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A Polyphosphoric Acid-Catalyzed Spiroamidation. The Conversion of *N*-[3-(1-Cyclohexen-1-yl)propyl]-2-(3,4-dimethoxyphenyl)acetamide to 1-Veratrylcarbonyl-1-azaspiro[4.5]decane

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Hill (1) has reported the polyphosphoric acid-induced spirolactamization of 4-(1-cyclohexen-1-yl)-butyramide (I) to 1-azaspiro[5.5]undecan-2-one (II). This Note is concerned with a related reaction, the spiroamidation of *N*-[3-(1-cyclohexen-1-yl)propyl]-2-(3,4-dimethoxyphenyl)acetamide (IX) to 1-veratryl-carbonyl-1-azaspiro[4.5]decane (X).

Treatment of the tosylhydrazone (IV) of 2-(2-cyanoethyl)cyclohexanone (III) (2) with sodium 2-ethoxyethoxide in boiling 2-ethoxyethanol by the method of Bamford and Stevens (3,4) gave the γ,δ-unsaturated nitrile (V) in 60% yield. Reduction of the nitrile (V) with lithium aluminum hydride (5) afforded the amine (VI) which was converted to the acetamide (IX).

Catalytic hydrogenation of IX in the presence of 10% palladium-on-carbon gave *N*-(3-cyclohexylpropyl)-2-(3,4-dimethoxyphenyl)acetamide (VIII) identical with an authentic sample obtained from 3-cyclohexylpropylamine (VII) (6) and 3,4-dimethoxyphenylacetic acid. The nuclear magnetic resonance spectra of the amide (IX) and the nitrile (V) showed one-proton multiplets at 5.60 p.p.m., the chemical shift characteristic of vinyl protons (7). These results established the structures of the amide (IX) and the unsaturated nitrile (V).

When a suspension of the amide (IX) and polyphosphoric acid was stirred at room temperature for approximately one day, a neutral substance, isomeric with IX, was obtained in 85% yield. By analogy to the conversion (1) of the amide (I) to the spiropiperidone (II) and the facile interconversion (8) of 3-(cyclohexen-1-yl)propionic acid (XII) and 1-oxaspiro[4.5]decan-2-one (XIII), the reaction product was assumed to be 1-azaspiro[4.5]decane (X). The spectral properties (see Experimental) of the cyclization product, while compatible with this assumption, did not exclude the possible alternatives, the *cis*- and *trans*-decahydroquinoline structures XIV and XV. Therefore the known (1,9) spiroamine (XI) was condensed with 3,4-dimethoxyphenylacetyl chloride (10). The tertiary amide (X), so obtained, was identical with the polyphosphoric acid-cyclization product.

Hydride reduction of X afforded the tertiary amine (XVI).

EXPERIMENTAL (11)

2-Oxocyclohexanepropionitrile *p*-toluenesulfonylhydrazone (IV).

2-(2-Cyanoethyl)cyclohexanone (III) (41.0 g., 0.272 mole) was added to a boiling saturated solution of *p*-toluenesulfonylhydrazine (50.8 g., 0.272 mole) and absolute ethanol. The solution was heated under reflux for one hour and then cooled in an ice-bath. The precipitate was collected, washed with ether and recrystallized from absolute ethanol; yield 42.5 g. (49.3%) of the hydrazone (IV), m.p. 121.0-122.0°.

A sample, recrystallized from absolute ethanol for analysis, had m.p. 121.0-122.0°; γ max ($CHCl_3$) 3000-3400 (NH), 2300 (C≡N), 1328, 1162 (O=S=O) cm^{-1}; λ max 227 mμ (ϵ, 12,300); δ 2.44 (singlet, 3H, CH_3-), 7.38, 7.85 (AB, J = 8 c.p.s., 4H, aromatic), 8.20 (broad singlet, 1H, -NH-) p.p.m.

Anal. Calcd. for $C_{16}H_{21}N_3O_2S$: C, 60.16; H, 6.63; N, 13.15; S, 10.04. Found: C, 60.24; H, 6.88; N, 12.93; S, 10.20.

2-(Cyclohexen-1-yl)propionitrile (V).

