Cyclic Acylimines and Cyclic Carbinolamides II. Isoquinolones.

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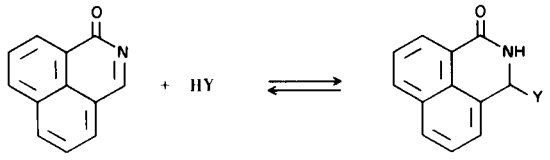
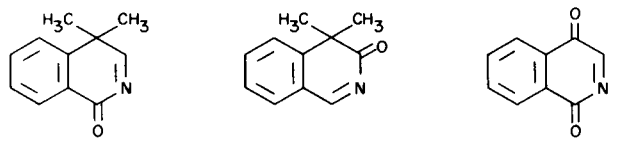
Three cyclic acylimines (X, XI, XXX) and six methoxyamides (VII, VIII, IX, XXIII, XXIX, XXXV) were synthesized and their chemical properties studied. The isoquinolone acylimines added readily, across the carbon-nitrogen double bond, weak nucleophiles such as alcohols and amides to give addition products. The methoxyamides can substitute, in the presence of an acid catalyst, the unsaturated compound in the various reactions. Diels-Alder type products were obtained with dienes and amidoalkylation derivatives with acetone and dimedone.

Acylimines are reactive compounds which readily add weak nucleophiles across the carbon-nitrogen double bond to give addition products (1,2,3). The reactivity of the system is retained even in 2-azaphenalone (I), a conjugated polycyclic acylimine (4), which is stable only as its hydrochloride or as an addition product (II) (4).



I II

The present investigation was aimed at the preparation of the two isomeric 4,4-dimethyl-1,4-dihydro-1-isoquinolone (III) and 4,4-dimethyl-3,4-dihydro-3-isoquinolone (IV), the azanaphthoquinone (V), the 1 or 3-phenyl derivatives, and a study of their chemical and physical properties. These compounds exhibit less conjugation than the azaphenalones and should therefore be more reactive toward addition reactions involving the C=N linkage.



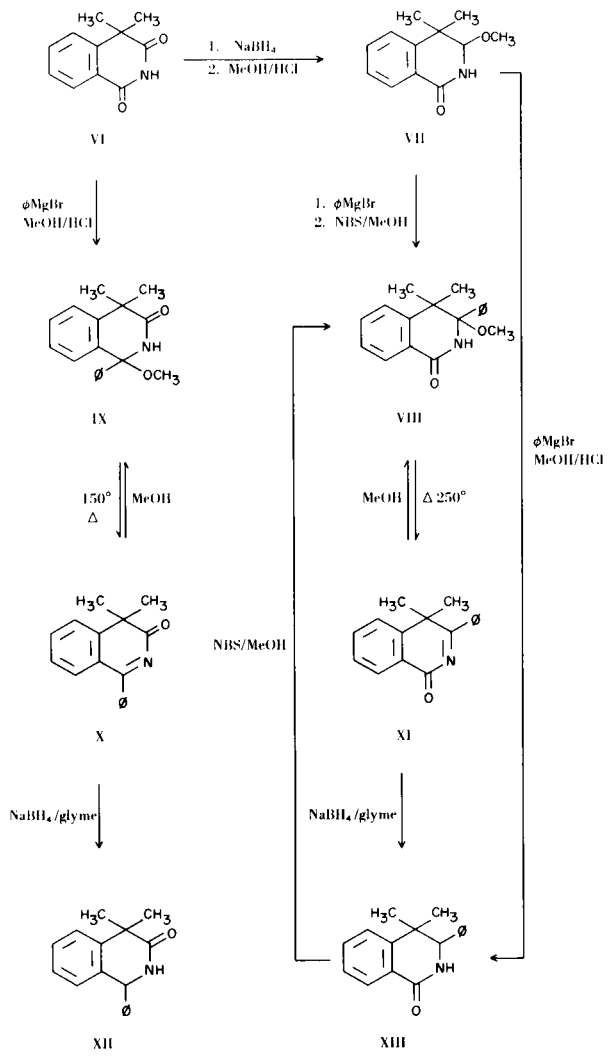
III IV V

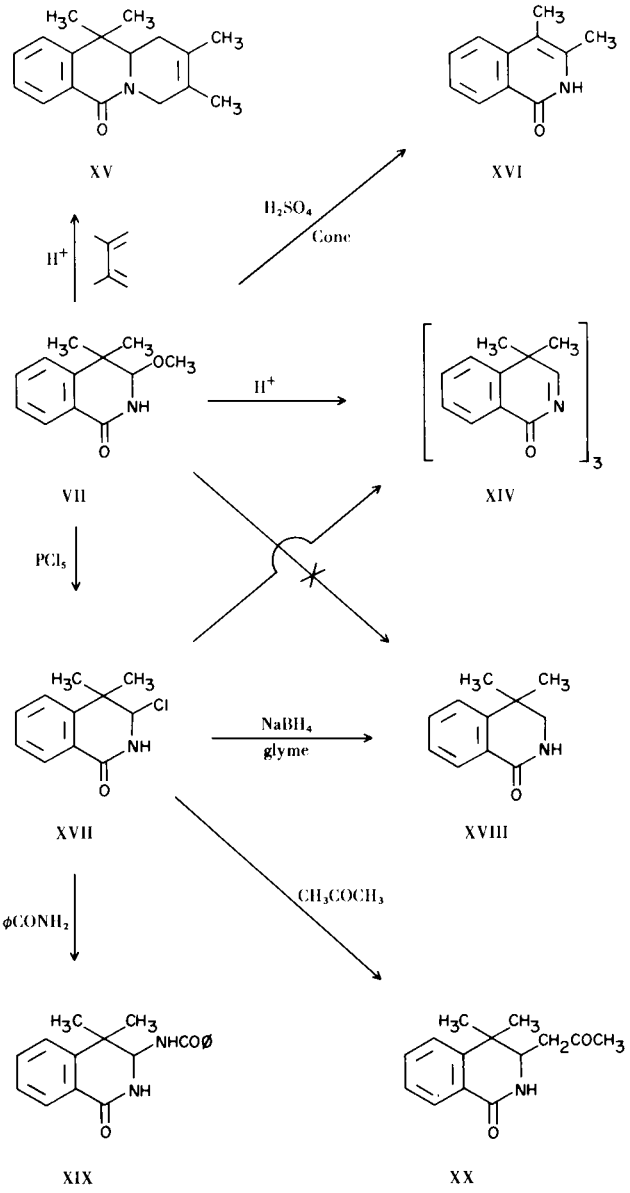
The 4-*gem*-dimethyl group should prevent the isomerization of III to the isocarbostyril and also prevent the enolization of IV to 3-hydroxyisoquinoline.

