DERIVATIVES OF ISOQUINOLINE. 30.* SYNTHESIS OF 4-SPIROSUBSTITUTED DIOXINOISOQUINOLINES

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Methods have been developed for the synthesis of 1,4-benzodioxanyl-6-ethylamine with cyclopentyl and tetrahydropyranyl substituents in the β-position. These compounds have been used as starting materials for the synthesis of new heterocyclic systems, the 4-spirocyclosubstituted dioxinoisoquinolines.

In the search for new drugs considerable attention has been paid to the synthesis of derivatives of both isoquinoline and 1,4-benzodioxane [1, 2]. We have shown on the basis of our previous work that the presence of spirotetrahydropyranyl and spirocyclopentyl substituents at position 4 of the isoquinoline have a favorable effect on the biological properties of the substituted isoquinolines. We have therefore attempted to synthesize new heterocyclic systems, dioxinoisoquinolines with spirocyclic substituents at position 4, which combine the benzodioxane, isoquinoline, and spirocyclic units in a single molecule.

Compounds X, XI and XVI-XXIII were synthesized starting from 1,4-benzodioxanyl-6-acetonitrile (III). Subsequent introduction of the cyclopentyl and tetrahydropyranyl substituents was realized with 1,4-dibromobutane (IV) and 2,2-dichlorodiethyl ether (V) in the presence of NaOH or benzyltriethylammonium chloride. Note that the best yields were obtained with powdered NaOH at 65-70°C [3], whereas compound VII was obtained in only 33% yield with benzyltriethylammonium chloride.

In previous papers $LiAlH_4$ was used to reduce the nitrile group in analogous compounds containing a cyclopentyl substituent but it was not satisfactory for compounds containing both a nitrile and a tetrahydropyranyl group [4]. However, when a 1,4-benzodioxane replaced the 3,4-dimethoxy substituent on the tetrahydropyrane ring, the aminomethyl derivatives VIII and IX were obtained in good yield (75% and 70%) by reduction of the nitrile groups with $LiAlH_4$.

The Pikte–Spengler cyclization is a suitable method for the synthesis of 1,2,3,4-tetrahydroisoquinolines with no substituent at position 1. In our examples it gave good yields of the 4-spirosubstituted dioxinoisoquinolines X and XI from the arylethylamines VIII and IX and 40% formalin.

The corresponding 3,4-dihydroisoquinolines XVI-XIX were obtained by Bischler–Napiral'ski cyclizations from the same amines VIII and IX via the corresponding N-acyl derivatives XII-XV. In view of their instability relative to atmospheric oxygen [3], compounds XVI-XIX were reduced with $NaBH_4$ without isolation to the corresponding 6-substituted 1,2,3,4-tetrahydrodioxinoisoquinolines XX-XXIII characterized as their insoluble hydrochlorides.

*For Communication 29, see [1].

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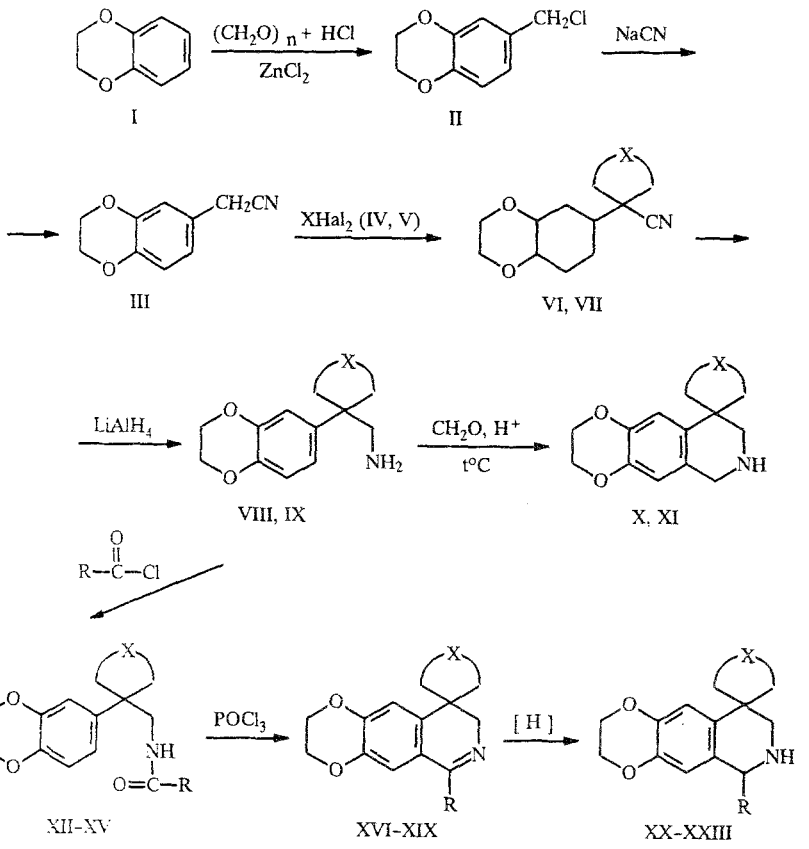
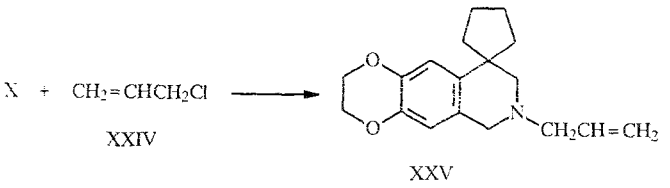


