REDUCTIVE CYCLIZATION OF o-CYANOCINNAMIC ACIDS AND THEIR ANALOGS*

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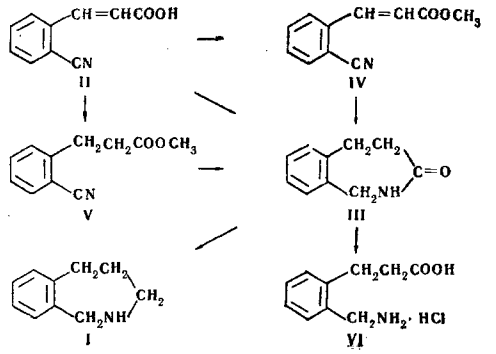
The hydrogenation of esters of o-cyanocinnamic acid or α-(o-cyanoaryloxy)carboxylic acids over Raney nickel leads to the corresponding seven-membered lactams. Subsequent reduction of these with lithium aluminum hydride gives 2,3,4,5-tetrahydro[1H]benzo[c]azepine and 1,2,3,5-tetrahydro[4H]benzo[*f*]-1,4-oxazepine.

Publications regarding the synthesis and pharmacological study of benzazepine derivatives have appeared in recent years [2,3]. It was also found that the alkaloids papaverrubine and roladine have benzazepine in their fundamental structures [4,5]. The most promising compounds for the synthesis of potential medicinals in the benzazepine series is 2,3,4,5-tetrahydro[1H]benzo[c]azepine (I), previously obtained by the cyclization of N-tosyl-N-phenylpropylglycine [6] or by the reduction of 6,7-dihydro[5H]tetrazolo[4,5-*a*]-benzo[c]azepine [7]. A number of its N-alkyl derivatives were synthesized by the reaction of o-(chloromethyl)phenylpropyl chloride with amines [8]. All of these routes are preparatively inconvenient, and we therefore set up a number of experiments involving the reductive cyclization of o-cyanocinnamic acids, which are readily formed by the Beckmann rearrangement of 1-nitroso-2-hydroxynaphthalene [9].



The experiments on the hydrogenation of cis-o-cyanocinnamic acid (II) over Raney nickel at room temperature and pressure were unsuccessful. 2,3,4,5-Tetrahydro[1H]benzo[c]azepin-3-one (III) could not be isolated after removal of the solvent and many hours of refluxing of the catalyzate at 150-175°. If, however, one hydrogenates the cis- or trans-methyl ester of o-cinnamic acid (IV) or, even better, the methyl ester of β-(o-cyanophenyl)propionic acid (V), lactam III can be obtained in 70% yield. The geometry of the double bond in esters IV does not have an appreciable effect on the course of the reduction, which makes it possible to assume the stepwise transformation of IV to V and then to III.

The PMR spectrum of lactam III contains a multiplet from the four protons of the CH_2CH_2- group at 2.37-3.10 ppm and a singlet from the CH_2N group (4.20 and 4.28 ppm), which is split due to interaction with

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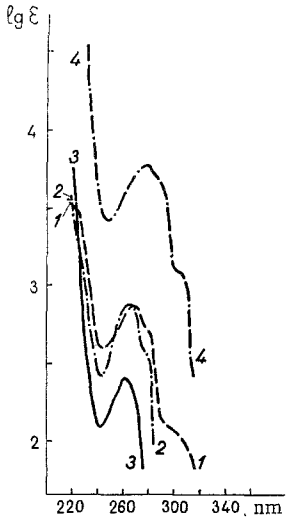
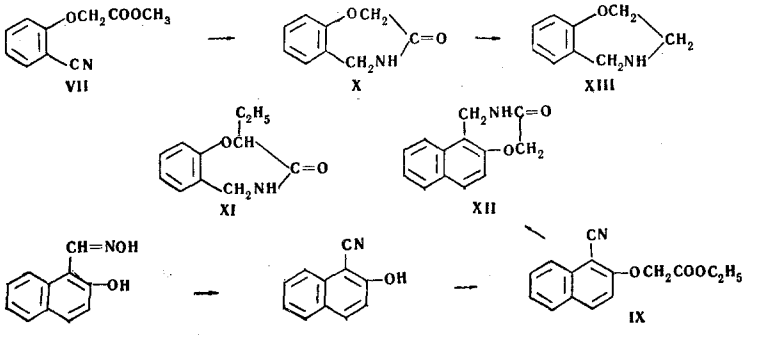


