Synthesis of Substituted Dihydrodibenzothiazepines and Related Compounds

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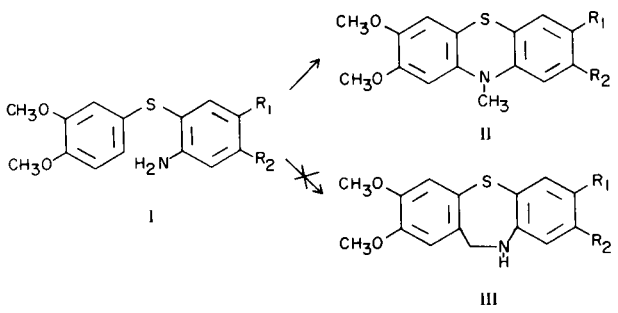
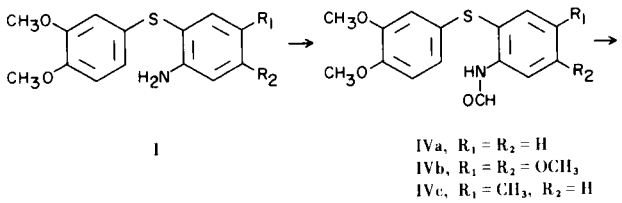
In a previous communication (2) we have demonstrated that condensation of 2-amino-(3′,4′-dimethoxyphenylthio)benzene, 2-amino-4,5-dimethoxy-(3′,4′-dimethoxyphenylthio)benzene and 2-amino-5-methyl-(3′,4′-dimethoxyphenylthio)benzene (I) with formaldehyde in acidic solution resulted in the formation of substituted 10-methylphenothiazines (II) instead of the expected dihydrodibenzothiazepines (III).



I II III

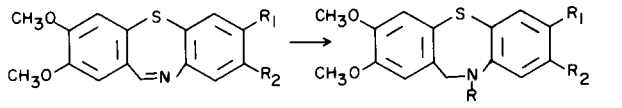
Obviously this reaction does not follow the generally accepted mechanism of the Pictet-Spengler reaction (3). Different workers (10-20) have shown that the alkylamino or acylamino functions on the nitrogen of the dihydrodibenzothiazepine nucleus exhibit pharmocological activity similar to phenothiazine derivatives. Thus, in conjunction with our study of heterocyclic compounds containing nitrogen and sulphur (4), it was of interest to synthesize polymethoxy dibenzothiazepines by a reaction similar to that of Bischler-Napieralski (5-9).

The following scheme was utilized for the synthesis. The formyl derivatives (IV) of amines (I) prepared in the usual manner, were heated with polyphosphoric acid at 100-110° to produce the dibenzo[*b*,*f*]-1,4-thiazepines (V) in excellent yields, exhibiting characteristic infrared absorption at 1600 cm^{-1} (C=N-). They were characterized as picrates. Reduction of V with lithium aluminum hydride-aluminum chloride in ether afforded the dihydro compounds (VI) in good yields with infrared absorption at 3400 cm^{-1} (-NH). The acetyl derivative VId was made in the usual manner.



I

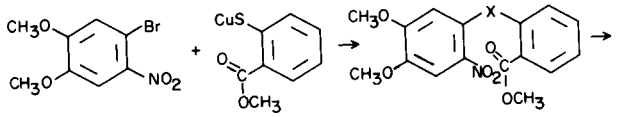
IVa, $R_1 = R_2 = H$
IVb, $R_1 = R_2 = OCH_3$
IVc, $R_1 = CH_3$, $R_2 = H$



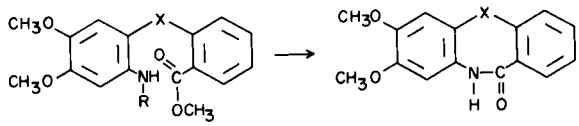
Va, $R_1 = R_2 = H$
Vb, $R_1 = R_2 = OCH_3$
Vc, $R_1 = CH_3$, $R_2 = H$

VIa, $R = R_1 = R_2 = H$
VIb, $R = H$, $R_1 = R_2 = OCH_3$
VIc, $R = R_2 = H$, $R_1 = CH_3$
VId, $R = COCH_3$, $R_1 = R_2 = H$

For the synthesis of the dihydrodibenzothiazepines (X), the preferred route was to convert the aminoesters (VIII) to lactams (IX).

