Synthesis of 6,11-Dihydrodibenzo[*b,e*]thiepin-11-yl 4-(Dimethylaminomethyl)phenyl Ketone and of Some Related Compounds

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Dedicated to Professor Ernest Campaigne on the occasion of his 75th birthday

Reactions of dibenzo[*b,e*]thiepin-11(6*H*)-one (**4**) with 2-, 3- and 4-(dimethylaminomethyl)phenylmagnesium bromide afforded the tertiary alcohols **5a,b,c**. The aldehydes **7** and **8** gave similarly the secondary alcohols **9a,b,c** and **10c**. Numerous attempts to prepare the corresponding ketones, especially by oxidation of **9a,b,c** and **10c** were unsuccessful. Only the oxidation of **9c** with tetrabutylammonium chromate in chloroform afforded the desired ketone **16**. Its formation was accompanied by an important side reaction consisting in a cleavage of the "retro-ene-reaction" type leading to compound **11** and the aldehyde **13c** which reacted with the chloroform present to give the alcohol **17**. Compounds **5a,b,c**, **9a,b,c** and **16** were tested as potential antidepressants but with the exception of some effects in the test of potentiation of yohimbine toxicity in mice, they proved inactive in this line.

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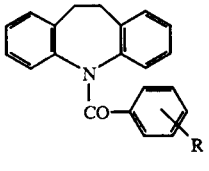
The announcement of psychotropic activity of compounds **1a,b,c** and analogs [1] induced us to investigate similarly constructed compounds derived from the antidepressant agent "prothiadene" (**2**) [2-4] by the insertion of the benzene nucleus between the terminal dimethylaminomethyl group and the tricycle connected with position 11 of this tricycle either by a direct bond or through a carbon atom. The first goal was the preparation of the tertiary alcohols **5a,b,c** which were obtained by reactions of the ketone **4** [2] with 2-, 3- and 4-(dimethylaminomethyl)-phenylmagnesium bromides in tetrahydrofuran. The preparation of the starting *N,N*-dimethylbromobenzylamines **3a,b,c** was described by reactions of bromobenzyl bromides with dimethylamine in acetonitrile [5]. Similar reactions have now been carried out in benzene and **3a,b,c** were obtained in higher yields. It was stated [5] that only **3a** is able to afford the Grignard reagent in ether when initiated by 1,2-dibromoethane; **3b,c** under similar



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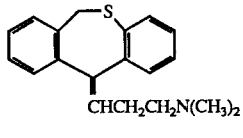

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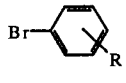

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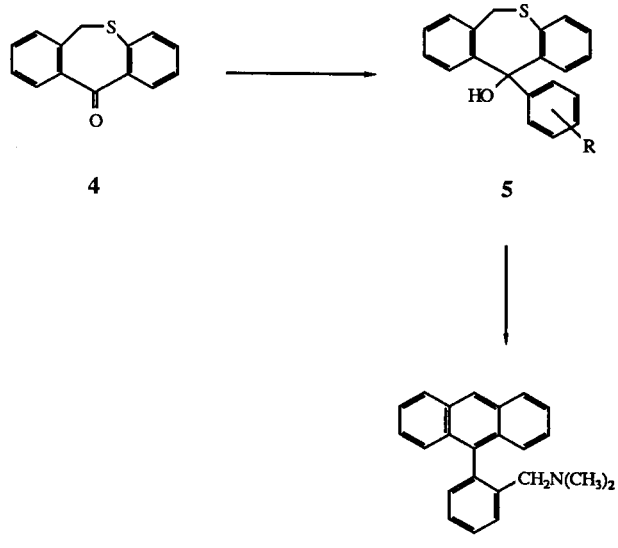
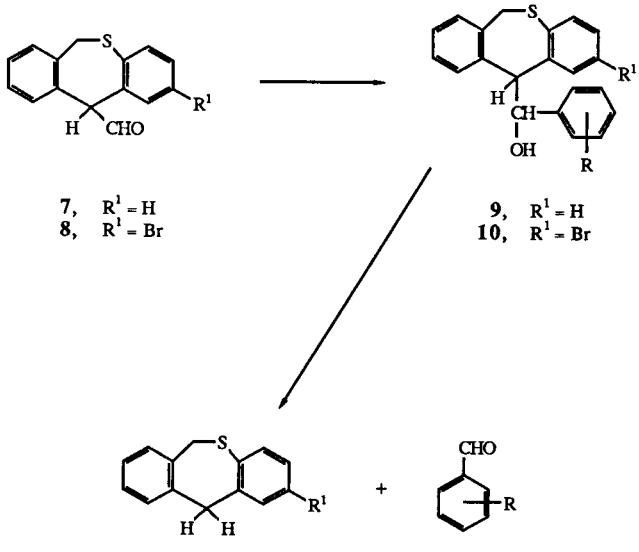
In all formulae: **a**, R = 2-$CH_2N(CH_3)_2$
b, R = 3-$CH_2N(CH_3)_2$
c, R = 4-$CH_2N(CH_3)_2$

