THE CYCLISATION REACTIONS OF γ-AMIDOALCOHOLS AND SYNTHESIS OF 2-BENZAZEPIN-3-ONE DERIVATIVES BY ACID CATALYSED REARRANGEMENT OF 1,3-OXAZEPIN-4-ONE DERIVATIVES

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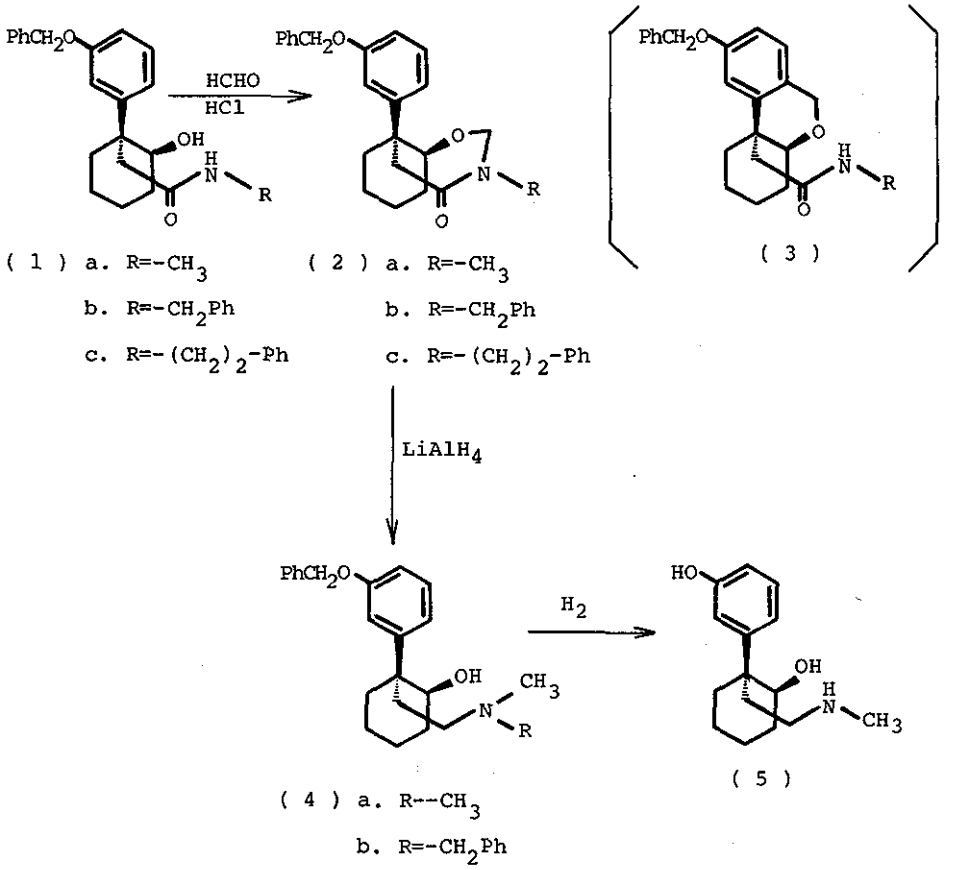
The cyclisation reaction of the secondary amides (1), possessing a hydroxyl group at γ-position, with formalin and hydrochloric acid gave the 1,3-oxazepin-4-one derivatives (2). The acid catalysed rearrangement of the resulting products was carried out successfully to give the 2-benzazepin-3-one derivatives (15) and (16).

A few papers on intramolecular condensation of amidoalcohols with carbonyl compounds have been reported[1], but reactions yielding lactam-type products are known only on primary amides with the exception of the formation of 7-membered ring products[2]. However many papers on amino-alcohols have been reported[3]. This communication presents examples of a condensation reaction of the secondary amidoalcohols with formalin giving new 1,3-oxazepin-4-one derivatives and of the rearrangement of these products with acid catalyst to form the new 2-benzazepin-3-one derivatives (15) and (16).

In previous papers[4], we reported that phenolic cyclization of alcohols with carbonyl compounds gave benzopyran derivatives. Although reaction of γ-amidoalcohols (1b and 1c) with formalin in the presence of hydrochloric acid gave the cyclised products showing no NH stretching due to amide in IR spectra, we tentatively assigned the structures to be 3.

