CARBAMATES AND UREAS DERIVED FROM 11-AMINO-6,11-DIHYDRODIBENZO[*b*,*e*]THIEPIN; SYNTHESIS AND PHARMACOLOGICAL SCREENING*

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A series of N-substituted carbamates *V*—*XIII* was prepared by reactions of 6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (*I*) with carbamates H_2NCOOR in acetic acid. Whereas the Leuckart reaction of dibenzo[*b*,*e*]thiepin-11(6*H*)-one yielded 9-formamido-10-methylene-9,10-dihydroanthracene (*XVIII*), a satisfactory method for preparing the amine *III* was found in heating the carbamate *V* with 2-aminoethanol to 170°C. Reactions of the amine *III* with isocyanates gave most of the disubstituted ureas *XX*—*XXV*. The expected anticonvulsant activity was found only in high doses with compounds *IX*, *XII*, *XV*, *XX*, *XXI* and *XXIII*.

In one of the preceding communications[1] of this series we described the synthesis and pharmacology of some carbamates and ureas derived from 10-amino-8-chloro--10,11-dihydrodibenzo[*b*,*f*]thiepin as potential anticonvulsant agents. The same reason led us to prepare a series of analogous derivatives of 11-amino-6,11-dihydrodibenzo[*b*,*e*]-thiepin, described in the present paper.

Ollmann and Witiak[2] prepared tert-butyl N-(6,11-dihydrodibenzo[*b*,*e*]thiepin--11-yl)carbamate (*VIII*) by treatment of the alcohol *I* (ref.[3]) with tert-butyl carbamate[4] in acetic acid at 25°C under the presence of 4-toluenesulfonic acid. We have now found that similar reactions (method *A*) are useful to prepare a series of analogous carbamates *V*—*XIII*; the starting carbamates H_2NCOOR were ethyl carbamate, isopropyl carbamate (*XIV*) (ref.[5]), n-butyl carbamate[4], propargyl carbamate[4], cyclopentyl carbamate (*XV*) (ref.[6]), 2-phenylethyl carbamate (*XVI*) (ref.[7]), 2-isopropyl-5-methylphenyl carbamate (*XVII*) and 2-methyl-2-propyl-1,3-propane-diol dicarbamate (meprobamate, ref.[8]). The carbamates *XIV*—*XVII* were obtained by reactions of the corresponding hydroxy compounds with potassium cyanate in benzene in the presence of trifluoroacetic acid (method *B*, ref.[4]). Out of these compounds, the thymol derivative *XVII* is new and for the cyclopentyl derivative *XV*, only biological data were published[6].

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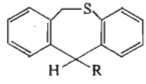
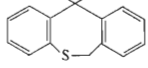
For further work, we needed 11-amino-6,11-dihydrodibenzo[*b*,*e*]thiepin (*III*), prepared by hydrazinolysis of the corresponding phthalimido derivative[9] and more recently by the acid hydrolysis of the carbamate *VIII* (ref.[2]). In the present work, we found that alkaline hydrolysis of the carbamate *VIII* likewise affords the amine *III*.



