

Synthesis of 1-Cyclohexyl-substituted Isoquinoline Derivatives

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In contrast with earlier literature data [7], both acrylic esters and acrylonitrile underwent Michael addition to 1-methyl-3,4-dihydroisoquinolines **1-4** to yield the diesters **5-9** or the dinitrile **10**, respectively. Compounds **5-10** were converted by Claisen condensation to 1-[(3'-methoxycarbonyl- or 1-[(3'-ethoxycarbonyl-4'-oxo)-1'-cyclohexyl]-3,4-dihydroisoquinoline derivatives **11-16**. Several derivatives of **12** were prepared. The new compounds possess various pharmacological actions.

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Introduction.

For some time we have investigated the reactions of compounds obtained by addition to the 1-methyl group of 1-methyl-6,7-dialkoxy-3,4-dihydroisoquinolines **2** and **3** [2-5]. From 1-[bis(hydroxymethyl)methyl]-6,7-dialkoxy-3,4-dihydroisoquinolines, prepared from **2** and **3** with paraformaldehyde, a number of azeto[2,1-*a*]isoquinoline, 1,3-oxazino- and 1,3-thiazino[4,3-*a*]isoquinoline derivatives have been prepared for pharmacological screening [6-11]. Our present aim was to utilize the reactivity of the 1-methyl group of 1-methyl-3,4-dihydroisoquinoline (**1**), 1-methyl-6,7-dialkoxy-3,4-dihydroisoquinolines **2** and **3** and 1-methyl-6,7-methylenedioxy-3,4-dihydroisoquinoline (**4**) with acrylates and acrylonitrile, and further transformations of the adducts, in order to obtain potential pharmaceuticals.

Synthesis.

Openshaw and Whittaker [12] reported that 1-methyl-3,4-dihydroisoquinoline (**1**) did not react with acrylonitrile. We have found that 1-methyl-3,4-dihydroisoquinoline (**1**), 1-methyl-6,7-dimethoxy- and 6,7-diethoxy-3,4-dihydroisoquinoline **2** and **3** and the corresponding 6,7-methylenedi-

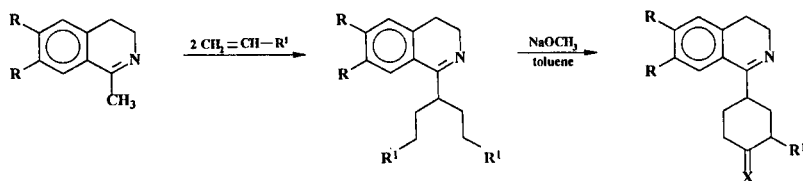
oxy derivative **4** undergo Michael addition in methanol with two moles of methyl or ethyl acrylate, or with acrylonitrile, to give the corresponding dicarboxylates **5-9** or dinitrile **10** *via* the monoadducts.

When the reactants were used in 1:1 molar ratio, a mixture of the mono- and diadducts of the acrylic ester or acrylonitrile were formed; the crude product also contained some unchanged starting material. The components of these mixtures were separated by fractional crystallization [13]. With two or more equivalents of acrylic esters or acrylonitrile, the diadducts were formed as the only products. The monoadducts could be transformed to the diadducts by using one or more equivalents of acrylic ester or acrylonitrile.

The resulting diadducts **5-10** were converted by Dieckmann condensation in toluene, in the presence of sodium methoxide, to β -ketocarboxylates **11-15** and the iminonitrile **16** (Scheme 1).