Chart 1



(1) a. R=-CH_3
b. R=-CH_2Ph
c. R=-$(CH_2)_2$-Ph

(2) a. R=-CH_3
b. R=-CH_2Ph
c. R=-$(CH_2)_2$-Ph

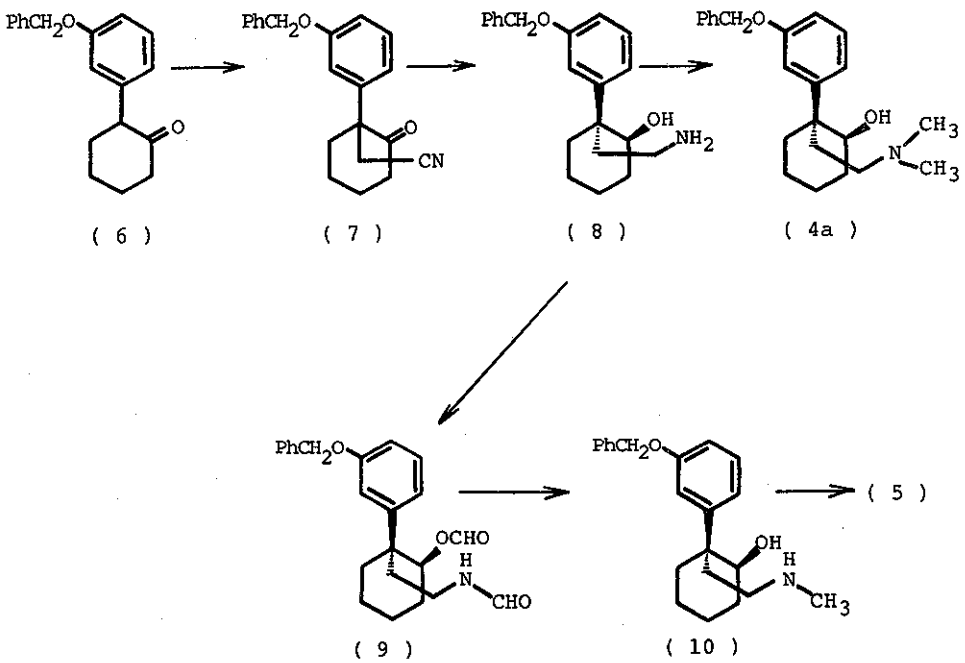
(3)

(4) a. R=-CH_3
b. R=-CH_2Ph

(5)

In order to clarify the structure of the above cyclised products, these products were reduced with lithium aluminium hydride to give the amines which showed a new signal due to N-methyl signal at ca. 2.7 ppm in NMR spectra. Consequently it was deduced that condensation products from 1 had not the structures (3), but the 1,3-oxazepin-4-ones (2b and 2c), and the amines could be assigned N-methyl derivatives (4a and 4b). Hydrogenolysis of the amine (4b) over palladium-charcoal furnished the phenol derivative (5).

Chart 2



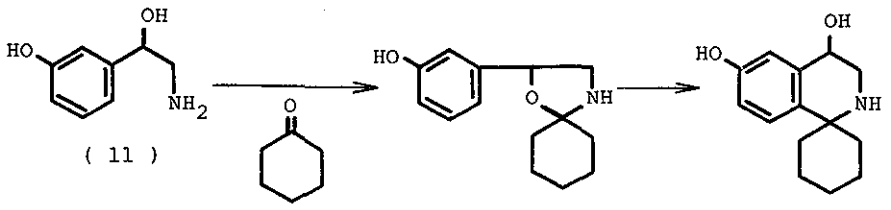
(6) (7) (8) (4a) (9) (10) (5)

For establishment of structure (2), an alternative synthesis of 4a and 5 was investigated. Namely, treatment of 2-(3-benzyloxyphenyl)-cyclohexanone (6) with iodoacetonitrile in the presence of sodium amide, according to Boekelheide's procedure[5], gave the nitrile (7), which was, without isolation, reduced by lithium aluminium hydride to afford 2-(2-aminoethyl)-2-(3-benzyloxyphenyl)cyclohexanol (8), which was isolated as the hydrochloride, m.p. 215 - 216°, [ν_{max} 3370 cm^{-1}; $\delta(CD_3OD)$ 3.90 (1H, broad, C<u>H</u>OH), 5.08 (2H, s, PhC<u>H</u>$_2$O)]. Eschweiler-Clarke reaction of 8 under usual conditions gave 2-(3-benzyloxyphenyl)-2-[2-(N,N-dimethylamino)ethyl]cyclohexanol (4a), which was characterised as the hydrochloride, m.p. 210 - 212° [ν_{max} 3350 cm^{-1}; $\delta(CD_3OD)$ 2.64, 2.73 (each 3H, each s, $N(CH_3)_2$), 3.90 (1H, t, <u>J</u> 6 Hz, C<u>H</u>OH), 5.10 (2H, s, PhC<u>H</u>$_2$)]. The melting point, IR spectrum and TLC of this product were identical with those of 4a derived from 2a.

