TRICYCLIC SYSTEMS CONTAINING A 3-THIENYLSULFIDE FRAGMENT; 10-(3-DIMETHYLAMINOPROPYLIDENE)-5,10-DIHYDROTHIENO[3,2-*c*]-2-BENZOTHIEPIN, A NEW EFFECTIVE ANTIHISTAMINE*

M. RAJŠNER, J. METYŠ, B. KAKÁČ and M. PROTIVA

Research Institute of Pharmacy and Biochemistry, 130 00 Prague 3

Received November 26th, 1974

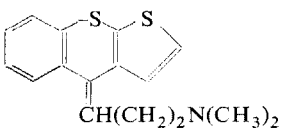
Acid *VI* obtained in a reaction of sodium 3-thiophenthiolate with phthalide was cyclized by a phosphate ester to thieno[3,2-*c*]-2-benzothiepin-10(5*H*)-one (*IV*) which was converted *via* the tertiary alcohol *V* to the title compound *III*. Acid *VII* obtained by bromination of *VI* yields by cyclization a mixture of 3-bromothieno[3,4-*c*]-2-benzothiepin-10(5*H*)-one (*VIII*) and ketone *IV*, formed after displacement of bromine during the acylation reaction. The thieno[3,2-*b*]-1-benzothiopyran-9-one (*X*) obtained in a modified procedure was converted in a reaction with 3-dimethylaminopropylmagnesium chloride to the tertiary alcohol *XI*, the dehydration of which did not result in the expected olefine because of lability of the latter in an acid medium. Hydrochloride of amine *III* was found to be a very potent antihistamine.

Of the six possible thieno-benzothiepins, linearly condensed tricycles with the sulfur atom in the two-unit bridge of the central seven-membered ring, only two have been described so far: thieno[2,3-*c*]-2-benzothiepin and thieno[2,3-*c*]-1-benzothiepin. Both were found to be suitable carrier systems for molecules of pharmacodynamically active compounds. The derivative of the first is the antihistamine and antiallergic "dithiadene" (*I*) developed by this group[1-7]; a derivative of the second is the piperidine analogue *II* with antihistamine, antiserotonin, bronchodilating and antitussic activities, prepared by Jucker and coworkers[8]. It is the aim of the present communication to describe the synthesis of *III* which is isomeric with dithiadene (*I*) and derived from another system of this type, *viz.* thieno[3,2-*c*]-2-benzothiepin (see also[9,10]). The work includes also an attempt to synthesize the derivatives of the fourth analogous system, *i.e.* thieno[3,4-*c*]-2-benzothiepin.

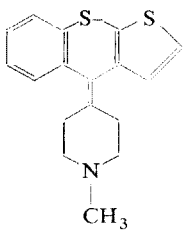
In the synthesis of *III*, similar methods as in the synthesis of *I* were used[2,4]. 3-Bromothiophene[11-13] was exposed to n-butyl lithium and then reacted with sulfur, yielding 3-thiophenthiol[14,15], the sodium salt of which reacted with phthalide[16] in boiling ethanol to yield 2-(3-thienylthiomethyl)benzoic acid (*VI*). This acid was

* Part LXXXIX in the series Neurotropic and Psychotropic Agents; Part LXXXVIII: This Journal *40*, 2887 (1975).

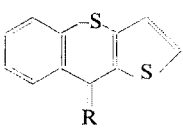
further cyclized by the action of a phosphate ester (for method see[17]) in boiling toluene, giving rise to thieno[3,2-*c*]-2-benzothiepin-10(5*H*)-one (*IV*). Reaction with 3-dimethylaminopropylmagnesium chloride[2] in tetrahydrofuran produced a fine yield of the tertiary alcohol *V*, which was dehydrated under acid catalysis (through the action of a small excess of hydrogen chloride in boiling acetone) to the olefinic amine *III*. The hydrochloride thus obtained appears homogeneous in paper chromatography after recrystallization, representing apparently one of the two possible geometric isomers of *III*; spectroscopic data which are available do not permit the definition of configuration of the present product.