As starting material, 4,4-dimethylhomophtalimide (VI) was employed which gave upon reduction with sodium borohydride and subsequent treatment with methanolic hydrogen chloride, 3-methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinolone (VII). The nonconjugated carbonyl of VI was selectively reduced leaving the conjugated one unaffected. Treatment of the methoxy-1-isoquinolone with phenylmagnesium bromide followed by bromination with *N*-bromosuccinimide in methanol introduced a phenyl substitutent in the 3 position of VII giving 3-methoxy-3-phenyl-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinolone (VIII). The isomeric 1-phenyl-1-methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-3-isoquinolone (IX) was obtained by reacting the starting material (VI) with phenylmagnesium bromide and treating the carbinolamide intermediate with methanolic hydrogen chloride.

The two cyclic methoxyamides VIII and IX lose methanol on heating (150-250°) to give the desired cyclic acylimines, X and XI, as yellow solids. The 1-phenyl-3,4-dihydro-3-isoquinolone derivative (X) has a carbon-nitrogen double bond conjugated to two phenyl groups and was therefore more stable than the other isomer; it was also formed at a lower temperature. Both isomers were reduced by sodium borohydride in glyme to the tetrahydroisoquinolones XII and XIII and both added methanol at room temperature to regenerate the methoxy amides. Compound XII was identified with a product obtained by the cyclization of dimethylphenylacetamide (XXI) and benzaldehyde. The isomer XI was found to be sensitive to moisture and on standing at room temperature, gave the corresponding carbinolamide.

The cyclic methoxyamides VIII and IX can be substituted for the acylimines in some of their chemical reactions. The two methoxy derivatives were found to react with acetone in the presence of an acid catalyst to give 1 or 3-acetonyl derivatives (type XXIV, XX). The 1-methoxy derivative (IX) was demethylated and reduced to XII with sodium borohydride while its isomer VIII was stable under the same experimental conditions. The more reactive the acylimine the less reactive was its methanol



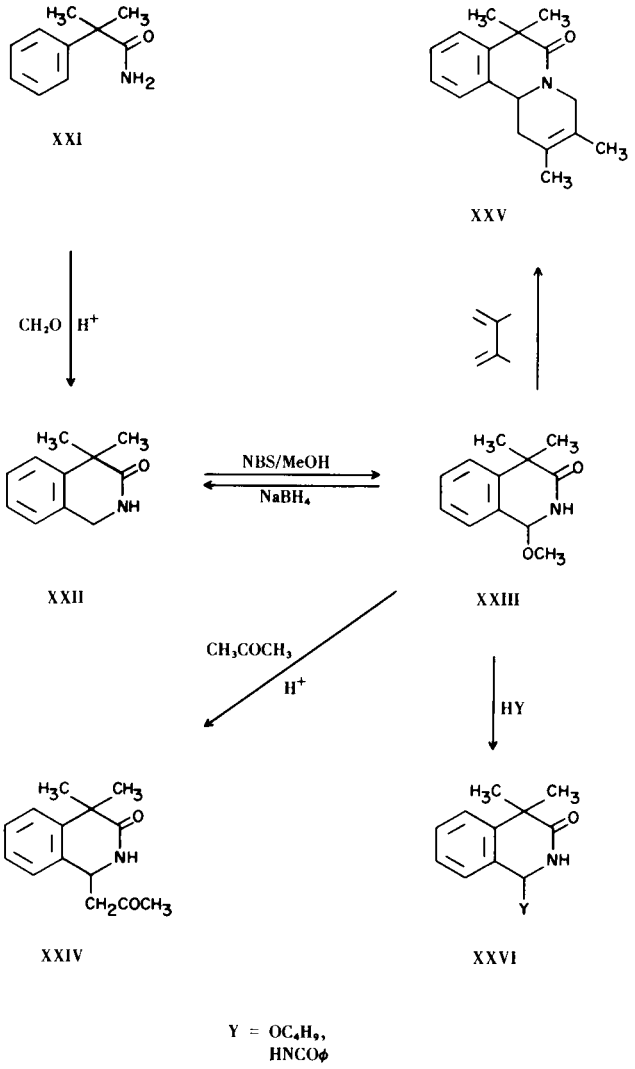


addition product.

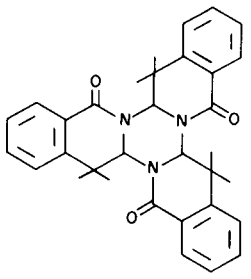
The 3-methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinolone (VII) which does not bear an additional phenyl group was found to be rather stable. It was distilled unchanged at 200° under reduced pressure and was not reduced with sodium borohydride in glyme after 40 hours In boiling benzene and in the presence of β-naphthalenesulfonic acid as catalyst, it was converted to a trimer, XIV, and in no case was the monomeric acylimine III isolated. This compound (VII) reacted with 2,3-dimethylbutadiene in boiling benzene containing an acid catalyst to give a Diels-Alder-type product (XV) whereas, in concentrated sulfuric acid it rearranged to 3,4-dimethyl isocarbostyril (XVI). Treatment of the methoxy derivative (VII) with phosphorus pentachloride afforded the chloro derivative (XVII) which was much more reactive than the corresponding methoxyamide. This was expected since chloride ion is a much better leaving group than the methoxy group. The chloro derivative reacted with benzamide and acetone to give the corresponding benzamide (XIX) and acetonyl (XX) derivatives. It was reduced with sodium borohydride to the lactam XVIII and was converted thermally to the triazine trimer (XIV). In its physical properties it differed from the chloro derivative in the azaphenalone series (4) which is a salt-like compound.

The isomeric 1-methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-3-isoquinolone (XXIII) was prepared by the cyclization of dimethyl phenylacetamide (XXI) with formaldehyde followed by NBS bromination in methanol of the lactam XXII. The reaction of the dimethyl phenylacetamide with benzaldehyde afforded the previously described 1-phenyl-1,2,3,4-tetrahydro-3-isoquinolone (XII).

This isomer XXIII was more reactive than the previous one (XII) in that it was reduced by sodium borohydride back to the lactam (XXII) and it lost methanol in boiling xylene to give a trimer. In this case, we also did not succeed in isolating the monomeric reactive cyclic acylimine IV. The 1-methoxy-1,2,3,4-tetrahydro-3-isoquinolone (XXIII) reacted thermally with weak nucleophiles to give the butoxy (XXVI, Y = C_4H_9O) or the benzamide dertive (XXVI; Y = ΦCONH). In the presence of an acid catalyst, it resembled the 3-methoxy isomer (VII) in its reaction with acetone to give the acetonyl derivative (XXIV).