A solution of the hydrazone (IV) (360 g., 1.13 moles) and 2-ethoxyethanolic sodium 2-ethoxyethoxide, prepared from sodium (68.8 g., 2.97 moles) and 2-ethoxyethanol (distilled from calcium hydride, 2 l.), was boiled under an atmosphere of nitrogen for two hours and allowed to stand at room temperature for 18 hours. The reaction mixture was poured onto ice-water and extracted with ether. The combined organic extracts were washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. Distillation of the residual oil through a spinning-band column (12) afforded 91.5 g. (60.0%) of the nitrile (V), b.p. 72.0-75.0° (2 mm.).

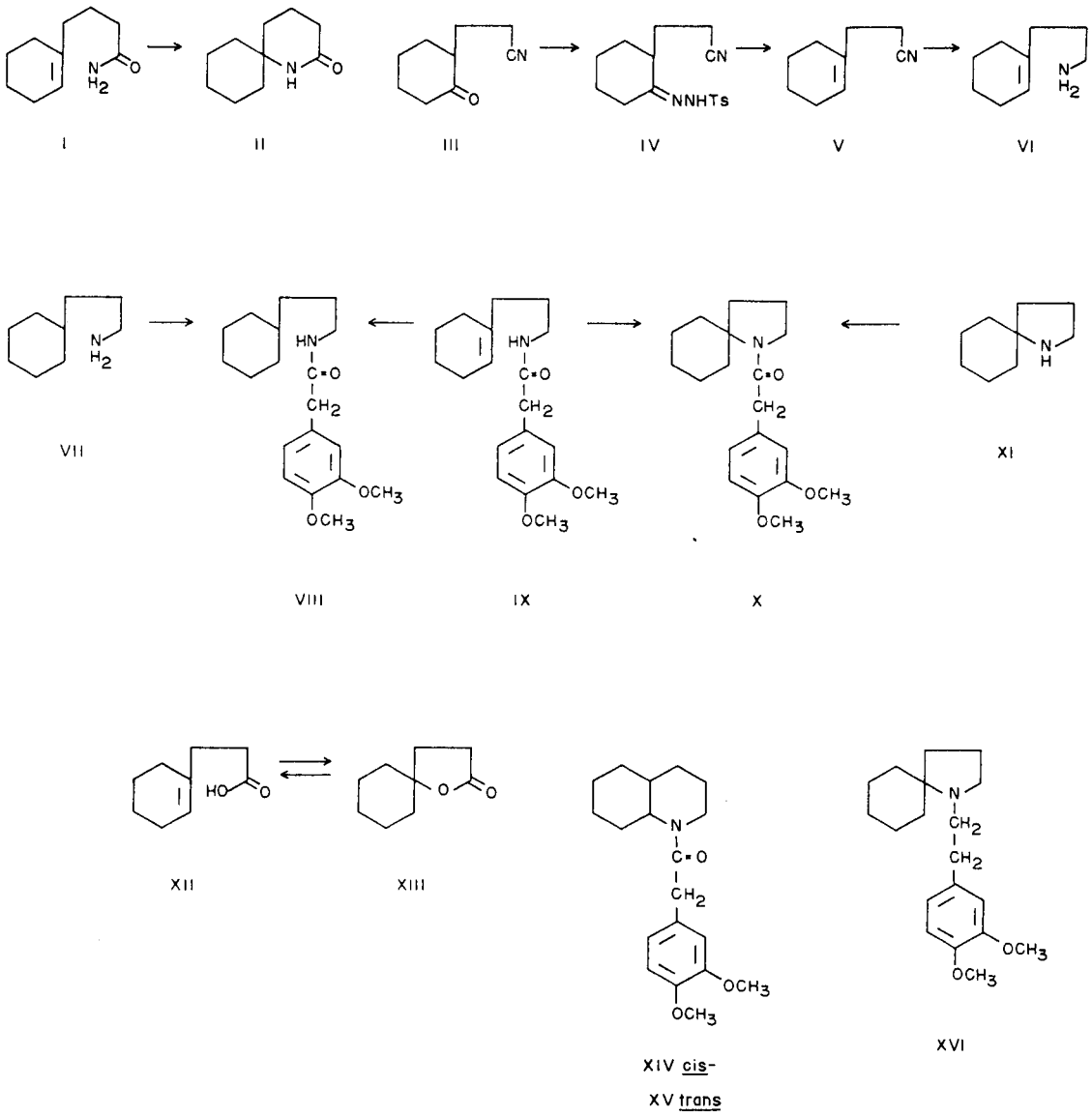
A sample, redistilled through a spinning-band column (12) for analysis, had b.p. 80° (3 mm.); γ max ($CHCl_3$) 2260 (C≡N) cm^{-1}; δ 5.60 (multiplet, 1H, vinyl proton) p.p.m.

