200. *The Preparation of Some* 2,3-*Dihydro*-1,4-*benzoxazepin*-5(4H)-*ones and Related Compounds.*

By D. Huckle, I. M. Lockhart, and M. Wright.

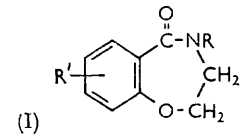
The action of hydrazoic acid on 4-chromanone leads to the formation of 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one. The syntheses of this and related compounds are described.

Treatment of 4-chromanone with sodium azide (1·3 mol.) in the presence of sulphuric acid under the conditions of the Schmidt reaction has given 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one (I; R = R′ = H). That the structure assigned was correct was confirmed by acid hydrolysis which yielded an amino-acid whose analysis and behaviour on potentiometric titration was consistent with the structure (II). The subsequent synthesis of 2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one, by thermal cyclisation of β-*o*-aminophenoxypropionic acid, whose properties were strikingly different from the product of the Schmidt reaction, provided further evidence of the correctness of the structure (I; R = R′ = H). 4-Chromanones substituted in the 6- or 8-positions with methyl or methoxy groups have been treated with sodium azide under the same conditions and the structures of the resulting benzoxazepinones (I; R = H; R′ = Me or OMe) confirmed similarly by identification of the amino-acids formed on hydrolysis.

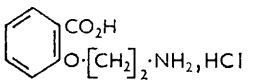
This method gives a simple route to the apparently novel dihydro-1,4-benzoxazepin-5(4*H*)-ones and thence to tetrahydro-1,4-benzoxazepines. A series of derivatives of 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one has been prepared where R (structure I) is an alkyl group or a basic side chain and R′ is hydrogen, methyl, or a methoxy substituent. Some analogous *N*-substituted derivatives of 2,3,4,5-tetrahydro-1,4-benzoxazepine (III) have been prepared by reduction of the appropriate benzoxazepinone with lithium aluminium hydride.

The Schmidt reaction with an unsymmetrical ketone can theoretically lead to two possible products. With 4-chromanone, whilst the yields did not preclude the formation

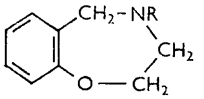
of both possible isomers no evidence of the alternative 2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one has been found in the work reported in this Paper. In view of the possible



(I)



(II)



(III)

analogy with acetophenone which yields acetanilide and α-tetralone which yields homodihydrocarbostyril under similar conditions,[1] the 1,5-benzoxazepinone might have been expected.

A striking difference has been noted in the rates of hydrolysis of the amide bonds in 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one and 2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one by 2N-hydrochloric acid at room temperature. As determined by the change in the ultraviolet spectrum, the former was unaffected after 18 days whereas hydrolysis was complete with the latter within 20 hours. This suceptibility of the 2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one to acid hydrolysis may explain its absence in a Schmidt reaction under acid conditions rather than that the reaction leads specifically to the 1,4-benzoxazepinone derivative.

The mechanism of the Schmidt reaction has been considered to have certain features which are similar to those of the Beckmann rearrangement.[2] It was of interest to find that Beckmann rearrangement of 4-chromanone oxime with polyphosphoric acid also gave 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one (I; R = R′ = H).

Experimental

Chromanones.—4-Chromanone and its 6- and 8-methyl derivatives were prepared by cyclisation of the appropriate phenoxypropionitrile [3] with polyphosphoric acid at 180° for 20 min.[4] This method was unsuitable for the methoxychromanones which were prepared from the methoxyphenoxypropionic acids by the method of Pfeiffer *et al.*[5]

2,3-*Dihydro*-1,4-*benzoxazepin*-5(4H)-*ones* (I).—The appropriate chromanone was stirred with twice its weight of concentrated sulphuric acid. Sodium azide (1·3 mol. relative to the chromanone) was added portionwise (*ca.* 10 g. per hr.), maintaining the internal temperature below 20°. The mixture was stirred for a further 2 hr. and poured on to crushed ice. Any solid which separated was filtered off. Sometimes ether extraction was used for isolation of the crude product, otherwise the aqueous solution was basified with 10N-sodium hydroxide and the solid which separated was filtered off. The full procedure was used routinely and the combined solids were extracted with light petroleum (b. p. 60—80°) in a Soxhlet apparatus or by boiling the solid with benzene and adding light petroleum (b. p. 60—80°) to the benzene solution. In both cases, the product crystallised on cooling. *Dihydrobenzoxazepinones* prepared by this method are listed in the Table.

