The pyrroles IIc, d, and f were obtained in an analogous manner.

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REDUCTION OF 4-OXO-4,6,7,8(5H)-TETRAHYDROPYRROLO[3,2-c]AZEPINES

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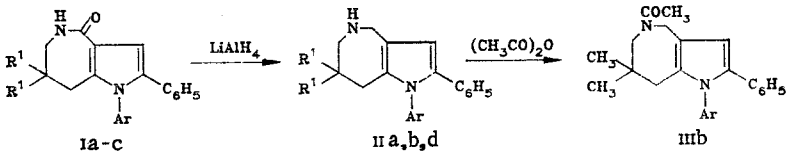
UDC 547.75'891.2:542.942

1,2-Diaryl-4,6,7,8(5H)-tetrahydropyrrolo[3,2-c]azepines are obtained via the reduction of 1,2-diaryl-4-oxo-4,6,7,8(5H)-tetrahydropyrrolo[3,2-c]azepines with lithium aluminum hydride. In the case of a bromophenyl substituent reduction of the bromine atom occurs as well; similarly, in the case of a nitroaryl-substituted lactam, reduction of the amide carbonyl function is accompanied by reduction of the nitro group to an azo group.

Recently we reported that the Beckmann rearrangement of aryl-substituted oximes of 4-oxo-4,5,6,7-tetrahydroindoles gave 4-oxo-4,6,7,8(5H)-tetrahydropyrrolo[3,2-c]azepines (I) [1]. Since derivatives of azepines and aminoalkylpyrroles possess interesting pharmacological properties, we have now investigated the reduction of the lactams Ia-c with lithium aluminum hydride, which has been frequently used to reduce cyclic amides [2, 3]. The reductions were carried out by extended (up to 30 h) reflux of a solution of the lactam in dry dioxane or dimethoxyethane with a fivefold excess of lithium aluminum hydride. The pyrroloazepines IIa, b, d were obtained in 50-67% yield. In the reduction of the lactam Ic hydroelimination of the halogen atom occurred simultaneously and resulted in the formation of the azepine Id. We note also, that since the azepine IIb was obtained as an oil, it was converted to the crystalline N-acetyl derivative IIIb for analysis.



a R^1=H, Ar=2-$CH_3C_6H_4$; b R^1=CH_3, Ar=4-$CH_3OC_6H_4$; c R^1=H, Ar=4-BrC_6H_4; d R^1=H, Ar=C_6H_5

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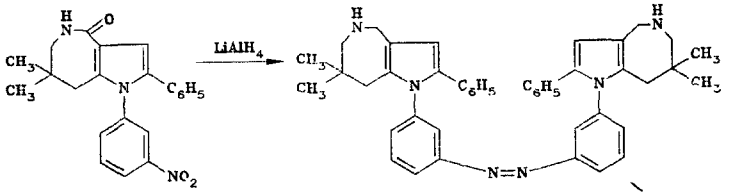
In the IR spectra of the azepines IIa and d, the carbonyl stretching frequency has disappeared from the 1600-1700 cm^{-1} region, and N–H stretching bands have appeared in the 3430-3460 cm^{-1} region. The mass spectra of compounds IIa and d contain peaks due to molecular ions* (at 302 and 288, respectively), which undergo loss of a hydrogen atom, followed by cleavage of C_2H_4, C_2H_5, C_3H_6, and C_3H_7 residues; this pattern is characteristic of the fragmentations of polymethylenearenes and hetarenes [4, 5]. The molecular ion of IIIb underwent facile elimination of the acetyl group, and the resulting ion (345) lost C_4H_7N and C_4H_8N to give ions at 276 and 275, characteristic of diaryltetrahydroindole derivatives [1, 6].

The reduction of the nitroaryl-substituted lactam Ie proceeded in an anomalous fashion, inasmuch as the reaction product IV displayed a molecular ion at 658; fragmentation of this ion occurred with loss of one or two hydrogen atoms, which is characteristic, as shown above, of hydropyrrolo[3,2-c]azepines. In addition, the mass spectrum of IV contained an intense peak at 315. The IR spectrum of this compound did not contain a carbonyl band; it did contain, however, the amino stretching vibration band at 3450 cm^{-1}, as well as an intense band in the 1450 cm^{-1} region, characteristic of an aromatic azo group [7, 8]. The formation of azo compounds via the reduction of aromatic nitro compounds is well known in the literature [9, 10].



Ie IV

The lithium aluminum hydride reduction of the lactams Ia-c constitutes a valuable new method for the preparation of 4,6,7,8(5H)-tetrahydropyrrolo[3,2-c]azepines.