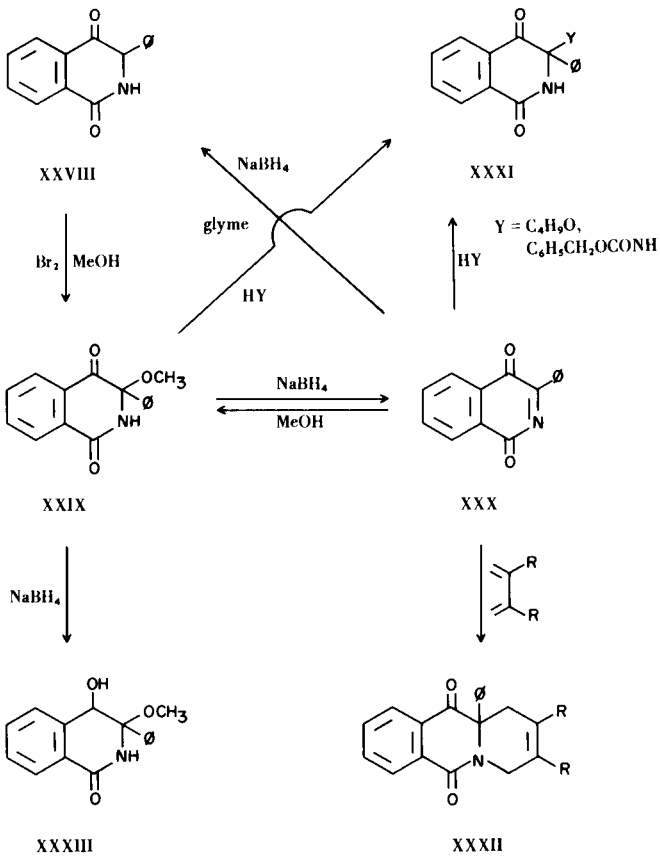
The two trimers mentioned above are symmetrical triazines (e.g. XIV) according to their physical properties. They showed weak molecular peaks in the mass spectra,



XIV

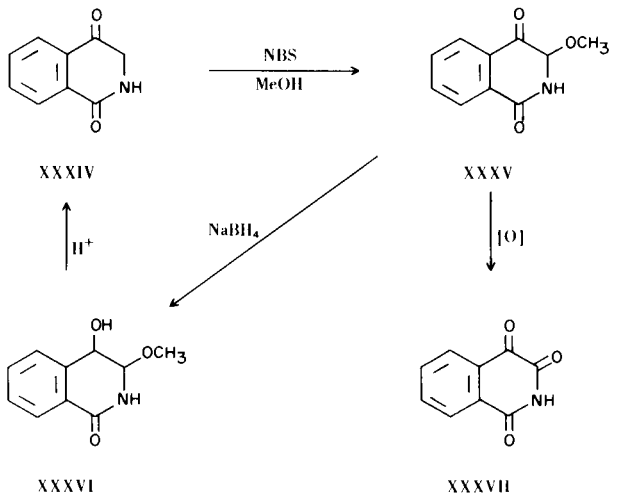
one carbonyl absorption at 1650-1660 cm^{-1} in the infrared and no NH absorptions. The N.M.R. spectrum of XIV showed six methyl singlets at δ 1-2 and three singlets at δ 6.80, δ 6.54 and δ 5.10 for the angular protons.

In the azanaphthaquinone series (V) we succeeded only in obtaining the phenyl derivative (XXX) or its methanol addition product (XXXV) described later. The phenylazanaphthoquinone was obtained, *via* its methanol addition product (XXIX) by the bromination in methanol in the presence of sodium methylate, of 3-phenyl-1,2,3,4-tetrahydroisoquinoline-1,5-dione (XXVIII). The methoxy derivative (XXIX) which is thermally quite stable, afforded the unsaturated azaquinone only after treatment with thionyl chloride and subsequent distillation of the reaction product. It was obtained as a very reactive red solid



which added alcohols, benzylcarbamate, dimedone and water readily at room temperature to give colorless products (XXXI). The azanaphthoquinone (XXX) reacted at room temperature in a benzene solution with butadiene and 2,3-dimethylbutadiene to give Diels-Alder type products (XXXII). The methoxy derivative (XXIX) can be substituted for the unsaturated azanaphthoquinone in some of its reactions. It reacted with butanol, benzyl carbamate and dimedone, in the presence of an acid catalyst, to give the addition products (XXXI). Its ketonic carbonyl group was preferentially reduced by sodium borohydride to give XXXIII. This type of compound, 3-phenyl-3-ethoxy-1,2,3,4-tetrahydroisoquinoline-1,4-dione is described in the literature and was obtained by a ring contraction of a 1,4-benzoxazepine (5).

We did not succeed in obtaining the unsubstituted azanaphthoquinone (V). Even the methoxy derivative (XXXV), which was obtained by the NBS bromination of the 1,2,3,4-tetrahydroisoquinoline-1,4-dione (XXXIV) in methanol, was unstable. It was oxidized, on standing at room temperature for three days, to phthalonimide (XXXVII). Sodium borohydride was found to reduce the ketonic carbonyl group of XXXV, in analogy to the reduction of the phenyl derivative (5) (XXIX) to give the methoxy hydroxy derivative (XXXVI). The latter, on treatment with an acid was further converted to the starting material (XXXIV). In the presence of an acid



XXXIV XXXV XXXVI XXXVII

catalyst the 3-methoxy-1,2,3,4-tetrahydroisoquinoline-1,4-dione reacted sluggishly with the nucleophiles described above to give a mixture of polymeric materials.

EXPERIMENTAL

Melting points are corrected, infrared spectra were measured in chloroform solutions and N.M.R. spectra in deuteriochloroform (unless otherwise indicated).

3-Methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinolone (VII).