N-*Substituted* 2,3-*Dihydro*-1,4-*benzoxazepin*-5(4H)-*ones.*—*Method A.* Sodium hydride (5·5 g.; 50% oil dispersion; 0·11 mol.) was washed with benzene and suspended in dried dimethylformamide–benzene (120 ml.). (The solvent was the residue obtained on mixing equal volumes of dimethylformamide and benzene, removing the water in a Dean and Stark apparatus, and distilling off one third of the volume of solvent.) 2,3-Dihydro-1,4-benzoxazepin-5(4*H*)-one (7 g.; 0·043 mol.) was rapidly added to the stirred suspension followed by dropwise addition of dry methyl iodide (13 ml.; 0·22 mol.). After the exothermic reaction had subsided, the mixture was heated at 70—90° for 2·5 hr. The reaction mixture was cooled, sodium iodide filtered off, and the filtrate evaporated to dryness *in vacuo*. The product was extracted from the residual oil with boiling light petroleum (b. p. 60—80°). The constants of the *methyl derivative* (4·3 g.) are given in the Table.

Method B. The benzoxazepinone (10 g.; 1 mol.) in dry dioxan (80 ml.) was refluxed with

[1] Briggs and DeAth, *J.*, 1937, 456.
[2] Wolff, *Org. Reactions*, 1946, **3**, 307.
[3] Bachman and Levine, *J. Amer. Chem. Soc.*, 1948, **70**, 599.
[4] U.S.P. 2,792,407.
[5] Pfeiffer, Oberlin, and Konermann, *Ber.*, 1925, **58**, 1947.

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

R *	R′	M. p. (or b. p.)	Cryst. form	Recryst. from	Yield (%)	*N*-Alkyln.	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
H	H	114—116°	*a*	*c*	56	—	$C_9H_9NO_2$	66·0	5·45	8·7	66·2	5·6	8·6
H	7-Me	108—109	*a*	*c*	44	—	$C_{10}H_{11}NO_2$	68·0	6·5	8·1	67·8	6·3	7·9
H	9-Me	82—84	*b*	*d*	36	—	$C_{10}H_{11}NO_2$	67·5	6·4	8·0	67·8	6·3	7·9
H	7-OMe	89—91	*b*	*c*	36	—	$C_{10}H_{11}NO_3$	62·1	6·1	7·3	62·2	5·7	7·25
H	9-OMe	128—129	*b*	*e*	66	—	$C_{10}H_{11}NO_3$	61·9	5·6	7·4	62·2	5·7	7·25
Me	H	69—70	*a*	*c*	57	A	$C_{10}H_{11}NO_2$	68·1	6·4	7·9	67·8	6·3	7·9
Me	9-OMe	86—87	*a*	*c*	22	B	$C_{11}H_{13}NO_3$	64·05	6·8	6·9	63·75	6·3	6·8
Et	H	59—61 †	*a*	*c*	64	B	$C_{11}H_{13}NO_2$	69·4	6·75	7·45	69·1	6·85	7·3
CH_2·CH:CH_2	H	B. p. 140°/0·8 mm.	‡	—	83	B	$C_{12}H_{13}NO_2$	70·95	6·4	6·6	70·9	6·45	6·9
Pr^n	H	B. p. 146/1·1 mm.	‡‡	—	50	§	$C_{12}H_{15}NO_2$	70·1	7·3	7·0	70·2	7·4	6·8
$[CH_2]_2$·NMe_2	H	69·5—70·5	*a*	*c*	24	C	$C_{13}H_{18}N_2O_2$	66·3	7·9	11·7	66·6	7·7	12·0
$[CH_2]_2$·Pyr	H	45—47	*a*	*c*	44	C	$C_{15}H_{20}N_2O_2$	68·85	7·55	10·9	69·2	7·7	10·8
$[CH_2]_2$·Pip	H	50—51	*a*	*c*	49	C	$C_{16}H_{22}N_2O_2$	70·0	8·4	10·0	70·0	8·1	10·2
$[CH_2]_2$·Mor	H	85—87	*a*	*c*	44	C	$C_{15}H_{20}N_2O_3$	65·3	7·4	10·2	65·2	7·3	10·1
$[CH_2]_2$·Mor	7-Me	B. p. 212—213/2 mm.	‖	—	73	C	$C_{16}H_{22}N_2O_3$	66·1	7·9	9·7	66·2	7·6	9·65
$[CH_2]_2$·Mor	9-Me	106—107 ¶	*b*	*f*	47	C	$C_{16}H_{22}N_2O_3$	66·8	8·1	10·0	66·2	7·6	9·65
$[CH_2]_2$·Mor	7-OMe	B. p. 192—194/0·15 mm.	**	—	67	C	$C_{16}H_{22}N_2O_4$	62·1	7·5	9·4	62·7	7·2	9·1
$[CH_2]_2$·Mor	9-OMe	66—68 ††	*b*	*e*	30	C	$C_{16}H_{22}N_2O_4$	62·7	7·65	8·8	62·7	7·2	9·1
$[CH_2]_3$·NMe_2	H	56—58	*a*	*c*	53	C	$C_{14}H_{20}N_2O_2$	67·7	8·2	10·9	67·7	8·1	11·3
$[CH_2]_3$·Mor	H	67—68	*a*	*e*	24	C	$C_{16}H_{22}N_2O_3$	66·55	7·7	9·6	66·2	7·6	9·65