The β -ketocarboxylates **11-16** contain the pharmacophore 3,4-dihydroisoquinoline unit, in which the 3'-ethoxy-carbonyl-4'-cyclohexanon-1'-yl substituent is suitable for various further transformations. Thus, the readily available compounds **11-16** are promising starting materials

Scheme 1



1: R = H
2: R = OCH₃
3: R = OC₂H₅
4: R,R = OCH₂O

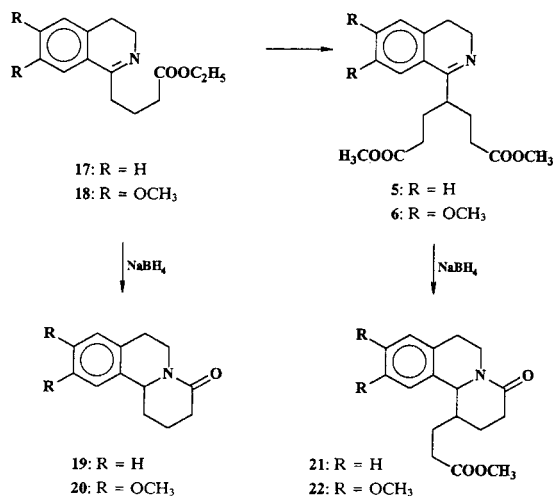
5: R = H, R' = COOCH₃
6: R = OCH₃, R' = COOC₂H₅
7: R = OCH₃, R' = COOCH₃
8: R = OC₂H₅, R' = COOCH₃
9: R,R = OCH₂O, R' = COOCH₃
10: R = OCH₃, R' = CN

11: R = H, R' = COOCH₃, X = O
12: R = OCH₃, R' = COOC₂H₅, X = O
13: R = OCH₃, R' = COOCH₃, X = O
14: R = OC₂H₅, R' = COOCH₃, X = O
15: R,R = OCH₂O, R' = COOCH₃, X = O
16: R = OCH₃, R' = CN, X = NH

for the syntheses of potential medicinal agents.

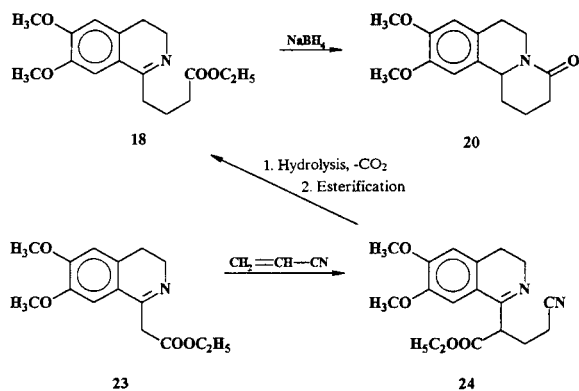
After the completion of our experiments [2], a paper dealing with related compounds was published by Indian authors [14]. They prepared the corresponding benzoquinolizinones **19-22** by sodium borohydride reduction of the mono- **17** and **18** and diadducts **5** and **6** (Scheme 2), and described the reaction as a new one-step synthesis of benzoquinolizinones. However, it probably escaped their attention that Agbalian *et al.* [15] reacted methyl acrylate with 1-methyl-3,4-dihydroisoquinoline (**1**), and isolated quinolizinones as by-products formed on heating.

Scheme 2



Similarly, the paper of the Indian authors [14] did not mention the result of Kóbor and Sohár [16] that 6,7-dimethoxy-1-(ethoxycarbonylpropyl)-3,4-dihydroisoquinoline (**18**) was synthesized by addition of acrylonitrile to 1-ethoxycarbonylmethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**23**), followed by hydrolysis and subsequent esterification of the intermediate **24**. Sodium borohydride reduction of **18** proceeded with ring closure and gave the benzoquinolizinone **20**. Its structure was elucidated *via* the spectroscopic data and *via* lithium aluminium hydride reduction

Scheme 3

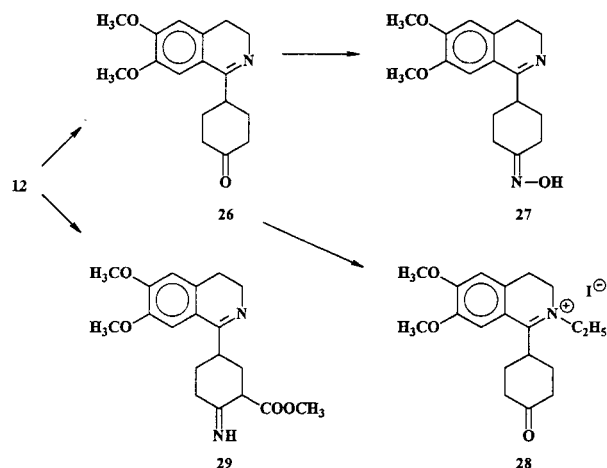


of the carbonyl group to yield the known benzoquinolizinone derivative (Scheme 3).