Scheme 1



conditions did not react. It has now been found that all three bromobenzenes **3a,b,c** react smoothly with magnesium when working in tetrahydrofuran. The advantage of this solvent for preparing the "basic Grignard reagents" was described earlier [6,7] *e.g.* for 3-dimethylaminopropyl chloride and similar amino chlorides. The ir spectrum of **5a** indicates a strong hydrogen bonding between the oxygen and nitrogen functions which means a rather rigid conformation for the molecule of **5a**. The attempt to dehydrate this alcohol **5a** by heating with phosphoric acid gave a sulfur-free product which was identified as the anthracene **6**. It is thus a new case of sulfur

Scheme 2



7, $R^1 = H$
8, $R^1 = Br$

9, $R^1 = H$
10, $R^1 = Br$

11, $R^1 = H$
12, $R^1 = Br$

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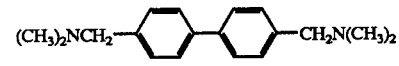
extrusion from the 6,11-dihydrodibenzo[*b,e*]thiepin system (for other cases *cf.* refs [8-12]).

The aldehyde **7** [13] was also reacted with 2-, 3- and 4-(dimethylaminomethyl)phenylmagnesium bromides in tetrahydrofuran to give mixtures of stereoisomeric secondary alcohols **9a,b,c**, isolated and characterized partly in the form of salts. In the last case **9c**, there was a basic by-product, separated by chromatography and identified as the biphenyl **14**, *i.e.* the usual type of by-product of reactions of arylmagnesium halides. The aldehyde **8** was prepared from 2-bromodibenzo[*b,f*]thiepin-11(6*H*)-one [14] by reaction with methoxymethylmagnesium chloride (for the starting chloromethyl methyl ether, *cf.* ref [15]) *via* the crude 2-bromo-11-(methoxymethyl)-6,11-dihydrodibenzo-[*b,e*]thiepin-11-ol in analogy to ref [13]. Its reaction with 4-(dimethylaminomethyl)phenylmagnesium bromide afforded the secondary alcohol **10c**.

The last step in our investigation were the attempts to prepare the corresponding ketones, *i.e.* the direct analogs of **1a,b,c**. This task proved to be more difficult than expected. The first experiment in this line started from 6,11-dihydrodibenzo[*b,e*]thiepin-11-carbonitrile [16] which was subjected to treatment with 4-(dimethylaminomethyl)-phenylmagnesium bromide and to the following hydrolysis (method [17]); no characterized product could be isolated. The same result gave the reaction of 6,11-dihydrodibenzo-[**b,e**]thiepin-11-carboxylic acid chloride (obtained from the acid [13] and thionyl chloride and used in crude state) with 3-(dimethylaminomethyl)phenylmagnesium bromide in tetrahydrofuran in the presence of catalytic amounts of tris(acetylacetonate)iron(III) ($Fe(acac)_3$) (method [18]).



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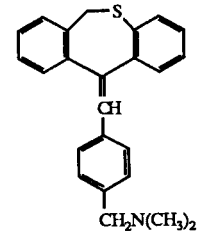
After this experience we concentrated our efforts to the oxidation of the secondary alcohols **9** and **10**. Only one experiment was successful: oxidation of **9c** with tetrabutylammonium chromate in chloroform (method [19]). A mixture was obtained which was separated by chromatography on alumina. The first product, which was eluted with cyclohexane, was surprisingly an oxygen- and nitrogen-free compound which was identified as the known **11** [20,21]. Its analysis, ^1H nmr spectrum and comparison of the melting point with the known value were sufficient for the identification. It was followed (elution with cyclohexane containing 10% of benzene) by a further oxygen-free but basic compound which was characterized in the form of its oxalate. It was identified as **15**, *i.e.* product of dehydration of **9c**, by combination of analysis, mass spectrum, uv (high degree of conjugation) and ir spectra. Further elution with a mixture of cyclohexane and benzene gave finally the desired ketone **16**. The base was crystalline and it gave a crystalline hydrogen fumarate and methanesulfonate. Its identity was corroborated mainly by the mass and ^1H nmr spectra; the ir spectrum showed the expected carbonyl band at 1 680 cm^{-1}. The last product to be eluted with chloroform was a crystalline substance $C_{11}H_{14}Cl_3NO$ which was identified as **17** (^1H nmr and ir spectra). This strange product was evidently formed from the aldehyde **13c** by reaction with chloroform (for similar reactions, *cf.* [22,23]). The most important side reaction proceeding along the oxidation, is a cleavage of **9c**, the products being **11** and **13c**. This cleavage looks like a "retro-ene-reaction" [24,25] which is a thermal cleavage of γ,δ-unsaturated alcohols, proceeding normally at high temperatures (170° and higher). The closest analogies to our reaction are the cleavages of aryl-2(or 4)-picolylmethanols at 170° to picolines and benzaldehydes