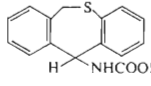
I, R = OH

II, R = O



III, R = NH_2

IV, R = H



V, R = C_2H_5

VI, R = $CH(CH_3)_2$

VII, R = $(CH_2)_3CH_3$

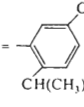
VIII, R = $C(CH_3)_3$

IX, R = $CH_2C{\equiv}CH$

X, R =

XI, R = $CH_2CH_2C_6H_5$

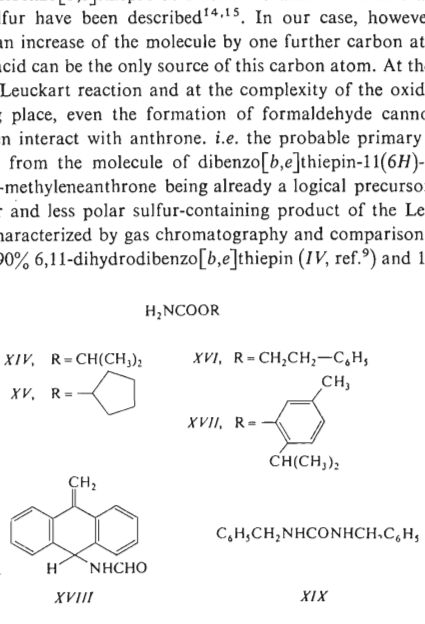
XII, R =



XIII, R = $CH_2C(CH_3)(CH_2OCONH_2)(CH_2)_2CH_3$

Quite unexpectedly we obtained the amine *III* also by a reaction of the carbamate *V* with 2-aminoethanol. Whereas a reaction of these two compounds at 130°C leads with excellent yield to the N,N'-disubstituted urea *XX*, the same reaction at 170°C (boiling point of 2-aminoethanol) yields almost quantitatively the amine *III*. This reaction was used for preparing larger quantities of this amine. We attempt to explain the formation of the amine *III* in this case by a thermic cleavage of the urea *XX*, 2-oxazolidinone being apparently the second product of the cleavage. The starting carbamate *V* and the urea *XX* are carbonic acid derivatives; the formation of 2-oxazolidinone by reactions of carbonic acid derivatives (phosgene, dialkyl carbonates, urea) with 2-aminoethanol is a general reaction[10,11].

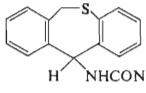
We attempted to use also the Leuckart reaction for preparing the amine *III* and dibenzo[*b*,*e*]thiepin-11(6*H*)-one[3] was heated with formamide and formic acid (180–190°C). A mixture of several products was formed from which we did not succeed to isolate the required N-formyl derivative of the amine *III*. The main product was characterized by means of the mass spectrum and analysis as a sulfur-free compound $C_{16}H_{13}NO$. On the basis of this composition and UV and IR spectra, the structure of 9-formamido-10-methylene-9,10-dihydroanthracene (*XVIII*) was suggested which, however, could not be confirmed by attempts at the alkaline hydrolysis or reduction with lithium aluminium hydride (no characterized products could be isolated). On the other hand, a synthetic proof did succeed: Leuckart reaction of 10-methyleneanthrone[12] gave a mixture of products which was separated; in a yield of 15% a substance was isolated which was found identical with our substance $C_{16}H_{13}NO$. In this way, structure *XVIII* is considered proven. A more complicated problem is the question of mechanism of formation of this compound in the Leuckart reaction[13] of dibenzo[*b*,*e*]thiepin-11(6*H*)-one[3]. Transformations of 6,11-dihydrodibenzo[*b*,*e*]thiepin derivatives to anthracene derivatives under the extrusion of sulfur have been described[14,15]. In our case, however, there comes additionally to an increase of the molecule by one further carbon atom and formamide or formic acid can be the only source of this carbon atom. At the high temperature during the Leuckart reaction and at the complexity of the oxidation-reduction reactions taking place, even the formation of formaldehyde cannot be excluded, which could then interact with anthrone. *i.e.* the probable primary product of the sulfur extrusion from the molecule of dibenzo[*b*,*e*]thiepin-11(6*H*)-one, under the formation of 10-methyleneanthrone being already a logical precursor of compound *XVIII*. A minor and less polar sulfur-containing product of the Leuckart reaction described was characterized by gas chromatography and comparison with standards as a mixture of 90% 6,11-dihydrodibenzo[*b*,*e*]thiepin (*IV*, ref.[9]) and 10% anthracene.



XVIII *XIX*

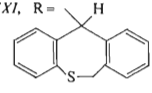
Heating the carbamate *V* with an excess of benzylamine to 185°C gave a mixture of products which was separated to the basic and the neutral fraction. The basic product was identified as the amine *III* and the neutral product as 1,3-dibenzylurea (*XIX*, ref.[16]). The primary product was apparently the unsymmetrically substituted urea *XXV* giving by the action of further benzylamine (transamidation) compounds *III* and *XIX*. An anomalous course was also noted in the reaction of the carbamate *V* with 2-diethylaminoethanol at 160–180°C; the only isolated product was a high-melting neutral compound having according to the mass spectrum and analysis the composition $C_{29}H_{24}N_2OS_2$. The IR spectrum indicated the presence of the fragment —NHCONH— and the compound is 1,3-bis(6,11-dihydrodibenzo[*b*,*e*]-thiepin-11-yl)urea (*XXI*). It is possible that we are dealing here with a product of a simple thermic reaction of the starting carbamate *V* and that 2-diethylaminoethanol had only the function of the reaction medium.

Reactions of the amine *III* with ethyl isocyanate[17], n- hexyl isocyanate[17], n-nonyl isocyanate (*XXVI*, ref.[18]) and benzyl isocyanate (*XXVII*, ref.[19]) in toluene (method *C*, ref.[20]) gave the unsymmetrically disubstituted ureas *XXII–XXV*. The starting isocyanates were prepared by reactions of the corresponding acid chlorides with sodium azide (for analogy, *cf.*[21]) as described here for n-nonyl isocyanate (*XXVI*)[18,22]. In an attempt to prepare the corresponding carbamate by reaction of the alcohol *I* with ethyl isocyanate in benzene (for the method, *cf.*[1]), bis(6,11-dihydrodibenzo[*b*,*e*]-thiepin-11-yl) ether (*II*) was obtained, prepared previously by a different method[9].