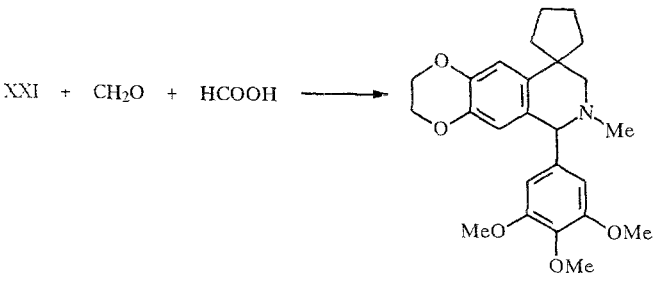
I, II, III, VI, VII, VIII, IX, X, XI, XII–XV, XVI–XIX, XX–XXIII

VI, VIII, X X = $(CH_2)_4$; VII, IX, XI X = $O(CH_2CH_2)_2$; XII, XVI, XX R = Me, X = $(CH_2)_4$; XIII, XVII, XXI R = $(MeO)_3C_6H_2$, X = $(CH_2)_4$; XIV, XVIII, XXII R = Me, X = $O(CH_2CH_2)_2$; XV, XIX, XXIII R = $(MeO)_3C_6H_2$, X = $O(CH_2CH_2)_2$

The corresponding N-allyl derivative XXV was obtained by interaction of compound X with allyl chloride (XXIV). Compound XXI was N-methylated quantitatively with a mixture of 40% formalin and formic acid [5].



XXIV XXV



XXVI

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	m.p., °C (b.p., °C/mm)	R_f	Yield, %	Compound	Empirical formula	m.p., °C (b.p., °C/mm)	R_f	Yield, %
VI	$C_{14}H_{15}NO_2$	180...185 /3 mm	0,64(a)	33	XIV	$C_{16}H_{21}NO_4$	124...125	0,80(d)	78
VII	$C_{14}H_{15}NO_3$	120...122	0,40(b)	54	XV	$C24H_{29}NO_7$	Oil	0,68(d)	64
VIII	$C_{14}H_{20}ClNO_2$	170...171	0,52(a)	75	XX	$C16H_{22}ClNO_2$	160...162	0,55(a)	75
IX	$C_{14}H_{20}ClNO_3$	223...224	0,65(a)	70	XXI	$C24H_{30}ClNO_5$	198...199	0,59(a)	72
X	$C_{15}H_{20}ClNO_2$	278...279	0,76(c)	73	XXII	$C16H_{22}ClNO_3$	140...141	0,73(a)	50
XI	$C_{15}H_{20}ClNO_3$	250...252	0,80(c)	61	XXIII	$C24H_{31}ClNO_6$	153...154	0,70(a)	76
XII	$C_{16}H_{21}NO_3$	Oil	0,56(d)	88	XXV	$C18H_{24}ClNO_2$	169...170	0,61(a)	71
XIII	$C_{24}H_{29}NO_6$	Oil	0,58(d)	89	XXVI	$C25H_{32}ClNO_5$	158...159	0,69(a)	81

EXPERIMENTAL

IR spectra were recorded in Nujol with a Zeiss UR—20 spectrometer, ^1H NMR spectra were obtained with a Varian T-60 instrument with TMS as internal standard, and mass spectra were recorded with an MX—1303 mass spectrometer at an ionizing voltage of 10 eV, an ionization chamber temperature of 150°C, and direct insertion of the sample into the ion source. Reaction course and purity of the products were monitored by TLC on Al_2O_3 with the following eluent mixtures: *a* 4:1 benzene–acetone, *b* 2:1 benzene–acetone, *c* 4:1:1 benzene–acetone–chloroform, and *d* 12:1 benzene–methanol. Characteristics of the compounds synthesized are given in Table 1.