To a suspension of dimethyl homophthalimide (XI) (6) (10.0 g., 0.053 mole) in methanol (120 ml.) there was added, with stirring and cooling (0°), sodium borohydride (4.0 g., 0.106 mole). After 20 minutes of additional stirring, methanolic hydrogen chloride was added slowly to the solution (60 ml., 20%). The acidic solution was poured into a cooled solution of sodium bicarbonate (200 ml., 2%). The product was extracted with ethyl acetate (3 x 200 ml.) and the organic solution was washed with water, dried over sodium sulphate and evaporated to dryness. The residue was triturated with hexane filtered and crystallized from cyclohexane. The product melted at 127°, yield 8.6 g. (79%). It showed NH absorption at 3410 cm^{-1} and CO absorption at 1675 cm^{-1} in the infrared. The N.M.R. spectrum showed singlets at δ 3.36 (3H), δ 1.49 (3H) and δ 1.30 (3H), doublets at δ 8.63 (1H, J = 5 cps), δ 8.10 (1H), and δ 4.29 (1H, J = 5 cps) and a multiplet at δ 7.6-7.2 (3H); mass spectrum m/e 205.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.88; H, 7.70; N, 7.02.

This compound was distilled unchanged at 200° (1 mm), and did not change in refluxing butanol for 24 hours.

3-Phenyl-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinolone (XIII).

The above described methoxytetrahydroisoquinolone (VII) (8.2 g., 0.040 mole) was added to a stirred solution of phenylmagnesium bromide (0.2 mole) in dry ether (300 ml.). Stirring and heating was continued for 16 hours. The solution was cooled, methanol (25 ml.) was added followed by methanolic hydrogen chloride (50 ml., 20%) and water. The aqueous layer was extracted with ether (3 x 100 ml.) and the ether solution was washed with water, dried and evaporated. The residue was chromatographed over neutral alumina (300 g.) and the product was eluted with chloroform. It was crystallized from ethyl acetate-hexane and melted at 142-143°, yield 5.40 g. (54%). It showed NH absorption at 3400 cm^{-1} and CO absorption at 1670 cm^{-1} in the infrared.

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.47. Found: C, 81.14; H, 7.22; N, 5.32.

3-Methoxy-3-phenyl-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinolone (VIII).

A mixture of the 3-phenyl derivative (XIII) described above (2.5 g.), *N*-bromosuccinimide (3.2 g.) in dry methanol (50 ml.) was refluxed by use of an infrared lamp; the red solution became colourless after a short period. After one hour another portion of *N*-bromosuccinimide (3.2 g.) was added and the reflux was continued for an additional 1.5 hour. The cooled solution was poured into aqueous bicarbonate (100 ml., 5%) and the product was extracted with ether. The ether solution was dried and evaporated to dryness. The solid residue obtained was chromatographed over deactivated alumina (100 g. alumina + 10 ml. methanol) and the product was eluted with hexane and crystallized from ethyl acetate-hexane. It melted at 193-194°, yield 2.3 g. (82%). The methoxyamide showed NH absorption at 3400 cm^{-1} and CO absorption at 1670 cm^{-1} in the infrared. The N.M.R. spectrum showed singlets at δ 3.03 (3H), δ 6.7 (1H, broad), δ 1.39 (3H) and δ 1.03 (3H) and a multiplet at δ 7.6-7.3 (3H); U.V. λ max (methanol) 258 mμ ($\epsilon = 1.8 \times 10^3$), 282 mμ ($\epsilon = 1.2 \times 10^3$); mass spectrum m/e 281.

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.54; H, 7.28; N, 4.67.

1-Methoxy-1-phenyl-4,4-dimethyl-1,2,3,4-tetrahydro-3-isoquinoline (IX).

The dimethylhomophthalimide (VI) (1.52 g., 0.008 mole) was

added to a stirred solution of phenylmagnesium bromide (0.040 mole) in dry ether (100 ml.) and stirring and heating were continued for one hour. To the cooled solution (0°) dry methanol (40 ml.) was added slowly followed by methanolic hydrogen chloride (20 ml., 20%). The solution was stirred for one hour at room temperature and then poured into aqueous sodium carbonate (0.80 ml., 10%). The organic layer was separated, washed with water, dried and evaporated to dryness. The solid residue was chromatographed over deactivated neutral alumina (50 g. alumina + 5 ml. methanol) and eluted with hexane to give 1.2 g. (53%) of product which melted at 130° after crystallization from ethyl acetate-hexane. The methoxyamide showed NH absorption at 3380 cm^{-1} and CO absorption at 1670 cm^{-1} in the infrared. The N.M.R. spectrum showed singlets at δ 6.32 (1H, broad), δ 3.09 (3H), δ 1.64 (6H) and a multiplet at δ 7.6-7.1 (9H); U.V. λ max (methanol) 212 mμ ($\epsilon = 1.4 \times 10^4$); mass spectra m/e 281.

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.97; H, 6.81; N, 5.01.

The same methoxy derivative (mixed m.p., I.R. and N.M.R.) was also obtained by the bromination of 1-phenyl-4,4-dimethyl-3,4-dihydro-3-isoquinolone with *N*-bromosuccinimide in methanol as described above for the preparation of 3-methoxy-3-phenyl-1-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolone.

1-Phenyl-4,4-dimethyl-3,4-dihydro-3-isoquinolone (X).

The methoxy derivative (IX) described above (1 g.) was heated in a sublimation apparatus at 150° (0.1 mm) and the yellow sublimate was crystallized from hexane. It melted at 87°; yield 0.7 g. (78%). The yellow product showed, in carbon tetrachloride solution, CO absorption at 1725 and C=N absorption at 1685 cm^{-1} in the infrared, but did not show any NH absorption. The N.M.R. spectrum showed one singlet at δ 1.50 (6H) and a multiplet at δ 7.8-7.1 (9H); U.V. λ max (carbon tetrachloride) 290 mμ ($\epsilon = 1.1 \times 10^4$); U.V. λ max (concentrated sulfuric acid) 203 mμ ($\epsilon = 5.5 \times 10^3$), 314 mμ ($\epsilon = 1.1 \times 10^4$), 360 mμ ($\epsilon = 1.2 \times 10^4$). The U.V. spectrum in concentrated sulfuric acid was identical with the spectrum of IX in the same solvent.

Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.96; H, 6.11; N, 5.63.

1-Phenyl-4,4-dimethyl-1,2,3,4-tetrahydro-3-isoquinolone (XII).

To a solution of the above 1-phenyl-3,4-dihydro-3-isoquinolone (X) (0.14 g.) in dry glyme (5 ml.) there was added excess sodium borohydride (0.1 g.). The yellow colour disappeared very rapidly. After 15 minutes the solution was acidified and extracted with ethyl acetate. The organic layer was dried and evaporated to dryness, and the residue was crystallized from ethyl acetate-hexane. The yield was 80 mg. (57%), m.p. 158°.

