4-Amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ols, 4-Amino-2,3,4,5-tetrahydro-1-benzothiepin-5-ols, and Related Compounds

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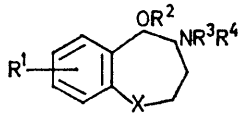
A number of 4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ols and related compounds in the 1-benzothiepin series have been prepared, and methods of separation of the *cis*- and *trans*-isomers have been studied. Pharmacological studies have revealed that some of the compounds show activity on the central nervous system in mice. The synthesis of a number of multicyclic molecules containing the 2,3,4,5-tetrahydro-1-benzothiepin system is described.

2-HYDROXY-2-PHENYLETHYLAMINES have long been of interest to medicinal chemists. Elliot [1] proposed that epinephrine might be the sympathetic transmitter of the autonomic nervous system and von Euler [2] showed that norepinephrine was the principal transmitter. A number of sympathomimetics, both natural and synthetic, contain the 2-hydroxy-2-phenylethylamine structure, of which ephedrine or adrenalin (1) is probably the most well known. This structural feature is also found in certain compounds that act as beta receptor blocking agents.

While working with compounds derived from 2,3,4,5-tetrahydro-1-benzoxepins and the corresponding 1-benzothiepins, we have synthesised a series of 4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ols (2; X = O, R^2 = H) and some analogous 1-benzothiepin-5-ols (2; X = S, R^2 = H), in order to examine the compounds for action on the central nervous system. We have also studied the stereochemistry of the products obtained.

3,4-Dihydro-1-benzoxepin-5(2*H*)-ones (3; R^2 = H) were prepared by cyclisation of the appropriate phenoxybutyric acids with polyphosphoric acid in xylene.[3] The formation of the corresponding 4-phenoxybutyric acid phenyl ester as a by-product, was noticed in certain cases, as reported by Fontaine.[3] Conversion of the ketone into its oxime followed by a Neber rearrangement of the oxime toluene-*p*-sulphonate,[4] normally afforded the 4-amino-3,4-dihydro-1-benzoxepin-5(2*H*)-one (3; R^2 = NH_2) hydrochloride. However, in certain cases, the method had limitations. When the Neber rearrangement was attempted with 3,4-dihydro-6,8-dimethyl-1-benzoxepin-5(2*H*)-one (3; R^1 = 6,8-Me_2, R^2 = H), instead of the expected product, the cyclic amide (4; R = H) was obtained, by a Beckmann rearrangement.

PhCH(OH)·CHMe·NHMe (1)



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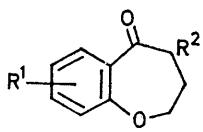

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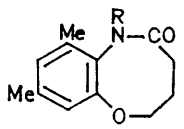

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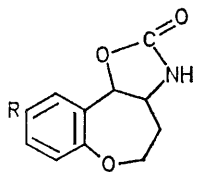

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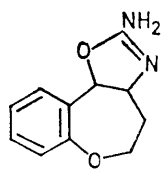

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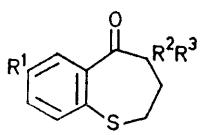

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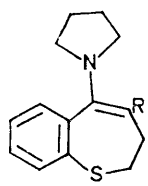

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Other routes from the 1-benzoxepin-5-one to the 4-amino-1-benzoxepin-5-one hydrochloride were, therefore,

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[1] T. R. Elliott, *J. Physiol.*, 1904, **31**, xx.
[2] U. S. von Euler, *Acta Physiol. Scand.*, 1946, **12**, 73.
[3] G. Fontaine, *Ann. Chim.* (*France*), 1968, 179.
[4] C. O'Brien, *Chem. Rev.*, 1964, **64**, 81.

examined. The most useful was the conversion of the 1-benzoxepin-5-one to the 4-isonitroso-derivative by the action of pentyl nitrite in the presence of hydrogen chloride. In certain cases, notably with 7-methyl-3,4-dihydro-1-benzoxepin-5(2*H*)-one (3; R^1 = 7-Me, R^2 = H), the isonitroso-derivative was unstable in the presence of hydrogen chloride, and careful control of the experimental conditions was necessary. However, this route was still not satisfactory for making the 6,8-dimethyl compound, which was finally prepared by hydrogenation of the 4-azido-3,4-dihydro-1-benzoxepin-5(2*H*)-one (3; R^1 = 6,8-Me_2, R^2 = N_3).

Hydrogenation, or sodium borohydride reduction, of the 4-amino-1-benzoxepin-5-one (3; R^1 = H, R^2 = NH_2) hydrochloride afforded 4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (2; R^1 = R^2 = R^3 = R^4 = H, X = O), normally as a mixture of *cis*- and *trans*-isomers (with respect to the hydrogen atoms on positions 4 and 5). However, sodium borohydride reduction of the 7-methyl analogue gave essentially the *trans*-amino-alcohol (2; R^1 = 7-Me; R^2 = R^3 = R^4 = H, X = O). Better methods were, therefore, sought to prepare samples of the pure isomers.

The aminobenzoxepinone (3; R^1 = H, R^2 = NH_2) hydrochloride was converted into its urethane (3; R^1 = H, R^2 = NH·CO_2Me), which on reduction with potassium borohydride (or on hydrogenation) afforded the oxazolone (5; R = H). A pure stereoisomer of the 4-amino-1-benzoxepin-5-ol (2; R^1 = R^2 = R^3 = R^4 = H, X = O) having the *trans*-configuration was obtained on hydrolysis with ethanolic sodium hydroxide.

Preparation of a sample of the corresponding *cis*-compound proved more difficult. The acetamido-alcohol (2; R^1 = R^2 = R^3 = H, R^4 = Ac, X = O) was prepared as a mixture of isomers by hydrogenation of the acetamido-ketone (3; R^1 = H, R^2 = NHAc). On stirring the mixed isomers in 2N-hydrochloric acid at room temperature, followed by recrystallisation of the undissolved material, a sample of the acetamido-alcohol having the *cis*-configuration was obtained. Subsequent hydrolysis with ethanolic sodium hydroxide afforded *cis*-4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (2; R^1 = R^2 = R^3 = R^4 = H, X = O). The hydrochloric acid solution contained the *O*-acetyl, compound (2; R^1 = R^3 = R^4 = H, R^2 = Ac, X = O) with H-4 and H-5 *trans*. On basification, $O \rightarrow N$ migration of the acetyl group occurred without inversion to give the acetamido-alcohol (2; R^1 = R^2 = R^3 = H, R^4 = Ac, X = O). This technique did not, however, prove satisfactory with the 7-methyl analogue; a sample of the *cis*-isomer has not been prepared.

Chlorinated 4-amino-1-benzoxepin-5-ols have been prepared by direct chlorination of the parent compound; *N*-substituted compounds were prepared by conventional procedures. Catalytic hydrogenation of 4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ols in sulphuric acid–acetic acid afforded 2,3,4,5-tetrahydro-1-benzoxepin-4-amines, and 2-amino-3a,4,5,10b-tetrahydro[1]benzoxepino[4,5-*d*]-oxazole (6) was obtained on treatment of the parent aminobenzoxepinol (2; R^1 = R^2 = R^3 = R^4 = H, X = O) with cyanogen bromide.

The 4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ols prepared are tabulated. Many of these compounds antagonised the action of reserpine in mice,[5] and some of the 2,3,4,5-tetrahydro-1-benzoxepin-4-amines suppressed the muricide response [6] in rats.

4-Amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ols and related compounds (2)

