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4, 5-Dihydro-1, 4-benzoxazepin-3(2*H*)-ones

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Several syntheses of 1,4-benzoxazepines (1,2,3) and 1,4-benzoxazepin-3,5-diones (4,5,6) have been reported in the literature. We now wish to describe a synthetic route to the previously unknown 4,5-dihydro-1,4-benzoxazepin-3(2*H*)-one ring system, from which the 2,3,4,5-tetrahydro-1,4-benzoxazepine system can be readily obtained. This method has been applied to the preparation of 4-phenyl derivatives and appears to be general (Table I).

The synthesis of the α-anilino-*o*-cresols (Ia-d) was effected by the condensation of the appropriate benzaldehyde with aniline, and subsequent reduction of the Schiff base. A variety of methods could be used for this reduction and sodium or tetramethylammonium borohydride, lithium aluminum hydride and catalytic hydrogenation in the presence of platinum were all found to be equally effective. The known compounds Ia (7) and Id (8) were identified by their melting points and infrared spectra. Compound Ic was reported by Paal (8) to have a melting point of 118°, but we obtained a compound of empirical formula $C_{13}H_{12}ClNO$, consistent spectrally with Ic, but melting at 55-57°. Reduction of the known Schiff base (9) with hydrogen over platinum or with lithium aluminum hydride gave the same low melting compound.

The condensation of salicylaldehyde with aniline in the presence of an excess of sodium borohydride gave directly α-anilino-*o*-cresol (Ia). Schiff base formation from salicylaldehyde was apparently much more rapid than reduction of the aldehyde function. The existence of a yellow color suggested that the Schiff base was an intermediate which probably existed as the intramolecular tertiary iminium salt. Such a salt would be rapidly reduced by sodium borohydride as has been suggested by Schellenberg (10) for similar reactions under acidic conditions. That such a reaction course is probably favored over initial reduction of the aldehyde is seen by the high yield of product obtained (75%).

The reaction of Ia-d with bromoacetyl bromide in the presence of a weak base afforded a good synthetic route to the 2-bromo-*N*-(2-hydroxybenzyl)-acetanilides (IIa-d). Although IIb and IIc were not isolated, the compounds were generally colorless crystalline solids whose infrared spectra were distinguished by an intense absorption at 1620-1645 cm^{-1}.

The treatment of IIa-d with a strong base effected ring closure to the corresponding 4,5-dihydro-4-phenyl-1,4-benzoxazepin-3(2*H*)-ones (IIIa-d). For compound IIId, bromoacetylation of Ib in the presence of sodium carbonate yielded the benzoxazepinone directly, and IIb was not isolated. Generally however, the cyclization was effected by treatment with sodium hydride in tetrahydrofuran.

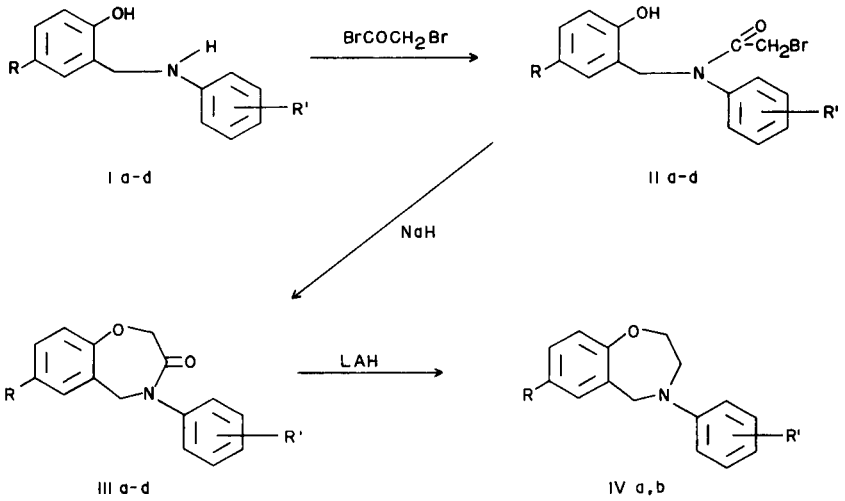
The reduction of IIIa and IIIb was effected with lithium aluminum hydride to give the 2,3,4,5-tetrahydro-4-phenyl-1,4-benzoxazepines (IVa) and (IVb), as low melting crystalline solids in good yield, (89 and 95% respectively). The split carbonyl absorption in the infrared associated with IIIa and IIIb (1675 and 1645-1650 cm^{-1}) was missing but the spectra of IVa and IVb still exhibited bands associated with the ether absorption at 1230 and 1050 cm^{-1}.