Anal. Calcd. for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found: C, 80.24; H, 9.53; N, 10.29.

The gas-liquid chromatogram (2% carbowax-on-Gas Chrom $Z^{80/100}$, column temp. 80°, flame detector) showed one symmetrical band.

3-(Cyclohexen-1-yl)propylamine (VI).

A solution of the nitrile (V) (18.0 g., 0.133 mole) and anhydrous ether (50 ml.) was added dropwise, with stirring, to a suspension of lithium aluminum hydride (10.2 g., 0.275 mole) and anhydrous ether (200 ml.) at a rate such as to maintain gentle reflux of the solvent. After the addition was complete, the reaction mixture was stirred at room temperature for 18 hours and then cooled in an ice-bath. Water (40 ml.) was added dropwise, with stirring, and, after two hours, the alumina was collected and washed with ether. The filtrate was extracted with 5% hydrochloric acid. The aqueous phase



was cooled in an ice-bath, basified with 20% sodium hydroxide solution and extracted with ether. The combined ethereal extracts were washed with saturated sodium chloride until the washings were neutral, dried over anhydrous magnesium sulfate, filtered and evaporated. Distillation of the residue through a spinning-band column (12) afforded 14.4 g. (71.0%) of the amine (VI), b.p. 103.0-104.0° (20 mm.); γ max ($CHCl_3$) 3200-3580, 1590 (NH_2) cm^{-1}; δ 1.09 (singlet, 2H, $-NH_2$), 5.50 multiplet, 1H, vinyl proton) p.p.m.

The rapid carbonation of VI precluded a satisfactory combustion analysis.

The hydrochloride of VI had m.p. 186.0-206.0° dec.; γ max (CH_2Cl_2) 2500-3200 ($\overset{+}{N}H_3$, $-CH_2-$), 1610 ($\overset{+}{N}H_3$) cm^{-1}; δ 2.91 (multiplet, 2H, $-CH_2\overset{+}{N}H_3$), 5.40 (multiplet, 1H, vinyl proton), 8.00 (multiplet, 3H-$\overset{+}{N}H_3$) p.p.m.

Anal. Calcd. for $C_8H_{18}ClN$: C, 61.52; H, 10.33; Cl, 20.18; N, 7.97. Found: C, 61.42; H, 10.28; Cl, 19.99; N, 7.75.

N-[3-(1-Cyclohexen-1-yl)propyl]-2-(3,4-dimethoxyphenyl)acetamide (IX).

A solution of the amine (VI) (6.37 g., 0.0458 mole), 3,4-dimethoxyphenylacetic acid (10.0 g., 0.0509 mole) and xylene (distilled from calcium hydride, 120 ml.) was heated under reflux with azeotropic water separation for 17 hours and allowed to cool to room temperature. The precipitate was collected, washed with cold xylene and cold Skelly B and dried in a vacuum desiccator. Recrystallization from cyclohexane gave 10.8 g. (74.2%) of the amide (IX), m.p. 93.5-94.0°.

An analytical sample of IX had m.p. 93.5-94.0°; γ max (CH_2Cl_2) 3400 (NH), 2830 (OCH_3), 1663 (C=O), 1606, 1591, 1514 (aromatic) cm^{-1}; λ max 231 mμ (ϵ, 7,800), 280 (2,840); λ inf 284 mμ (ϵ, 2,560); δ 3.52 (singlet, 2H, $-CH_2CO-$), 3.87 (singlet 6H, $-OCH_3$), 5.33 (multiplet, 1H, -NH-), 5.60 (multiplet, 1H, vinyl proton), 6.85 (singlet, 3H, aromatic) p.p.m.