R^1	R^2	R^3	R^4	X	Method of prepn.	M.p.	Form	Cryst. from	Formula	Found (%) C	H	N	Required (%) C	H	N	Doublet in n.m.r. spectrum: τ	*J* (Hz)	Solvent	*cis* or *trans*
H	H	H	H	O	A, B	234 *c*	*d*	*g*	$C_{10}H_{14}ClNO_2$	55·6	6·6	6·3	55·8	6·5	6·5	4·9	9	D_2O	*trans*
H	H	Me	Me	O	F	115—120 *b*	*e*	*g*	$C_{12}H_{18}ClNO_3$,0·5H_2O	56·95	7·6	6·0	56·9	7·55	5·5	(prepared from *trans*-amine)			
7-Me	H	H	H	O	A	250 *c*	*d*	*g*	$C_{11}H_{16}ClNO_2$	57·3	7·1	5·8	57·5	7·0	6·1				*trans*
7-Me	H	H	H	O	B	151—153 *b*	*e*	*g*	$C_{11}H_{15}NO_2$	69·0	7·9	7·3	68·4	7·8	7·25	5·6	9	$(CD_3)_2SO$	*trans*
7-Me	H	H	Et	O	G	181—183 *c*	*e*	*h*	$C_{13}H_{20}ClNO_2$	60·5	8·0	5·3	60·55	7·8	5·4	4·9	9	D_2O	*trans*
7-Me	H	H	Me	O	G	204—205 *c*	*d*	*h*	$C_{12}H_{18}ClNO_2$	58·9	7·6	5·7	59·1	7·4	5·75				
7-Me	Ac	H	H	O	H	166—165 *c*	*e*	*g*	$C_{13}H_{19}ClNO_3$,H_2O	53·7	7·0	4·7	53·9	6·95	4·8				
7-MeO	H	H	H	O	B	199·5—200 *c*	*d*	*g*	$C_{11}H_{16}ClNO_3$,0·25H_2O	52·7	6·7	5·6	52·8	6·65	5·6	4·9	10	D_2O	*trans*
7,9-Me_2	H	H	H	O	D	255—256 *c*	*d*	*g*	$C_{12}H_{19}ClNO_2$	58·6	7·55	5·9	59·0	7·4	5·7	4·9	9	D_2O	*trans*
7,9-Me_2	H	H	Ac	O	D	196—197	*e*	*g*	$C_{14}H_{19}NO_3$	67·2	7·8	5·4	67·4	7·7	5·6				
9-Me	H	H	H	O	D	216—217 *c*	*d*	*g*	$C_{11}H_{14}ClNO_2$,0·25H_2O	56·6	7·1	5·7	56·4	7·1	6·0	4·95	9·5	D_2O	*trans*
7-Cl	H	H	H	O	E	250—251 *c*	*d*	*g*	$C_{10}H_{13}Cl_2NO_2$	48·0	5·2	5·5	48·0	5·2	5·6	5·0	10	D_2O	*trans*
7,9-Cl_2	H	H	H	O	E	263—264 *c*	*d*	*g*	$C_{10}H_{13}Cl_2NO_2$,0·5H_2O	41·2	4·3	4·5	40·9	4·5	4·8				
6 (or 8)-Cl,7-Me	H	H	H	O	E	253—254 *c*	*e*	*h*	$C_{11}H_{14}Cl_2NO_2$,0·5H_2O	42·9	4·75	4·3	42·9	4·9	4·55				
H	H	H	Ac	O	H	169—170	*e*	*g*	$C_{12}H_{15}NO_3$	65·2	6·95	6·2	65·1	6·8	6·3	4·9	2	D_2O	*cis* *n*
H	Ac	H	H	O	H	163—165 *c*	*d*	*g*	$C_{12}H_{16}ClNO_3$	55·5	6·2	5·7	55·9	6·2	5·4				
H	H	H	Ac	O	D *a*	138—139	*f*	*g*	$C_{12}H_{15}NO_3$	65·4	6·0	6·4	65·1	6·8	6·3				
H	H	H	CO_2Me	O	I	144—145			$C_{12}H_{15}NO_4$	60·8	6·5	5·7	60·75	6·4	5·9				
H	H	H	H	**S**	**J**	256—257 *c*	*e*	*i*	$C_{10}H_{14}ClNOS$	51·6	5·9	6·3	51·8	6·1	6·05	4·4	2·5	D_2O	*cis*
H	H	H	H	S	J	247—248 *c*	*e*	*i*	$C_{10}H_{14}ClNOS$	51·6	6·3	5·8	51·8	6·1	6·05	*cis*–*trans*—see text			
7-Me	H	H	Ac	S	K	216—217	*e*	*g*	$C_{13}H_{17}NO_2S$	62·05	7·0	6·15	62·1	6·8	5·6				*cis*
7-Me	H	H	H	S	K	131—132 *b*	*d*	*j*	$C_{11}H_{15}NOS$	63·1	7·4	6·45	63·1	7·2	6·7	4·6	2	$CDCl_3$	*cis*
7-Me	H	H	H	S	K	270—271 *c*	*d*	*k*	$C_{11}H_{16}ClNOS$	53·8	6·7	5·5	53·7	6·6	5·7				
7-Me	H	H	H	S	K	161—161·5 *b*	*d*	*j*	$C_{11}H_{15}NOS$	63·0	7·3	6·4	63·1	7·2	6·7	5·35	8	$CDCl_3$	*trans*
7-Me	H	H	H	S	K	252—253 *c*	*d*	*k*	$C_{11}H_{16}ClNOS$	53·8	6·7	5·5	53·7	6·6	5·7				*trans*
7-Me	H	Me	Me	S	F	108—109 *b*	*e*	*l*	$C_{13}H_{19}NOS$	65·7	8·2	5·65	65·8	8·1	5·9				*cis*
7-Me	H	Me	Me	S	F	225—227 *c*	*d*	*m*	$C_{13}H_{20}ClNOS$	57·1	7·6	5·1	57·0	7·1	5·1				*cis*
7-Me	H	Me	Me	S	F	97—99 *b*	*e*	*l*	$C_{13}H_{19}NOS$	65·6	8·0	5·7	65·8	8·1	5·9				*trans*
7-Me	H	Me	Me	S	F	236—237 *c*	*e*	*i*	$C_{13}H_{20}ClNOS$	57·0	7·5	4·9	57·0	7·1	5·1				*trans*
7-Me	H	H	H	SO_2	J	285—287 *c*	*e*	*m*	$C_{11}H_{16}ClNO_3S$	47·6	5·7	5·2	47·6	5·8	5·0	*cis*–*trans*—see text			
7-Me	H	H	H	S	J	116—118 *b*	*e*	*j*	$C_{11}H_{15}NOS$	63·3	7·4	6·4	63·1	7·2	6·7				*cis*–*trans*
7-Me	H	H	H	S	J	267—268 *c*	*e*	*i*	$C_{11}H_{16}ClNOS$	54·0	6·8	5·6	53·7	6·6	5·7				*cis*–*trans*

a PtO_2 instead of 10% Pd–C. *b* Free base. *c* Hydrochloride. *d* Needles. *e* Prisms. *f* Microcrystalline. *g* Ethanol *h* Acetone. *i* Methanol–ether. *j* Benzene–light petroleum (b.p. 60—80°). *k* Methanol–propan-2-ol. *l* Propan-2-ol. *m* Propan-2-ol–ether. *n* After alkaline hydrolysis of the acetyl group.

[5] L. O. Randall and R. E. Bagdon, *Ann. New York Acad. Sci.*, 1959, **80**, 626.

[6] Z. P. Horovitz, J. J. Piala, J. P. High, J. C. Burke, and R. C. Leaf, *Internat. J. Neuropharmacol.*, 1966, **5**, 405.

Work with the 1-benzothiepin system has been confined to compounds originating from 3,4-dihydro-1-benzothiepin-5(2*H*)-one (7; $R^1 = R^2 = R^3 = H$) and its 7-methyl analogue (7; $R^1 = Me$, $R^2 = R^3 = H$). Although the general synthetic procedures were similar to those applied to the 1-benzoxepin series, differences in the chemistry were encountered, particularly in the separation of isomers of the 4-amino-2,3,4,5-tetrahydro-1-benzothiepin-5-ols.

Whilst the Neber reaction again afforded a ready route to the amino-ketone (7; $R^1 = Me$, $R^2 = H$, $R^3 = NH_2$) hydrochloride, it was surprising to find that a slightly better yield was obtained on catalytic reduction of the 4-isonitroso-ketone (7; $R^1 = Me$, $R^2R^3 = :N{\cdot}OH$). Subsequent reduction of the amino-ketone hydrochlorides with sodium borohydride in methanol afforded the appropriate 4-amino-1-benzothiepin-5-ols (2; X = S). In the case of the parent compound (2; $R^1 = R^2 = R^3 = R^4 = H$, X = S), the product was rich in the *cis*-isomer, which was readily separated, whereas, with the 7-methyl analogue, the isomers were present in similar proportions and a separation was not achieved. A more satisfactory procedure in this case involved potassium borohydride reduction of the acetamido-ketone (7; $R^1 = Me$, $R^2 = H$, $R^3 = NHAc$) in methanol. The isomers of the resulting 4-acetamido-1-benzothiepin-5-ol (2; $R^1 = 7\text{-}Me$, $R^2 = R^3 = H$, $R^4 = Ac$, X = S) were separated by use of their differing solubility in chloroform. The parent amines were liberated by alkaline hydrolysis and subsequently converted into the *NN*-dimethyl analogues (2; $R^1 = 7\text{-}Me$, $R^2 = H$, $R^3 = R^4 = Me$, X = S) with formic acid–formaldehyde.

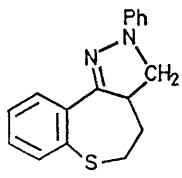
The enamine (8; R = H) was used as a source of a 4-methyl-1-benzothiepin-5-one (7; $R^1 = R^2 = H$, $R^3 = Me$). Bromination of the latter was followed by conversion of the bromo-ketone (7; $R^1 = H$, $R^2 = Br$, $R^3 = Me$) into an azide (7; $R^1 = H$, $R^2 = N_3$, $R^3 = Me$). Subsequent reduction with sodium dihydrobis-(2-methoxyethoxy)aluminate [7] gave a 4-amino-4-methyl-1-benzothiepin-5-ol.

The preparation of 2,3,4,5-tetrahydro-1-benzothiepin-4-amines by reduction of the analogous 4-amino-2,3,4,5-tetrahydrobenzothiepin-5-ols was not successful; poisoning prevented the use of catalytic methods, and the action of phosphorus and hydriodic acid led to the 2,3,4,5-tetrahydro-1-benzothiepin.

A representative sulphone analogue of the 4-amino-2,3,4,5-tetrahydro-1-benzothiepin-5-ols (2; $R^1 = 7\text{-}Me$, $R^2 = R^3 = R^4 = H$, $X = SO_2$) was prepared. The ketone (7; $R^1 = Me$, $R^2 = R^3 = H$) was oxidised with hydrogen peroxide to the corresponding sulphone. Neber rearrangement of the oxime tosylate, followed by potassium borohydride reduction, afforded the amino-alcohol as a mixture of *cis*- and *trans*-isomers.

The sulphur-containing amino alcohols prepared are listed in the Table. Like their oxygen analogues, several of the 4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ols were quite potent antagonists of the action of reserpine in mice. However, there was a clear-cut distinction between the isomers. Whereas *trans*-4-amino-2,3,4,5-tetrahydro-7-methyl-1-benzothiepin-5-ol hydrochloride showed potent antireserpine activity and definite gastric antisecretory properties, these were virtually absent in the *cis*-isomer.