XX, R = CH_2CH_2OH

XXI, R =



XXII, R = C_2H_5
XXIII, R = $(CH_2)_5CH_3$
XXIV, R = $(CH_2)_8CH_3$
XXV, R = $CH_2C_6H_5$

$$R{-}N{=}C{=}O$$

XXVI, R = $(CH_2)_8CH_3$
XXVII, R = $CH_2C_6H_5$

The compounds prepared by the general methods *A–C* are assembled in Table I.

Compounds *V–XII*, *XV* and *XX–XXV* were pharmacologically tested in a general screening programme with the emphasis on the expected anticonvulsant activity. The basic data are summarized in Table II. All the compounds tested are little soluble

TABLE I
Carbamates and Ureas

Compound	Method (% yield)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found			
				% C	% H	% N	% S
V	*A* (98)	160—161 (toluene–light petroleum)	$C_{17}H_{17}NO_2S$ (299·4)	68·20 67·90	5·72 5·73	4·68 4·75	10·71 10·99
VI	*A* (95)	192—193[a] (benzene)	$C_{18}H_{19}NO_2S$ (313·4)	68·98 69·15	6·11 6·20	4·47 4·29	10·23 10·12
VII	*A* (95)	137—139[b] (toluene–light petroleum)	$C_{19}H_{21}NO_2S$ (327·4)	69·69 69·86	6·46 6·41	4·28 4·24	9·79 10·00
VIII	*A* (99)	169—171[c] (ethanol)	— —	— —	— —	— —	— —
IX	*A* (95)	141·5—143·5[d] (benzene)	$C_{18}H_{15}NO_2S$ (309·4)	69·88 70·44	4·89 4·94	4·53 4·47	10·36 10·46
X	*A* (97)	174—175[e] (benzene)	$C_{20}H_{21}NO_2S$ (339·4)	70·76 70·96	6·24 6·27	4·12 3·95	9·45 9·46
XI	*A* (98)	187—188[f] (benzene)	$C_{23}H_{21}NO_2S$ (375·5)	73·57 73·83	5·64 5·68	3·73 3·76	8·54 8·78
XII	*A* (82)	153—154[g] (ethanol)	$C_{25}H_{25}NO_2S$ (403·5)	74·41 74·63	6·24 6·45	3·47 3·42	7·94 8·02
XIII[h]	*A* (83)	75—77[i] (benzene–light petroleum)	$C_{25}H_{30}N_2O_4S$ (454·6)	66·05 66·03	6·65 6·77	6·16 6·52	7·06 7·40
XIV	*B* (58)	89—93[j] —	— —	— —	— —	— —	— —
XV	*B* (67)	114·5[k] (benzene–light petroleum)	$C_6H_{11}NO_2$ (129·2)	55·79 55·78	8·58 8·31	10·85 10·90	— —
XVI	*B* (95)	91—92·5[l] —	— —	— —	— —	— —	— —
XVII	*B*[m] (85)	134·5—135·5 (benzene–light petroleum)	$C_{11}H_{15}NO_2$ (193·2)	68·36 68·51	7·82 7·79	7·25 7·23	— —
XXII[n]	*C* (86)	208·5—209·5[o] (aqueous ethanol)	$C_{17}H_{18}N_2OS$ + + 0·5 H_2O (307·4)	66·42 66·78	6·23 6·24	9·11 9·04	10·48 10·59

TABLE I
(*Continued*)

Compound	Method (% yield)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found			
				% C	% H	% N	% S
XXIII	*C*[m]	175—176	$C_{21}H_{26}N_2OS$	71·15	7·39	7·90	9·04
	(89)	(aqueous ethanol)	(354·5)	71·82	7·51	7·99	8·92
XXIV	*C*	142—143[p]	$C_{24}H_{32}N_2OS$	72·68	8·13	7·06	8·08
	(86)	(aqueous ethanol)	(396·6)	73·05	8·29	7·13	8·37
XXV	*C*	229—229·5[q]	$C_{22}H_{20}N_2OS$	73·30	5·59	7·77	8·89
	(94)	(dimethylformamide–ethanol)	(360·5)	73·52	5·60	7·75	8·99