* Pyr = Pyrrolidino; Pip = Piperidino; Mor = Morpholino. *a*, Needles; *b*, Prisms; *c*, Light petroleum (b. p. 60—80°); *d*, Benzene; *e*, Benzene–light petroleum (b. p. 60—80°); *f*, Acetone. † B. p. 144—147°/1 mm. ‡ n_D^{21} 1·5695. ‡‡ n_D^{21} 1·5590. § Prepared by catalytic hydrogenation of the corresponding *N*-allyl compound. ‖ *Hydrochloride* as prisms, m. p. 170—172° (Found: C, 55·7; H, 7·6; N, 7·9. $C_{16}H_{23}ClN_2O_3,H_2O$ requires C, 55·7; H, 7·3; N, 8·1%); *oxalate* as needles, m. p. 182—183° (Found: C, 56·4; H, 6·65; N, 7·6. $C_{18}H_{24}N_2O_7$ requires C, 56·8; H, 6·4; N, 7·4%). ¶ *Hydrochloride* as prisms (from ethanol), m. p. 178—179° (Found: C, 55·7; H, 7·4; N, 8·2. $C_{16}H_{23}ClN_2O_3,H_2O$ requires C, 55·7; H, 7·3; N, 8·1%). ** *Hydrochloride* as needles, m. p. 212—213° (Found: C, 56·1; H, 6·95; N, 7·9. $C_{16}H_{23}ClN_2O_4$ requires C, 56·2; H, 6·8; N, 8·2%). †† *Hydrochloride* as prisms, m. p. 192—193° (Found: C, 53·4; H, 7·2; N, 7·7. $C_{16}H_{23}ClN_2O_4,H_2O$ requires C, 53·25; H, 7·0; N, 7·8%).

sodamide (1·1 mol.) until evolution of ammonia ceased. Alkyl iodide (1·2 mol.) was added and the mixture stirred at reflux temperature for 4 hr. The mixture was cooled, methanol (5 ml. per g. of sodamide) was added, and stirring continued for 1 hr. Filtration through a supercel pad and evaporation of the filtrate yielded a crude product which was purified by distillation or crystallisation. *Compounds* prepared by this method are listed in the Table.