On the other hand, reaction of 8 with acetic anhydride and formic acid gave diformyl derivative (9) as a colorless oil [m/e 381 M^+)], and lithium aluminium hydride reduction of 9 yielded 2-(3-benzyloxyphenyl)-2-[2-(N-methylamino)ethyl]cyclohexanol (10) which was purified as the hydrochloride, m.p. 180 - 181° [ν_{max} 3420 cm^{-1}; $\delta(CD_3OD)$ 2.37 (3H, s, N-CH_3), 3.90 (1H, t, <u>J</u> 6 Hz, C<u>H</u>OH), 5.05 (2H, s, PhC<u>H</u>$_2$O)]. Catalytic hydrogenation over palladium-charcoal gave 2-(3-hydroxyphenyl)-2-[2-(N-methylamino)ethyl]cyclohexanol (5), m.p. 125 - 126° (δ(DMSO d_6) 2.13 (3H, s, NCH_3), 3.62 (1H, broad, C<u>H</u>OH), m/e 249 (M^+)], which was also identical with 5 derived from 4b on spectroscopic comparisons. Therefore, the previously reported structure (3)[4b] should be revised to 2b and 2c. This fact also revealed that relative configuration of the hydroxyl and phenyl groups of 8 was <u>cis</u>.

In the previous synthesis of isoquinoline (13) by phenolic cyclisation of phenethylamine (11) having a hydroxyl group, the oxazolidine (12) had been formed as an intermediate[6]. On this finding, transformation of 1,3-oxazepin-4-ones (2) into 2-benzazepin-3-one derivatives was investigated.

Chart 3



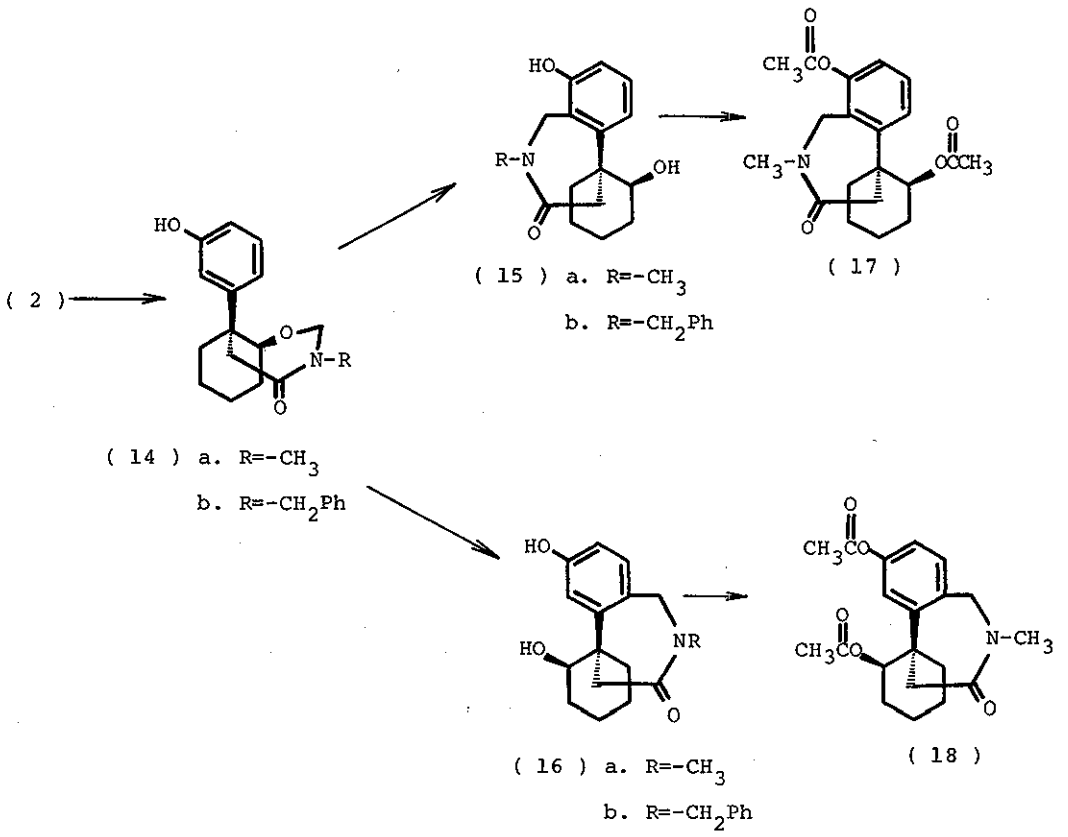
(11) (12) (13)