Finally, a comment should be made on the differentiation of the *cis*- and *trans*-isomers of the amino-alcohols. N.m.r. spectra of the hydrochlorides were run for solutions in deuterium oxide, and free bases were examined in [$^2H_6$]dimethyl sulphoxide solution. The 4- and 5-protons of the 4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ols gave a doublet centred at about τ 4·9 in the hydrochloride and at about τ 5·6 in the free base. In the *trans*-configuration, the coupling constant had a value of about 9 Hz whereas in the *cis*-isomer it was about 2 Hz. In the case of 4-amino-2,3,4,5-tetrahydro-1-benzothiepin-5-ols (free bases in [^{2}H]chloroform) the *trans*-isomer showed a doublet at τ 5·35 (J 8 Hz) whereas the coupling constant in the *cis*-isomer was *ca.* 2 Hz for a doublet centred around τ 4·6.



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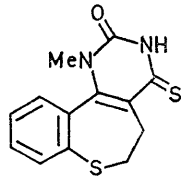

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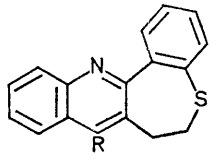

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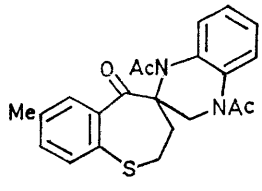

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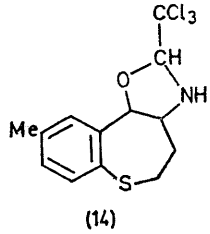

(14)

In addition to the work designed to prepare amino-alcohols, the synthesis of a number of multicyclic molecules containing the 2,3,4,5-tetrahydro-1-benzothiepin system was undertaken.

The reaction of the Mannich base (7; $R^1 = R^2 = H$, $R^3 = CH_2{\cdot}NMe_2$) with phenylhydrazine in the presence of sodium hydroxide afforded the pyrazole (9). The enamine (8; R = H) provided a starting point for a fused pyrimidine system (10). Reaction with ethoxy-

[7] J. Vit, B. Čásenský, and J. Macháček, Fr. Pat., 1,515,582; V. Bažant, M. Čapka, M. Černý, V. Chvalovský, K. Kochloefl, M. Kraus, and J. Malek, *Tetrahedron Letters*, 1968, 3303.

carbonyl isothiocyanate [8] afforded the thiocarbamoyl ester (8; R = CS·NHCO$_2$Et) which was converted into the pyrimidinethione (10) by the action of aqueous methylamine. Some uncyclised material (11) was, however, also isolated from the reaction.

The benzothiepino[5,4-*b*]quinolinecarboxylic acid (12; R = CO$_2$H) was obtained by treatment of 3,4-dihydro-1-benzothiepin-5(2*H*)-one with isatin under alkaline conditions; a similar reaction in which the isatin was replaced by anthranilic acid afforded a benzothiepino-[5,4-*b*]quinolinol (12; R = OH).

The 4-hydroxymethylene compound (7; R^1 = Me, R^{2}R^3 = :CH·OH) was obtained by treatment of 7-methyl-3,4-dihydro-1-benzothiepin-5(2*H*)-one with methyl formate and sodium hydride in benzene. Subsequent reaction with *o*-phenylenediamine afforded the enamine (7; R^1 = Me, R^{2}R^3 = :CH·NH·C$_6$H$_4$·NH$_2$-*o*), which on acetylation with acetic anhydride, afforded the spiro-compound (13).

Finally, a benzothiepino[4,5-*d*]oxazole (14) was prepared by treatment of 4-amino-2,3,4,5-tetrahydro-7-methyl-1-benzothiepin-5-ol with anhydrous chloral.

EXPERIMENTAL

M.p.s are corrected and were determined for samples in capillary tubes; b.p.s are uncorrected. N.m.r. spectra were determined with a Varian A60 spectrometer. Catalytic hydrogenations were carried out at atmospheric temperature and pressure unless otherwise stated.

4-Phenoxybutyric Acids.—3-Phenoxypropyl bromides were prepared from the appropriate phenols and trimethylene dibromide, and converted into the corresponding nitriles as described by Marvel and Tanenbaum.[9,10] Refluxing the crude 4-phenoxybutyronitriles with concentrated hydrochloric acid for 17 hr. afforded the 4-phenoxybutyric acids. These were normally obtained as oils that slowly crystallised. They were not usually purified, but cyclised directly.

3,4-Dihydro-1-benzoxepin-5(2H)-ones (3; R^2 = H).—Cyclisation of 4-phenoxybutyric acids with polyphosphoric acid in xylene in a manner similar to that described by Fontaine [3] afforded the appropriate 3,4-dihydro-1-benzoxepin-5(2*H*)-ones. The ketones were finally distilled *in vacuo* to free them from the corresponding 4-phenoxybutyric acid phenyl esters that were frequently formed as by-products.[3] The product obtained after a single distillation was adequate for subsequent work but was not always analytically pure, owing to traces of the lactone by-product [$\nu_{max.}$ 1740 cm.$^{-1}$ (CO)]. The ketones showed $\nu_{max.}$ *ca.* 1680 cm.$^{-1}$.

3,4-Dihydro-1-benzothiepin-5(2H)-ones (7; R^2 = R^3 = H).—4-(Phenylthio)butyric acid was prepared and converted into 3,4-dihydro-1-benzothiepin-5-(2*H*)-one by the method of Traynelis and Love.[11]

The 7-methyl analogue (7; R^1 = 7-Me, R^2 = R^3 = H) was prepared as follows: 4-(Tolylthio)butyric acid [12] (255 g.) was added in portions with vigorous stirring to polyphosphoric acid (3·35 kg.) at 100°. The red solution was stirred at 100° for 2 hr., then poured on crushed ice (*ca.* 6 kg.), and the cooled mixture was extracted with ether. The extract was washed with 2N-sodium hydroxide and water, dried, and evaporated. Distillation of the residue afforded 3,4-dihydro-7-methyl-1-benzothiepin-5(2*H*)-one as a liquid (199 g.), b.p. 138—142°/0·7 mm.

3,4-Dihydro-7-methyl-1-benzothiepin-5(2H)-one 1,1-Dioxide.—3,4-Dihydro-7-methyl-1-benzothiepin-5(2*H*)-one (30 g.), glacial acetic acid (250 ml.), and hydrogen peroxide (28% aq. solution; 100 ml.) were heated on a steam-bath for 2 hr. and poured into water (750 ml.). The mixture was cooled in ice and the solid that separated was filtered off. The *sulphone* (31·25 g.) was obtained as needles (from ethanol), m.p. 153·5—154° (Found: C, 58·6; H, 5·2. C$_{11}$H$_{12}$O$_3$S requires C, 58·9; H, 5·4%).

3,4-Dihydro-1-benzoxepin-5(2H)-one Oximes and 3,4-Dihydro-1-benzothiepin-5(2H)-one Oximes.—The benzoxepinones and benzothiepinones were converted into their oximes in virtually quantitative yield. Previously unreported oximes were *3,4-dihydro-7-methyl-1-benzoxepin-5(2H)-one oxime*, prisms (from ethanol), m.p. 65—68° (Found: C, 69·4; H, 7·0; N, 7·0. C$_{11}$H$_{13}$NO$_2$ requires C, 69·1; H, 6·85; N, 7·3%), and *3,4-dihydro-7-methyl-1-benzothiepin-5(2H)-one oxime*, plates (from aqueous ethanol), m.p. 122—123° (Found: C, 63·3; H, 6·5; N, 6·7. C$_{11}$H$_{13}$NOS requires C, 63·7; H, 6·3; N, 6·7%). Although 3,4-dihydro-6,8-dimethyl-1-benzoxepin-5-(2*H*)-one oxime has not been previously reported, the sample obtained in this work was not adequately characterised.

The *oxime* of 3,4-dihydro-7-methyl-1-benzothiepin-5(2*H*)-one 1,1-dioxide was obtained as plates (71% yield), m.p. 192—193° (from ethanol) (Found: C, 54·8; H, 5·3; N, 6·0. C$_{11}$H$_{13}$NO$_3$S requires C, 55·2; H, 5·5; N, 5·9%).

3,4-Dihydro-1-benzoxepin-5(2H)-one O-(p-Tolylsulphonyl)oximes and 3,4-Dihydro-1-benzothiepin-5(2H)-one O-(p-Tolylsulphonyl)oximes.—Oximes were converted into the O-(*p*-tolylsulphonyl)oximes by the method of ref. 13. They were not purified but were converted directly into the amino-ketone hydrochlorides. The *O-(p-tolylsulphonyl)-oxime* of 3,4-dihydro-7-methyl-1-benzothiepin-5(2H)-one 1,1-dioxide was obtained (69%) as needles (from benzene–methanol), m.p. 146—147° (Found: C, 55·3; H, 5·0; N, 3·2. C$_{18}$H$_{19}$NO$_3$S$_2$ requires C, 54·95; H, 4·9; N, 3·55%).

3,4-Dihydro-4-hydroxyimino-7-methyl-1-benzoxepin-5(2H)-one (3; R^1 = 7-Me, R^2 = :N·OH).—3,4-Dihydro-7-methyl-1-benzoxepin-5(2*H*)-one (8·8 g.) in ether (20 ml.) was cooled to 0° and saturated with dry hydrogen chloride. Redistilled pentyl nitrite (9·5 ml.) in ether (20 ml.) was added during 0·5 hr., with the temperature maintained below 5°. Within 10 min. of completing the addition, the yellow solid was rapidly filtered off and dried in a desiccator, and the crude isonitroso-compound (4·8 g.; m.p. 139—144°) was reduced directly to the amino-ketone as described later. Further purification proved difficult.