EXPERIMENTAL

1-(2-Methylphenyl)-2-phenyl-4,6,7,8(5H)-tetrahydropyrrolo[3,2-c]azepine (IIa). To a solution of 270 mg (0.85 mmole) of lactam Ia in 40 ml of absolute dimethoxyethane was added dropwise over a period of 30 min a suspension of 100 mg (3 mmole) of lithium aluminum hydride in 200 ml of absolute dimethoxyethane. The resulting mixture was refluxed 5 h, cooled, 40 ml of ethyl acetate was added, followed by 8 ml of water dropwise with stirring. The resulting precipitate was removed, washed with ethyl acetate, and the organic filtrate was concentrated *in vacuo*. The residue was taken up in ether, extracted once with 10 ml of 10% aqueous hydrochloric acid, and three times with water. The combined aqueous extracts were neutralized with sodium hydroxide and extracted with methylene chloride. The methylene chloride solution was dried over anhydrous sodium sulfate, concentrated *in vacuo*, and the residue was recrystallized from ether–methylene chloride (1:1). Yield: 130 mg (50%), mp 234-237°C (decomp.). Found: C 83.6; H 7.3%. $C_{21}H_{22}N_2$. Calculated: C 83.4; H 7.3%. M 302. UV spectrum (ethanol); λ_{max} (log ε): 212 (4.87), 280 nm (4.18). IR spectrum (KBr): 3460 cm^{-1} (NH). Mass spectrum: 302 (100), 301 (30), 273 (48), 272 (76), 260 (43), 259 (46), 252 (39), 244 (39), 155 (39), 151 (48), 149 (76).

Reduction of 1-(4-Bromophenyl)-4-oxo-2-phenyl-4,6,7,8-tetrahydropyrrolo[3,2-c]azepine (Ic). To a solution of 450 mg (1.2 mmole) of lactam Ic in 80 ml dry dimethoxyethane was added dropwise over a period of 45 min a solution of 130 mg (3.6 mmole) of lithium aluminum hydride in 20 ml of absolute dimethoxyethane. The reaction mixture was refluxed 5 h and worked up as described above. 1,2-Diphenyl-4,6,7,8(5H)-tetrahydropyrrolo[3,2-c]azepine was obtained as cream-colored crystals, yield 220 mg (67%), mp 211-214°C. A Beilstein test was negative. IR spectrum (KBr): 3480-3430 cm^{-1} (NH). Mass spectrum 288 (M) (100), 287 (23), 271 (57), 259 (48), 258 (88), 246 (26, 245 (66), 244 (60), 116 (28), 63 (31), 60 (31). $C_{20}H_{20}N_2$. Calculated: M 288.

5-Acetyl-7,7-dimethyl-1-(4-methoxyphenyl)-2-phenyl-4,6,7,8(5H)-tetrahydropyrrole[3,2-c]-azepine (IIIb). A solution of 80 mg (0.2 mmole) of lactam Ib in 20 ml dry dioxane at 20°C was treated dropwise with a suspension of 50 mg (1.5 mmole) of lithium aluminum hydride in 20 ml of dry dioxane with vigorous stirring; the mixture was worked up in the manner described

*Mass spectral data is presented as m/z values for all ion peaks.

above to give 50 mg of a colorless oil which could not be crystallized. This oil was dissolved in 1 ml pyridine, 0.5 ml of acetic anhydride was added, and the resulting solution was heated 40 min on a water bath. The solution was cooled, 10 ml of cold water was added, and the resulting precipitate was removed by filtration, washed with 2% aqueous hydrochloric acid, dried, and chromatographed on a plate with a thick layer of alumina using ether–chloroform (1:1). The band with R_f 0.55 gave 35 mg (41%) of N-acetylamine IIIb, mp 155-157°C. IR spectrum (KBr): 1660 cm^{-2} (C=O). Mass spectrum: 388 (100) (M), 373 (25), 345 (18), 329 (22), 316 (84), 314 (29), 302 (25), 289 (24), 276 (74), 275 (93), 274 (44). Found: M^+ 388. $C_{25}H_{28}N_2O_2$. Calculated: M 388.

Reduction of 7,7-Dimethyl-1-(3-nitrophenyl)-2-phenyl-4,6,7,8(5H)-tetrahydropyrrolo[3,2-c]-azepine. A solution of 220 mg (0.6 mmole) of lactam Ie in 20 ml dry dioxane was treated with a suspension of 100 mg (3 mmole) of lithium aluminum hydride in 30 ml dry dioxane. The mixture was refluxed 30 h and worked up as described above; orange crystals of the azo derivative IV were obtained in 90 mg (22%) yield, mp 233-235°C (from chloroform). IR spectrum (KBr): 3450 cm^{-1} (NH), 1605 (C=N), 1450 cm^{-1} (N=N). UV spectrum (ethanol), λ_{max} (log ε): 248 (4.5), 285 nm (4.6). Mass spectrum: 658 (57), 656 (32), 629 (34), 628 (20), 330 (45), 329 (100), 328 (29), 315 (98), 299 (52), 298 (39), 359 (30). Found: M^+ 658. $C_{44}H_{46}N_6$. Calculated: M 658.

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