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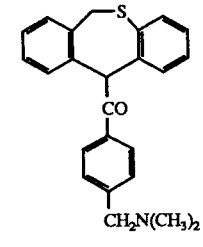

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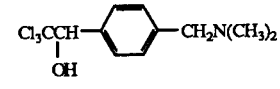

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[26] and the analogy in the pyrazine series [27]. The most interesting point with our reaction is the low temperature (boiling point of chloroform) at which it proceeds. Oxidation of the alcohol **10c** with the same reagent led only to **12** and **13c**, *i.e.* the only reaction observed was the cleavage of the "retro-ene-reaction" type. An attempt to oxidize **9a** with the same reagent led only to recovery of the starting material.

Oxidation of **9b** with a combination of lead tetraacetate with manganous diacetate [28] gave a product which was not the desired ketone (seemed to be isomeric with it -mass spectrum) and which was not identified. An attempt to oxidize **9c** with manganese dioxide [29,30] in chloroform did not lead to any characterized product. A trial to use the same reagent for oxidizing **9a** led to recovery of the starting compound. The same results gave the attempts to oxidize **9b** with potassium bromate-ammonium cerium(IV) nitrate in aqueous acetonitrile [31] or by using the Oppenauer reaction (acetone and aluminium isopropoxide) [32]. From the attempt to oxidize **9b** with cetyltrimethylammonium permanganate [33,34], only the aldehyde **13b** was isolated and characterized as the hydrogen oxalate. It is again a product of the cleavage of the "retro-ene-reaction" type; the tricyclic product of the cleavage escaped in this case to isolation. The tendency of the alcohols **9a,b,c** to undergo this type of cleavage is evidently very high, this cleavage is probably not of oxidative nature and is completely independent of the oxidation reagent used.

Compounds **5a,b,c**, **9a,b,c** and **16** were tested in the form of salts described in the Experimental by methods of pharmacology and biochemical pharmacology (oral administration in the animal tests). In concentration of 100 n*M* they did not significantly inhibit the binding of 4 n*M* [^{3}H] imipramine and 4 n*M* [^{3}H] desipramine in the hypothalamus of the rat brains. In doses of 100-500 mg/kg they did not significantly influence the behavior of mice and had no ataxic activity. In doses of 10 mg/kg they did not show antihistamine activity in tests of histamine aerosol and histamine detoxication in guinea pigs. In doses of 100-300 mg/kg they did not show antireserpine effects in the test of reserpine ptosis in mice. The only effect found was the potentiation of yohimbine toxicity in mice in rather high doses, ED_{50} in mg/kg: **5a**, 323; **5b**, 396; **5c**, 218; **9a**, the dose of 100 mg/kg potentiated in 20% of the animals; **9c**, 56.8; **16**, the dose of 100 mg/kg potentiated in 70% of the animals.

EXPERIMENTAL

All melting points were determined in the Mettler FP-5 melting point recorder. Ultraviolet (uv) spectra were determined in methanol (λ max in nm (log ϵ)) on a Unicam SP 8000 spectrophotometer, infrared (ir) spectra were recorded in Nujol (unless otherwise stated) on a Perkin-Elmer 298 spectrophotometer (ν in cm^{-1}). Nuclear magnetic resonance (^{1}H nmr) spectra were obtained on Tesla BS 487C (80 MHz) and Tesla BS 567A (100 MHz) in deuteriochloroform (unless stated otherwise). Chemical shifts are reported in delta units (in ppm) relative to tetramethylsilane (J in Hz). Mass spectra (m/z, fragments and/or %) were recorded on MCH 1320 and/or Varian MAT 44S (GC-MS) spectrometers. The homogeneity of the substances was checked by thin-layer chromatography (tlc) on silica gel. Column chromatography was performed with neutral alumina (activity II), unless otherwise stated. Solutions were dried over magnesium sulfate or potassium carbonate. All concentrations of solutions were carried out under reduced pressure on a rotary evaporator.

N,N-Dimethyl-2-bromobenzylamine (**3a**).

A solution of dimethylamine (25 g) in benzene (200 ml) was stirred and treated at 4-7° with 2-bromobenzyl bromide (42.7 g) in benzene (100 ml). The mixture was stirred and cooled for 1.5 hours, allowed to stand for 48 hours at room temperature, the basic product was extracted with 3*M* hydrochloric acid (3 x 120 ml), the acid solution was made alkaline with 20% sodium hydroxide, and the base was isolated by extraction with benzene. Processing gave **3a**, 30.1 g, 82%, bp 102-103°/1.6 kPa. Ref [5] gave a yield of 62% and bp 104-106°/1.2 kPa.

