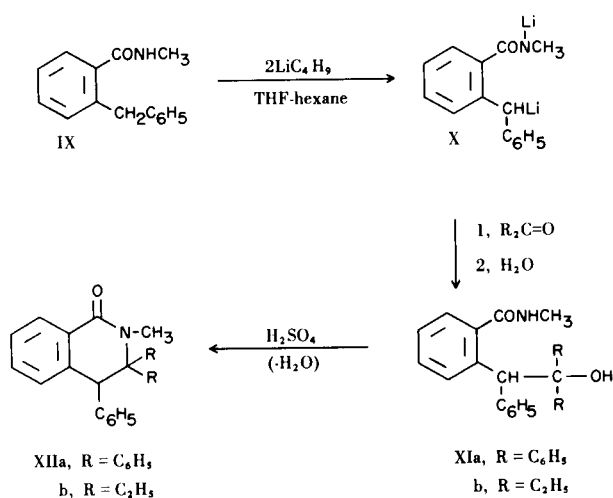
| Compound | Infrared (cm ⁻¹) C=O | Formula | Calcd. | | | Found | | |
|----------|-------------------------------------|------------------------------------|--------|------|------|-------|------|------|
| | | | C | H | N | C | H | N |
| IVa | 1650 | C ₂₁ H ₁₉ NO | 83.69 | 6.35 | 4.65 | 83.90 | 6.10 | 4.63 |
| IVb | 1660 | C ₁₆ H ₁₅ NO | 80.98 | 6.37 | 5.99 | 80.89 | 6.48 | 5.70 |
| IVc | 1660 | C ₁₈ H ₁₉ NO | 81.47 | 7.22 | 5.28 | 81.55 | 7.41 | 5.22 |
| IVd | 1670 | C ₁₄ H ₁₉ NO | 77.37 | 8.81 | 6.45 | 77.32 | 8.82 | 6.32 |
| IVe | 1640 | C ₂₇ H ₂₁ NO | 86.37 | 5.64 | 3.73 | 85.90 | 5.71 | 3.91 |
| IVf | 1645 | C ₂₁ H ₁₇ NO | 84.25 | 5.72 | 4.68 | 84.34 | 5.67 | 4.55 |
| VII | 1650 | C ₁₅ H ₁₉ NO | 78.56 | 8.35 | 6.10 | 78.81 | 8.55 | 5.97 |
| VIII | 1645 | C ₂₂ H ₁₇ NO | 84.86 | 5.50 | 4.49 | 84.54 | 5.69 | 4.68 |
| XIIa | 1660 | C ₂₈ H ₂₃ NO | 86.34 | 5.96 | 3.60 | 85.99 | 5.84 | 3.57 |
| XIIb | 1660 | C ₂₀ H ₂₃ NO | 81.87 | 7.90 | 4.77 | 81.89 | 8.19 | 4.54 |

TABLE V

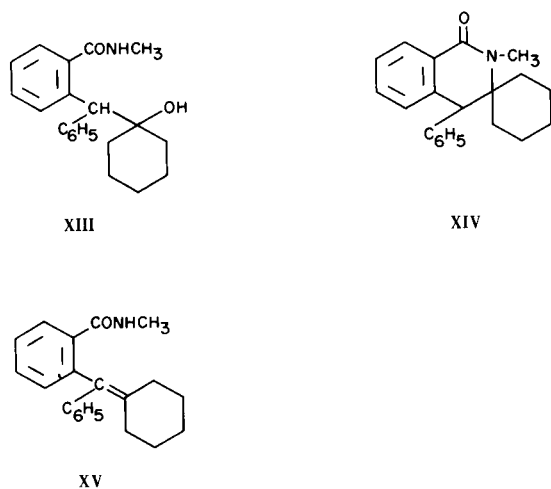
Nmr Data for Substituted 3,4-Dihydroisocarbostyrils
Types of Hydrogen and Chemical Shifts, δ (ppm)