Crude 3,4-dihydro-4-isonitroso-1-benzoxepin-5(2*H*)-one was similarly prepared (75%), m.p. 146—148°. *3,4-Dihydro-4-hydroxyimino-7-methoxy-1-benzoxepin-5(2H)-one* (49%) had m.p. 157—162° (Found: C, 59·9; H, 5·2; N, 6·2. C$_{11}$H$_{11}$NO$_4$ requires C, 59·7; H, 5·0; N, 6·3%), 3,4-dihydro-4-hydroxyimino-9-methyl-1-benzoxepin-5(2*H*)-one (16%) had m.p. 160—162°, and the 7,9-dimethyl

[8] R. W. Lamon, *J. Heterocyclic Chem.*, 1968, **5**, 837.
[9] C. S. Marvel and A. L. Tanenbaum, *Org. Synth.*, Coll. Vol. I, 1956, p. 435.
[10] C. S. Marvel and A. L. Tanenbaum, *J. Amer. Chem. Soc.*, 1922, **44**, 2647.
[11] V. J. Traynelis and R. F. Love, *J. Org. Chem.*, 1961, **26**, 2728.
[12] W. Reppe, *Annalen*, 1955, **596**, 195.
[13] C. O'Brien, E. M. Philbin, S. Ushioda, and T. S. Wheeler, *Tetrahedron*, 1963, **19**, 373.

analogue (60%) had m.p. 158—160°. The nature of the crude products was confirmed by their i.r. spectra; the Nujol spectra showed peaks around 1660 (CO) and 3250 cm.$^{-1}$ (OH).

3,4-*Dihydro*-4-*hydroxyimino*-7-*methyl*-1-*benzothiepin*-5(2H)-*one* (7; R^1 = Me, R^2R^3 = :N·OH) was similarly prepared (63%) as needles (from aqueous ethanol), m.p. 162—163° (Found: C, 60·0; H, 5·2; N, 6·2. $C_{11}H_{11}NO_2S$ requires C, 59·7; H, 5·0; N, 6·3%).

4-*Azido*-3,4-*dihydro*-6,8-*dimethyl*-1-*benzoxepin*-5(2H)-*one* (3; R^1 = H, R^2 = N_3).—Bromine (14·4 g.) was added dropwise to a refluxing solution of 3,4-dihydro-6,8-dimethyl-1-benzoxepin-5(2*H*)-one (16 g.) in ether (100 ml.). The solution was refluxed for 2·5 hr. and evaporated. The crude bromo-compound (23 g.) and glacial acetic acid (1 ml.) were dissolved in dimethylformamide (75 ml.). Sodium azide (7 g.) in water (40 ml.) was added and the mixture was stirred at room temperature for 2 days, poured into water (300 ml.), and extracted with ethyl acetate. Evaporation of the extracts *in vacuo* afforded the crude azide (20 g.) [$\nu_{max.}$ 1680 (CO) and 2125 cm.$^{-1}$ (N_3)].

4-*Azido*-3,4-*dihydro*-4-*methyl*-1-*benzothiepin*-5(2H)-*one* (7; R^1 = H, R^2 = Me, R^3 = N_3).—4-Methyl-3,4-dihydro-1-benzothiepin-5(2*H*)-one (19·2 g.) was dissolved in carbon tetrachloride (100 ml.) and a solution of bromine (5·1 ml.) in carbon tetrachloride (20 ml.) was added dropwise at room temperature during 1·5 hr. The solution was stirred overnight, and evaporated. The residual oil was dissolved in ether (100 ml.), washed with saturated sodium hydrogen carbonate solution, dried, and evaporated to give the crude 4-bromo-ketone as an oil (30 g.). The bromo-compound was converted into the crude 4-azido-compound [an orange oil (24·2 g.)] in a manner similar to that already described.

4-*Amino*-3,4-*dihydro*-1-*benzoxepin*-5(2H)-*one* (3; R^2 = NH_2) *Hydrochlorides and* 4-*Amino*-3,4-*dihydro*-1-*benzothiepin*-5(2H)-*one* (7; R^2 = H, R^3 = NH_2) *Hydrochlorides*. —(a) *By the Neber reaction*. The *O*-(*p*-tolylsulphonyl)-oximes were converted into the appropriate amino-ketone hydrochlorides by the methods of refs. 13 and 14. Previously unreported compounds prepared by this method were: 4-*amino*-3,4-*dihydro*-1-*benzoxepin*-5(2H)-*one hydrochloride* (80%), needles (from ethanol), m.p. 209—212° (Found: C, 50·8; H, 5·8; N, 5·8. $C_{10}H_{12}ClNO_2$,1·25H_2O requires C, 50·8; H, 6·2; N, 5·9%), and 4-*amino*-3,4-*dihydro*-7-*methyl*-1-*benzoxepin*-5(2H)-*one hydrochloride* (70%), needles (from ethanol), m.p. 201—203° (Found: C, 57·1; H, 6·25; N, 6·25. $C_{11}H_{14}ClNO_2$ requires C, 57·2; H, 6·2; N, 6·2%).

4-Amino-3,4-dihydro-1-benzothiepin-5(2*H*)-one hydrochloride (58%) had m.p. 219—221° (lit.,[14] 209·5—210°) and 4-*amino*-3,4-*dihydro*-7-*methyl*-1-*benzothiepin*-5(2H)-*one hydrochloride* (72%) formed prisms (from methanol), m.p. 223—225° (Found: C, 53·9; H, 5·8; N, 5·5. $C_{11}H_{14}ClNOS$ requires C, 54·2; H, 5·75; N, 5·7%). 4-*Amino*-3,4-*dihydro*-7-*methyl*-1-*benzothiepin*-5(2H)-*one* 1,1-*dioxide hydrochloride* (61%) formed prisms (from methanol–ether), m.p. 232—233° (Found: C, 47·8; H, 5·1; N, 4·9. $C_{11}H_{14}ClNO_3S$ requires C, 47·9; H, 5·1; N, 5·1%).

(b) *By reduction of the isonitroso-ketone*. 3,4-Dihydro-4-hydroxyimino-7-methoxy-1-benzoxepin-5(2*H*)-one (18·1 g.) in glacial acetic acid (500 ml.) was hydrogenated in the presence of 10% palladium–charcoal (2 g.). The catalyst was filtered off and excess of ethereal hydrogen chloride was added to the filtrate. Evaporation afforded 4-*amino*-3,4-*dihydro*-7-*methoxy*-1-*benzoxepin*-5(2H)-*one hydrochloride* (8·9 g.) as plates (from ethanol), m.p. 202—203° (Found: C, 54·2; H, 5·9; N, 5·6. $C_{11}H_{14}ClNO_3$ requires C, 54·2; H, 5·8; N, 5·75%). Samples of the parent amino-ketone (3; R^1 = H; R^2 = NH_2) hydrochloride and the 7-methyl analogue (3; R^1 = 7-Me, R^2 = NH_2) were identical with the samples prepared before. Other compounds similarly prepared were 4-*amino*-3,4-*dihydro*-9-*methyl*-1-*benzoxepin*-5(2H)-*one hydrochloride* (61%) as prisms (from ethanol), m.p. 145—147° (Found: C, 54·0; H, 6·6; N, 5·7. $C_{11}H_{14}ClNO_2$,H_2O requires C, 53·8; H, 6·6; N, 5·7%), and 4-*amino*-3,4-*dihydro*-7,9-*dimethyl*-1-*benzoxepin*-5(2H)-*one hydrochloride* (92%) as prisms (from ethanol), m.p. 196—198° (Found: C, 59·6; H, 6·8; N, 5·7. $C_{12}H_{16}ClNO_2$ requires C, 59·6; H, 6·7; N, 5·8%).

4-Amino-3,4-dihydro-7-methyl-1-benzothiepin-5(2*H*)-one (7; R^1 = Me, R^2 = H, R^3 = NH_2) hydrochloride was obtained (77%) by the same procedure; the product was identical with the sample prepared by the Neber reaction.

(c) *By reduction of the azido-ketone*. Crude 4-azido-3,4-dihydro-6,8-dimethyl-1-benzoxepin-5(2*H*)-one (20 g.; prepared as already described) in glacial acetic acid (250 ml.) was hydrogenated over 10% palladium–charcoal (2 g.). The catalyst was filtered off, excess of ethereal hydrogen chloride was added, and the solution was evaporated. The crude amino-ketone hydrochloride in water (125 ml.) containing sodium acetate (48 g.), acetic anhydride (64·8 g.), and ethyl acetate (400 ml.) was stirred at room temperature for 5 hr. The organic phase was separated, washed with water, dried, and evaporated. The residual oil was dissolved in benzene and applied to a column of neutral Woelm alumina (16 × 3·5 cm.). The acetamido-ketone emerged after 150 ml. of benzene had been passed through the column (rate of elution 8 ml./hr.). Evaporation afforded 4-*acetamido*-3,4-*dihydro*-6,8-*dimethyl*-1-*benzoxepin*-5(2H)-*one* as needles (1·8 g.), m.p. 144—146° (from benzene–light petroleum) (Found: C, 67·2; H, 6·9; N, 5·4. $C_{14}H_{17}NO_3$ requires C, 68·0; H, 6·9; N, 5·7%).