N,N-Dimethyl-3-bromobenzylamine (**3b**).

A similar reaction of dimethylamine (36 g) with 3-bromobenzyl bromide (61 g) in benzene (420 ml) (3 days standing at room temperature) gave **3b**, 36 g, 69%, bp 113-116°/2 kPa. Ref [5] gave a yield of 43% and bp 104.5-105.5°/1.26 kPa.

N,N-Dimethyl-4-bromobenzylamine (**3c**).

A similar reaction of dimethylamine (25 g) with 4-bromobenzyl bromide (42.7 g) in benzene (300 ml) gave **3c**, 22.1 g, 69%, bp 116-118°/2.4 kPa. Ref [5] gave a yield of 48% and bp 104-105.5°/-1.26 kPa.

11-(2-(Dimethylaminomethyl)phenyl)-6,11-dihydrodibenzo[*b,e*]-thiepin-11-ol (**5a**).

The Grignard reagent was prepared from **3a** (14.3 g) and Mg (1.9 g) in tetrahydrofuran (60 ml) and was treated dropwise under stirring with a solution of **4** [2] (6.9 g) in tetrahydrofuran (30 ml). The mixture was refluxed for 4 hours, allowed to stand overnight at room temperature, diluted with ether, and decomposed by 20% ammonium chloride (70 ml). The organic layer was shaken with 10% hydrochloric acid and the precipitated hydrochloride of **5a** was filtered, 11.35 g, 94%, mp 227-232° (ethanol-ether) of **5a** was obtained.

Anal. Calcd. for $C_{25}H_{24}ClNOS$: C, 69.41; H, 6.08; Cl, 8.91; N, 3.52; S, 8.06. Found: C, 69.48; H, 6.15; Cl, 8.93; N, 3.59; S, 8.14.

The released base crystallized from cyclohexane, mp 225.5-226°; uv: 260.4 (4.30), infl 296 (3.93), infl 308 (3.86), infl 344 (3.17); ir: 3095, 3075, 3015, 2730, 2675, 1588, 1571, 1562, 1501, 760, 750, 740; ^{1}H nmr: 2.10 (s, 6H), 3.20 (m, 2H), 2.55 and 3.55 (2 d, 1 + 1H, J = 13.0), 7.00-7.50 and 8.19 (2 m, 10 + 2H).

Anal. Calcd. for $C_{25}H_{23}NOS$: C, 76.42; H, 6.41; N, 3.87; S, 8.87. Found: C, 76.13; H, 6.74; N, 3.81; S, 8.73.

11-(3-(Dimethylaminomethyl)phenyl)-6,11-dihydrodibenzo[*b,e*]-thiepin-11-ol (**5b**).

The Grignard reagent was similarly prepared from **3b** (25.2 g) and Mg (0.7 g) in tetrahydrofuran (30 ml) and was reacted with **4** [2] (2.5 g) in tetrahydrofuran (20 ml). Similar processing, decom-

position of the crude hydrochloride with aqueous ammonia and extraction with ether gave **5b**, 2.4 g, 55%, mp 154.5-155.5° (benzene-cyclohexane); ir (potassium bromide): 3200, 3048, 3015, 2820, 2775, 1599, 1586, 1374, 1030, 763, 759, 750; ^{1}H nmr: 2.00 (s, 6H), 3.15 (bs, 1H), 3.20 (s, 2H), 3.10 and 3.60 (2 d, 1 + 1H, J = 13.0), 6.90-7.40 (m, 10H), 8.00 (m, 2H).

Anal. Calcd. for $C_{23}H_{23}NOS$: C, 76.42; H, 6.41; N, 3.87; S, 8.87. Found: C, 76.72; H, 6.54; N, 3.59; S, 8.90.

The neutral oxalate hemihydrate had mp 196-199° (ethanol).

Anal. Calcd. for $C_{23}H_{23}NOS \cdot 0.5\ C_2H_2O_4 \cdot 0.5\ H_2O$: C, 69.37; H, 6.06; N, 3.37; S, 7.72. Found: C, 69.57; H, 6.23; N, 3.07; S, 7.78.

11-(4-(Dimethylaminomethyl)phenyl)-6,11-dihydrodibenzo[*b,e*]-thiepin-11-ol (**5c**).

The Grignard reagent was prepared from **3c** (10.4 g) and Mg (1.4 g) in tetrahydrofuran (50 ml) and was similarly reacted with **4** [2] (5.0 g) in tetrahydrofuran (30 ml). Similar processing and shaking of the extract with dilute hydrochloric acid gave directly **5c** hydrochloride hemihydrate, 6.8 g, 76%, mp 239-241° dec (aqueous ethanol-ether).