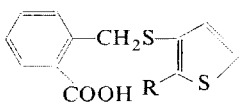
I



II

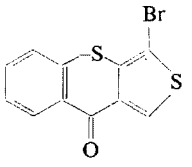


III, R = $CH(CH_2)_2N(CH_3)_2$
IV, R = O
V, R = $\begin{matrix} OH \\ (CH_2)_3N(CH_3)_2 \end{matrix}$



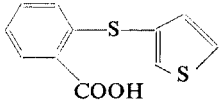
VI, R = H
VII, R = Br

Bromination of *VI* in acetic acid led to a monobromo derivative which, on the basis of NMR spectrum, is assumed to be the 2-bromo-3-thienyl derivative *VII*. Attempts at cyclization of acid *VII* with phosphorus pentoxide in boiling toluene resulted in a neutral product but its bromine content was substantially lower than corresponds to product *VIII*. Using thin-layer chromatography on silica gel it was found that the product is a mixture of principally two components, the predominating one being ketone *IV*. Repeated crystallization finally led to a sample of pure 3-bromothieno[3,4-*c*]-2-benzothiepin-10(5*H*)-one (*VIII*). The unexpected formation of ketone *IV* can be explained by a primary displacement of halogen from position 2 of thiophen. A similar type of reaction was observed during acylation of 2,5-dichloro, 2,5-dibromo and 2,5-diiodothiophene[18-20]. Attempts at removing the bromine atom from the molecule of ketone *VIII* by applying zinc in acetic acid did not result in the desired product.

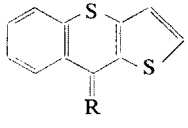


VIII

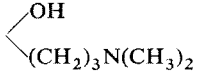
Finally we attempted to synthesize the thiophen analogue of prothixene[21] with the little known thieno[3,2-*b*]-1-benzothiopyran skeleton. The described procedure[22] was applied to the preparation of 2-(3-thienylthio)benzoic acid (*IX*) in a reaction of 3-bromothiophene[12] with thiosalicylic acid[23]. Acid *IX* was then cyclized in the presence of polyphosphoric acid at 140°C to ketone *X*. This procedure appears to be superior to the previously described cyclization using sulfuric acid[24] which gives a lower yield and a less pure product. Reaction of ketone *X* with 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran resulted without complications



IX



X, R = O

XI, R = 

in amino alcohol *XI* which was used in an attempt at dehydration by heating with dilute sulfuric acid. The usual processing resulted in an oily basic product which resisted all attempts at preparing crystalline maleate, hydrochloride or fumarate. The situation remained unchanged even after chromatography of the crude base which appears to be unstable in the presence of acids.

In view of the structural similarity with dithiadene (*I*) compound *III* was tested pharmacologically mainly from the point of view of antihistamine activity and effects which usually accompany it[4–6]. It was applied in the form of hydrochloride. The acute toxicity was determined in mice; with an *i.v.* administration the LD_{50} was 18·5 mg/kg, with a *p.o.* one it was 180 mg/kg. The compound displayed an intense antihistamine effect in tests using guinea-pigs *in vivo*. In the aerosol test, its ED_{50} is 0·209 mg/kg when applied *i.v.* 15 min prior to histamine (this is almost the same as with cyproheptadine with a ED_{50} = 0·23 mg/kg but by almost an order of magnitude lower than with dithiadene[4]). In the test of histamine detoxication, the compound *III* was administered subcutaneously (30 min prior to histamine); its ED_{50} = 0·054 mg/kg (approximately the same as with promethazine or cypro-