[a] IR spectrum: 740 (4 adjacent Ar—H), 1041, 1089, 1121, 1141, 1160, 1182, 1278 (COOR), 1550, 1645 (NHCOOR), 3075 (Ar), 3340 cm^{-1} (NH); ^{1}H-NMR spectrum: δ 8·48 (bd, J = 9·0 Hz, 1 H, NH), 6·80—7·50 (m, 8 H, Ar—H), 6·35 (d, J = 9·0 Hz, 1 H, Ar_2CH), 4·70 (m, 1 H, CH of isopropyl), 4·62 and 3·95 (2 d, J = 13·0 Hz, 2 H, $ArCH_2S$), 1·12 (d, J = 6·0 Hz, 6H, 2 CH_3). [b] IR spectrum (KBr): 743 (4 adjacent Ar—H), 1044, 1094, 1121, 1270 (COOR), 1553, 1693 (NHCOOR), 1445, 1594, 3073 (Ar), 3339 cm^{-1} (NH); ^{1}H-NMR spectrum ($CDCl_3$): δ 6·90 to 7·50 (m, 8 H, Ar—H), 6·28 (bd, J = 7·0 Hz, 1 H, NH), 6·03 (d, J = 7·0 Hz, 1 H, Ar_2CH), 4·22 (s, 2 H, $ArCH_2S$), 4·03 (t, 2 H, OCH_2), c. 1·40 (m, 4 H, remaining 2 CH_2), 0·90 (def. t, 3 H, CH_3). [c] The literature[2] reported a m.p. of 168—170°C. [d] IR spectrum (KBr): 748 (4 adjacent Ar—H), 1265 (COOR), 1550, 1704 (NHCOOR), 2140 (RC≡CH), 3065 (Ar), 3310, 3325 (C≡C—H), 3435 cm^{-1} (NH); ^{1}H-NMR spectrum ($CDCl_3$): δ 7·00—7·50 (m, 8 H, Ar—H), 6·48 (bd, J = = 8·0 Hz, 1 H, NH), 6·04 (d, J = 8·0 Hz, 1 H, Ar_2CH), 4·67 (d, J = 2·5 Hz, 2 H, OCH_2C≡), 4·20 (s, 2 H, $ArCH_2S$), 2·43 (t, J = 2·5 Hz, 1 H, C≡CH). [e] IR spectrum: 747, 773 (4 adjacent Ar—H), 1043, 1090, 1166, 1269 (COOR), 1551, 1686 (NHCOOR), 3075 (Ar), 3322 cm^{-1} (NH); ^{1}H-NMR spectrum ($CDCl_3$): δ 6·90—7·50 (m, 8 H, Ar—H), 6·10 (m, 2 H, NH and Ar_2CH), 5·10 (m, 1 H, OCH), 4·15 (s, 2 H, $ArCH_2S$), 1·65 (bs, 8 H, 4 CH_2 of cyclopentyl). [f] IR spectrum: 703, 745 (5 and 4 adjacent Ar—H), 1038, 1094, 1120, 1140, 1159, 1270 (COOR), 1552, 1693 (NHCOOR), 3040, 3070 (Ar), 3335 cm^{-1} (NH). [g] IR spectrum (KBr): 755, 826, 883 (4 and 2 adjacent and solitary Ar—H), 1036, 1093, 1164, 1246 (COOR), 1508 (Ar), 1540, 1724 (NHCOO. .Ar), 3330 cm^{-1} (NH). [h] Solvate with 1/3 C_6H_6. [i] Mass spectrum, *m/e*: 428 (M^+, $C_{23}H_{28}N_2$. .O_4S); IR spectrum: 750 (4 adjacent Ar—H), 1041, 1080, 1253 (COOR), 1540, 1700 (CONH), 1700 (H_2NCOOR), 1600, 3070 (Ar), 3375, 3460 cm^{-1} (NH, NH_2). [j] The literature[5] reported a m.p. of 92—93°C for a product prepared differently. [k] IR spectrum: 1056, 1130, 1172, 1317, 1343 (COOR), 1528 (Ar), 1617 (NH_2), 1684 (H_2NCOOR), 3220, 3277, 3340, 3440 cm^{-1} (NH_2). [l] The literature[7] reported a m.p. of 91—91·5°C for a product prepared differently. — [m] See Experimental. [n] Hemihydrate. [o] IR spectrum: 741, 753, 763 (4 adjacent Ar—H), 1570, 1627 (CONH), 3030, 3060 (Ar), 3320, 3360 cm^{-1} (NH, H_2O). [p] IR spectrum: 742 (4 adjacent Ar—H), 1525, 1638 (CONH), 1582, 1596, 3067 (Ar), 3310, 3389 cm^{-1} (NH); ^{1}H-NMR spectrum: δ 6·90—7·50 (m, 9 H, 8 Ar—H and Ar_2C—NH), 6·40 (d, J = 9·0 Hz, 1 H, Ar_2CH), 6·08 (t, J = 5·0 Hz, 1 H, remaining NH), 4·67 and 4·15 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$), 3·03 (bm, 2 H, NCH_2), 1·25 (bs, 14 H, remaining 7 CH_2), 0·86 (def. t, 3 H, CH_3). [q] IR spectrum: 702, 750 (5 and 4 adjacent Ar—H), 1577, 1640 (CONH), 3300, 3380 cm^{-1} (NH); ^{1}H-NMR