The ketoester **12** itself, besides being a versatile synthon, exerts anti-ulcer and sedatohypnotic actions; therefore, it seemed worthwhile to study the conversions of this compound and prepare several of its derivatives.

On heating with hydrochloric acid, the hydrolysis of **12** proceeds with decarboxylation, as is usual with β -ketoacids, and the 4'-oxo compound **26** was obtained. This 1-isoquinolylcyclohexanone derivative was converted to the oxime **27** with hydroxylamine or to the corresponding quaternary salt **28** with ethyl iodide. Reaction of **12** with ammonia furnished the corresponding imino derivative **29** (Scheme 4).

Scheme 4



The ketoester **12** showed good anti-ulcer, and sedatohypnotic effects; **27** is a sedatohypnotic agent, while the cyanoimide derivative **16** displays strong antihypertensive action. Of the starting diadducts, the dinitile **10** exerts cardiotoxic and anticonvulsive actions [17].

EXPERIMENTAL

Melting points were determined on a Boetius micro melting point apparatus and are uncorrected. The homogeneity of the compounds prepared was tested by tlc (silica gel G layer; developing solvent: benzene-ethanol 4:1; detection in iodine vapour).

The structures of the compounds were confirmed by ir and ¹H- and ¹³C-nmr spectroscopy. The ir spectra were recorded in potassium bromide pellets on a Spectromom 2000 instrument. The ¹H nmr spectra were recorded on Bruker spectrometer at 400 MHz, with tetramethylsilane as internal standard. The spectra obtained corresponded to the structures given in the Schemes.

1-Methyl-6,7-dimethoxy-3,4-dihydroisoquinoline and 1-methyl-3,4-dihydroisoquinoline were prepared according to published methods ([18,19] and [20,21], respectively). Double adducts **6** and **7** were prepared as described earlier [13]. Melting points were as follows: **6**, 54-56° (ether); **7**·HCl, 147-150° (acetone-ether).

Dimethyl or Diethyl [4-(3',4'-Dihydro-1'-isoquinolin-1-yl)]pimelates **5**, **8**, and **9**.

1-Methyl-3,4-dihydroisoquinoline **1**, **3** or **4** (0.1 mole) was dissolved in benzene (50 ml), methyl or ethyl acrylate (0.3 mole) was added, and the solution was refluxed for 24 hours. The progress of the reaction was followed by tlc. The solvent and the excess of acrylate were removed by distillation, and the residual brown oil was used for the further reactions without purification.

4-(6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)pimelonitrile **10**.

A mixture of 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline (**1**) (23.3 g, 0.1 mole) and acrylonitrile (26.5 g, 0.5 mole) was refluxed in benzene (150 ml) under a nitrogen atmosphere for 48 hours. The progress of the reaction was monitored by tlc. When the conversion was complete, the solvent and the excess of acrylonitrile were removed by evaporation and the residue was crystallized from ethanol. Repeated recrystallization gave 19.9 g (64%) of **10**, mp 105-106°. The hydrochloride was crystallized from ethanol, mp 168-169°.

Anal. Calcd. for $C_{18}H_{22}ClN_3O_2$ (347.85): C, 62.15; H, 6.38; Cl, 10.19; N, 12.08. Found: C, 62.23; H, 6.58; Cl, 10.08; N, 12.26.

1-[(3'-Methoxycarbonyl- or ethoxycarbonyl-4'-oxo)-1'-cyclohexyl]-3,4-dihydroisoquinolines **11-15**.