Anal. Calcd. for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41; O, 15.12; mol. wt. 317. Found: C, 71.93; H, 8.49; N, 4.69; O, 15.35; mol. wt. (mass spectrometry) 317.

N-(3-Cyclohexylpropyl)-2-(3,4-dimethoxyphenyl)acetamide (VIII). A. Reaction of 3-Cyclohexylpropylamine (VII) with 3,4-Dimethoxyphenylacetic Acid.

A solution of 3-cyclohexylpropylamine (6) (VII) (10.4 g., 0.0737 mole), 3,4-dimethoxyphenylacetic acid (15.7 g., 0.0802 mole) and xylene (distilled from calcium hydride, 100 ml.) was heated under reflux with azeotropic water separation for seven hours and allowed to stand at room temperature for 16 hours. The precipitate was collected on a filter, washed with cold xylene and dried; yield 23.0 g. (98.1%) of the amide (VIII), m.p. 100.0-100.5°.

An analytical sample, prepared by recrystallization from cyclohexane had m.p. 100.5-101.0°; γ max (CH_2Cl_2) 3400 (NH), 2840 (OCH_3), 1660 (C=O), 1605, 1590, 1510 (aromatic) cm^{-1}; λ max 232

mμ (ε, 7,800), 280 (3,000); λ inf 285 mμ (ε, 2,560); δ 3.47 (singlet, 2H, $-CH_2CO-$), 3.84 (singlet, 6H, $-OCH_3$), 6.07 (multiplet, 1H, -NH-), 6.82 (singlet, 3H, aromatic) p.p.m.

Anal. Calcd. for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.38. Found: C, 71.28; H, 9.16; N, 4.45.

B. Catalytic Hydrogenation of *N*-[3-(1-Cyclohexen-1-yl)propyl]-2-(3,4-dimethoxyphenyl)acetamide (IX).

A mixture of the amide (IX) (2.00 g., 0.00631 mole), 10% palladium-on-carbon (0.3 g.) and absolute ethanol (50 ml.) was shaken on a Paar pressure reaction apparatus at room temperature and an initial pressure of 43 p.s.i. of hydrogen. After five minutes the theoretical quantity of hydrogen was absorbed and there was no additional uptake. The catalyst was collected, washed with absolute ethanol and the filtrate was evaporated under reduced pressure. Recrystallization of the residual solid from cyclohexane afforded 1.50 g. (74.8%) of the amide (VIII), m.p. 98.0-99.5°.

A sample, recrystallized from cyclohexane and from ether, had m.p. 99.0-99.5°, alone or admixed with the authentic sample prepared by method A.

The infrared, ultraviolet and nuclear magnetic resonance spectra of the saturated amides, prepared by methods A and B, were identical.

1-Veratrylcarbonyl-1-azaspiro[4.5]decane (X). A. Treatment of *N*-[3-(1-Cyclohexen-1-yl)propyl]-2-(3,4-dimethoxyphenyl)acetamide (IX) with Polyphosphoric Acid.

A mixture of the amide (IX) (20.0 g., 0.0631 mole) and polyphosphoric acid, prepared from 85% phosphoric acid (140 g.) and phosphoric pentoxide (140 g.), was stirred at room temperature for 21 hours. The reaction mixture was poured onto ice and extracted with methylene chloride. The combined organic extracts were washed with saturated sodium chloride solution until the washings were neutral, dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent under reduced pressure gave 19.5 g. of a tan solid. Recrystallization from cyclohexane (Darco-G) afforded 17.0 g. (85.0%) of the amide (X), m.p. 98.0-98.5°.

A constant melting sample, prepared by two recrystallizations from cyclohexane, had m.p. 99.0-99.5°; γ max (CH_2Cl_2) 2850 (OCH_3), 1638 (sh), 1631 (C=O), 1594, 1515 (aromatic) cm^{-1}; λ max 280 mμ (ε, 3,020); λ inf 284 mμ (ε, 2,660); δ 3.54 (singlet, 2H, $-CH_2CO-$), 3.84 (singlet, -6H, $-OCH_3$), 6.80 (singlet, 3H, aromatic) p.p.m.