The catalytic hydrogenation of 5a-(3-benzyloxyphenyl)-2,3,4,5,5a,6,7,8,9,9a-decahydro-3-methyl-1,3-benzoxazepin-4-one (2a), m.p. 114 - 115° [ν_{max} 1660 cm^{-1}; $\delta(CDCl_3)$ 2.50, 2.96 (each 1H, each d, J 14 Hz, CH_2CO), 2.80 (3H, s, NCH_3), 3.60 (1H, dd, J 9 and 6 Hz, CHO), 4.73, 5.07 (each 1H, each d, J 13 Hz, OCH_2N), 4.99 (2H, s $PhCH_2O$)], which was obtained as the cases of 2b and 2c[4b], gave 2,3,4,5,5a,6,7,8,9,9a-decahydro-5a-(3-hydroxyphenyl)-3-methyl-1,3-benzoxazepin-4-one (14a) without hydrogenolysis of the oxazepine ring, m.p. 255 - 257° [ν_{max} 3280, 1630 cm^{-1}; δ(DMSO d_6) 2.25, 3.15 (each 1H, each d, J 14 Hz, CH_2CO), 2.72 (3H, s, NCH_3), 3.70 (1H, broad, CHO), 4.82, 5.16 (each 1H, each d, J 13 Hz, OCH_2N)].

Heating 14a in n-propanol in the presence of a catalytic amount of hydrochloric acid, gave the two products in a ratio of ca. 1:2,

separable by silica gel chromatography. Both products showed similar signal patterns in NMR spectrum except aromatic region. The first product could be assigned 2,3,4,5-tetrahydro-9-hydroxy-2-methyl-5-spiro(2-hydroxycyclohexyl)-1H-2-benzazepin-3-one (15a) (20 % yield), m.p. 263 - 266° [ν_{max} 3370, 3240, 1605 cm^{-1}; δ(DMSO d_6) 2.79 (3H, s, NCH_3), 3.43 (1H, broad, C<u>H</u>OH), 4.59 (2H, s, NC<u>H</u>$_2$Ph), 6.66 (1H, dd, <u>J</u> 8 and 2 Hz, C_8-proton), 6.94 (1H, t, <u>J</u> 8 Hz, C_7-proton), 7.16 (1H, dd, <u>J</u> 8 and 2 Hz, C_6-proton)] and the aromatic protons of the corresponding diacetate (17) showed a typical ABC type coupling at 6.93 (dd, <u>J</u> 8 and 2 Hz), 7.24 (t, <u>J</u> 8 Hz) and 7.57 (dd, <u>J</u> 8 and 2 Hz) in its NMR ($CDCl_3$) spectrum. On the other hand, the second one (44 % yield), m.p. 250 - 253° [ν_{max} 3590, 3100, 1610 cm^{-1}, δ(DMSO d_6) 2.79 (3H, s, N-CH_3), 2.87 (2H, s, CH_2CO), 3.38 (1H, broad, C<u>H</u>OH), 4.39 (2H, s, NC<u>H</u>$_2$Ph), 6.46 (1H, dd, <u>J</u> 8 and 2 Hz, C_8-proton), 6.89 (1H, d, <u>J</u> 8 Hz, C_9-proton), 7.17 (1H, d, <u>J</u> 2 Hz, C_6-proton)] was assigned 16a, whose diacetate (18), m.p. 176 - 178°, exhibited aromatic protons as ABX pattern [6.87 (1H, dd, <u>J</u> 8 and 2 Hz, C_8-proton)], 7.09 (1H, d, <u>J</u> 8 Hz, C_9-proton) and 7.36 (1H, d, <u>J</u> 2 Hz, C_6-proton)].

Chart 4



Similarly, N-benzyl derivative (15b), m.p. 214 - 216° [ν_{max} 3570, 3280, 1620 cm^{-1}; δ(DMSO d_6) 2.97 (2H, s, CH_2CO), 3.53 (1H, broad, CHOH), 4.27, 4.61 (each 1H, each d, J 15 Hz, benzyl methylene), 4.56 (2H, s, C_1-methylene), 6.63 (1H, dd, J 8 and 2 Hz, C_8-proton), 6.95 (1H, t, J 8 Hz, C_7-proton)] and (16b), m.p. 210 - 213° [ν_{max} 3550, 3160, 1620 cm^{-1}; δ($CDCl_3$, DMSO d_6) 3.04 (2H, s, CH_2CO), 3.56 (1H, broad, CHOH), 4.31 (2H, s, C_1-methylene), 4.36, 4.66 (each 1H, each d, J

15 Hz, methylene due to benzyl group), 6.44 (1H, dd, J 8 and 2 Hz, C_8-proton), 6.69 (1H, d, 8 Hz, C_9-proton)] were obtained in 20 and 44 % yield, respectively, from 14b.

Application and limitation of these reactions are now in progress.

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