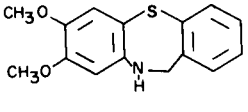


VII, X = S
VIIa, X = SO_2



VIII, R = H, X = S
VIIIa, R = $COCH_3$, X = S
VIIIb, R = H, X = SO_2
VIIIc, R = $COCH_3$, X = SO_2

IX, X = S
IXa, X = SO_2



X

The nitroester (VII) was obtained in 66% yield, when 4-bromo-5-nitroveratrole was heated in quinoline with cuprous salt of methyl thiosalicylate (4). Hydrogen peroxide oxidation gave the corresponding sulfone (VIIa) in 88% yield. Catalytic reduction in the presence of Raney Nickel produced the corresponding amines (VIII). The aminoesters VIII and VIIIb were cyclized at 220° to the corresponding lactams in 83% yield. An attempt to hydrolyse the lactam (IXa) to the 2(2'-amino-3',4'-dimethoxybenzenesulfonyl)benzoic acid resulted in recyclization of the amino acid to the starting lactam (22). Lithium aluminum hydride reduction of IX yielded the dihydrodibenzothiazepine X. Beckmann's rearrangement of 2,3-dimethoxythioxanthone 5,5-dioxide oxime (4) yielded the isomer of IXa (23).

EXPERIMENTAL

Procedure for the Preparation of Substituted 2-(3',4'-Dimethoxyphenylthio)formanilides.

To a solution of 2 g. of amine I (9) (21) in 15 ml. of anhydrous benzene was added 20 ml. of 98% formic acid. The mixture was heated under reflux for 2.5 hours. The solvent was evaporated under reduced pressure and the residue was obtained in crystalline form by addition of ice-water in 75-80% yield. The following compounds were obtained.

2-(3',4'-Dimethoxyphenylthio)formanilide (IVa).

This compound, m.p. 110-111°, was crystallized from methanol.

Anal. Calcd. for $C_{15}H_{15}NO_3S$: C, 62.28; H, 5.19; N, 4.84; S, 11.07. Found: C, 61.88; H, 5.21; N, 4.70; S, 11.28.

2-(3',4'-Dimethoxyphenylthio)-4,5-dimethoxyformanilide (IVb).

This compound, m.p. 101-102°, was crystallized from aqueous ethanol.

Anal. Calcd. for $C_{17}H_{19}NO_5S$: C, 58.48; H, 5.44; N, 4.01. Found: C, 58.32; H, 5.20; N, 3.90.

2-(3',4'-Dimethoxyphenylthio)-5-methylformanilide (IVc).

This compound, m.p. 116-117°, was crystallized from aqueous methanol.

Anal. Calcd. for $C_{16}H_{17}NO_3S$: C, 63.36; H, 5.61; N, 4.62. Found: C, 63.10; H, 5.50; N, 4.70.

General Procedure for the Preparation of Substituted Dibenzo-[*b,f*]-1,4-thiazepines.

In a two-necked flask fitted with a stirrer and a reflux condenser was placed 1 g. of IV and 15 g. of polyphosphoric acid. The mixture was sitrred and heated at 100° for one hour. The warm reaction mixture was poured into ice-water and made basic with concentrated ammonium hydroxide. The solution was extracted four times with 150 ml. of chloroform. The organic layer was washed with water, dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue was crystallized from methanol. The following compounds were obtained.

2,3-Dimethoxydibenzo[*b,f*]-1,4-thiazepine (Va).

This compound had m.p. 136-137°, yield, 78%.

Anal. Calcd. for $C_{15}H_{13}NO_2S$: C, 66.42; H, 4.79; N, 5.20. Found: C, 66.30; H, 4.42; N, 5.35.

2,3,7,8-Tetramethoxydibenzo[*b,f*]-1,4-thiazepine (Vb).

This compound had m.p. 166-167°, yield, 67%.

Anal. Calcd. for $C_{17}H_{17}NO_4S$: C, 61.63; H, 5.13; N, 4.23. Found: C, 61.30; H, 5.02; N, 4.29.

2,3-Dimethoxy-7-methyldibenzo[*b,f*]-1,4-thiazepine (Vc).

This compound had m.p. 122-123°, yield, 71%.

Anal. Calcd. for $C_{16}H_{15}NO_2S$: C, 67.36; H, 5.26; N, 4.91. Found: C, 67.49; H, 4.98; N, 5.04.

Reduction of Dibenzo[*b,f*]-1,4-thiazepines.

In a 150 ml. three-necked flask fitted with stirrer, condenser and addition funnel, both protected from moisture, was placed 0.001 mole of lithium aluminum hydride and 0.001 mole of aluminum chloride in 25 ml. of anhydrous ether. With gentle heating and stirring 0.0005 mole of dibenzothiazepine V in 50 ml. of ether was added dropwise over a period of 20 minutes. The mixture was heated under reflux for two hours. After cooling the excess reducing agent was decomposed by a dropwise addition of a solution of 10% sodium hydroxide. The solids were removed by filtration and washed with 100 ml. of warm ether. The combined filtrate was washed with water, dried over magnesium sulfate and evaporated under reduced pressure to yield a residue which on recrystallization from methanol gave compounds VI as follows.