Method C. The benzoxazepinone (10 g.; 1 mol.) in dry dioxan (80 ml.) was stirred at reflux temperature with sodamide (1·1 mol.) until evolution of ammonia ceased. The freshly prepared morpholinoethylchloride (or other base as appropriate) (1·4 mol.) was added and the mixture stirred under reflux for 3 hr. After cooling, methanol was added and the mixture filtered (supercel). Evaporation of the filtrate gave the crude base which was extracted into 2N-hydrochloric acid and after basifying the acid solution, the base was isolated with ethyl acetate and purified by recrystallisation. *Compounds* prepared by this method are listed in the Table.

N-*Substituted* 2,3,4,5-*Tetrahydro*-1,4-*benzoxazepines* (III).—4-*Ethyl*-2,3,4,5-*tetrahydro*-1,4-*benzoxazepine hydrochloride.* 4-Ethyl-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one (9 g.) in benzene (200 ml.) was added dropwise with stirring to lithium aluminium hydride (10 g.) in ether (180 ml.). The mixture was refluxed for 2 hr. Water (100 ml.) or wet ether was added to the cooled mixture followed by 10N-sodium hydroxide (30 ml.). The mixture was refluxed for 2 hr., filtered hot, and the filtrate evaporated. The residue was dissolved in 2N-hydrochloric acid, the solution basified with 10N-sodium hydroxide, and the base extracted into ether. The ethereal solution was dried (sodium sulphate) and the hydrochloride precipitated by addition of ethereal hydrogen chloride. Recrystallisation from ethyl acetate gave the *benzoxazepine hydrochloride* (7·1 g.) as prisms, m. p. 199—200° (Found: C, 61·45; H, 7·4; N, 6·5. $C_{11}H_{16}ClNO$ requires C, 61·8; H, 7·55; N, 6·6%).

Other compounds similarly prepared were 4-allyl-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrochloride as prisms, m. p. 190—192° (Marson [6] gives m. p. 197°) from ethyl acetate (Found: C, 63·4; H, 7·2; N, 6·4. Calc. for $C_{12}H_{16}ClNO$: C, 63·8; H, 7·15; N, 6·2%) and 4-(2-*morpholinoethyl*)-2,3,4,5-*tetrahydro*-1,4-*benzoxazepine dihydrochloride* as needles, m. p. 258—260°, from ethanol (Found: C, 53·45; H, 7·3; N, 8·4; Cl, 21·4. $C_{15}H_{24}Cl_2N_2O_2$ requires C, 53·7; H, 7·2; N, 8·4; Cl, 21·15%).

2,3-*Dihydro*-1,5-*benzoxazepin*-4(5H)-*one.*—β-*o*-Aminophenoxypropionic acid [7] (45 g.) was heated at 150—155° (bath)/0·5 mm. for 1·5 hr. Cyclisation occurred and distillation *in vacuo* afforded 2,3-*dihydro*-1,5-*benzoxazepin*-4(5H)-*one* (b. p. 172—174°/0·7 mm.) which crystallised from benzene–light petroleum (b. p. 60—80°) as needles (23·8 g.), m. p. 126—127° (Found: C, 66·4; H, 5·5; N, 8·6. $C_9H_9NO_2$ requires C, 66·2; H, 5·6; N, 8·6%).

β-o-*Aminophenoxypropionic Acid Hydrochloride.*—Trituration of β-*o*-aminophenoxypropionic acid [7] under ethereal hydrogen chloride yielded the *hydrochloride* as rods (from ethanol–ether), m. p. 174—175° (Found: C, 49·5; H, 5·65; N, 6·4. $C_9H_{12}ClNO_3$ requires C, 49·7; H, 5·6; N, 6·4%); pK_a 3·8, 5·5 (in 50% ethanol); $\lambda_{max.}$ (in 0·1N-NaOH) 213, 232, and 283 mμ (ε 31,900, 6610, and 2650); $\lambda_{max.}$ (in 0·1N-HCl) 211sh, 216, 268, and 274 mμ (ε 7600, 8080, 2240, and 2010).