| Compound | Aromatic | <i>o</i> -CH-ph | ph-CH- <i>N</i> - | <i>o</i> -CH ₂ - | <i>N</i> -CH ₃ | -CH ₂ -C | CH ₃ - |
|----------|-------------------|-----------------|-------------------|-----------------------------|---------------------------|---------------------|-------------------|
| IVa | 8.1 (m), 7.25 (m) | --- | --- | 3.79 (s) | 2.88 (s) | --- | --- |
| IVb | 8.1 (m), 7.25 (m) | --- | 5.0 (m) | 2.85 (m) | 3.12 (s) | --- | --- |
| IVc | 8.1 (m), 7.20 (m) | --- | --- | 3.25 (s) | 3.22 (s) | 1.91 (m) | 0.78 (t) |
| IVd | 8.1 (m), 7.15 (m) | --- | --- | 2.77 (s) | 3.13 (s) | 1.60 (m) | 0.88 (t) |
| IVe | 8.2 (m), 7.25 (m) | --- | --- | 3.71 (s) | --- | --- | --- |
| VII | 8.1 (m), 7.20 (m) | --- | --- | 2.78 (s) | 3.20 (s) | 1.50 (m) | --- |
| XIIa | 8.0 (m), 7.10 (m) | 5.05 (s) | --- | --- | 3.45 (s) | --- | --- |
| XIIb | 8.2 (m), 7.15 (m) | 3.96 (s) | --- | --- | 3.38 (s) 3.27 (s) | 1.50 (m) | 0.82 (t) |

SCHEME II



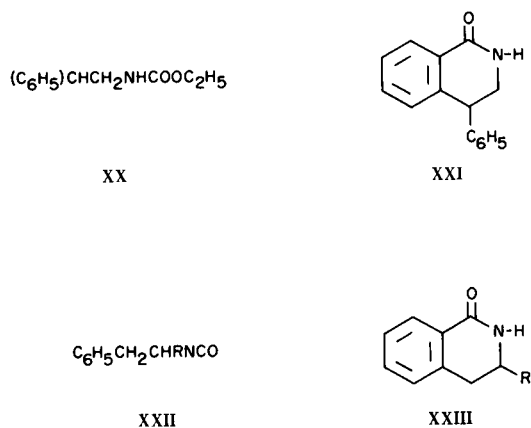
Also, δ -hydroxyamide (XIII), which was prepared from dilithioamide (X) and cyclohexanone, was cyclodehydrated to form evidently 3,4-dihydroisocarbostyril (XIV) but, surprisingly, the olefin-amide (XV) was obtained on distillation.



The data for the new δ -hydroxyamides and for the substituted 3,4-dihydroisocarbostyrils, all of which appeared to be new, are summarized in Tables I-II and III-V, respectively. Tables I and III show that the yields of these compounds were generally good to excellent. The structures of these products were supported by absorption spectra and analyses (see Tables II and IV-V). The infrared spectra for the δ -hydroxyamides showed peaks for the OH and NH groups at 3000 to 3400 cm^{-1} , whereas those for the 3,4-dihydroisocarbostyrils lacked such absorption. The carbonyl absorption appeared at 1620 to 1650 cm^{-1} for the former compounds, and 1640 to 1670 cm^{-1} for

the latter. The nmr spectra for both types of compounds supported the assigned structures.

This method of synthesis of 2,3-disubstituted, 2,3,3-trisubstituted and 2,3,3,4-tetrasubstituted 3,4-dihydroisocarbostyrils, which involves a rather unusual acid-catalyzed cyclodehydration, is convenient and, apparently, quite general. No previous examples of the two latter types of compounds seem to have been reported. Two earlier methods for the preparations of certain 3,4-dihydroisocarbostyrils have involved cyclizations of an appropriate urethane with polyphosphoric acid (3) and an isocyanate with aluminum chloride in the presence of nitrobenzene (4). For example, cyclization of urethane (XX) has produced XXI and that of isocyanate (XXII) has yielded XXIII; compound XXI has been methylated to form the 2-methyl derivative (3). Our method appears much simpler for synthesis of polysubstituted 3,4-dihydroisocarbostyrils having a 2-substituent.



EXPERIMENTAL

Melting points and boiling points are uncorrected. Elemental analyses were performed by Janssen Pharmaceutica, Beerse, Belgium and M-H-W Laboratories, Garden City, Michigan. IR spectra were produced on a Perkin-Elmer Infracord Model 137 and 237. The nmr spectra were obtained with a Varian A-60 Spectrometer using deuteriochloroform as solvent and tetramethylsilane as internal standard. Chemical shifts are measured to the center of a singlet or multiplet. In each spectrum the peak areas were consistent with the assignments given in the Tables.

Conversion of Amides (Ia-b) to Dilithioamides (IIa-b).

To a stirred solution of 0.025 mole of *N*-methyl-*o*-toluamide (Ia) in 50 ml. of tetrahydrofuran (THF) (5) cooled in an ice bath was added, under nitrogen, 0.05 mole of *n*-butyllithium in hexane (6) by a modification of a previous method (1). After stirring for 30 minutes, the red solution was assumed to contain 0.025 mole of dilithioamide (IIa).