Diadduct **5-9** (0.1 mole) was dissolved in toluene (15 ml) and the solution was added to sodium methoxide, freshly prepared from 7 g of sodium with methanol and evaporated to dryness. Dissolution was effected by gently heating the mixture on a rotary evaporator. Simultaneously with the dissolution, separation of the sodium salt started; reduced pressure (30 mm Hg) was then applied, and a part of the solvent was evaporated off. The evaporated toluene was replaced, the reaction mixture was refluxed in an oil bath for 3 hours, and the evaporation and replacement of the solvent were repeated during refluxing for a further 6 hours. After removal of most of the toluene, the mixture was allowed to cool and was acidified with 25% hydrochloric acid under cooling. The thus dissolved reaction product was separated from the remaining toluene in a separatory funnel. The aqueous phase was clarified with activated carbon, filtered, and made alkaline with a saturated solution of potassium carbonate. After cooling, the separated crystals were filtered off, washed with a small amount of water, then with ether, and dried.

The hydrochlorides were prepared from the bases dissolved in absolute ethanol by the addition of a solution of hydrogen chloride in dry ethanol. The acidified solutions were evaporated to dryness, the residues were dissolved in dry ethanol and the hydrochlorides were precipitated by addition of ether.

Compound **11** was obtained in a yield of 76%, mp 98-101° (ethyl acetate).

Anal. Calcd. for $C_{17}H_{19}NO_3$ (285.35): C, 71.56; H, 6.71; N, 4.91. Found: C, 71.64; H, 6.96; N, 4.73.

Compound **12** was obtained in a yield of 91%, mp 125-126° (ethyl acetate).

Anal. Calcd. for $C_{19}H_{23}NO_5$ (345.40): C, 66.07; H, 6.71; N, 4.06. Found: C, 66.25; H, 7.01; N, 4.26.

Compound **12**·HCl had mp 200° (methanol-ether).

Anal. Calcd. for $C_{19}H_{24}ClNO_5$ (381.86): C, 59.76; H, 6.34; Cl, 9.28; N, 3.67. Found: C, 59.50; H, 6.61; Cl, 9.49; N, 3.75.

Compound **13** was obtained in a yield of 83%; mp 103-105° (ether).

Anal. Calcd. for $C_{20}H_{25}NO_5$ (359.43): C, 66.84; H, 7.01; N, 3.90.

Found: C, 67.08; H, 7.08; N, 4.01.

Compound **13**·HCl had mp 213-214° (ethanol).

Anal. Calcd. for $C_{20}H_{26}ClNO_5$ (395.89): C, 60.68; H, 6.62. Found: C, 60.75; H, 6.55.

Compound **15** was obtained in a yield of 66%, mp 135-135° (ethyl acetate).

Anal. Calcd. for $C_{18}H_{19}NO_5$ (329.36): C, 65.65; H, 5.81; N, 4.25. Found: C, 65.74; H, 5.97; N, 4.18.

With the above method, diester **8** did not give a crystalline product **14**. The crude product was extracted with ether. However, column chromatographic purification of the extract still failed to give a crystalline compound; the preparation of a crystalline hydrochloride also remained unsuccessful. The structures of the compounds were proved by preparing 1-isoquinolinylquinazolinones [17] from the crude oily products and by characterizing these by elementary analysis and nmr spectroscopy.

1-[(3'-Cyano-4'-imino)-1'-cyclohexyl]-6,7-dimethoxy-3,4-dihydroisoquinoline (**16**).

4-(6,7-Dimethoxy-3,4-dihydroisoquinolin-1'-yl)pimelonitrile (**10**) (12.4 g, 0.04 mole) was dissolved in toluene (200 ml), and the solution was poured onto sodium methoxide freshly prepared from sodium 2.3 g, 0.1 g-atom) in methanol and evaporated to dryness. The suspension was refluxed under a nitrogen atmosphere for 12 hours. The progress of the reaction was followed by tlc. When the conversion was complete, the reaction mixture was cooled and washed with water (2 x 250 ml). The toluene solution was dried over anhydrous sodium sulphate and evaporated to dryness. The residue was crystallized from a mixture of ethanol and acetone to give 8.5 g (68%) of **16**, mp 189-190°.