Anal. Calcd. for $C_{23}H_{24}ClNOS \cdot 0.5\ H_2O$: C, 67.88; H, 6.19; Cl, 8.71; N, 3.44; S, 7.88. Found: C, 67.85; H, 6.49; Cl, 8.73; N, 3.51; S, 7.58.

The base was released and crystallized from cyclohexane, mp 146-147°; uv: 260.9 (3.94); ir: 3270, 3045, 2820, 2785, 2770, 1586, 1506, 1479, 1150, 1019, 1010, 810, 740; ^{1}H nmr: 2.12 (s, 6H), 3.35 (s, 2H), 3.15 and 3.65 (2 d, 1 + 1H, J = 13.0), 7.15 and 8.05 (2 m, 10 + 2H).

Anal. Calcd. for $C_{23}H_{23}NOS$: C, 76.42; H, 6.41; N, 3.87; S, 8.87. Found: C, 76.16; H, 6.50; N, 3.91; S, 8.98.

9-(2-(Dimethylaminomethyl)phenyl)anthracene (**6**).

A mixture of **5a** (3.6 g) and 85% phosphoric acid (25 ml) was heated for 2.5 hours to 120-130°. After cooling the mixture was diluted with water, made alkaline with aqueous ammonia, and extracted with chloroform. Processing of the extract gave a mixture (4.0 g) which was chromatographed on silica gel (160 g). The main product **6** (2.10 g, 68%) was eluted with a mixture of benzene, chloroform and ethanol, mp 128-130° and after resolidification 137.5-138.5° (methanol and then ether); ms: 131 (M^+), 105 (base); uv: 253.4 (4.99), 346.3 (3.80), 364.1 (4.00), 383.8 (3.98); ir: 3045, 2815, 2770, 1620, 1527, 893, 757, 739; ^{1}H nmr: 1.88 (s, 6H), 2.90 (s, 2H), 7.00-8.10 (m, 12H), 8.40 (s, 1H).

Anal. Calcd. for $C_{23}H_{21}N$: C, 88.70; H, 6.80; N, 4.50. Found: C, 89.00; H, 7.06; N, 4.44.

2-Bromo-6,11-dihydrodibenzo[*b,e*]thiepin-11-carbaldehyde (**8**).

A mixture of Mg (14.5 g), mercuric chloride (0.72 g) and tetrahydrofuran (30 ml) was cooled to -10° and was treated under stirring at -5 to -10° over 1 hour with chloromethyl methyl ether [15] (45 ml) in tetrahydrofuran (50 ml). The mixture was stirred under cooling for 2 hours and then treated over 1 hour with a solution of 2-bromodibenzo[*b,e*]thiepin-11(6*H*)-one [14] (91.6 g) in tetrahydrofuran (500 ml) still at -10°. The mixture was stirred under cooling for 1 hour, allowed to warm to room temperature, diluted with ether (150 ml) and poured onto a solution of ammonium chloride (60 g) in water (500 ml). The aqueous solution was separated and extracted with ether. The organic layers were combined, dried, and evaporated giving the crude 2-bromo-11-(methoxymethyl)-6,11-dihydrodibenzo[*b,e*]thiepin-11-ol (109.3 g) containing an important amount of the starting ketone.

The crude product was treated with 99% formic acid (215 ml), the mixture was heated for 15 minutes to 75-90°, 10% sulfuric acid (30 ml) was added and the mixture was stirred and refluxed (bath temperature 120°) for 15 minutes. It was then poured onto a mixture of ice (200 g), water (400 ml), and benzene (200 ml). The aqueous layer was extracted with benzene, the benzene layers were combined, dried, and evaporated. The residue (100 g) was chromatographed on silica gel (1 kg of "Kieselgel 40"). Elution with a mixture of benzene and light petroleum (1:1) led first to recovery of the starting ketone (14.47 g), mp 147-150° (ref [14], mp 151-156°). Continued elution with the same mixture of solvents afforded **8**, 19.48 g, 24% (per conversion), mp 118-120° (benzene-light petroleum); ms: 318 (M^+), 178 (base); ir: 3058, 3015, 2820, 2720, 1705, 1577, 1556, 1495, 889, 820, 754, 740, 726; ^{1}H nmr: 3.75 and 4.05 (2d, 1 + 1H, J = 13.0), 4.40 (s, 1H), 6.90-7.50 (m, 7H), 9.80 (s, 1H).

Anal. Calcd. for $C_{15}H_{11}BrOS$: C, 56.43; H, 3.47; Br, 25.04; S, 10.04. Found: C, 56.48; H, 3.61; Br, 24.83; S, 10.07.

α-(6,11-Dihydrodibenzo[*b,e*]thiepin-11-yl)-2-(dimethylaminomethyl)benzyl Alcohol (**9a**).