TABLE I

Physical and Experimental Data for New Compounds Prepared

Compound	Yield %	Solvent (a)	M.P., °C	Formula	Calcd. % C	Calcd. % H	Calcd. % N	Found % C	Found % H	Found % N
IIa	93	A	99-101	$C_{15}H_{14}BrNO_2$	56.27	4.41	4.39	56.34	4.43	4.19
IIIa	68.7	B	147-148	$C_{15}H_{13}NO_2$	75.30	5.48	5.85	74.98	5.63	5.96
IVa	89.2	A+C	64-65	$C_{15}H_{15}NO$	79.97	6.71	6.22	80.26	6.46	6.19
Ib	81.4	D+E	114-118	$C_{13}H_{12}ClNO$	66.81	5.18	5.99	66.51	5.05	5.85
IIIb	59.4	A	135-136	$C_{15}H_{12}ClNO_2$	65.82	4.42	5.12	66.06	4.61	5.10
IVb	94.8	A	77-78.5	$C_{15}H_{14}ClNO$	69.36	5.43	5.39	69.73	5.65	5.45
IIIc	84.2	A+F	105-107	$C_{15}H_{12}ClNO_2$	65.82	4.42	5.12	65.72	4.31	5.19
IId	93.5	A	115-118	$C_{15}H_{13}BrClNO_2$	50.66	3.68		50.88	3.85	
IIId	68.3	F	147.5-150	$C_{15}H_{12}ClNO_2$	65.82	4.42	5.12	65.86	4.41	5.06

(a) A = hexane, B = acetone, C = methylene chloride, D = ethanol, E = water, F = ether.



a, R = R' = H

b, R = Cl, R' = H

c, R = H, R' = oCl

d, R = H, R' = pCl

EXPERIMENTAL (11, 12).

α-Anilino-*o*-cresols (Ia-d).

A solution of the appropriate salicyladehyde (0.5 mole) and aniline (0.5 mole) in 350 ml. of benzene was azeotropically distilled until 8 ml. of water had been collected. The benzene was removed *in vacuo* giving 0.5 mole of the α-phenylimino-*o*-cresol as a yellow oil which solidified on standing. The crude Schiff base, dissolved in 500 ml. of ethanol containing 5 ml. of concentrated ammonium hydroxide, was then treated portionwise over 1.5 hours with 20 g. of sodium borohydride. The reaction mixture was allowed to stir for several hours and was then diluted with an equal volume of ice water. The crystalline product was removed by filtration.

The synthesis was greatly simplified in the case of Ia by combining the two steps as follows: A solution of 0.2 mole of aniline and 0.2 mole of salicylaldehyde in 250 ml. of ethanol and 2 ml. of concentrated ammonium hydroxide was treated portionwise over 1 hour with 10 g. of sodium borohydride. The reaction mixture was then diluted with cold water and the crystalline product was removed by filtration.

2-Bromo-*N*-(2-hydroxybenzyl)acetanilides (IIa-d).

A vigorously stirred mixture of 0.1 mole of the appropriate cresol (Ia-d), 150 ml. of methylene chloride and 250 ml. of a saturated solution of sodium carbonate in water was treated by the dropwise addition of a solution of 0.11 mole of bromoacetyl bromide in 100 ml. of methylene chloride. The resulting mixture was then stirred overnight. The organic layer was separated, washed with 3 *N* sodium hydroxide, dried over magnesium sulfate and evaporated *in vacuo* to an oil, which on standing, gave the crude crystalline product.

4,5-Dihydro-4-phenyl-1,4-benzoxazepin-3(2*H*)-ones (IIIa-d).

A solution of IIa-d in tetrahydrofuran was treated with a slight excess of a 53% sodium hydride-mineral oil dispersion and was stirred for 4 hours at 35°. The excess sodium hydride was destroyed with ethanol and the reaction mixture poured into ice water. Filtration gave the crude product.

2,3,4,5-Tetrahydro-4-phenyl-1,4-benzoxazepines (IVa-b).

To a mixture of 5.0 g. of lithium aluminum hydride and 250 ml. of ether, 74 mmole of IIIa,b was added carefully. The reaction mixture was stirred overnight at reflux and then treated carefully with 10 ml. of water and 8 ml. of 10 *N* sodium hydroxide. The mixture was stirred at reflux for 30 minutes and filtered. Removal of the solvent *in vacuo* gave the crude product as a light yellow oil which could be crystallized from either hexane or a mixture of methylene chloride and hexane.

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REFERENCES

(1) K. Schenker and J. Druey, *Helv. Chim. Acta*, 46, 1696 (1963).
(2) L. M. Marson, *Farmaco* (*Pavia*), *Ed. Sci.*, 14, 159 (1959).
(3) B. Belleau, U. S. Patent 2,807,628, Sept. 24, 1957.
(4) J. Gilbert and H. Gault, *Compt. Rend.*, 254, 884 (1962).
(5) H. Schafer, German Patent 1,085,879, July 1960.
(6) P. Galimberti, V. Gerosa and M. Melandri, *Farmaco* (*Pavia*), *Ed. Sci.*, 14, 96 (1959).
(7) C. Paal and H. Senninger, *Ber.*, 27, 1802 (1894).
(8) C. Paal, *Arch. Pharm.*, 240, 689 (1902).
(9) A. Senier and F. G. Shepheard, *J. Chem. Soc.*, 95, 1946 (1909).
(10) K. A. Schellenberg, *J. Org. Chem.*, 28, 3260 (1963).
(11) All melting points were determined microscopically on a hot stage and are corrected.
(12) Data on the isolation and characterization of the materials presented below is given in Table I.

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