Similarly, *N*-phenyl-*o*-toluamide (Ib) was dilithiated to form a red solution of 0.025 mole of dilithioamide (IIb). This solution as well as that of IIa, was employed in condensations.

Preparation of Amide (IX) and Its Conversion to Dilithioamide (X).

A stirred solution of 0.05 mole of 2-benzylbenzoic acid (7) and 0.10 mole of thionyl chloride in 30 ml. of dry ether was heated at 60-70° for 20 minutes, and the excess thionyl chloride was then removed under reduced pressure at room temperature. The residual oil was dissolved in 30 ml. of dry ether and the solution was added dropwise to a stirred mixture of 100 ml. of 40% aqueous methylamine and 200 ml. of ether cooled in an ice bath. The layers were separated, the organic layer was combined with ethereal extracts of the aqueous layer, and the solution was washed with cold 10% sodium hydroxide solution. The solvent was removed and the residue recrystallized from aqueous ethanol to give 9.0 g. (80%) of *N*-methyl-2-benzylbenzamide (IX), m.p. 106-107°; ν (potassium bromide) cm^{-1} , 3300 (NH), 1640 (C=O).

Anal. Calcd. for $\text{C}_{15}\text{H}_{15}\text{NO}$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.14; H, 6.49; N, 6.25.

A solution of 0.01 mole of amide (IX) in 30 ml. of THF (5) was treated with 0.02 mole of *n*-butyllithium in hexane (6) as described above for the dilithiation of amide (Ia) to form a red solution of 0.01 mole of dilithioamide (X), which was used in condensations.

Condensations of Dilithioamides (IIa-b and X) with Ketones or Aldehydes to form δ -Hydroxyamides.

In Tables I and II are summarized the results obtained for the new δ -hydroxyamides. The general procedure is described below.

To a stirred solution of 0.025 mole of the dilithioamide (IIa or IIb) or 0.01 mole of X in THF-hexane (see above) cooled in an ice bath or Dry Ice-acetone bath, was added, under nitrogen, 0.025 mole or 0.01 mole of the appropriate ketone or benzaldehyde in 20 ml. of THF (5). The reaction mixture was stirred for 30 minutes, and then poured onto 300 ml. of stirred ice-cooled water. The solid was removed by filtration. The two layers of the filtrate were separated. The organic layer was combined with two ethereal extracts of the aqueous layer, and the solvent was removed. The residue was combined with the original solid and recrystallized from an appropriate solvent (see Table I).

Cyclodehydration of δ -Hydroxyamides to Form Substituted 3,4-Dihydroisocarbostyrils.

In Tables III-V are the summarized results. General procedures are described below.

(A) With Concentrated Sulfuric Acid.

The δ -hydroxyamide (2.0 g.) was dissolved over a period of about 1 hour in 20 g. of concentrated sulfuric acid cooled in an ice bath. After another hour, the solution was poured onto 100 g. of crushed ice and then 50 ml. of water was added. The mixture was neutralized with 6 *N* sodium hydroxide solution. The product was removed either by filtration or by extraction with ether, and isolated and purified by crystallization or by distillation.

In the case of δ -hydroxyamides XIa-b, the sulfuric acid solution was poured onto ice after 30 minutes.

The δ -hydroxyamide VI failed to give the cyclic amide VIII; instead, the product was water soluble and was not identified.

(B) With Glacial Acetic Acid-Sulfuric Acid.

The δ -hydroxyamide (1.0 g.) was dissolved in 20 ml. of glacial acetic acid containing a few drops of concentrated sulfuric acid, and the solution was refluxed for 20 minutes. After cooling to room temperature, the solution was diluted with 50 ml. of water. The resulting white precipitate was collected and crystallized from acetonitrile.

Acknowledgment.

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- (2) I. T. Barnish, C. L. Mao, R. L. Gay and C. R. Hauser, *Chem. Commun.*, **10**, 564 (1968).
- (3) See S. Karady, *J. Org. Chem.*, **27**, 3720 (1962), and G. Berti, *Gazz. Chim. Ital.*, **90**, 559 (1960).
- (4) See T. C. Aschner, U. S. Patent, 2,647,902; *Chem. Abstr.*, **48**, 17, 330d (1954).
- (5) Freshly distilled from lithium aluminum hydride.
- (6) Used as obtained from Foote Mineral Company, Exton Pennsylvania.
- (7) E. B. Barnett, J. W. Cook and I. G. Nixon, *J. Chem. Soc.*, 504 (1927).

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