3,4-*Dihydro*-7,9-*dimethyl*-2H-1,6-*benzoxazocin*-5(6H)-*one* (4; R = H). —3,4-Dihydro-6,8-dimethyl-1-benzoxepin-5(2*H*)-one (39 g.) was converted into its oxime and thence into the *O*-(*p*-tolylsulphonyl)oxime. The latter was subjected to the Neber reaction but the expected amino-ketone hydrochloride was not obtained. The hydrochloric acid extracts slowly deposited a white crystalline solid (7 g.) and a further 15 g. was obtained when the acid was evaporated. The solids showed identical i.r. spectra [$\nu_{max.}$ 1660 (CO) and 3200 cm.$^{-1}$ (NH) (Nujol)] and afforded prisms (from ethanol), m.p. 214—215°, of the *benzoxazocinone* (4; R = H) (Found: C, 69·7; H, 7·5; N, 6·7. $C_{12}H_{15}NO_2$ requires C, 70·2; H, 7·3; N, 6·8%).

The structure was confirmed by acid hydrolysis as previously described.[15] 4-(2-Amino-3,5-dimethylphenoxy)-butyric acid hydrochloride was obtained as prisms, m.p. 214—215°. Potentiometric titration showed pK_a 3·9 (base) and 5·7 (carboxylic acid) (50% ethanol), with an equivalent weight of 129 for two groups (*i.e.* molecular weight 258; required 260). This indicated a weak base as opposed to the strong base that would have been expected from the corresponding 1,5-benzoxazocin-6-one.

6-[3-(*Dimethylamino*)*propyl*]-3,4-*dihydro*-7,9-*dimethyl*-2H-1,6-*benzoxazocin*-5(6H)-*one* (4; R = $[CH_2]_3$·NMe_2) *Hydrochloride*.—The 1,6-benzoxazocin-5-one (4; R = H) was

[14] N. V. Dudykina and V. A. Zagorevskii, *J. Org. Chem.* (*U.S.S.R.*), 1966, **2**, 2179.

[15] D. Huckle, I. M. Lockhart, and M. Wright, *J. Chem. Soc.*, 1965, 1137.

converted into the *N*-dimethylaminopropyl derivative by alkylation with dimethylaminopropyl chloride in dimethylformamide in the presence of sodium hydride, essentially as described previously.[15] The product (4; R = $[CH_2]_3$·NMe_2) was obtained as the *hydrochloride*, m.p. 200—201° (from ethanol) (Found: C, 61·95; H, 8·3; N, 8·5. $C_{17}H_{26}N_2O_2$,HCl requires C, 62·4; H, 8·3; N, 8·6%).

Methyl 2,3,4,5-Tetrahydro-7-methyl-5-oxo-1-benzoxepin-4-carbamate (3; R^1 = 7-Me, R^2 = NH·CO_2Me).—Methyl chloroformate (20 ml.) and potassium hydrogen carbonate (40 g.) were added alternately and in portions to 4-amino-3,4-dihydro-7-methyl-1-benzoxepin-5(2*H*)-one hydrochloride (6·7 g.) in water (200 ml.). The mixture was stirred for 1 hr.; the solid was filtered off, washed with water, and dried to give the *keto-urethane* (6·2 g.) as plates (from ethanol), m.p. 129·5—130·5° (Found: C, 62·6; H, 6·2; N, 5·4. $C_{13}H_{15}NO_4$ requires C, 62·6; H, 6·1; N, 5·6%).

Other keto-urethanes prepared similarly were *methyl 2,3,4,5-tetrahydro-5-oxo-1-benzoxepin-4-carbamate* (3; R^1 = H, R^2 = NH·CO_2Me), needles (from ethanol), m.p. 133—134·5° (Found: C, 61·2; H, 5·6; N, 5·9. $C_{12}H_{13}NO_4$ requires C, 61·3; H, 5·6; N, 6·0%), and the *7-methoxy-analogue* (3; R^1 = 7-MeO, R^2 = NH·CO_2Me), prisms (from ethanol), m.p. 87—91° (Found: C, 59·0; H, 5·9; N, 5·8. $C_{13}H_{15}NO_5$ requires C, 58·9; H, 5·7; N, 5·3%).

trans-3a,4,5,10b-*Tetrahydro-9-methyl*[1]*benzoxepino*-[4,5-d]*oxazol*-2(3H)-*one* (5; R = Me).—Methyl 2,3,4,5-tetrahydro-7-methyl-5-oxo-1-benzoxepin-4-carbamate (3; R^1 = 7-Me, R^2 = NH·CO_2Me) (6 g.) in ethanol (100 ml.) and water (15 ml.) was stirred with potassium borohydride (3·5 g.) at room temperature for 4 hr. Ethanol was removed by evaporation; the solid was filtered off, washed with water, dried, and recrystallised from ethanol. The trans-*benzoxepino-oxazolone* (2·9 g.) was obtained as needles, m.p. 214—215° (Found: C, 66·0; H, 5·9; N, 6·4. $C_{12}H_{13}NO_3$ requires C, 65·7; H, 6·0; N, 6·4%), τ [$(CD_3)_2SO$] 4·7 (d, *J* 11 Hz).

Other compounds prepared similarly were trans-3a,4,5,10b-*tetrahydro*[1]*benzoxepino*[4,5-d]*oxazol*-2(3H)-*one*, a microcrystalline solid, m.p. 201—202° (Found: C, 64·0; H, 5·5; N, 6·9. $C_{11}H_{11}NO_3$ requires C, 64·4; H, 5·4; N, 6·8%), τ [$(CD_3)_2SO$] 4·6 (d, *J* 11 Hz), and trans-3a,4,5,10b-*tetrahydro-9-methoxy*[1]*benzoxepino*[4,5-d]*oxazol*-2(3H)-*one*, plates, m.p. 205—207° (Found: C, 61·2; H, 5·7; N, 6·1. $C_{12}H_{13}NO_4$ requires C, 61·3; H, 5·6; N, 6·0%).

4-Amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (2; R^2 = R^3 = R^4 = H, X = O) *Hydrochlorides and 4-Amino-2,3,4,5-tetrahydro-1-benzothiepin-5-ol* (2; R^2 = R^3 = R^4 = H, X = S) *Hydrochlorides*.—The physico-chemical properties of the various *amino-benzoxepinols* and *-benzothiepinols* are listed in the Table.

Method A. The appropriate 4-amino-3,4-dihydro-1-benzoxepino-5(2*H*)-one hydrochloride (*ca.* 0·15 mole) in ethanol (250 ml.) was added to a stirred suspension of sodium borohydride (10 g.) in ethanol (250 ml.). The mixture was stirred for 3 hr., 2N-hydrochloric acid (250 ml.) was added, and the clear solution was evaporated. The residue was purified by acid–base extraction and/or by recrystallisation from a suitable solvent. In certain cases, the free base was converted into the hydrochloride.

Method B. The appropriate *trans*-3a,4,5,10b-tetrahydro-[1]benzoxepino[4,5-*d*]oxazol-2(3*H*)-one (2 g.) in ethanol (75 ml.) and 2N-sodium hydroxide (30 ml.) was stirred and refluxed for 2·5 hr. Ethanol was evaporated off and the alkaline suspension was extracted with chloroform. The extracts were extracted with 2N-hydrochloric acid and the aqueous solution was basified (10N-sodium hydroxide) and re-extracted with chloroform. The chloroform extracts were dried and evaporated to give a residue of the amino-alcohol that was recrystallised, and, in certain cases converted into the hydrochloride.

Method C. 4-Amino-3,4-dihydro-1-benzoxepin-5(2*H*)-one hydrochloride (12·75 g.) in ethanol (250 ml.) was hydrogenated over 10% palladium–charcoal (1 g.). The catalyst was filtered off, the filtrate was evaporated, and the amino-alcohol hydrochloride (11 g.)) was isolated from the residue; m.p. 223—225° (mixture of isomers). A mixture of isomers was also obtained when 4-amino-3,4-dihydro-7,9-dimethyl-1-benzoxepin-5(2*H*)-one hydrochloride was hydrogenated to the corresponding amino-alcohol hydrochloride.

Method D. 4-Amino-3,4-dihydro-1-benzoxepin-5(2*H*)-one hydrochlorides were converted into the *N*-acetyl derivatives by the method described previously.[16] *4-Acetamido-3,4-dihydro-7,9-dimethyl-1-benzoxepin-5*(2H)-*one* (3; R^1 = 7,9-Me_2, R^2 = NHAc) was obtained as prisms (from benzene), m.p. 186—187° (Found: C, 68·0; H, 6·9; N, 5·5. $C_{14}H_{17}NO_3$ requires C, 68·0; H, 6·9; N, 5·7%), and 4-*acetamido-3,4-dihydro-7-methyl-1-benzoxepin-5*(2H)-one (3; R^1 = 7-Me, R^2 = NHAc) as needles (from ethanol), m.p. 159—160° (Found: C, 66·8; H, 6·5; N, 5·6. $C_{13}H_{15}NO_3$ requires C, 66·9; H, 6·5; N, 6·0%). The 9-methyl analogue (3; R^1 = 9-Me, R^2 = NHAc) was not characterised; the crude product was directly converted into the acetamido-alcohol.

4-Acetamido-1-benzoxepin-5(2*H*)-ones were converted into the corresponding 4-acetamido-1-benzoxepin-5-ols by hydrogenation in ethanol over 10% palladium–charcoal. The acetamido-1-benzoxepin-5-ols (0·02 mole) were finally converted into the 4-amino-1-benzoxepin-5-ols by refluxing with ethanol (20 ml.) and 10N-sodium hydroxide (10 ml.) for 3·5 hr. The products were isolated by conventional procedures and converted into their hydrochlorides.