spectrum: δ 6·80—7·60 (m, 14 H, Ar—H and Ar_2C—NH), 6·58 (t, J = 5·0 Hz, 1 H, the other NH), 6·45 (d, J = 9·0 Hz, 1 H, Ar_2CH), 4·68 and 4·18 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$), 4·31 (d, J = 5·0 Hz, 2 H, $ArCH_2$).

TABLE II

Pharmacology of the Carbamates and Ureas (doses in mg/kg, oral administration)

Compound	Code number	Acute toxicity LD_{50}	Dose screened D	Anticonvulsant activity ED
V	VÚFB-12.438	>2 500	300	>300
VI	VÚFB-12.446	>2 500	300	>300
VII	VÚFB-12.448	>2 500	300	>300
VIII	VÚFB-12·447	>2 500	300	>300
IX	VÚFB-12.442	>2 500	300	200
X	VÚFB-12.444	>2 500	300	>300
XI	VÚFB-12.443	>2 500	300	>300
XII	VÚFB-12.445	>2 500	300	200
XV	VÚFB-12.440	1 000	200	150
XX	VÚFB-12.436	2 000	300	200
XXI	VÚFB-12.441	>2 500	300	200
XXII	VÚFB-12.507	>2 500	300	>300
XXIII	VÚFB-12.508	>2 500	300	300
XXIV	VÚFB-12.509	>2 500	300	>300
XXV	VÚFB-12.510	>2 500	300	>300
Phenytoine	—	—	—	100

in water and, therefore, they were administered only orally. The acute toxicity in mice was estimated in the first line; groups by five animals were used and the survival was followed for 5 days. The toxicity of all compounds was very low; in most cases, the LD_{50} were higher than 2500 mg/kg. This could be the result of a poor absorption. The further column in the Table II indicates the dose which was used in the usual battery of tests. The anticolvulsant activity was determined by estimating the antagonism towards pentetrazole. The effective dose ED significantly prolongs the latency of convulsions elicited by a standard dose of pentetrazole in mice. Most of the compounds were inactive in the dose D; only *IX*, *XII*, *XV*, *XX*, *XXI* and *XXIII* showed clear activity but this was lower than that of phenytoine included in the Table II as a standard. All compounds were ineffective in the test of electroshock. Only in doses higher than D, compound *VIII* showed some central depressant activity:

inhibition of spontaneous activity and reactivity of mice and hypothermic effect in rats. Compound *XV*, the pharmacology of which was mentioned in the literature[6], was found to inhibit spontaneous motility of mice in a dose of 50 mg/kg. Doses higher than D bring about a general depression of activity and reactivity, ataxia and muscle hypotony in mice. In doses D, all the compounds were inactive in tests for analgesic, thiopental potentiation, mydriatic, antihistamine, antiarrhythmic, hypotensive, diuretic, hypoglycaemic and antiinflammatory activity (mice and rats).

The compounds prepared were also tested for antimicrobial activity *in vitro* (Dr J. Turinová and Dr A. Čapek, bacteriological department of this Institute). The tested microorganisms, compounds and minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Mycobacterium tuberculosis* H37Rv, *V* 100, *VII* 100, *VIII* 100, *IX* 50, *X* 100, *XI* 50, *XXI* 25, *XXIII* 50; *Saccharomyces pasterianus*, *XXI* 50; *Trichophyton mentagrophytes*, *V* 50, *VII* 50, *IX* 50, *XI* 50, *XXI* 50, *XXII* 50, *XXIV* 50. All compounds were inactive towards *Streptococcus* β-*haemolyticus*, *Streptococcus faecalis*, *Staphylococcus pyogenes aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus vulgaris*, *Candida albicans* and *Aspergillus niger*.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or at 77°C. The UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (in Nujol unless stated otherwise) with a Unicam SP 200G spectrophotometer, the ^{1}H-NMR spectra (in CD_3SOCD_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra with a MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by chromatography on thin layers of silica gel (Silufol).