Anal. Calcd. for $C_{18}H_{21}N_3O_2$ (311.39): C, 69.43; H, 6.80; N, 13.49. Found: C, 69.51; H, 7.09; N, 13.25.

The hydrochloride was prepared from the base with an equivalent amount of hydrogen chloride in ethanol; it was recrystallized from a mixture of ethanol and acetone; mp 250-255° dec.

1-(4'-Oxo-1'-cyclohexyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**26**).

β -Ketoester **12** (16.7 g, 0.05 mole) was dissolved in 100 ml of 4 N hydrochloric acid and the mixture was gently boiled until the evolution of carbon dioxide had ceased (about 1 hour). The reaction mixture was evaporated to dryness, the residue was dissolved in water, and the aqueous solution was made alkaline with ammonium hydroxide. The separated crystals were recovered by filtration and recrystallized from ether to give 10.6 g (74%) of **26**, mp 103-106°.

Anal. Calcd. for $C_{17}H_{21}NO_3$ (287.36): C, 71.06; H, 7.37; N, 4.87. Found: C, 70.82; H, 7.29; N, 4.90.

The hydrochloride was prepared in the usual way from the base **27**, after recrystallization from a mixture of methanol and acetone, mp 207-208°.

Anal. Calcd. for $C_{17}H_{22}ClNO_3$ (323.82): C, 63.06; H, 6.85; Cl, 10.95; N, 4.33. Found: C, 63.17; H, 6.81; Cl, 10.63; N, 4.45.

1-(4'-Oxo-1'-cyclohexyl)-6,7-dimethoxy-3,4-dihydroisoquinoline Oxime (**27**).

1-(4'-Oxo-1'-cyclohexyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**26**) (11.5 g, 0.04 mole) and hydroxylamine hydrochloride (3.46 g, 0.05 mole) were dissolved in methanol (100 ml). A solution of sodium (1.14 g, 0.05 g-atom) in methanol (20 ml) was added, and the mixture was stirred for 2 hours at room temperature, and

then gently refluxed for 10 hours. After evaporation to dryness, the residue was triturated with water, filtered off, and recrystallized from methanol to give 10.6 g (88%) of **27**, mp 200-202°.

Anal. Calcd. for C₁₇H₂₂N₂O₃ (302.38): C, 67.53; H, 7.33; N, 9.26. Found: C, 67.51; H, 7.43; N, 9.36.

1-(4'-Oxo-1'-cyclohexyl)-2-ethyl-6,7-dimethoxy-3,4-dihydroisoquinolinium Iodide (**28**).

1-(4'-Oxo-1'-cyclohexyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**26**) (5.7 g, 0.02 mole) was dissolved in benzene (50 ml), and ethyl iodide (3.1 g, 0.04 mole) was added to the solution. The reaction mixture was gently boiled, with stirring, for 6 hours. The excess of the solvent and ethyl iodide were then removed by distillation. The residue was recrystallized from ethanol to give 5.6 g (64%) of **28**, mp 218-219° dec.

Anal. Calcd. for C₁₉H₂₆INO₃ (443.33): C, 51.48; H, 5.91; N, 3.16. Found: C, 51.27; H, 5.73; N, 3.31.

1-[(3'-Methoxycarbonyl-4'-imino)-1'-cyclohexyl]-6,7-dimethoxy-3,4-dihydroisoquinoline (**29**).

A 28% methanolic solution of ammonia (200 ml) was added to 1-[(3'-methoxycarbonyl-4'-oxo)-1'-cyclohexyl]-6,7-dimethoxy-3,4-dihydroisoquinoline (**12**), and the reaction mixture was allowed to stand at room temperature for 72 hours, with occasional shaking. It was then evaporated to dryness under reduced pressure (30 mm Hg) and the residue was collected with methanol on a filter to obtain 15.2 g (88%) of **29**, mp 114-115°. The compound was recrystallized from methanol.

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