The Grignard reagent was prepared from **3a** (14.4 g) and Mg (1.62 g) in tetrahydrofuran (60 ml) (starting with a grain of iodine and 5 drops of 1,2-dibromoethane). The mixture was refluxed for 45 minutes, cooled and treated at 15° with a solution of **7** [13] (9.6 g) in tetrahydrofuran (30 ml), added dropwise. It was stirred for 2 hours at room temperature, decomposed by a solution of ammonium chloride (14 g) in water (60 ml) and the aqueous layer was extracted with ether. The organic layers were combined, dried, and evaporated. The residue was crystallized from a mixture of benzene (80 ml) and light petroleum (50 ml) to give **9a**, 8.95 g, 60%, mp 165-167°; uv: 260 (3.82); ir: 3160, 3050, 3025, 1600, 1575, 1485, 1055, 750, 742; ^{1}H nmr proved the compound to be a mixture of two stereoisomers.

Anal. Calcd. for $C_{24}H_{25}NOS$: C, 76.76; H, 6.71; N, 3.73; S, 8.54. Found: C, 77.07; H, 6.77; N, 3.54; S, 8.54.

The hydrochloride had mp 138-141° (ether).

Anal. Calcd. for $C_{24}H_{26}ClNOS$: C, 69.96; H, 6.36; Cl, 8.61; N, 3.40; S, 7.78. Found: C, 69.74; H, 6.41; Cl, 8.46; N, 3.44; S, 7.77.

α-(6,11-Dihydrodibenzo[*b,e*]thiepin-11-yl)-3-(dimethylaminomethyl)benzyl Alcohol (**9b**).

The Grignard reagent was prepared from **3b** (20.4 g) and Mg (2.5 g) in tetrahydrofuran (80 ml) and was treated at room temperature with a solution of **7** [13] (14.8 g) in tetrahydrofuran (50 ml), added dropwise over 15 minutes. The mixture was refluxed for 3 hours, decomposed with 20% ammonium chloride (60 ml), and extracted with ether. Processing of the extract gave an oily mixture which was chromatographed on alumina (500 g). Elution with benzene and with chloroform afforded the oily mixture of stereoisomers (23.1 g) which was transformed to the neutral fumarate, mp 207.5-208° (ethanol).

Anal. Calcd. for $C_{24}H_{25}NOS \cdot 0.5\ C_4H_4O_4$: C, 72.03; H, 6.28; N, 3.23; S, 7.40. Found: C, 72.11; H, 6.37; N, 3.41; S, 7.41.

A sample of the released base was transformed to the hydrochloride which proved to be the monohydrate, mp 139-143° (ether); ms: 375 (M^+), 164 (base); uv: 260 (4.10), 297 (3.69), infl 310 (3.59); ir: 3340, 2640, 2500, 1055, 1040, 1020, 753; ^{1}H nmr: 1.98 and 2.02 (2s, Σ 6H), 3.18 (s, 2H), 3.50-5.00 (flat signals, Σ 4H), 5.78 (m, 1H), 6.20-7.50 (m, 12H).

Anal. Calcd. for $C_{24}H_{26}ClNOS \cdot H_2O$: C, 67.03; H, 6.56; Cl, 8.25;

N, 3.26; S, 7.46. Found: C, 66.73; H, 6.54; Cl, 8.31; N, 3.31; S, 7.53.

α-(6,11-Dihydrodibenzo[*b,e*]thiepin-11-yl)-4-(dimethylaminomethyl)benzyl Alcohol (**9c**).

The Grignard reagent was prepared from **3c** (17.1 g) and Mg (1.92 g) in tetrahydrofuran (75 ml) with the help of a small quantity of iodine and 1,2-dibromoethane (0.3 ml). It was reacted similarly with **7** [13] (14.4 g) in tetrahydrofuran (45 ml) at 15°. The mixture was stirred for 2 hours at room temperature, decomposed with ammonium chloride (17 g) in water (70 ml), and extracted with ether. The crude product was chromatographed on alumina (400 g). A mixture of benzene and cyclohexane (1:3) eluted oily 4,4'-bis(dimethylaminomethyl)biphenyl (**14**), 1.68 g, which was transformed to the dihydrochloride, mp above 300° (ref [35] mentioned the low-melting base, the picrate and the dimethiodide, ref [36] mentioned its bisquaternary salts); uv: 255 (4.33) (a biphenyl-like spectrum); ir: 3060, 3010, 2573, 2515, 2470, 2385, 1587, 1501, 1480, 791.

Anal. Calcd. for $C_{18}H_{26}Cl_2N_2$: C, 63.34; H, 7.68; Cl, 20.78; N, 8.21. Found: C, 63.28; H, 7.77; Cl, 20.62; N, 8.04.