2,3-Dimethoxy-10,11-dihydrodibenzo[*b,f*]-1,4-thiazepine (VIa).

This compound had m.p. 139-140°, yield, 82%.

Anal. Calcd. for $C_{15}H_{15}NO_2S$: C, 65.98; H, 5.49; N, 5.12. Found: C, 65.73; H, 5.53; N, 5.00.

2,3,7,8-Tetramethoxy-10,11-dihydrodibenzo[*b,f*]-1,4-thiazepine (VIb).

This compound had m.p. 153-155°, yield, 61%.

Anal. Calcd. for $C_{17}H_{19}NO_4S$: C, 61.26; H, 5.70; N, 4.20. Found: C, 61.14; H, 5.40; N, 3.95.

2,3-Dimethoxy-7-methyl-10,11-dihydrodibenzo[*b,f*]-1,4-thiazepine (VIc).

This compound had m.p. 132-133°, yield, 75%.

Anal. Calcd. for $C_{16}H_{17}NO_2S$: C, 66.81; H, 5.92; N, 4.87. Found: C, 67.20; H, 5.98; N, 4.94.

N-Acetyl Derivative of VIa.

Dihydrothiazepine (VIa) 0.3 g. was heated under reflux with 3 ml. of acetic anhydride for 45 minutes. The acetate VId was obtained in 75% yield after crystallization from methanol, m.p. 153-155°.

Anal. Calcd. for $C_{17}H_{17}NO_3S$: C, 64.76; H, 5.39. Found: C, 64.69; H, 5.61.

Methyl 2-(2'-Nitro-4',5'-dimethoxyphenylthio)benzoate (VII).

The cuprous salt of methyl thiosalicylate 25.5 g., (0.11 mole) was added to a solution prepared by dissolving 26.2 g. (0.1 mole) of 2-nitro-4,5-dimethoxybromobenzene in 100 ml. of quinoline and 10 ml. of anhydrous pyridine. The solution was refluxed for 2.5 hours. The warm reaction mixture was poured into ice-water containing 120 ml. of concentrated hydrochloric acid. The precipitate was collected by filtration and extracted with warm chloroform. The organic layer was washed with water, dried over anhydrous magnesium sulfate and purified by filtration over a column of 100 g. of aluminum oxide (eluant, chloroform). After removal of the solvent the semisolid product was crystallized from ethanol to yield 23 g. of VII, m.p. 109-110°.

Anal. Calcd. for $C_{16}H_{15}NO_6S$: C, 55.01; H, 4.29; N, 4.01.

Found: C, 55.17; H, 4.35; N, 3.86.

Methyl 2-(2′-Nitro-4′,5′-dimethoxybenzenesulfonyl)benzoate (VIIa).

To a solution of VII (3 g.) in 30 ml. of glacial acetic acid was added 10 ml. of 35% hydrogen peroxide and the mixture was heated on a steam bath for 2 hours. After pouring the solution into cold water, the yellow crystalline material was collected by filtration and crystallized from chloroform-methanol to give compound VIIa in 88% yield, m.p. 126-127°.

Anal. Calcd. for $C_{16}H_{15}NO_8S$: C, 50.39; H, 3.93; N, 3.67. Found: C, 50.35; H, 3.99; N, 3.53.

Methyl 2-(2′-Amino-4′,5′-dimethoxyphenylthio)benzoate (VIII).

Ten g. of the nitro compound (VII) were dissolved in 500 ml. of pure ethanol and to this solution was added 3-4 g. of freshly prepared Raney Nickel. The solution was hydrogenated at room temperature and normal pressure for 7 hours. The catalyst was filtered and the solvent was removed under vacuum to yield the amine VIII (7.5 g.) m.p. 129-130°. Recrystallization from ethanol increased the m.p. 130-131°.

Anal. Calcd. for $C_{16}H_{17}NO4S$: C, 60.20; H, 5.32; N, 4.38. Found: C, 60.18; H, 5.37; N, 4.19.

Methyl 2-(2′-Acetamino-4′,5′-dimethoxyphenylthio)benzoate (VIIIa)

The aminoester (VIII) (0.2 g.) was acetylated with 2 ml. of pyridine and 3 ml. of acetic anhydride at room temperature for 12 hours. Work up as usual afforded compound (VIIIa) in 85% yield. Recrystallization from methanol increased the m.p. to 177-179°.

Anal. Calcd. for $C_{18}H_{19}NO_5S$: C, 59.83; H, 5.26; N, 3.87. Found: C, 59.94; H, 5.34; N, 3.65.

Methyl 2-(2′-Amino-4′,5′-dimethoxybenzenesulfonyl)benzoate (VIIIb).

Following the procedure for the reduction of compound VIII, there was prepared the aminoester VIIIb in 86% yield. Recrystallization from ethanol-water gave a product with m.p. 101-102°.