Method E. 4-Amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ol hydrochlorides were dissolved in chloroform and a few crystals of iodine were added. An appropriate weight of chlorine in chloroform was then added, and the solution was stirred at room temperature for 2 days. The chloro-compound was isolated by conventional procedures.

Method F. 4-Amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ol hydrochloride (4·5 g.) was converted into the free base and refluxed with 90% formic acid (4 ml.) and formaldehyde (6 ml.) for 5 hr. The solution was basified and extracted with ether; the 4-(dimethylamino)-1-benzoxepin-5-ol was isolated from the extract and converted into the hydrochloride (3·8 g.).

Method G. 4-Amino-3,4-dihydro-7-methyl-1-benzoxepin-5(2*H*)-one hydrochloride (6 g.), sodium acetate (1·8 g.), 98% formic acid (100 ml.), and acetic anhydride (200 ml.) were heated on a steam-bath for 3 hr. after the exothermic reaction had subsided. The mixture was evaporated, the residue was dissolved in chloroform, and the organic solution was washed with water, dried, and evaporated, to give *4-formamido-3,4-dihydro-7-methyl-1-benzoxepin-5*(2H)-*one* (4·0 g.) (3; R^1 = 7-Me, R^2 = NH·CHO) as needles (from ethanol), m.p. 132—133° (Found: C, 65·9; H, 6·15; N, 6·1. $C_{12}H_{13}NO_3$ requires C, 65·7; H, 6·0; N, 6·4%).

[16] D. Huckle, I. M. Lockhart, and M. Wright, *J. Medicin. Chem.*, 1969, **12**, 277.

The formamido-ketone was converted into the 4-formamido-1-benzoxepin-5-ol by catalytic reduction in ethanol over 10% palladium–charcoal. The crude product (3·5 g.) was dissolved in benzene (50 ml.), added to a suspension of lithium aluminium hydride (1·5 g.) in benzene (50 ml.), and refluxed for 10 hr. Saturated aqueous ammonium chloride was added to the cooled mixture, which was refluxed for 2 hr. and filtered; the residue was washed with ethyl acetate. The combined organic phases were washed with water, dried, and evaporated. The residual 2,3,4,5-tetrahydro-7-methyl-4-(methylamino)-1-benzoxepin-5-ol (2·0 g.) was converted into the *hydrochloride*.

The corresponding 4-(ethylamino)-2,3,4,5-tetrahydro-7-methyl-1-benzoxepin-5-ol was similarly prepared by lithium aluminium hydride reduction of the 4-acetamido-analogue.

Separation of cis- *and* trans-*Isomers of 4-Acetamido-2,3,4,5-tetrahydro-1-benzoxepin-5-ol.—Method H.* 4-Amino-3,4-dihydro-1-benzoxepin-5(2*H*)-one hydrochloride was converted into the 4-acetamido-compound (method D), which on catalytic hydrogenation (method D) afforded a mixture of *cis*- and *trans*-isomers of 4-acetamido-2,3,4,5-tetrahydro-1-benzoxepin-5-ol. The sample of the mixed isomers (10·5 g.) was stirred at room temperature with 2N-hydrochloric acid (50 ml.) for 2 hr. Recrystallisation of the undissolved residue from ethanol afforded the *cis*-isomer of the 4-acetamido-1-benzoxepin-5-ol (3 g.). A sample of the *cis*-acetamido-compound was converted into the 4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ol by alkaline hydrolysis (see method D). The n.m.r. spectrum of the hydrochloride (m.p. 255—256°) showed a doublet at τ (D_2O) 4·93 (J 2 Hz) indicating the *cis*-configuration.

On stirring with 2N-hydrochloric acid, the *trans*-4-acetamido-2,3,4,5-tetrahydro-1-benzoxepin-5-ol was apparently converted into *trans*-4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-yl acetate (2; $R^1 = R^3 = R^4 = H$, $R^2 = Ac$, X = O), which dissolved in the acid and was isolated as the *hydrochloride* on evaporation and recrystallisation from ethanol. Basification and extraction with solvent effected $O \rightarrow N$-acyl migration and reconverted the *O*-acetyl compound into the *trans*-4-acetamido-2,3,4,5-tetrahydro-1-benzoxepin-5-ol.

Similar experiments with the 4-acetamido-2,3,4,5-tetrahydro-7-methyl-1-benzoxepin-5-ol did not effect a separation of isomers but did enable trans-4-*amino*-2,3,4,5-*tetrahydro*-7-*methyl*-1-*benzoxepin*-5-*yl acetate* (2; R^1 = 7-Me, R^2 = Ac, $R^3 = R^4 = H$, X = O) *hydrochloride* to be isolated.

Methyl trans-2,3,4,5-*Tetrahydro*-5-*hydroxy*-1-*benzoxepin*-4-*carbamate* (2; $R^1 = R^2 = R^3 = H$, $R^4 = CO_2Me$, X = O). —*Method I.* *trans*-4-Amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ol hydrochloride (0·2 g.) in water (10 ml.) and ethyl acetate (50 ml.) was stirred, and potassium carbonate (0·3 g.) was added, followed by methyl chloroformate (1·2 g.). The mixture was stirred for 4 hr.; the organic layer was then washed with water, dried, and evaporated. The residue was washed with light petroleum (b.p. 60—80°), filtered, and dried to give the 1-*benzoxepin*-4-*carbamate*.

cis-4-*Amino*-2,3,4,5-*tetrahydro*-1-*benzothiepin*-5-*ol* (2; $R^1 = R^2 = R^3 = R^4 = H$, X = S) *Hydrochloride*.—*Method J.* Potassium borohydride (15·9 g.) was added in portions to a stirred suspension of 4-amino-3,4-dihydro-1-benzothiepin-5(2*H*)-one hydrochloride monohydrate (22·9 g.) in methanol (250 ml.), with the temperature kept below 30°. The mixture was stirred for 6 hr. at room temperature, water (250 ml.) was added, and excess of methanol was removed by distillation. The mixture was extracted with ether; the extract was dried ($MgSO_4$) and evaporated, and ether (150 ml.) was added to the residue. The *cis*-isomer was filtered off and converted into its *hydrochloride* (2·8 g.).

Ethereal hydrogen chloride was added to the ether solution from the foregoing separation. The hydrochloride that separated (8·1 g.) had m.p. 247—248° and was shown to be a mixture of *cis*- and *trans*-isomers (approx. 1 : 1) by t.l.c. [a 5 µl. sample of a 5% solution in methanol run on plates of Keiselgel HF 254 developed with chloroform–methanol–diethylamine (90 : 10 : 5); the plates were examined at 254 and 350 nm.].

cis- *and* trans-4-*Acetamido*-2,3,4,5-*tetrahydro*-7-*methyl*-1-*benzothiepin*-5-*ols.—Method K.* 4-Amino-3,4-dihydro-7-methyl-1-benzothiepin-5(2*H*)-one hydrochloride was converted [16] into the 4-*acetamido-compound* (7; R^1 = 7-Me, $R^2 = H$, $R^3 = NHAc$), which was obtained as cubes (56%), m.p. 178—179° (from ethanol) (Found: C, 63·2; H, 6·4; N, 5·35. $C_{13}H_{15}NO_2S$ requires C, 62·6; H, 6·1; N, 5·6%).

Potassium borohydride (17·2 g.) was added in portions to the 4-acetamido-ketone (31 g.) in 96% ethanol (350 ml.). The mixture was stirred at room temperature for 6 hr. Water (75 ml.) was added, the mixture was filtered, and the precipitate was washed with ethanol; the combined filtrates were evaporated to give the mixed isomers as a yellow gum. Chloroform (200 ml.) was added and trans-4-*acetamido*-2,3,4,5-*tetrahydro*-7-*methyl*-1-*benzothiepin*-5-*ol* (11·4 g.) (2; R^1 = 7-Me, $R^2 = R^3 = H$, R^4 = Ac, X = S) was purified by recrystallisation.

Evaporation of the chloroform solution afforded the crude *cis*-isomer as a yellow gum (17·9 g.), which was not characterised but was converted directly into the amino-alcohol.

The 4-acetamido-1-benzothiepin-5-ols were converted into the corresponding 4-*amino*-1-*benzothiepin*-5-*ols* by hydrolysis (method D) and subsequently converted into their *hydrochlorides*.

4-*Amino*-2,3,4,5-*tetrahydro*-4-*methyl*-1-*benzothiepin*-5-*ol*.—The crude 4-azido-4-methyl-3,4-dihydro-1-benzothiepin-5(2*H*)-one (24·2 g.) (see before) was dissolved in benzene and added dropwise to a solution of sodium dihydrobis-(2-methoxyethoxy)aluminate [7] in benzene (50 ml.; 70% w/v). The solution was stirred for 16 hr. Water (100 ml.) was added dropwise, the mixture was filtered, and the residue was washed with benzene. The combined benzene extracts were washed with water and extracted with 2N-hydrochloric acid. The acid solution was basified (K_2CO_3) and extracted with ethyl acetate, and the organic phase was dried and evaporated. The 4-*amino*-2,3,4,5-*tetrahydro*-4-*methyl*-1-*benzothiepin*-5-*ol* (14 g.) was obtained as cubes (from propan-2-ol), m.p. 145—146° (Found: C, 63·0; H, 7·4; N, 6·2. $C_{11}H_{15}NOS$ requires C, 63·1; H, 7·2; N, 6·7%).