This product was identical with a product obtained by refluxing a solution of α,α-dimethylphenylacetamide (20 g., 0.12 mole), benzaldehyde (25 ml., 0.25 mole) in glacial acetic acid (250 ml.) containing concentrated sulfuric acid (50 ml.) for 24 hours. The cooled solution was poured into water and extracted with ethyl acetate (3 x 150 ml.). The ethyl acetate solution was washed with aqueous bicarbonate (10%), water and dried over magnesium sulfate. The residue obtained after the removal of the solvent was crystallized from ethyl acetate-hexane to give 13.5 g. (44%) of a crystalline product, m.p. 159°. It showed NH absorption at 3400 cm^{-1} and CO absorption at 1668 cm^{-1} in the infrared. The N.M.R. spectrum showed singlets at δ 7.26 (5H), δ 5.57 (1H), δ 1.62 (3H), δ 1.52 (3H) and a multiplet at δ 7.4-6.7 (5H); U.V. λ max (methanol) 216 mμ ($\epsilon = 8.2 \times 10^3$); m/e 251.

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.14; H, 6.74; N, 5.52.

3-Phenyl-4,4-dimethyl-1,4-dihydro-1-isoquinolone (XI).

3-Methoxy-3-phenyl-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinolone (VIII) (0.5 g.) was heated at 250° for 10 minutes. The pale yellow product was unstable, it absorbed water on standing and reacted immediately with methanol to regenerate the methoxy derivative. It showed (dry carbon tetrachloride) CO absorption at 1690, C=N absorption at 1680 cm^{-1} and no NH absorption in the infrared. The N.M.R. spectrum showed a singlet at δ 1.64 (6H) and multiplets at δ 8.3-8.1 (1H) and δ 7.7-7.3 (8H); U.V. (carbon tetrachloride) λ max 268 mμ (ϵ 2.1 x 10^4), 280 mμ ($\epsilon = 2.0 \times 10^4$) and 286 mμ ($\epsilon = 2.0 \times 10^4$); U.V. (concentrated sulfuric acid) λ max 232 mμ ($\epsilon = 1.9 \times 10^3$), 310 mμ ($\epsilon = 3.6 \times 10^3$). The spectrum in concentrated sulfuric acid was identical with the spectrum of the methoxy derivative (VIII) in concentrated sulfuric acid.

3-Phenyl-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinolone (XIII).

3-Phenyl-4,4-dimethyl-1,4-dihydro-1-isoquinolone (XI) (0.1 g.) in dry glyme (2 ml.) was reduced with sodium borohydride as described above for the 1-phenyl-3,4-dihydro-3-isoquinolone. The residue obtained after the removal of the solvent was identical with 3-phenyl-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinolone described above.

3-Acetonyl-3-phenyl-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinolone.

A solution of the methoxylactam (VIII, 0.28 g.) and 2-naphtalenesulfonic acid (50 mg.) in dry acetone was refluxed for 48 hours. The solvent was evaporated and the residue was chromatographed over neutral alumina (20 g.). The product was eluted with benzene-methylene chloride (1:1) and crystallized from ethyl acetate-hexane. It melted at 162°, yield 0.19 g. (62%). The product showed NH absorption at 3385 cm^{-1} and two carbonyl absorptions at 1730 and 1665 cm^{-1}. The N.M.R. spectrum showed singlets at δ 7.38 (5H), δ 6.95 (1H, J = 18), and multiplets at δ 9.3-8.1 (1H), and δ 7.6-7.3 (3H); mass spectrum m/e 307.

Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89, N, 4.56. Found: C, 78.32; H, 7.05; N, 4.47.

1-Acetonyl-1-phenyl-4,4-dimethyl-1,2,3,4-tetrahydro-3-isoquinolone.

The methoxylactam (IX) was treated with acetone as described above for the 3-methoxylactam (VIII). The product melted at 153° after crystallization from ethyl acetate-hexane, yield 0.29 g. (94%). It showed NH absorptions at 3360 cm^{-1} and two carbonyl absorptions at 1725 and 1665 cm^{-1} in the infrared. The N.M.R. spectrum showed singlets at δ 7.5 (1H, broad), δ 7.28 (5H), δ 2.10 (3H), δ 1.65 (3H), δ 1.53 (3H), doublets at δ 3.82 (1H, J = 17), δ 3.17 (1H, J = 17) and a multiplet at δ 7.6-7.0 (4H).

Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56. Found: C, 77.83; H, 6.97; N, 4.50.

Tri(4,4-dimethyl-1,4-dihydro-1-isoquinolone) (XIV).

A solution of the methoxy derivative VII (0.34 g.) in benzene (20 ml.) and β-naphtalenesulfonic acid (50 mg.) was refluxed for 16 hours. The benzene was removed *in vacuo* and the residue chromatographed over alumina (14 g.) and eluted with benzene. The product melted at 255° after crystallization from hexane, yield 0.15 g. (53%). It showed CO absorption at 1660 cm^{-1} and no NH absorption in the infrared. The N.M.R. spectrum showed singlets at δ 8.18 (1H), δ 8.06 (1H), δ 6.80 (1H), δ 5.10 (1H),

δ 1.98 (3H), δ 1.58 (3H), δ 1.51 (3H), δ 1.42 (3H), δ 1.36 (3H), δ 1.08 (3H) and a multiplet at δ 7.8-7.1 (10H); mass spectrum m/e 519.

Anal. Calcd. for $(C_{11}H_{11}NO)_3$: C, 76.27; H, 6.40; N, 8.09. Found: C, 75.94; H, 6.64; N, 7.89.

3-Chloro-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinolone (XVII).

A suspension of the methoxy compound (VII, 1.0 g.) and phosphorus pentachloride (1.1 g.) in dry ether (10 ml.) was stirred for 15 minutes. The starting materials went first into solution and the product then precipitated out. The suspension was cooled in the refrigerator and filtered to give a crystalline product that melted at 121-122°, yield 0.93 g. (91%). It was kept in a desiccator over potassium hydroxide. It showed NH absorption at 1670 cm^{-1} in the infrared. The N.M.R. spectrum showed singlets at δ 5.69 (1H, broad), δ 1.51 (6H) and multiplets at δ 8.8-8.0 (2H) and δ 7.6-7.2 (3H); mass spectrum m/e 173 (M-HCl).

Anal. Calcd. for $C_{11}H_{12}ClNO$: Cl, 16.90. Found: Cl, 16.45.

Thir product was unstable and decomposed on standing.

Diels-Alder Adduct with 2,3-Dimethylbutadiene,2,3,11,11-Tetramethyl-4,6-11,11a-tetrahydro-1*H*-pyrido[1,2-*b*]-6-isoquinolone (XV).