Elemental analysis results for C, H, N, and Cl corresponded with calculated values.

1-(1,4-Benzodioxan-6-yl)-1-cyanocyclopentane (VI). A. Powdered NaOH (16.0 g, 0.14 mole) was suspended in the oily nitrile III [6] (20.3 g, 0.12 mole), and 1,4-dibromobutane (35.0 g, 0.16 mole) was added dropwise while the stirred mixture was heated to 55°C. The mixture was then heated at 90-95°C for 12 h. It was extracted with toluene (250 ml), washed with water and dried over K_2CO_3. The residue after removal of the solvent was distilled in vacuum to give compound VI (53 %), b.p. 180-182°C/3 mm. IR spectrum: 2240 cm^{-1} (C–N). ^1H NMR spectrum (CCl_4): 7.0 (3H, m, H_{arom}), 4.3 (4H, s, OCH_2CH_2O), 2.0-2.6 ppm (8H, m, $(CH_2)_4$).

B. Benzyltriethylammonium chloride (7 g, 0.02 mole) was added to a solution of NaOH (20 g, 0.5 mole) in water (20 ml), the temperature was raised to 75-80°C, and nitrile III (4.3 g, 0.025 mole) and dibromide IV (8.6 g, 0.04 mole) were added dropwise at that temperature. The mixture was heated at 75-80°C for 1 h. Workup of the reaction mixture and isolation of the nitrile were analogous to A. Yield 1.4 g (33%), b.p. 180-185°C/3 mm.

4-(1,4-Benzodioxan-6-yl)tetrahydropyran-4-carbonitrile (VII) was obtained from nitrile III (25 g, 0.14 mole), powdered NaOH (20 g, 0.5 mole) and 2,2-dichlorodiethyl ether (V) (40 g, 0.28 mole) as for the synthesis of compound VI (method A). Yield 12.2 g (54.2 %), m.p. 120-122°C. IR spectrum: 2230 cm^{-1} (C≡N). ^1H NMR spectrum ($CDCl_3$): 7.3 (3H, d, H_{arom}), 4.4 (4H, s, OCH_2CH_2O), 3.8-4.2 (4H, m, CH_2OCH_2), 1.8-2.0 ppm (4H, m, $CH_2CH_2OCH_2CH_2$). Mass spectrum: M^+ 245.

6-(1-Aminomethyl-1-cyclopentyl)-1,4-benzodioxane Hydrochloride (VIII). Absolute ether (200 ml) was added to $LiAlH_4$ (15.2 g, 0.4 mole) and the mixture was boiled for 20 min. Nitrile VI (23 g, 0.1 mole) in benzene (100 ml) was added dropwise to the cooled solution, the mixture was boiled for 18 h, then cooled in ice water while 5% NaOH (20 ml) and then water (20 ml) were added dropwise. The mixture was filtered, the residue after removal of solvent was dissolved in absolute ether and treated with ethereal HCl to give the hydrochloride VIII (20.3 g, 75%). ^1H NMR spectrum (D_2O): 1.5-1.9 (8H, m, $(CH_2)_4$), 3.0 (2H, s CH_2N), 4.1 (4H, s $(-CH_2O)_2$), 6.7 ppm (3H, s, H_{arom}).

4-Aminomethyl-4-(1,4-benzodioxan-6-yl)tetrahydropyran hydrochloride (IX) was prepared analogously to compound VIII from nitrile VII (10 g, 0.04 mole) and $LiAlH_4$ (4 g). Yield 8.0 g (70%). ^1H NMR spectrum (D_2O): 1.6-2.3 (4H, m, CH_2-C-CH_2), 3.1 (2H, s, CH_2NH_2), 3.3-3.7 (4H, m, CH_2OCH_2), 4.2 (4H, s, OCH_2CH_2O), 7.0 ppm (3H, s, H_{arom}).

9-Spirocyclopentan-2,3,6,7,8,9-hexahydrodioxino[2,3-*d*]isoquinoline Hydrochloride (X). 20% Formalin (3.1 g) was added dropwise with stirring over 30 min to amine VIII (4.6 g, 0.02 mole) and the mixture was heated on a water bath for

1 h. The cooled mixture was extracted with benzene, the benzene removed, the residue dissolved in 10% aqueous hydrochloric acid and evaporated to dryness on a water bath. The hydrochloride was recrystallized from ethanol. ^{1}H NMR spectrum (D_2O): 1.8 (8H, m $(CH_2)_4$), 3.2 (2H, s, CH_2N), 4.2 (6H, s, CH_2N and OCH_2CH_2O), 6.7 and 6.9 ppm (2H, s, H_{arom}). Mass spectrum : M^+ 245.