Confirmation of the Structure of 2,3-*Dihydro*-1,4-*benzoxazepin*-5(4H)-*ones Prepared by the Schmidt Reaction.*—The supposed 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one (120 mg.) was heated in a sealed tube with 6N-hydrochloric acid at 110° for 16 hr. The acid solution was diluted to 10 ml. with water and extracted with ether. Evaporation of the aqueous solution *in vacuo* and crystallisation of the residue from ethanol–ether gave needles (75 mg.), m. p. 177—178° (Found: C, 49·8; H, 5·4; N, 6·9. $C_9H_{12}ClNO_3$ requires C, 49·7; H, 5·6; N, 6·4%); pK_a 3·84, 9·64 (in 50% ethanol); $\lambda_{max.}$ (in 0·1N-NaOH) 219 and 278 mμ (ε 4410 and 1430); $\lambda_{max.}$ (in 0·1N-HCl) 234 and 289 mμ (ε 3840 and 2110). The compound gave a m. p. 142—148° when mixed with β-*o*-aminophenoxypropionic acid hydrochloride and from this and the different infrared spectrum, it was concluded that the hydrolysis product was o-2-*aminoethoxybenzoic acid hydrochloride* (II), confirming that the correct structure had been assigned to the product from the Schmidt reaction.

Similar experiments to confirm the structure of the other 1,4-benzoxazepinones (I; R = H, R′ = 7- or 9-Me and 7- or 9-OMe) resulted in the isolation of the following amino-acid hydrochlorides: 2-2′-*aminoethoxy*-3-*methylbenzoic acid hydrochloride*, m. p. 198—200°, microcrystalline from ethanol–ether (Found: C, 51·8; H, 5·9; N, 6·1. $C_{10}H_{14}ClNO_3$ requires C, 51·8; H, 6·1; N, 6·0%); 2-2′-*aminoethoxy*-5-*methylbenzoic acid hydrochloride*, m. p. 204—205°, microcrystalline

[6] Marson, *Il Farmaco* (*Pavia*), 1959, **14**, 159.
[7] Skinner, Martinez, and Baker, *J. Org. Chem.*, 1961, **26**, 152.

from ethanol–ether (Found: C, 51·6; H, 5·9; N, 6·0. $C_{10}H_{14}ClNO_3$ requires C, 51·8; H, 6·1; N, 6·0%); *2-2′-aminoethoxy-3-methoxybenzoic acid hydrochloride*, m. p. 180—182°, rods from ethanol–ether (Found: C, 48·4; H, 5·75; N, 5·6. $C_{10}H_{14}ClNO_4$ requires C, 48·5; H, 5·7; N, 5·7%); *2-2′-aminoethoxy-5-methoxybenzoic acid hydrochloride*, m. p. 212—214°, microcrystalline from ethanol–ether (Found: C, 47·85; H, 5·9; N, 6·0. $C_{10}H_{14}ClNO_4,0{\cdot}25H_2O$ requires C, 47·6; H, 5·8; N, 5·6%).

Beckmann Rearrangement of 4-Chromanone Oxime.—4-Chromanone oxime [8] (7 g.) and polyphosphoric acid (80 ml.) were stirred at 130—135° (internal temp.) for 15 min. The mixture was poured into water (450 ml.), extracted with chloroform, the extracts dried (Na_2SO_4), and evaporated. Repeated recrystallisation from benzene–light petroleum (b. p. 60—80°) afforded needles (2·3 g.), m. p. 106—108°. When mixed with authentic 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one (m. p. 110—112°) the mixture had m. p. 107—109° whilst admixture with authentic 2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one (m. p. 123—124°) gave a mixed m. p. of 85—92°. The infrared spectrum confirmed the identity of the product with 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one.

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RESEARCH DEPARTMENT, PARKE DAVIS & COMPANY,
HOUNSLOW, MIDDLESEX.

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[8] Powell, *J. Amer. Chem. Soc.*, 1923, **45**, 2708.