2,3,4,5-*Tetrahydro*-1-*benzoxepin*-4-*amine Hydrochlorides*.—4-Amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (13·4 g.) in glacial acetic acid (250 ml.) and concentrated sulphuric acid (10 ml.) was stirred at room temperature for 0·5 hr. 10% palladium–charcoal (1 g.) was added and the mixture was hydrogenated at 60°. The catalyst was filtered off and washed with a little acetic acid. The combined filtrates were neutralised with potassium carbonate, and evaporated The residue was dissolved in water, basified (10N-sodium hydroxide), and extracted with chloroform. The organic solution was extracted with 2N-hydrochloric acid and the combined acid extracts were evaporated. The 2,3,4,5-*tetrahydro*-1-*benzoxepin*-4-*amine hydrochloride* (5·3 g.) was

obtained as prisms (from ethanol), m.p. 201—203° (Found: C, 59·6; H, 7·1; N, 6·75. $C_{10}H_{14}ClNO$ requires C, 60·0; H, 7·0; N, 7·0%).

2,3,4,5-*Tetrahydro*-7-*methyl*-1-*benzoxepin*-4-*amine hydrochloride* was similarly prepared (50%) as prisms (from ethanol), m.p. 226—228° (Found: C, 61·8; H, 7·6; N, 6·5. $C_{11}H_{16}ClNO$ requires C, 61·8; H, 7·6; N, 6·6%), and 2,3,4,5-*tetrahydro*-7-*methoxy*-1-*benzoxepin*-4-*amine hydrochloride* (42%) as prisms (from ethanol), m.p. 225—226° (Found: C, 57·9; H, 7·1; N, 5·9. $C_{11}H_{16}ClNO_2$ requires C, 57·6; H, 7·0; N, 6·1%).

Methylation of 2,3,4,5-tetrahydro-1-benzoxepin-4-amine with formic acid and formaldehyde (*cf.* method F) afforded 2,3,4,5-*tetrahydro*-NN-*dimethyl*-1-*benzoxepin*-4-*amine hydrochloride* (75%) as prisms (from ethanol), m.p. 199—201° (Found: C, 63·1; H, 8·05; N, 5·9. $C_{12}H_{18}ClNO$ requires C, 63·25; H, 7·95; N, 6·2%).

N-Formylation of 2,3,4,5-tetrahydro-1-benzoxepin-4-amine, followed by reduction with lithium aluminium hydride (*cf.* method G), afforded 2,3,4,5-*tetrahydro*-N-*methyl*-1-*benzoxepin*-4-*amine hydrochloride* (55%) as prisms (from acetone), m.p. 150—151° (Found: C, 62·3; H, 7·8; N, 6·4. $C_{11}H_{16}ClNO$ requires C, 62·2; H, 7·5; N, 6·6%). A similar *N*-acetylation followed by lithium aluminium hydride reduction afforded N-*ethyl*-2,3,4,5-*tetrahydro*-1-*benzoxepin*-4-*amine hydrochloride* (68%) as prisms (from ethanol), m.p. 208—210° (Found: C, 63·2; H, 8·0; N, 5·8. $C_{12}H_{18}ClNO$ requires C, 63·3; H, 7·9; N, 6·2%).

Reduction of 4-*Amino*-2,3,4,5-*tetrahydro*-1-*benzothiepin*-5-*ols*.—Catalytic hydrogenation of aminobenzothiepinols as described for the analogous aminobenoxepinols had no effect, presumably owing to catalyst poisoning.

4-Amino-2,3,4,5-tetrahydro-1-benzothiepin-5-ol hydrochloride (2·3 g.), red phosphorous (1·24 g.), and aqueous 55% hydriodic acid (30 ml.) were refluxed for 5 hr. The mixture was diluted with water (100 ml.) and filtered, and the residue was washed with benzene. The aqueous layer was separated from the combined filtrates, basified, and extracted with ether. Only a trace of tar was isolated from the ether, from which no hydrochloride was obtained. The benzene phase was washed with saturated sodium thiosulphate and extracted with 2N-hydrochloric acid. No basic material was obtained from the latter. Evaporation of the benzene afforded 2,3,4,5-*tetrahydro*-1-*benzothiepin* (1·6 g.) as a yellow oil, b.p. 82—84°/0·6 mm. (Found: C, 76·9; H, 6·7. $C_{10}H_{12}S$ requires C, 77·3; H, 6·7%).

2-*Amino*-3a,4,5,10b-*tetrahydro*[1]*benzoxepino*[4,5-d]*oxazole Hydrochloride* (6).—4-Amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (8·9 g.) and sodium acetate (11·0 g.) in methanol (200 ml.) were cooled in an ice-bath. Cyanogen bromide (5·5 g.) in methanol (200 ml.) was added dropwise to the stirred suspension and stirring was continued for 4 hr. The solvent was evaporated off below 40°. The residual solid was slurried with aqueous ice-cold potassium carbonate solution and set aside overnight. The separated solid was filtered off and dried. The product (4·9 g.) was boiled with 2N-hydrochloric acid (50 ml.) (charcoal); the solution was filtered and evaporated. The *oxazole* was obtained (from ethanol) as prisms, m.p. 150—152° (Found: C, 53·8; H, 5·65; N, 11·6. $C_{11}H_{13}ClN_2O_2,0{\cdot}25H_2O$ requires C, 53·9; H, 5·55; N, 11·4%).

2,3-*Dihydro*-5-*pyrrolidino*-1-*benzothiepin* (8; R = H).—3,4-Dihydro-1-benzothiepin-5(2*H*)-one (17·8 g.), pyrrolidine (9·6 g.), and toluene-*p*-sulphonic acid (250 mg.) in benzene (250 ml.) were refluxed for 5 hr.; water was removed by use of a Dean and Stark head. The solution was evaporated and the residue was distilled *in vacuo* to give the *enamine* as an oil (14·5 g.), b.p. 136—140°/0·3 mm, n_D^{22} 1·6250 (Found: C, 72·5; H, 7·5; N, 5·7. $C_{14}H_{17}NS$ requires C, 72·5; H, 7·4; N, 6·1%).

3,4-*Dihydro*-4-*methyl*-1-*benzothiepin*-5(2H)-*one* (7; R^1 = R^3 = H, R^4 = Me).—The foregoing enamine (8; R = H) (30·3 g.), methyl iodide (19·4 g.), and dry dioxan (100 ml.) were refluxed with stirring for 24 hr. The yellow solid was filtered off, washed with ether, and dissolved in a mixture of water (100 ml.), 2N-sulphuric acid (100 ml.), and ethanol (200 ml.). The solution was refluxed for 48 hr., ethanol was distilled off *in vacuo*, and the aqueous solution was extracted with ether. The extract was washed with water, dried, and evaporated, and the residue was distilled *in vacuo* to give the 4-*methyl compound* as an oil (17·1 g.), b.p. 124—126°/0·8 mm. and n_D^{22} 1·6010 (Found: C, 68·5; H, 6·3. $C_{11}H_{12}OS$ requires C, 68·7; H, 6·3%).

Ethyl [(2,3-*Dihydro*-5-*pyrrolidino*-1-*benzothiepin*-4-*yl*)*thiocarbonyl*]*carbamate* (8; R = CS·NH·CO_2Et).—Ethoxycarbonyl isothiocyanate [8] (5·2 g.) in sodium-dried ether (15 ml.) was added dropwise to a solution of the enamine (8; R = H) (9·1 g.) in dry ether (30 ml.). After the mild exothermic reaction had ceased, the mixture was stirred overnight at room temperature. The orange precipitate was filtered off to give the *thiocarbonylcarbamate* (9·1 g.) as orange plates (from propan-2-ol), m.p. 152—153° (Found: C, 59·8; H, 6·2; N, 7·6. $C_{18}H_{22}N_2O_2$ requires C, 59·65; H, 6·1; N, 7·7%).

Ethyl [(2,3-*Dihydro*-5-*methylamino*-1-*benzothiepin*-4-*yl*)-*thiocarbonyl*]*carbamate* (11) *and* 3,4,5,6-*Tetrahydro*-1-*methyl*-4-*thioxo*-1-*benzothiepino*[5,4-d]*pyrimidin*-2(1H)-*one* (10).—The foregoing pyrrolidino-1-benzothiepin (8; R = CS·NH·CO_2Et) (6·0 g.) was dissolved in hot methanol (60 ml.), aqueous methylamine (50 ml.; 40%) was added, and the mixture was stirred for 20 hr. Water (100 ml.) was added and the 5-(*methylamino*)-*compound* (11) was filtered off to give orange prisms (2·6 g.) (from aqueous methanol), m.p. 131—132° (Found: C, 62·2; H, 6·45; N, 9·55. $C_{15}H_{18}N_2O_2S$ requires C, 62·05; H, 6·25; N, 9·65%). The filtrate was acidified (concentrated hydrochloric acid) with cooling. The precipitate was filtered off and recrystallised to give the *pyrimidine* (10) (0·6 g.) as yellow prisms (from methanol), m.p. 231—232° (Found: C, 56·4; H, 4·5; N, 10·1. $C_{13}H_{12}N_2OS_2$ requires C, 56·5; H, 4·4; N, 10·1%).

4-*Dimethylaminomethyl*-3,4-*dihydro*-1-*benzothiepin*-5(2H)-*one* (7; R^1 = R^2 = H, R^3 = CH_2·NMe_2) *Hydrochloride*.—3,4-Dihydro-1-benzothiepin-5(2*H*)-one (17·8 g.), dimethylamine hydrochloride (9·0 g.), paraformaldehyde (4·5 g.), absolute ethanol (100 ml.), and a few drops of concentrated hydrochloric acid were refluxed with stirring for 5 hr. Evaporation of the solution followed by recrystallisation of the residue from propan-2-ol afforded the *Mannich base* (16·2 g.) as needles, m.p. 168·5—169° (Found: C, 57·1; H, 6·9; N, 5·15. $C_{13}H_{18}ClNOS$ requires C, 57·4; H, 6·7; N, 5·2%).