Ethyl N-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-yl)carbamate (*V*)
(Method *A*)

A mixture of 70 g 6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (*I*), (ref.[3]), 37 g ethyl carbamate, 750 ml acetic acid and 3·0 g 4-toluenesulfonic acid was stirred for 6 h at 37°C and allowed to stand overnight. It was then diluted with 3 l water, stirred for 30 min and the product filtered, washed with water and dried *in vacuo*; 89 g (98%), m.p. 157—160°C. Analytical sample, m.p. 160—161°C (toluene–light petroleum). IR spectrum: 748 (4 adjacent Ar—H), 1046, 1096, 1124, 1164, 1270 (COOR), 1556, 1697 (NHCOOR), 3075 (Ar), 3336 cm^{-1} (NH). ^{1}H-NMR spectrum ($CDCl_3$): 6·90—7·50 (m, 8 H, Ar—H), 6·25 (bd, J = 7·0 Hz, 1 H, NH), 6·08 (d, J = 7·0 Hz, 1 H, Ar_2CH—N), 4·28 (s, 2 H, $ArCH_2S$), 4·15 (q, J = 7·0 Hz, 2 H, $COOCH_2$), 1·25 (t, J = 7·0 Hz, 3 H, CH_3).

2-Isopropyl-5-methylphenyl Carbamate (*XVII*) (Method *B*)

A stirred mixture of 15·0 g thymol, 16·2 g KCNO and 50 ml benzene was treated over 30 min with 23 g trifluoroacetic acid. The stirring was continued for 4 h and the mixture allowed to stand for 48 h at room temperature. It was then diluted with 100 ml water and extracted with chloroform. The extract was dried with K_2CO_3 and evaporated under reduced pressure; 16·4 g (85%), m.p. 131—135°C. Analytical sample, m.p. 134·5—135°C (benzene–light petroleum). IR spectrum:

819, 871 (2 adjacent and solitary Ar—H), 1065, 1109, 1160, 1250, 1284 (COOAr), 1378 (CH_3CHCH_3), 1467, 1510, 1616 (Ar), 1664 ($H_2NCOOAr$), 3218, 3290, 3357, 3442 cm^{-1} (NH_2).

11-Amino-6,11-dihydrodibenzo[*b,e*]thiepin (*III*)

A. A mixture of 16·5 g *VIII*, 66 g KOH and 150 ml 95% ethanol was stirred and refluxed for 6 h. After cooling, the mixture was diluted with 250 ml water and the product isolated by extraction with ether. The extract was shaken with 250 ml 5M-HCl, the separated solution of the hydrochloride was decomposed with NH_4OH and the base isolated by extraction with ether. Processing of the extract gave a residue which crystallized from 70 ml 70% aqueous ethanol; 6·0 g (53%), m.p. 146—149°C. The product is identical with the compound obtained by hydrolysis of *VIII* with hydrochloric acid in methanol[2] for which the literature[2] reported a m.p. of 146—147°C.

Hydrochloride, m.p. 221—223°C with decomposition (ethanol–ether). For $C_{14}H_{14}ClNS$ (263·8) calculated: 63·74% C, 5·35% H, 13·44% Cl, 5·31% N, 12·15% S; found: 63·56% C, 5·32% H, 13·62% Cl, 5·63% N, 12·32% S.

B. A mixture of 21·0 g *V* and 43 g 2-aminoethanol was heated for 5·5 h under reflux in a bath of 175°C (the temperature of the mixture was 160—168°C). After cooling to 120°C, it was diluted with 300 ml water and the product was filtered, washed with water and dried *in vacuo*; 15·2 g (96%), 145—148°C. Analytical sample, m.p. 146·5—148°C. IR spectrum: 748, 759 (4 adjacent Ar—H), 1590, 1615, 3065 (Ar), 3428, 3488 cm^{-1} (NH_2). The product was identical with the compound, prepared according to *A* (mixed melting point, TLC).