Methyl 2-(2′-Acetamido-4′,5′-dimethoxybenzenesulfonyl)benzoate (VIIIc).

Acetylation of the amine with an excess of acetic anhydride-pyridine at room temperature overnight yielded compound VIIIc, m.p. 150-151° after crystallization from methanol.

Anal. Calcd. for $C_{18}H_{19}NO_7S$: C, 55.0; H, 4.83. Found: C, 55.33; H, 5.01.

2,3-Dimethoxydibenzo[*b*,*f*]-1,4-thiazepin-10-one (IX).

The aminoester (VIII) (6.5 g.) was immersed in an oil bath at 220-230°, under nitrogen for 6.5 hours. The compound after cooling was crystallized from methanol, yield 5.45 g. of IX. Recrystallization from acetic acid increased the m.p. to 235-237°.

Anal. Calcd. for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.52; N, 4.87. Found: C, 62.34; H, 4.61; N, 4.45.

2,3-Dimethoxydibenzo[*b*,*f*]-1,4-thiazepin-10-one 5,5-Dioxide (IXa).

Following the procedure for the preparation of compound IX, lactam IXa was obtained in 82% yield after recrystallization from acetic acid-methanol, m.p. 224-225°.

Anal. Calcd. for $C_{15}H_{13}NO_5S$: C, 56.42; H, 4.07; N, 4.38. Found: C, 56.20; H, 4.09; N, 4.21.

2,3-Dimethoxy-10,11-dihydrodibenzo[*b*,*f*]-1,4-thiazepine (X).

To a solution of 1.4 g. of IX in 50 ml. of anhydrous tetrahydrofuran was added 1 g. of lithium aluminum hydride over a period of ten minutes. After the reaction mixture was refluxed for 20 hours, the excess reducing agent was decomposed by dropwise addition of dilute sodium hydroxide. The mixture was extracted several times with 100 ml. of chloroform. The chloroform was evaporated in vacuum to give 750 mg. of X, m.p. 128-129°.

Anal. Calcd. for $C_{15}H_{15}NO_2S$: C, 65.93; H, 5.49. Found: C, 65.71; H, 5.32.

REFERENCES

(1) Present address: School of Pharmacy, University of California, San Francisco, California 94122.

(2) R. Quelet, C. Broquet and P. Catsoulacos, *Compt. Rend.*, 258, 3504 (1964)

(3) W. M. Whaley and T. R. Govindachari, *Organic Reactions*, 6, 151 (1951).

(4) P. Catsoulacos, *J. Heterocyclic Chem.*, 4, 645 (1967).

(5) C. I. Brodrick, J. S. Nicholson and W. F. Short, *J. Chem. Soc.*, 3857 (1954).

(6) R. H. B. Galt and J. D. Loudon, *J. Chem. Soc.*, 885 (1959).

(7) M. Protiva, J. O. Jilek and K. Pelz, IUPAC, XIXth International Congress, Abstracts A, 244 (London, 1963).

(8) J. O. Jilek, K. Pelz, D. Pavlickova and M. Protiva, *Collect. Czech. Chem. Commun.*, 30, 1676 (1965).

(9) R. Quelet and P. Catsoulacos, *Compt. Rend.*, 258, 1251 (1964).

(10) V. Hach and M. Protiva, *Chem. Listy*, 51, 1909 (1957).

(11) M. Protiva and V. Hach, Czech. Patent, 86,660 (1957).

(12) R. Jaques, A. Rossi, E. Urech, H. J. Bein and K. Hoffman, *Helv. Chim. Acta*, 42, 1265 (1959).

(13) G. Stille, H. Laurer, E. Eichenberger, F. Hunziker and J. Schmutz, *Arzneim.-Forsch.*, 15, 841 (1965).

(14) F. A. Sowinski and H. L. Yale, U. S. Patent, 3,188,320 (1965).

(15) F. A. Sowinski and H. L. Yale, *ibid.*, 3,188,323 (1965).

(16) G. Stille, H.-Ackermann, E. Eichenberger and H. Lauener, *Int. J. Nuropharmacol.*, 4, 375 (1965).

(17) F. Hunziker, F. Kunzle and J. Schmutz, *Helv. Chim. Acta*, 49, 244 (1966).

(18) M. Protiva, V. Hach and M. Borovicka, Czech. Patent, 88,128 (1958).

(19) M. Protiva and V. Hach, *Collect. Czech. Chem. Commun.*, 24, 207 (1959).

(20) H. L. Yale and F. A. Sowinski, U. S. Patent, 3,258,459 (1966).

(21) P. Catsoulacos, *Pharm. Deltion*, 4, 93 (1964); *Chem. Abstr.*, 63, 8364 (1966).

(22) W. E. Truce and J. A. Simms, *J. Org. Chem.*, 22, 617 (1957).

(23) Unpublished results.

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