Anal. Calcd. for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41; O, 15.12; mol. wt. 317. Found: C, 71.99; H, 8.61; N, 4.64; O, 15.58; mol. wt. (mass spectrometry) 317.

B. Treatment of 1-Azaspiro[4.5]decane (XI) with 3,4-Dimethoxyphenylacetyl Chloride.

A mixture of 1-azaspiro[4.5]decane (1,9) (XI) (10.0 g., 0.0720 mole), freshly distilled 3,4-dimethoxyphenylacetyl chloride (11) (18.6 g., 0.0864 mole), 85% potassium hydroxide (5.69 g., 0.0861 mole), water (50 ml.) and ether (150 ml.) was shaken for 72 hours at room temperature. The layers were separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with 5% hydrochloric acid, 5% sodium bicarbonate solution, saturated sodium chloride solution, dried over anhydrous magnesium sulfate and filtered. Recrystallization of the residual solid (20.4 g.), obtained by concentration of the filtrate, from cyclohexane afforded 18.0 g. (78.8%) of the amide (X), m.p. 101.0-102.0°.

A sample, recrystallized from cyclohexane for analysis, had m.p. 101.0-102.0°, alone or admixed with a sample prepared by method A.

Anal. Calcd. for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 72.12; H, 8.78; N, 4.42.

The infrared, ultraviolet and nuclear magnetic resonance spectra of the authentic sample (method B) and the polyphosphoric acid-cyclization product (method A) were superimposable. The thin-layer chromatoplates were identical.

1-(3,4-Dimethoxyphenethyl)-1-azaspiro[4.5]decane (XVI).

To a suspension of lithium aluminum hydride (2.40 g., 0.0635 mole) and anhydrous ether (50 ml.) was added, dropwise, with stirring, a solution of the amide (X) (10.0 g., 0.0635 mole) and anhydrous ether (750 ml.) at a rate such as to maintain gentle reflux of the solvent. After the addition was complete, the reaction mixture was stirred at room temperature for 48 hours and cooled in an ice-bath. Water (9.4 ml.) was added dropwise, with stirring. The alumina was collected, washed with ether and the filtrate was extracted with 5% hydrochloric acid. The aqueous phase was cooled in an ice-bath, basified with 20% sodium hydroxide solution and extracted with ether. The ethereal extracts were washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The residual oil (6.70 g.) was dissolved in the minimum volume of anhydrous ether and ethereal hydrogen bromide was added. The precipitate was collected, washed with ether and dried. Recrystallization from 2-propanol-anhydrous ether afforded 7.04 g. (58.3%) of the amine (XVI) hydrobromide, m.p. 196.0-197.5°.

A sample, recrystallized from 2-propanol-anhydrous ether for analysis, had m.p. 197.5-198.5°; γ max (CH_2Cl_2), 2850 (OCH_3), 2300-2700 ($\overset{+}{N}H$) 1610, 1495, 1515 (aromatic) cm^{-1}; λ max 229 mμ (ε, 8,420), 278 (2,960); inf 283 mμ (ε, 2,610); δ 3.85, 3.89 (singlets, 6H, $-OCH_3$), 6.80 (broad singlet, 3H, aromatic), 10.7 (multiplet, 1H, $-\overset{+}{N}H-$) p.p.m.

Anal. Calcd. for $C_{19}H_{30}BrNO_2$: C, 59.37; H, 7.87; Br, 20.79; N, 3.64. Found: C, 59.58; H, 8.10; Br, 20.73; N, 3.77.

The tertiary amine XVI had b.p. 160.0-170.0° (bath temp., 0.1 mm.), λ max (CH_2Cl_2), 2850 (OCH_3), 1604, 1590, 1511 (aromatic) cm^{-1}; λ max 229 mμ (ε, 9,030), 280 (3,180); λ inf 285 mμ (ε, 2,650); δ 2.70 (singlet, 4H, $-CH_2CH_2-$), 3.85, 3.89 (singlets, 6H, $-OCH_3$), 6.80 (singlet, 3H aromatic) p.p.m.

Anal. Calcd. for $C_{19}H_{29}NO_2$: C, 75.20; H, 9.63; N, 4.62. Found, C, 75.33; H, 9.66; N, 4.88.

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