A solution of VII (2.0 g.), dimethylbutadiene (4.0 ml.) and trifluoroacetic acid (2.0 ml.) in benzene (60 ml.) was refluxed for 60 hours. The solution was washed with aqueous bicarbonate (5%) and dried over anhydrous sodium sulfate. The residue obtained after the removal of the solvent was chromatographed over basic alumina (80 g.) and the product, 1.3 g. (53%) showed a CO absorption at 1640 cm^{-1} and no NH absorptions in the infrared. The N.M.R. spectrum showed singlets at δ 1.67 (3H, broad), δ 1.55 (3H, broad), δ 1.36 (6H), doublets at δ 4.87 (1H, J = 17), δ 3.36 (1H, J = 17), a quartet at δ 3.37 (1H) and multiplets at δ 8.1-7.9 (1H), δ 7.4-7.1 (3H), δ 2.1-1.7 (2H); mass spectrum m/e 255.

Anal. Calcd. for $C_{21}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.70; H, 8.26; N, 5.18.

3,4-Dimethylisocarbostyril (XVI).

A solution of VII (0.27 g.) in concentrated sulfuric acid (3 ml.) was left at room temperature for 3 hours and then poured onto crushed ice. The aqueous suspension was extracted with ethyl acetate and the solid obtained after the evaporation of the solvent was triturated with ether and crystallized from methanol. The dimethylisocarbostyril melted at 265-266°, yield 0.10 g. (44%).

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.33; H, 6.81; N, 8.08.

Sodium Borohydride Reduction of XVII.

To a stirred suspension of the chloro compound (XVII) (0.3 g., 1.4 mmoles) in dry glyme (2 ml.) there was added sodium borohydride (0.056 g., 1.4 mmoles). After stirring for half an hour the suspension was distributed between ethyl acetate and aqueous hydrochloric acid (3%). The organic layer was separated, dried over magnesium sulfate and evaporated. The residue was crystallized from hexane to give 0.17 g. (67%) of the lactam (XVIII) which melted at 133°. The lactam showed NH absorption at 3420 cm^{-1} and CO absorption at 1670 cm^{-1} in the infrared. The N.M.R. spectrum showed a singlet at δ 1.38 (6H), a doublet at δ 3.37 (2H, J = 3) and multiplets at δ 8.2-8.0 (1H) and δ 7.6-7.33 (4H); mass spectrum m/e 175.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 74.92; H, 7.52; N, 7.70.

Under the same experimental conditions and stirring for 40 hours, the methoxy derivative VII was recovered unchanged.

3-Benzamido-4,4-dimethyl-1,2,3,4-tetrahydro-1-isoquinolone (XIX).

A suspension of the chloro compound XVII (0.212 g., 1 mmole), benzamide (0.123 g., 1 mmole) in dry ether (10 ml.) was stirred for 16 hours at room temperature. The product was filtered and crystallized from benzene-hexane. The yield was 0.13 g. (42%); m.p. 182-183°. It showed NH absorption at 3400 cm^{-1} and 1500 cm^{-1} and CO absorption at 1670 cm^{-1} broad, mass spectrum m/e 294.

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.70; H, 6.59; N, 9.41.

3-Acetonyl-4,4dimethyl-1,2,3,4-tetrahydro-1-isoquinolone (XX).

A solution of the chloro compound (XVII) (0.35 g.) in dry acetone (10 ml.) was refluxed for 16 hours. The acetone was evaporated and the residue was chromatographed over basic alumina (10 g.). Elution with methylene chloride afforded an oil which solidified in the refrigerator. It melted at 120-121° after crystallization from hexane, yield 0.2 g. (52%). It showed NH absorption at 3410 cm^{-1} and two CO absorptions at 1718 and 1665 cm^{-1}, mass spectrum m/e 231.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.42; H, 7.41; N, 6.08.

4,4-Dimethyl-1,2,3,4-tetrahydro-3-isoquinolone (XXII).

A suspension of α,α-dimethylphenylacetamide (XXI) (41 g., 0.25 mole), paraformaldehyde (8.6 g., 0.29 mole) and sulfuric acid (20 ml.) in glacial acetic acid (400 ml.) was stirred until it became homogeneous (0.5 hour). The solution was then refluxed for 16 hours, cooled and poured onto crushed ice. The mixture was extracted three times with ethyl acetate and the organic layer was washed with water, aqueous bicarbonate (10%) and dried over magnesium sulfate. The residue obtained after the removal of the solvent was triturated with ether. It is sensitive to oxidation and was therefore purified only by repeated trituration with ether. It melted at 122-123°, yield 36 g. (82%). The lactam showed singlets at δ 7.78 (1H, broad), δ 1.49 (6H), a doublet at δ 4.51 (2H, J = 2.5) and a multiplet at δ 7.4-7.1 (4H); mass spectrum m/e 175.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.12; H, 7.68; N, 7.84.

1-Methoxy-4,4-dimethyl-1,2,3,4-tetrahydro-3-isoquinolone (XXII).

A suspension of the lactam described above (XXII, 46 g., 0.26 mole) and *N*-bromosuccinimide (51 g., 0.29 mole) in absolute methanol (46.0 ml.) was refluxed by use of an infrared lamp until the red color disappeared (3 hours). The cooled solution was neutralized with anhydrous potassium carbonate (30 g.), filtered, and the methanol was evaporated. The residue was chromatographed on a deactivated neutral alumina (800 g. alumina + 80 ml. methanol). The product was eluted with hexane to give a crystallized product which melted after trituration with ether at 133-135°, yield 12 g. (21%). This product is also sensitive to air oxidation. It showed NH absorption at 3400 cm^{-1} and CO absorption at 1675 cm^{-1} in the infrared. The N.M.R. spectrum showed singlets at δ 7.98 (1H, broad), δ 3.33 (3H), δ 1.61 (3H) and δ 1.57 (3H), a doublet at δ 5.55 (1H, J = 4) and multiplet at δ 7.5-7.2 (4H); mass spectrum m/e 205; λ max (sulfuric acid), 335 mμ ($\epsilon = 6.2 \times 10^3$); λ max (methanol), 212 mμ ($\epsilon = 4.5 \times 10^3$).

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.24; H, 7.41; N, 6.53.

Tri(4,4-dimethyl-3,4-dihydro-3-isoquinolone) (XXVII).