3,4-*Dihydro*-4-[(4-*methylpiperazin*-1-*yl*)*methyl*]-1-*benzothiepin*-5(2H)-*one* (7; R^1 = R^2 = H, R^3 = 4-Me-piperazin-1-yl) *hydrochloride* was similarly obtained (23%) as a microcrystalline solid (from methanol–propan-2-ol), m.p. 173—174° (Found: C, 51·7; H, 6·55; N, 7·7. $C_{16}H_{24}Cl_2N_2OS,0{\cdot}5H_2O$ requires C, 51·65; H, 6·8; N, 7·5%); and 3,4-*dihydro*-4-*dimethylaminomethyl*-7-*methyl*-1-*benzothiepin*-5(2H)-*one* (7; R^1 = Me, R^2 = H, R^3 = CH_2·NMe_2) *hydrochloride* (24%) as plates (from propan-2-ol–ether), m.p.

161—163° (Found: C, 58·5; H, 7·2; N, 4·6. $C_{14}H_{20}ClNOS$ requires C, 58·8; H, 7·1; N, 5·0%).

3,3a-4,5-*Tetrahydro*-2-*phenyl*-2H-1-*benzothiepino*[5,4-c]-*pyrazole* (9).—Treatment of 3,4-dihydro-4-dimethylaminomethyl-1-benzothiepin-5(2*H*)-one hydrochloride (2·7 g.) with phenylhydrazine hydrochloride (1·7 g.) in the presence of ethanolic sodium hydroxide by a method similar to that described by Chase and Evans [17] afforded the *pyrazole* (2·0 g.) as pale yellow needles (from ethanol), m.p. 89—90° (Found: C, 72·7; H, 5·8; N, 9·4. $C_{17}H_{16}N_2S$ requires C, 72·8; H, 5·75; N, 10·0%).

NN-*Diethyl*-6,7-*dihydro*[1]*benzothiepino*[5,4-b]*quinoline*-8-*carboxamide* (12; R = CO·NEt_2).—Thionyl chloride (6 ml.) was added to 6,7-dihydro[1]benzothiepino[5,4-*b*]quinoline-8-carboxylic acid [18] (3·1 g.) in benzene (50 ml.); the mixture was refluxed for 10 hr. and filtered. The filtrate was evaporated *in vacuo*, benzene (25 ml.) was added, and the mixture was re-evaporated. Diethylamine (3 ml.) was added to the residue in benzene (25 ml.) and the mixture was refluxed for 3 hr. Water (50 ml.) was added; the benzene extracts were washed with 2N-sodium hydroxide and water, dried, and evaporated. The residue afforded the *diethylamide* (3·3 g.) as needles (from aqueous ethanol), m.p. 160—162° (Found: C, 72·7; H, 6·3; N, 7·5. $C_{22}H_{22}N_2OS$ requires C, 72·9; H, 6·1; N, 7·7%).

6,7-*Dihydro*[1]*benzothiepino*[5,4-b]*quinolin*-8-*ol* (12; R = OH).—3,4-Dihydro-1-benzothiepin-5(2*H*)-one (3·6 g.) was treated with anthranilic acid (2·7 g.) by the method described by Cromwell and Nielson.[19] The *quinolin*-8-*ol* (2·2 g.) was obtained as needles (from dimethylformamide), m.p. 305—306° (Found: C, 73·3; H, 5·1; N, 5·4. $C_{17}H_{13}NOS$ requires C, 73·1; H, 4·7; N, 5·0%). Subsequent treatment with thionyl chloride afforded 8-*chloro*-6,7-*dihydro*-1-*benzothiepino*[5,4-b]*quinoline* (12; R = Cl) as a microcrystalline solid (3·55 g.), m.p. 166—167° (from ethanol) (Found: C, 68·7; H, 4·15; N, 4·65. $C_{17}H_{12}ClNS$ requires C, 68·5; H, 4·1; N, 4·7%).

8-[2-(*Diethylamino*)*ethoxy*]-6,7-*dihydro*[1]*benzothiepino*-[5,4-b]*quinoline* (12; R = O·$[CH_2]_2$·NEt_2) *Hydrochloride*.—The quinolin-8-ol (12; R = OH) (5·6 g.) was added in portions to a stirred suspension of sodium hydride (0·96 g.; 50% dispersion in oil washed with light petroleum) in dimethylformamide (40 ml.). The mixture was heated at 50° for 0·5 hr. 2-(Diethylamino)ethyl chloride [freshly prepared from the hydrochloride (4·0 g.)] in dimethylformamide (10 ml.) was added dropwise, and the solution was heated at 50° for 5 hr. It was poured into water (300 ml.) and extracted with ether. The dried extracts were evaporated and the residue was converted into the *hydrochloride* (3·8 g.), which was obtained as a microcrystalline solid (from propan-2-ol), m.p. 287—290° (Found: C, 59·0; H, 6·2; N, 6·0. $C_{23}H_{30}Cl_2SO_2$ requires C, 58·8; H, 6·4; N, 6·0%).

3,4-*Dihydro*-4-(*hydroxymethylene*)-7-*methyl*-1-*benzothiepin*-5(2H)-*one* [20] (7; R^1 = Me, R^2R^3 = :CH·OH).—To a stirred suspension of sodium hydride (4·9 g.; 50% dispersion in oil previously washed with light petroleum) in dry ether (100 ml.) was added methanol (1 ml.) followed dropwise by a mixture of 3,4-dihydro-7-methyl-1-benzothiepin-5(2*H*)-one (19·2 g.) and methyl formate (9·05 g.) in dry ether (25 ml.) during 1 hr. The suspension was refluxed with stirring for 4 hr. Water (200 ml.) was added. The organic phase was washed with water and the aqueous layer was extracted with ether. The combined aqueous phases were acidified with 6N-hydrochloric acid and extracted with ether. Evaporation of the extract followed by distillation of the residue afforded the 4-*hydroxymethylene compound* as a liquid (21·4 g.), b.p. 162—164°/0·8 mm. (Found: C, 65·4; H, 5·5. $C_{12}H_{12}O_2S$ requires C, 65·4; H, 5·5%).

4-[(o-*Aminoanilino*)*methylene*]-3,4-*dihydro*-7-*methyl*-1-*benzothiepin*-5(2H)-*one* (7; R^1 = Me, R^2R^3 = :CH·NH·C_6H_4·NH_2-*o*).—A solution of *o*-phenylenediamine (2·2 g.) in ethanol (100 ml.) was added to a solution of the foregoing 4-hydroxymethylene compound (4·4 g.) in ethanol (50 ml.). After 10 min., the mixture was cooled in ice and the yellow precipitate was filtered off, washed with cold ethanol, and dried to give the 4-(o-*aminoanilinomethylene*)-1-*benzothiepin*-5(2H)-*one* (5·8 g.) as needles (from ethanol), m.p. 189—190° (Found: C, 70·0; H, 6·0; N, 8·5. $C_{18}H_{18}N_2OS$ requires C, 69·7; H, 5·85; N, 9·0%).

1′,4′-*Diacetyl*-2,3,3′,4′-*tetrahydro*-7-*methylspiro*[1-*benzothiepin*-4(5H),2′(1′H)*quinoxalin*]-5-*one* (13).—The foregoing [(*o*-aminoanilino)methylene]benzothiepinone (6·2 g.) was suspended in glacial acetic acid (40 ml.) and acetic anhydride (20 ml.) and refluxed for 0·5 hr. The mixture was cooled; the precipitate was filtered off and washed with ether to give the *spiro-compound* (13) as a microcrystalline solid (3·4 g.), m.p. 227—228° (from chloroform–ether) (Found: C, 66·8; H, 5·6; N, 6·8. $C_{22}H_{22}N_2O_3S$ requires C, 70·0; H, 5·6; N, 7·1%).

2,3,3a,4,5,10b-*Hexahydro*-9-*methyl*-2-(*trichloromethyl*)[1]-*benzothiepino*[4,5-d]*oxazole* (14).—Redistilled chloral (3·0 g.) was added to a *cis–trans* mixture of 2,3,4,5-tetrahydro-7-methyl-1-benzothiepin-5-ol (2·1 g.) in benzene (50 ml.) and the mixture was refluxed for 3 hr. The clear solution was evaporated *in vacuo*, the residue was boiled with light petroleum (b.p. 60—80°), and the decanted supernatant liquid was cooled in ice. The *oxazole* (14) separated as needles (1·25 g.), m.p. 120—121° (Found: C, 46·3; H, 4·3; N, 4·1. $C_{13}H_{14}Cl_3NOS$ requires C, 46·2; H, 4·2; N, 4·1%).

2,3,4,5-*Tetrahydro*-5-*oxo*-1-*benzothiepin*-4-*ylurea* (7; R^1 = R^2 = H, R^3 = NH·CO·NH_2).—A solution of potassium cyanate (1·0 g.) in water (5 ml.) was added to 4-amino-3,4-dihydro-1-benzothiepin-5(2*H*)-one hydrochloride (2·7 g.) in hot water (30 ml.). The mixture was stirred at 60° for 0·25 hr., cooled, and filtered. The residue was washed with water and recrystallised from ethanol to give the *urea* (1·7 g.) as prisms, m.p. 248—250° (decomp.) (Found: C, 56·0; H, 5·2; N, 11·5. $C_{11}H_{12}N_2O_2S$ requires C, 55·9; H, 5·1; N, 11·8%).

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