9-(4-Spirotetrahydropyran)-2,3,6,7,8,9-hexahydrodioxino[2,3-*d*]isoquinoline hydrochloride (XI) was prepared analogously to compound X from amine IX (5.5 g, 0.02 mole), 20% formalin (3.3 g) and 20% hydrochloric acid. Yield 46 g (61%). Mass spectrum: M^+ 261.

N-Methyl 4-(1,4-benzodioxan-6-yltetrahydropyranyl)-4-acetamide (XIV). A mixture of amine IX (11 g, 0.04 mole) and pyridine (3.4 g, 0.044 mole) in benzene (20 ml) was added dropwise at 0°C to acetyl chloride (3.4 g, 0.04 mole) in absolute benzene (30 ml). The mixture was stirred for 1 h at room temperature and then boiled for 6 h. The reaction mixture was acidified with 10% hydrochloric acid, the organic layer was washed with 10% aqueous NaOH, dried over Na_2SO_4, the solvent evaporated, and the residue recrystallized from ether, yield 9 g (78%).

The amides XIII and XV were obtained analogously.

6-Methyl-9-spiro-(4-tetrahydropyran)-2,3,6,7,8,9-hexahydrodioxino[2,3-d]isoquinoline Hydrochloride (XXII). $POCl_3$ (30 g, 0.20 mole) was added to a solution of amide XIV (7 g, 0.02 mole) in toluene (70 ml) and the mixture was boiled for 6 h. The solvent was evaporated from the cooled solution. The residue was dissolved in methanol (70 ml), $NaBH_4$ (3.6 g, 0.1 mole) was added with stirring at 0°C, stirring was continued at 0°C for a further 2 h and the mixture was kept overnight. The solvent was evaporated, water was added, the mixture was extracted with benzene, the benzene solution was washed with water, and the solvent was evaporated.

The hydrochloride XXII (3.5 g, 50%) was obtained by treatment of a solution of base XXII in chloroform with aqueous HCl. IR spectrum (base): 1580 (aromatic C=C), 3250-3450 cm^{-1} (associated N−H). Mass spectrum: M^+ 275.

Compounds XX, XXI and XXIII were obtained analogously from the corresponding amides.

N-Allyl-9-spirocyclopentan-2,3,6,7,8,9-hexahydrodioxino[2,3-*d*]isoquinoline Hydrochloride (XXV). Powdered Na_2CO_3 (2.6 g, 0.024 mole) was added to a solution of compound X (5.0 g, 0.02 mole) in benzene (250 ml) and then freshly distilled allyl bromide (3.0 g, 0.024 mole) was added dropwise. The mixture was stirred at room temperature for 1 h, boiled for 10 h, filtered, the filtrate evaporated, the residue dissolved in absolute ether (150 ml) and the hydrochloride obtained by treatment with ethereal HCl. Yield 4.5 g (70%). ^{1}H NMR spectrum (CD_3OD): 1.8-2.2 (8H, m, $(CH_2)_4$), 3.5 (2H, s, CH_2N), 4.0 (2H, d, $CH_2-CH=CH_2$), 4.3 (4H, s, OCH_2CH_2O), 4.4 (2H, s, $ArCH_2$), 5.6-6.0 (3H, m, $CH_2=CH$), 6.9 ppm (2H, d, H_{arom}).

7-Methyl-6-(3,4,5-trimethoxyphenyl)-9-spirocyclopentan-2,3,6,7,8,9-hexahydrodioxino[2,3-*d*]isoquinoline hydrochloride (XXVI). Formalin (4.7 g, 0.15 mole) and formic acid (5.0 g, 0.11 mole) were added to compound XXI (4.0 g, 0.01 mole) and the mixture was boiled for 8 h. The mixture was made basic with aqueous ammonia (pH 10) and extracted with ether. The ether extract was washed with water, the solvent was evaporated and the residue was converted to the hydrochloride (yield 3.7 g, 81%). ^{1}H NMR spectrum ($CDCl_3$): 1.7-1.9 (8H, m. $(CH_2)_4$), 2.0 (3H, s, CH_3N), 2.5 (2H, d, CH_2NCH_3), 3.8 (9H, s, 3 CH_3O), 3.9 (1H, s, Ar_2CHN), 4.2 (4H, s, OCH_2CH_2O), 6.1, 6.5, 6.7 ppm (4H, s, H_{arom}).

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