9-Formamido-10-methylene-9,10-dihydroanthracene (*XVIII*)

A. A mixture of 11·3 g dibenzo[*b,e*]thiepin-11(6*H*)-one[3], 70 g formamide and 7 g formic acid was heated for 1 h to 120°C, for 1 h to 160°C and for 10 h to 185—190°C; H_2S formation was observed. After cooling to 100°C, the residue was mixed with 150 ml water and the suspension stirred and boiled for 20 min. After cooling, the inhomogeneous solid was filtered and extracted for 10 min with 180 ml boiling ethanol. The undissolved compound was filtered off, washed with ethanol and dried; 4·3 g (37%), m.p. 277—280°C. Analytical sample, m.p. 278—279°C (dimethylformamide). Mass spectrum, *m/e*: 235·099 (M^+, $C_{16}H_{13}NO$), 206 (M—CHO), 128·0499 (base peak, C_9H_6N). UV spectrum: λ_{max} 256 nm (log ε 5·20), 354 nm (3·78), 372 nm (3·96), 393 nm (3·94). IR spectrum: 728, 736, 752 (4 adjacent Ar—H), 875 ($R_2C{=}CH_2$), 1520, 1562, 3035, 3055, 3075 (Ar), 1650 (NHCHO), 3175, 3215 cm^{-1} (NH). For $C_{16}H_{13}NO$ (235·3) calculated: 81·68% C, 5·57% H, 5·95% N; found: 81·40% C, 5·81% H, 6·10% N.

Evaporation of the ethanol mother liquor gave 1·2 g inhomogeneous solid which was repeatedly crystallized from ethanol and finally chromatographed on 20 g Al_2O_3. Elution with benzene gave a compound melting at 96·5—98·5°C which was shown by the mixed melting point, TLC and the ^{1}H-NMR spectrum (2 s at δ 4·40 and 4·13 corresponding to $ArCH_2S$ and $ArCH_2Ar$) to consist mainly of 6,11-dihydrodibenzo[*b,e*]thiepin (*IV*) (ref.[9] reported the m.p. of 101—102°C). By means of gas chromatography, the presence of about 10% anthracene was proven.

B. A mixture of 4·1 g 10-methyleneanthrone[12], 30 g formamide and 3 g formic acid was successively heated to 170°C and kept for 2 h at this temperature. It was then diluted with 150 ml water, the solid filtered and extracted with 30 ml boiling ethanol. The undissolved substance was filtered, washed with water and dried; 0·75 g (15%), m.p. 266—270°C with decomposition. Analytical sample, m.p. 278—279°C (ethanol–dimethylformamide). The product was identical with *XVIII* prepared according to *A*.

Reaction of the Carbamate *V* with Benzylamine

A mixture of 3·0 g *V* with 10·7 g benzylamine was heated for 2·5 h to 180°C. After cooling, it was decomposed with 75 ml warm water, the suspension was stirred for 2 h and allowed to stand overnight. The inhomogeneous solid was filtered, dissolved in 150 ml chloroform and the solution shaken with 30 ml 5M-HCl. A solid precipitated, was filtered and dried; 2·05 g (78%) 11-amino-6,11-dihydrodibenzo[*b*,*e*]thiepin hydrochloride, m.p. 218—221°C (ethanol–ether). Treatment with NH_4OH released the base *III*, m.p. 147—148°C. The identity of the base and of the hydrochloride was established by comparison with authentic samples.

The chloroform solution was evaporated and the residue crystallized from ethanol; 0·8 g (22%) 1,3-dibenzylurea (*XIX*), m.p. 171—171·5°C (ethanol). The literature[16] reported a m.p. of 167°C for a product prepared differently.

1-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-yl)-3-(2-hydroxyethyl)-urea (*XX*)

A mixture of 9·0 g *V* and 37 g 2-aminoethanol was stirred and heated for 4 h to 126—128°C (bath temperature 135—140°C). The product was diluted with 50 ml chloroform, 350 ml water were added and the mixture stirred. After complete cooling, the solid was filtered, washed with water and dried *in vacuo*; 7·7 g (82%) melting unsharply at about 174°C. Analytical sample, m.p. 183—184·5°C (aqueous ethanol). IR spectrum (KBr): 750 (4 adjacent Ar—H), 1 050 (CH_2OH), 1 569, 1 636 (CONH), 3 080 (Ar), 3 320, 3 370 cm^{-1} (OH, NH). ^{1}H-NMR spectrum: δ 6·70—7·50 (m, 8 H, Ar—H), c. 6·25 (m, 3 H, Ar_2CH—NHCONH), 4·65 (t, 1 H, OH), 4·60 and 4·08 (2 d, J = 13·0 Hz, 2 H, $ArCH_2S$), 3·30 (m, 2 H, CH_2O), 3·09 (m, 2 H, CH_2N). For $C_{17}H_{18}N_2O_2S$ (314·4) calculated: 64·94% C, 5·77% H, 8·91% N, 10·20% S; found: 65·30% C, 5·89% H, 8·59% N, 10·02% S.