Fig. 1. UV spectra of lactams in 96% ethanol: 1) 2-ethyl-1,2,3,5-tetrahydro-[4H]benzo[*f*]-1,4-oxazepin-3-one (XI); 2) 1,2,3,5-tetrahydro[4H]benzo[*f*]-1,4-oxazepin-3-one (X); 3) 2,3.4,5-tetra-hydro[1H]benzo[c]azepin-3-one (III); 4) 1,2,3,5-tetrahydro[4H]naphtho[1,2-*f*]-1,4-oxazepin-3-one (XII).

the NH group. o-(Aminomethyl)hydrocinnamic acid (VI) forms readily during the acid hydrolysis of III, while the reduction of III with lithium aluminum hydride leads to I, the physical constants of which are in agreement with those described in the synthesis by another path [6]. Our III melted at 136°C, while the formation of this lactam with mp 109-110° was described in the Schmidt rearrangement from 2-tetralone [10]. We repeated this rearrangement and obtained a mixture of substances with mp about 110°, from which a pure lactam with mp 136° that was identical to our compound could be isolated by repeated crystallization and preparative chromatography on aluminum oxide.

We have thus developed a route to the synthesis of tetrahydrobenzazepine I and its 3-oxo derivatives, and this compelled us to make an evaluation of the applicability of this method to the synthesis of homologs and analogs. In particular, it was desireable to find a route to the synthesis of 1,2,3,5-tetrahydro-[4H]benzo[*f*]-1,4-oxazepine, for which accessible methods could not previously be found (see [11, 12], for example). With this end in mind, we synthesized the methyl ester of o-cyanophenoxyacetic acid (VII), and the ethyl esters of α-(o-cyanophenoxy)butyric acid (VIII) and 1-cyano-2-naphthoxyacetic acid (IX) by alkylation of the corresponding o-cyanophenols. A priori it might have been expected that the trans-annular interaction of the ester oxygen atom with the carbalkoxy group would promote cyclization, but simultaneously would also facilitate hydrolysis of the C–O bond. The introduction of branching (compound VIII) also might have promoted cyclization (the Thorpe–Ingold effect). In fact, the introduction of an oxygen atom in place of a CH_2 group or branching of the hydrocarbon chain did not affect the course of the reductive cyclization under our conditions. In all cases, the corresponding lactams (X-XII) were obtained in about equal yields. It is possible that the deciding factor in the process is the approach of the functional groups to the catalyst surface leading to the formation of an amide bond, similar to the situation in which the approach of groupings facilitates the acyloin condensation [13].

1,2,3,5-Tetrahydro[4H]benzo[*f*]-1,4-oxazepine (XIII) was obtained by the reduction of lactam X with lithium aluminum hydride. The PMR spectrum of lactam X has a singlet from the OCH_2 group (4.73 ppm) and a doublet of the second CH_2 group (4.40 and 4.33 ppm), the protons of which interact with the proton of the NH group. The UV spectra of all of the lactams are similar (Fig. 1). Replacement of the CH_2 group in lactam III by an oxygen atom in lactam X results in a shift of the absorption maximum to the long-wave region and appreciably raises the absorption intensity, which corresponds to transition of the electrons to the antibonding σ orbitals.



EXPERIMENTAL

The homogeneity of the compounds obtained and the selection of the reaction conditions were evaluated by means of chromatography in a loose, thin layer of activity II aluminum oxide. The chromatograms were developed with iodine vapors. A benzene–absolute ethanol (10 : 1) system was used for the lactams, while a benzene–hexane (4 : 1) system was used for the esters. The UV spectra of $1 \cdot 10^{-4}$ M ethanol solutions were recorded with an SF-4A spectrophotometer. The PMR spectra of pyridine solutions were recorded with an RS-60 spectrometer with an operating frequency of 60 MHz with hexamethyldisiloxane as the internal standard.

2,3,4,5-Tetrahydro[1H]benzo[c]azepin-3-one (III). A) A total of 17.5 g of a pulverized Raney alloy was added in small portions with stirring to 80 ml of 25% sodium hydroxide. To complete hydrogen evolution, the mixture was heated on a water bath, and the catalyst was then washed with distilled water (by decantation) until it no longer gave an alkaline reaction to litmus, and was then washed twice with 20 ml portions of methanol. After this, a solution of 8.95 g (0.05 mole) of methyl o-cyanophenylpropionate [1] in 30 ml of methanol was added to the catalyst, and, after hydrogen had been bubbled through, the compound was hydrogenated at the normal pressure for 3-4 h with periodic shaking of the flask. About 2.5 liter of hydrogen was absorbed (the calculated amount necessary for reduction of the nitrile group to an amino group). The methanol solution was then poured off, and the catalyst was washed twice with 15 ml of methanol. The solutions were combined, the solvent was removed by vacuum distillation on a water bath, and the residue was recrystallized from 100 ml of carbon tetrachloride to give 5.5 g (70%) of lactam III with mp 134-135°. The compound melted at 136° after repeated crystallization with activated charcoal.