A solution of XXIII (0.20 g.) in xylene (4.0 ml.) was refluxed for 6 hours. The yellow color slowly disappeared. The xylene was removed under reduced pressure and the residue was chromatographed over florisil (10 g.). The column was eluted with benzene to give the trimer which melted at 278-280° after crystallization from methanol, yield 0.1 g. (58%). The trimer showed a CO absorption at 1670 cm^{-1}, no NH band was observed. The N.M.R. spectrum showed singlets at δ 7.74 (1H), δ 6.0 (1H), δ 5.8 (1H), δ 1.61 (6H), δ 1.52 (3H), δ 1.40 (3H), δ 1.35 (3H) and multiplets at δ 8.2-7.9 (1H) and δ 7.5-7.1 (11H). The N.M.R. of the trimer was identical in concentrated sulfuric acid with the N.M.R. of the methoxy derivative XXIII, except for the δ 4.01 band (CH_3OSO_3-H).

The U.V. spectrum of the trimer and XXIII were also identical in concentrated sulfuric acid; mass spectrum m/e 519.

Anal. Calcd. for $(C_{11}H_{11}NO)_3$: C, 76.27; H, 6.40; N, 8.09. Found: C, 75.96; H, 6.53; N, 7.89.

Sodium Borohydride Reduction of XXIII.

The methoxy-tetrahydro-3-isoquinolone (XXIII, 0.205 g., 1 mmole) in 2-propanol (2 ml.) was treated with sodium borohydride (0.05 g., 1.3 mmoles). After two hours the solution was poured onto cold hydrochloric acid (3%), extracted with ethyl acetate and the organic layer dried over anhydrous magnesium sulfate. The residue 0.05 g. (87%) was identical with the lactam XXII.

The Reaction of XXIII with Benzamide.

A mixture of the methoxy-tetrahydro-3-isoquinolone (XXIII) (0.205 g., 1 mmole) and benzamide (0.13 g., 1.05 mmoles) in xylene (10 ml.) was refluxed for 16 hours. Hexane (20 ml.) was added to the cooled solution and the solid was filtered and crystallized from benzene. The yield was 0.15 g. (51%), m.p. 164-165°. It showed NH absorption at 3440, 3390 and 1500 cm^{-1} and a broad CO absorption at 1670 cm^{-1}; mass spectrum m/e 294.

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.55; H, 6.30; N, 9.31.

The Reaction of XXIII with Acetone.

A solution of the methoxy derivative XXIII (0.205 g., 1 mmole) and acetone (0.3 ml.) in trifluoroacetic acid (1 ml.) was left at room temperature for 16 hours. The solution was poured onto crushed ice and extracted with ethyl acetate. The ethyl acetate solution was washed with water, aqueous bicarbonate (5%) and dried over magnesium sulfate. The residue obtained after the removal of the solvent was crystallized from carbon tetrachloride. The yield of the acetonyl derivative (XXIV) was 0.21 g. (91%), m.p. 100-101°. It showed NH absorption at 3400 cm^{-1} and two CO absorptions at 1720 and 1660 cm^{-1}. The N.M.R. spectrum showed singlets at δ 7.48 (1H, broad), δ 2.13 (3H), δ 1.48 (3H) and δ 1.46 (3H), a doublet at δ 2.90 (2H, J = 6), a triplet at δ 5.0 (1H) and a multiplet at δ 7.3-7.0 (4H); mass spectrum m/e 231.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.39; H, 7.26; N, 6.67.

3-Methoxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline-1,4-dione (XXIX).

To a cold solution of the sodium salt of XXVIII, which was prepared from sodium (0.22 g., 9.6 mmoles) and the lactam (1.0 g., 4.2 mmoles), in methanol (35 ml.) there was added, dropwise with stirring, a solution of bromine (0.74 g., 4.6 mmoles) in methanol (10 ml.). The neutral solution was stirred for another 15 minutes and was poured onto crushed ice. It was extracted with ethyl acetate and the organic layer was washed with water and dried over sodium sulfate. The residue obtained after the removal of the solvent was crystallized from methanol. The yield was 1.1 g. (98%), m.p. 152° dec. The product showed NH absorption at 3380 cm^{-1} and two CO absorptions at 1700 and 1680 cm^{-1}. The N.M.R. spectrum showed a singlet at δ 3.4 (3H) and a multiplet at δ 7.2-8.5 (10H); mass spectrum m/e 267.

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.84; H, 4.88; N, 5.08.

3-Phenylazanaphthaquinone (XXX).

A mixture of the methoxy derivative (XXIX, 1 g.) and thionyl chloride (1.5 ml.) was heated for 15 minutes in an oil bath (100°). The excess thionyl chloride was removed *in vacuo* and the residue was distilled at 180° (0.1 mm). The red oil solidified to give a reactive compound which melted at 99-103°, yield 0.8 g. (72%). On exposure to air it absorbed water to give the colorless hydroxy compound. The red solid showed two absorptions in the CO region at 1600 and 1690 cm^{-1} (carbon tetrachloride). It was too reactive to be submitted to elementary analysis.

The Reaction of XXX with Butanol.

To a solution of the azanaphthoquinone (0.1 g.) in dry benzene (3 ml.) was added, butanol (0.2 ml.) with stirring. The color disappeared upon the addition of the butanol. The excess benzene was removed under reduced pressure and the residue was crystallized from benzene-hexane. The yield was 0.10 g. (81%), m.p. 194° dec. It showed NH absorption at 3380 cm^{-1}, CO absorption at 1680 and 1700 cm^{-1} in the infrared; mass spectrum m/e 309.

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.81; H, 6.01; N, 4.44.

The Reaction of XXX with Benzylcarbamate.

The procedure described above was used. After 15 minutes the solvent was evaporated and the product crystallized from benzene. The yield was 97%, m.p. 194-195°. The 3-carbobenzoxyamino derivative (XXXI, Y = C_6H_5OCONH) showed NH absorptions at 3400, 3350 and 1505 cm^{-1} and CO absorptions at 1680, 1710 and 1735 cm^{-1} in the infrared. The N.M.R. spectrum showed a singlet at δ 5.1 (2H) and a multiplet at δ 7.2-8.5 (11H); mass spectrum m/e 386.

Anal. Calcd. for $C_{23}H_{18}N_2O_4$: C, 71.49; H, 4.70; N, 7.25. Found: C, 71.77; H, 4.84; N, 6.97.

The Reaction of XXX with Butadiene (XXXII, R = H).