1,3-Bis(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yl)urea (*XXI*)

Na (0·05 g) was dissolved in 10 ml 2-diethylaminoethanol, 3·0 g *V* were added and the mixture was stirred for 8 h at 160—180°C. An attempt to achieve a separation by mixing with 200 ml chloroform and 200 ml water led do 2·1 g (44%) insoluble product, m.p. 295°C with decomposition. Analytical sample, m.p. 298°C with decomposition (dimethylformamide–toluene). Mass spectrum, *m/e*: 480 (M^+, $C_{29}H_{24}N_2OS_2$), 269·0755, 211. IR spectrum: 742 (4 adjacent Ar—H), 1 567, 1 636 (NHCONH), 3 348 cm^{-1} (NH). For $C_{29}H_{24}N_2OS_2$ (480·6) calculated: 72·46% C, 5·03% H, 5·83% N, 13·34% S; found: 71·91% C, 5·19% H, 5·80% N, 12·90% S.

Nonyl Isocyanate (*XXVI*)

A stirred solution of 23 g NaN_3 in 75 ml water was treated dropwise over 1 h with a solution of 47·7 g decanoyl chloride[23] in 75 ml acetone at 10—15°C. The mixture was stirred for 1 h at 10—13°C and then separated. The organic layer was dried with $MgSO_4$ and added dropwise over 30 min under stirring to 250 ml benzene at 60—68°C. After 2 h stirring at 70°C, the mixture was evaporated *in vacuo* at 30—40°C. The precipitated solid was filtered off and the filtrate was distilled; 25·2 g (60%), b.p. 106—108°C/1·3 kPa. For analysis, a sample was redistilled, b.p. 105 to 106°C/1·3 kPa. The IR spectrum (film): 1 359, 2 280 (N=C=O), 1 470 cm^{-1} (CH_2). ^{1}H-NMR spectrum ($CDCl_3$): δ 3·21 (t, J = 6·0 Hz, 2 H, CH_2NCO), 1·60 (m, 2 H, CH_2 adjacent to methyl), 1·28 (bs, 12 H, remaining 6 CH_2), 0·86 (def. t, 3 H, CH_3). For $C_{10}H_{19}NO$ (169·3) calculated: 70·95% C, 11·31% H, 8·28% N; found: 70·68% C, 11·61% H, 8·67% N. The literature[18,22] mentioned this compound but experimental data are not available.

Benzyl Isocyanate (*XXVII*)

Phenylacetyl chloride (30·9 g) and 20 g NaN_3 were processed similarly like in the preceding experiment; 11·2 g (42%), b.p. 88°C/1·3 kPa. The literature[19] reported a b.p. of 88—90°C/1·3 kPa for a product prepared differently.

1-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-yl)-3-(n-hexyl)urea (*XXIII*) (Method *C*)

A solution of 2·3 g *III* in 20 ml toluene was stirred and treated dropwise over 15 min with a solution of 1·3 g n-hexyl isocyanate[17] in 6 ml toluene at 65—72°C. The mixture was stirred for 1·5 h at 70—80°C and the product was precipitated by a slow addition of 30 ml light petroleum under cooling. After standing for 48 h, the product was filtered, washed with light petroleum and dried; 3·1 g (89%), m.p. 175—176°C. Crystallization from 90% ethanol did not change the melting point. IR spectrum: 748, 751 (4 adjacent Ar—H), 1568, 1622 (CONH), 3058 (Ar), 3333, 3380 cm^{-1} (NH). ^{1}H-NMR spectrum: δ 7·00—7·50 (m, 9 H, 8 Ar—H and Ar_2C—NH), 6·40 (d, J = 9·0 Hz, 1 H, Ar_2CH), 6·10 (t, J = 5·0 Hz, 1 H, remaining NH), 4·70 and 4·19 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$), 3·08 (m, 2 H, NCH_2), 1·30 (bs, 8 H, remaining 4 CH_2), 0·89 (def. t, 3 H, CH_3).

Bis(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-yl) Ether (*II*)

A solution of 5·7 g *I* (ref.[3]) in 90 ml benzene was treated dropwise with 3·55 g ethyl isocyanate at 35—40°C, the mixture was stirred for 3 h and heated for 30 min to 50°C. After standing overnight at room temperature, the solvent was evaporated *in vacuo*. The residue 5·48 g (100%), m.p. 175—180°C. Analytical sample, m.p. 191—192°C (benzene–cyclohexane). Mass spectrum, *m/e* (%): 438·1102 (M^+, 2, $C_{28}H_{22}OS_2$), 227 (100), 211 (100), 178 (100), 165 (36), 91 (29). The analysis was in full agreement with the mass spectrum and the melting point is identical with that of *II*, prepared by different methods[9].

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