Continued elution with the same mixture of solvents afforded **9c** (oily mixture of stereoisomers), 12.5 g, 56%, which was transformed to the hydrochloride, appearing to be a hemihydrate, mp 150-151°; ms: 164 ($C_{10}H_{14}NO$, base); ir: 3340, 2670, 2470, 1050, 810, 754.

Anal. Calcd. for $C_{24}H_{24}ClNOS \cdot 0.5\ H_2O$: C, 68.47; H, 6.46; Cl, 8.42; N, 3.33; S, 7.62. Found: C, 68.39; H, 6.46; Cl, 8.28; N, 3.00; S, 7.87.

α-(2-Bromo-6,11-dihydrodibenzo[*b,e*]thiepin-11-yl)-4-(dimethylaminomethyl)benzyl Alcohol (**10c**).

The Grignard reagent was prepared from **3c** (19.9 g) and Mg (2.5 g) in tetrahydrofuran (80 ml) and after 30 minutes of refluxing it was treated under cooling with a solution of **8** (19.5 g) in tetrahydrofuran (50 ml), added dropwise under stirring over 15 minutes. The mixture was refluxed for 3 hours, diluted with ether, decomposed with 20% ammonium chloride (60 ml), and extracted with ether. Processing of the extract gave an oily mixture which was chromatographed on alumina (500 g). Elution with chloroform gave **10c** as a mixture of stereoisomers (A/B 3:2 according to nmr), 14.7 g, 53%. The product was transformed to the neutral fumarate which proved to be a hemihydrate, mp 221-224° (ethanol); ms: (ci) 454 ($M^+ + 1$); (ei) 58 (base).

Anal. Calcd. for $C_{24}H_{24}BrNOS \cdot 0.5\ C_4H_4O_4 \cdot 0.5\ H_2O$: C, 59.88; H, 5.22; Br, 15.32; N, 2.69; S, 6.15. Found: C, 60.00; H, 5.20; Br, 15.01; N, 2.71; S, 6.11.

The released base was oily; ^1H nmr: 2.13 and 2.18 (2 s, Σ 6H), 3.30 and 3.38 (2 s, Σ 2H), 3.90 and 4.90 (flat signals, 4H), 5.85 (d, 1H), 6.90-7.60 (m, 11H).

6,11-Dihydrodibenzo[*b,e*]thiepin-11-yl 4-(Dimethylaminomethyl)phenyl Ketone (**16**).

A stirred solution of chromic anhydride (6.1 g) in water (50 ml) was treated with tetrabutylammonium hydrogen sulfate (21.3 g) in water (100 ml) and the formed tetrabutylammonium chromate was extracted with chloroform (500 ml). The extract was evaporated to 50 ml, the residue was treated with a solution of **9c** (11.35 g) in chloroform (50 ml) and the mixture was refluxed for 5 hours. Chloroform was evaporated, the residue was distributed between ether and 10% sodium hydroxide, after filtration the organic layer was dried and evaporated. The inhomogeneous residue (9.1 g) was chromatographed on alumina (400 g). Cyclohexane eluted first 6,11-dihydrodibenzo[*b,e*]thiepin (**11**), mp 99-100.5° (ethanol) (refs [20,21], mp 101-102° and 103-105°, respectively); the analysis is in agreement with $C_{14}H_{12}S$; ^1H nmr: 4.05 and 4.20 (2 s, 2 + 2H), 6.80-7.20 (m, 8H).

The elution was continued with cyclohexane containing 10% of benzene. The first fraction (0.3 g) was homogeneous and was identified as 11-(4-(dimethylaminomethyl)benzylidene)-6,11-dihydrodibenzo[*b,e*]thiepin (**15**) affording the crystalline hydrogen oxalate hemihydrate, mp 212-215° (acetone-ether); ms: 357 (M^+), 58 (base); uv: 260 (4.27), 285 (4.17), infl 315 (3.85).

Anal. Calcd. for $C_{26}H_{25}NO_4S \cdot 0.5\ H_2O$: C, 68.40; H, 5.74; N, 3.07; S, 7.02. Found: C, 68.29; H, 5.88; N, 3.36; S, 6.81.

The released base was oily; ir (carbon disulfide): 2805, 2760, 761, 745.

Continued elution with a mixture of cyclohexane and benzene afforded the desired **16**, 1.36 g, 12%, which was transformed to the hydrogen fumarate, mp 198-201° (ethanol); ms: 373 (M^+), 162 (base).

Anal. Calcd. for $C_{28}H_{27}NO_5S$: C, 68.69; H, 5.56; N, 2.86; S, 6.55. Found: C, 68.86; H, 5.75; N, 2.83; S, 6.55.