B) Similarly, 4.6-5 g (56-60%) of lactam III with mp 133-135° was obtained from 8.85 g (0.05 mole) of methyl cis-o-cyanocinnamate [14] after the absorption of 3.5 liter of hydrogen (in 4-5 h). Under the same conditions, III with mp 136° and R_f 0.51 was obtained in 50-55% yield from methyl trans-o-cyanocinnamate [14] (trans-IV). UV spectrum: λ_{max} 250 nm (log ε 2.43).

o-Hydroxybenzonitrile. Salicylaldoxime [50 g (0.365 mole)] was stirred thoroughly with 150 ml of acetic anhydride. The solution was allowed to stand until the exothermic reaction was complete (30 min) and was then refluxed on a metal bath for 2 h. The solution was poured into 0.5 liter of hot water and shaken thoroughly. The mixture was then allowed to stand, and the aqueous layer was decanted. A total of 400 ml of 10% sodium hydroxide was added to the residue, and the mixture was refluxed until it was completely homogeneous, while maintaining an alkaline reaction to litmus. The mixture was cooled, and acidified with concentrated hydrochloric acid relative to Congo while stirring throughly in order to prevent the formation of lumps. The material was removed by suction filtration, washed with water, and air dried to give 25 g (57%) of nitrile with mp 98° (mp 98° [15]), which did not require special purification for the subsequent syntheses.

Methyl o-Cyanophenoxyacetate (VII). o-Hydroxybenzonitrile [24 g (0.2 mole)], 21.7 g (0.2 mole) of methyl chloroacetate, and 0.2 g of calcined sodium iodide were added successively with stirring to sodium ethoxide (from 4.6 of sodium in 200 ml of absolute ethanol), after which the mixture was refluxed for 2 h. It was then cooled, and the copious precipitate of sodium chloride was separated and washed with ethanol. The combined filtrates were evaporated, 200 ml of petroleum ether with bp 70-100° was added to the residue, and the mixture was stirred and cooled. The precipitate was removed by filtration and washed with petroleum ether and water to give 18.5 g (48%) of ester VII with mp 60° (from aqueous ethanol with activated charcoal) and R_f 0.51. Found %: N 7.42, 7.47. $C_{10}H_9NO_3$. Calculated %: N 7.33.

1,2,3,5-Tetrahydro[4H]benzo[*f*]-1,4-oxazepin-3-one (X). As in the synthesis of III, 3.6 g (94%) of lactam X with mp 113-114° (from CCl_4) and R_f 0.48 was obtained from 4.62 g (0.025 mole) of methyl ester VII in 50-60 ml of methanol after hydrogenation (for 2.5-3 h). Found %: N 8.63; 8.66. $C_9H_9NO_2$. Calculated %: N 8.69. UV spectrum: λ_{max} 268 nm (log ε 2.88).

Ethyl α-(o-Cyanophenoxy)butyrate (VIII). As in the synthesis of ester VII, 35 g (74%) of ester VIII with mp 65-66° (from aqueous ethanol) and R_f 0.54 was obtained from 24 g (0.2 mole) of o-hydroxybenzonitrile, 4.6 g of sodium in 200 ml of ethanol, and 39 g (0.2 mole) of ethyl α-bromobutyrate. Found %: N 6.60, 6.55. $C_{13}H_{15}NO_3$. Calculated %: N 6.43.

2-Ethyl-1,2,3,5-tetrahydro-[4H]-benzo[*f*]-1,4-oxazepin-3-one (XI). As in the synthesis of III, 4.2 g (73%) of lactam XI with mp 110-111° and R_f 0.66 was obtained from 7 g (0.03 mole) of ester VIII in 50 ml of methanol after hydrogenation. Found %: N 7.44, 7.51. $C_{11}H_{13}NO_2$. Calculated %: N 7.33. UV spectrum: λ_{max} 270 nm (log ε 2.89).