To a solution of butadiene in benzene (5 ml., 80%) there was added phenylazanaphthoquinone (XXX, 1.34 g.) and trifluoroacetic acid (0.5 ml.). The red color disappeared after 2 hours. The solution was concentrated under reduced pressure and the residue was chromatographed over neutral alumina (40 g.). The column was eluted with hexane to give 1.27 g. (77%) of a product (XXXII, R = H) which melted at 128° after crystallization from benzene-hexane. It showed (carbon tetrachloride) three absorptions in the carbonyl region at 1650, 1580 and 1700 cm^{-1}. The N.M.R. spectrum showed a singlet at δ 7.25 (5H), quartets at δ 2.7-3.5 (2H) and δ 3.5-5.9 (2H), and multiplets at δ 5.4-5.9 (2H) and δ 7.5-8.5 (4H); mass spectrum m/e 289.

Anal. Calcd. for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.70; H, 5.19; N, 5.22.

Catalytic hydrogenation in ethyl acetate over palladium-

charcoal (10%), afforded the reduced product which melted at 104°.

The Reaction of XXX with 2,3-Dimethylbutadiene (XXXII, R = CH_3).

A solution of phenylazanaphthoquinone (XXX, 0.4 g.) 2,3-dimethylbutadiene (1 ml.) and trifluoroacetic acid (0.1 ml.) in benzene (5 ml.) was treated as described above for the butadiene. The crude product was chromatographed over neutral alumina (15 g.) and the column was eluted with methylene chloride to give 0.30 g. (55%) of product (XXXII, R = CH_3) which melted at 165° after crystallization from benzene-hexane. It showed (carbon tetrachloride) absorption in the CO region at 1655, 1665 and 1700 cm^{-1}. The N.M.R. spectrum showed singlets at δ 1.55 (3H), δ 1.75 (3H) and δ 7.28 (5H), quartets at δ 2.7-3.4 (2H) δ 3.4-4.8 (2H) and a multiplet at δ 7.5-8.5 (4H).

Anal. Calcd. for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.85; H, 6.06; N, 4.58.

The same product was obtained in 92% yield when the reaction was carried out at room temperature for 24 hours without an acid catalyst.

The Reaction of the Methoxy XXIX with Butanol.

A solution of XXIX (0.1 g.) in butanol (7 ml.) was refluxed for 1 hour in the presence of β-naphthalenesulfonic acid (0.01 g.). The product obtained after the removal of the solvent was identical with the butoxy derivative described above (XXXI, Y = C_4H_9O), yield 95%.

The reaction was also carried out in refluxing butanol for 3 hours in the presence of sodium butylate (0.01 g.) or thermally for 4 days in refluxing butanol.

The Reaction of XXXIX with Benzyl Carbamate.

A solution of XXXIX (0.10 g.), benzyl carbamate (57 mg.) and β-naphthalenesulfonic acid in benzene (5 ml.) was refluxed for 3 hours. The benzene solution was washed with water, dried and evaporated to dryness. Trituration with ether afforded the carbobenzoxyamino derivative described above (XXXI, Y = $HNCO_2CH_2C_6H_5$) in 93% yield.

The Reaction of XXXIX with Dimedone.

A suspension of XXIX (0.1 g.), dimedone (0.053 g., 1 eq.) was refluxed in benzene (10 ml.) and in the presence of β-naphthalenesulfonic acid (0.01 g.) for 3 hours. The solid which separated on cooling was filtered, triturated with methanol and then crystallized from methanol. The yield was 85%, m.p. 236° dec. It showed (potassium bromide) OH and NH absorptions in the 3500-3000 region (broad) and CO absorption at 1675 (broad); mass spectrum m/e 375.

Anal. Calcd. for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.37; H, 5.92; N, 3.89.

The same product was also obtained by stirring a benzene suspension of the unsaturated compound XXX with dimedone for 20 minutes at room temperature.

The Reducation of XXIX with Sodium Borohydride (XXXIII).

To a solution of XXIX (0.1 g.) in absolute methanol there was added, with stirring, sodium borohydride (0.060 g.). After stirring for 24 hours the solution was poured onto water and extracted with ethyl acetate. After the removal of the solvent there was obtained a white crystalline material which melted at 145-146° dec., yield 0.075 g. (74%). It showed OH absorption at 3560 cm^{-1}, NH absorption at 3395 cm^{-1} and CO absorption at 1680 cm^{-1} in the infrared. The N.M.R. spectrum showed a singlet at δ 3.1 (3H), a doublet at δ 4.8 (1H, J = 10 cps.) and a multiplet at δ 7.2-8.3 (10H).

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.38; H, 5.61; N, 5.20. Found: C, 71.46; H, 5.82; N, 5.07.

3-Methoxy-1,2,3,4-tetrahydroisoquinoline-1,4-dione (XXXV).

To a cold suspension (-10°) of 1,2,3,4-tetrahydro-isoquinoline-1,4-dione (3.0 g.) (XXXIV) in absolute methanol there was added, under nitrogen, freshly prepared *N*-bromosuccinimide (3.3 g., 1 eq.). After 10 minutes, the solid was filtered off and was washed with cold absolute methanol. It was crystallized from methanol and kept in a vacuum desiccator over phosphorus pentoxide. The yield was 2.2 g. (63%), m.p. 154-155° dec. This compound is unstable and slowly oxidizes to phthalonimide. It showed NH absorption at 3400 cm^{-1} and CO absorptions at 1690 and 1700 cm^{-1}. The N.M.R. spectrum showed a methoxy singlet at δ 3.48, a doublet at δ 4.90 (1H) and a multiplet at δ 7.6-8.4 (5H); mass spectrum m/e 191.

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82, H, 4.75; N, 7.33. Found: C, 62.54; H, 5.14; N, 7.96.

In most of its reactions the methoxy derivative was oxidized to phthalonimide or converted, in the presence of an acid to a polymeric mixture.

Sodium Borohydride Reduction of XXXV.

To a suspension of the methoxy derivative (0.25 g.) in absolute methanol (8 ml.) there was added, portionwise with stirring, sodium borohydride (0.1 g.). Stirring was continued until the yellow color disappeared (2 hours). The methanol solution was diluted with water and extracted into ethyl acetate. The solid residue obtained after the removal of the solvent was crystallized from chloroform. The yield of XXXVI was 72%, m.p. 198° dec. The hydroxymethoxylactam showed OH absorption at 3430 cm^{-1} and a CO absorption at 1690 cm^{-1} in the infrared. The N.M.R. spectrum (pyridine d_5) showed a singlet at δ 3.37 (3H); multiplets at δ 5.2 (1H) and δ 7.10-8.5 (5H) and broad peaks at δ 5.45 (1H) and δ 9.95 (1H); mass spectrum m/e 193.

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N. 7.25. Found: C, 62.12; H, 5.80; N, 7.20.

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Received December 20, 1969 Haifa, Israel