The base was released by treatment with aqueous ammonia and isolated by extraction with ether, oil; ir (carbon disulfide): 3060, 3020, 3000, 2815, 2765, 1680, 750, 740; ^1H nmr: 2.22 (s, 6H), 3.40 (s, 2H), 3.68 and 4.40 (2 d, 1 + 1H, J = 13.0), 5.55 (s, 1H), 7.00-7.60 (m, 10H), 7.92 (d, 2H, J = 8.5).

The methanesulfonate monohydrate had mp 197-203° (ethanol-ether).

Anal. Calcd. for $C_{25}H_{27}NO_4S_2 \cdot H_2O$: C, 61.58; H, 5.99; N, 2.87; S, 13.15. Found: C, 61.38; H, 5.77; N, 2.96; S, 13.33.

The chromatography was concluded by elution with chloroform which afforded 2,2,2-trichloro-1-(4-(dimethylaminomethyl)phenyl)ethanol (**17**), 1.72 g, mp 165-166° (benzene); ms: 281 (M^+), 58 (base); uv: 220.4 (4.05), 259.2 (2.52), 266 (2.51), infl 271 (2.35); ir: 3073, 3030, 3010, 2650, 1513, 1095, 808, 793; ir (chloroform): 3585, 2820, 2775, 1071; ^1H nmr (hexadeuteriodimethyl sulfoxide): 2.15 (s, 6H), 3.40 (s, 2H), 5.15 (s, 1H), 7.22 and 7.55 (2 d, 2 + 2H, J = 8.5), 8.30 (bs, 1H).

Anal. Calcd. for $C_{11}H_{14}Cl_3NO$: C, 46.75; H, 4.99; N, 4.96. Found: C, 46.91; H, 5.18; N, 4.83.

Oxidation of **10c** with Tetrabutylammonium Chromate.

A solution of chromic anhydride (5.0 g) in water (50 ml) was treated with a solution of tetrabutylammonium hydrogen sulfate (17.6 g) in water (100 ml) and the formed tetrabutylammonium chromate was extracted with chloroform (500 ml). The extract was evaporated to the volume of 100 ml, a solution of **10c** (21.3 g) in chloroform (50 ml) was added and the mixture was refluxed for 5 hours. Chloroform was evaporated, the residue was distributed between 10% sodium hydroxide and ether, the mixture was filtered, the organic layer was dried, and evaporated. The semisolid residue (15.8 g) was chromatographed on alumina (400 g). Benzene eluted in the first fractions crystalline 2-bromo-6,11-dihydrodibenzo[*b,e*]thiepin (**12**), 8.65 g, mp 138.5-139.5° (ethanol-benzene); ms: 290 (M^+), 178 (base); ^1H nmr: 4.02 and 4.20 (2 s, 2 + 2H), 6.82 (d, 1H J = 9.5), 7.06 (dd, 1H, J = 9.5, 3.0), 7.14 (s, 4H), 7.20 (d, 1H, J = 3.0).

Anal. Calcd. for $C_{14}H_{11}BrS$: C, 57.74; H, 3.81; Br, 27.44; S, 11.01. Found: C, 57.65; H, 3.79; Br, 27.26; S, 10.79.

In the last fractions benzene eluted the oily 4-(dimethylaminomethyl)benzaldehyde (**13c**), 1.42 g, which gave a crystalline

fumarate, mp 125-127.5° (ethanol-ether); ms: 163 (M^+), 58 (base); ir: 3080, 2500, 1700, 1610, 1560, 1262, 1188, 974, 957, 817, 780. Ref [37] described the hydrobromide and the succinate; **13c** was mentioned in a patent [38] as a starting material.

Anal. Calcd. for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.13; N, 5.02. Found: C, 59.98; H, 6.14; N, 5.18.

The chromatography was concluded by elution with chloroform which afforded **17**, 2.58 g, mp 165-167° (compared also by tlc with the product described above).

Oxidation of **9b** with Cetyltrimethylammonium Permanganate.

A solution of **9b** (1.5 g) in dichloromethane (10 ml) was treated with a solution of hexadecyltrimethylammonium permanganate (CTAP) [34] (1.6 g) in dichloromethane (10 ml), the mixture was stirred for 1.5 hours at room temperature, dissolved in ether, filtered through a layer of magnesium sulfate, and the filtrate was evaporated. The residue (1.3 g, containing according to tlc a small amount of the starting **9b**) was transformed to the oxalate, 0.75 g, mp 151-156° (ethanol-acetone). It was identified as 3-(dimethylaminomethyl)benzaldehyde (**13b**) hydrogen oxalate hemihydrate; ms: 163 (M^+), 58 (base). Ref [38] characterized **13b** only as a "liquid".

Anal. Calcd. for $C_{12}H_{15}NO_5 \cdot 0.5\ H_2O$: C, 54.95; H, 6.15; N, 5.34. Found: C, 54.66; H, 5.94; N, 5.36.

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