1-Cyano-2-naphthol. A mixture of 8.61 g (0.05 mole) of 2-hydroxy-1-naphthaldehyde, 6 g of sodium hydroxide in 50 ml of water, and 3.35 g (0.05 mole) of hydroxylamine hydrochloride was heated for 30 min on a water bath. The mixture was cooled, filtered, and acidified with hydrochloric acid with respect to Congo. The precipitate was removed by suction filtration and washed with water to give 8.6 g (91%) of oxime with mp 156° from aqueous ethanol [16].

A mixture of 8.42 g (0.045 mole) of this oxime and 30 ml of acetic anhydride was refluxed for 2 h. The hot solution was diluted with hot water, stirred, and allowed to stand. The aqueous layer was decanted, and the organic layer was again washed with water. The residue was dissolved in ethanol, 50-80 ml of 25% sodium hydroxide was added, and the mixture was heated until the solid dissolved completely. (The solution should be alkaline to litmus.) When the mixture was cooled (and sometimes even from the hot solution), a slightly soluble cyanonaphthoxide precipitated; after drying, this can be used for the subsequent experiments. In order to obtain the pure substance, this naphthoxide was dissolved with heating in water, and the solution was filtered and acidified with respect to Congo with hydrochloric acid. The precipitate was removed by filtration, washed with water, and crystallized from water to give 6 g (64%) of the hydroxynitrile with mp 152-153° [17].

Ethyl 1-Cyano-2-naphthoxyacetate (IX). 1-Cyano-2-naphthol [16.9 g (0.1 mole)], 12.3 g (0.1 mole) of ethyl chloroacetate, and 0.3 g of calcined sodium acetate were added to a solution of 2.3 g of sodium metal in 200 ml of absolute ethanol, and the mixture was refluxed until it was completely homogeneous (about 30 h). The hot solution was filtered and cooled. Water (100 ml) was added to the precipitate, and the residue was removed by suction filtration, washed with water, and air dried to give 17 g (67%) of ester IX with mp 99° (from CCl_4) and R_f 0.52. Found %: N 5.56, 5.59. $C_{15}H_{13}NO_3$. Calculated %: N 5.49.

1,2,3,5-Tetrahydro[4H]naphtho[1,2-*f*]-1,4-oxazepin-3-one (XII). As in the synthesis of III, 1.3 g (61%) of lactam XII with mp 213° (from aqueous ethanol or benzene) and R_f 0.63 was obtained by the hydrogenation of 2.55 g (0.01 mole) of ester IX in methanol over Raney nickel. Found %: N 6.62, 6.71. $C_{13}H_{11}NO_2$. Calculated %: N 6.67. UV spectrum: λ_{max} 278 nm (log ε 3.78).

o-(Aminomethyl)hydrocinnamic Acid (VI). A 0.5 g (0.003 mole) sample of lactam III was heated on a boiling-water bath in 3 ml of concentrated hydrochloric acid until it dissolved. The solution was then cooled to room temperature, and the precipitate was removed by suction filtration, squeezed, and dried in a vacuum desiccator over potassium carbonate to give 0.4 g (60%) of the hydrochloride of amino acid VI with mp 210° (dec., from ethanol). Found %: N 6.70, 6.75; Cl 16.44, 16.39. $C_{10}H_{13}NO_2 \cdot HCl$. Calculated %: N 6.49; Cl 16.47.

2,3,4,5-Tetrahydro[1H]benzo[c]azepine (I). A benzene solution of 7.65 g (0.05 mole) of lactam III was added dropwise to a solution of lithium aluminum hydride (from 4 g of lithium hydride in 200 ml of ether) in such a way that the ether boiled vigorously. The mixture was then refluxed for 20 h, and the excess aluminum hydride was decomposed initially with moist ethyl acetate and then with water. The precipitate was dissolved by adding water, the ether–benzene layer was separated, and the aqueous layer was extracted twice with 5 ml portions of ether. The combined extracts were dried with sodium sulfate, the solvent was removed by distillation, and the residue was vacuum distilled to give 5.5 g (80%) of compound I with bp 105° (6 mm). The chloroplatinate melted at 195°. The tosyl derivative melted at 134-135°, which is in agreement with the literature data [6].

2,3,4,5-Tetrahydro[1H]benzo[*f*]-1,4-oxazepines (XIII). As in the previous experiment, 4.1 g (50%) of XIII with bp 103-105° (4 mm) was isolated by the reduction of 9.2 g (0.06 mole) of lactam X after refluxing for 15 h and subsequent workup of the reaction mixture. The IR spectrum did not contain frequencies corresponding to a carbonyl group. According to [18], this compound boils at 122-129° (15 mm).

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