heptadine and 50% of the dithiadene activity[4]). Compound *III* has practically no anti-serotonin activity in the test of rat foot edema (in a dose of 5 mg/kg applied *i.p.* 30 min prior to serotonin). It has a slight antianaphylactic effect from a dose of 25 mg/kg *s.c.* up, but even a dose of 100 mg/kg does not block fully the anaphylactic reaction after dextran in rats. The depressant effect of *III* is very low. In the rotating-rod test in mice it does not cause incoordination at a dose of 5 mg/kg *i.v.* while 10 mg/kg has an almost 100% effect which is of short duration only. The compound prolongs the duration of thiopental sleep in mice with statistical significance starting with the dose corresponding to 5% intravenous LD_{50} (for mice). Compound *III* has no antireserpine effect in tests on mice or rats. It does not affect the apomorphine chewing or agitation in rats in the test of Janssen and coworkers[25]. Compound *III* showed a certain antitubercular activity in an *in vitro* test (Dr J. Turinová); the minimum inhibitory concentration for *Mycobacterium tuberculosis* H37Rv is 50 μg/ml.

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* at 0·5 Torr over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, IR spectra (in Nujol unless stated otherwise) in a Unicam SP 200G spectrophotometer and NMR spectra (in $CDCl_3$ unless stated otherwise) in a ZKR 60 (Zeiss, Jena) spectrometer. The homogeneity of the samples was checked by thin-layer chromatography on silica gel.

2-(3-Thienylthiomethyl)benzoic Acid (*VI*)

3-Thiophenthiol[14] (50 g, b.p. 54°C/10 Torr) was combined with a solution of C_2H_5ONa (200 ml ethanol, 11·7 g Na) and then 68 g phthalide[16] was added and the mixture was refluxed under stirring for 2 h. The solution obtained was diluted with 750 ml water, filtered with charcoal and the filtrate was acidified with hydrochloric acid. On standing overnight and on filtration, 90·5 g (71%) crude product was obtained which was recrystallized from aqueous ethanol and melted at 108—109°C. NMR spectrum: δ 11·75 (bs, 1 H, COOH), 8·20 (m, 1 H, 6-H in the benzoic acid residue), 4·48 (s, 2 H, CH_2S). For $C_{12}H_{10}O_2S_2$ (250·3) calculated: 57·57% C, 4·03% H, 25·62% S; found: 57·51% C, 4·13% H, 25·35% S.

Thieno[3,2-*c*]-2-benzothiepin-10(5*H*)-one (*IV*)

Ethanol (18·7 ml) was added dropwise to a mixture of 37·5 g P_2O_5 and 300 ml toluene under stirring and the mixture was refluxed for 20 min. After cooling, 37·5 g *VI* was added and the mixture was refluxed under stirring for further 5 h. After cooling, it was decomposed with 200 ml water, the toluene layer was separated, washed with 10% NaOH, dried with K_2CO_3, filtered with charcoal and evaporated at reduced pressure. A total of 34·3 g (98%) crude product was obtained which crystallized from 125 ml ethanol to 26·1 g (75%) pure compound, m.p. 116—118°C. UV spectrum: λ_{max} 254 nm (log ε 3·69), 304 nm (3·93), 373 nm (3·83). IR spectrum: 737, 743, 767, 819, 851 (Ar—H), 1280 (CO), 1600 (Ar), in CCl_4 1621 cm^{-1} (Ar_2CO). For $C_{12}H_8OS_2$ (232·3) calculated: 62·03% C, 3·47% H, 27·61% S; found: 61·76% C, 3·47% H, 27·42% S.

10-(3-Dimethylaminopropyl)-5,10-dihydrothieno[3,2-*c*]-2-benzothiepin-10-ol (*V*)

Reaction of 12·7 g 3-dimethylaminopropyl chloride with 2·5 g Mg in 35 ml tetrahydrofuran (a grain of iodine and 3 drops of 1,2-dibromoethane) yielded a solution of Grignard's reagent (1 h of refluxing)[2]. After cooling, a solution of 15·0 g *IV* in 70 ml benzene was added dropwise under stirring over a period of 30 min, the mixture was stirred for 1 h at room temperature and, after standing overnight, it was decomposed with a solution of 24 g NH_4Cl in 100 ml water. The organic phase was separated, dried with K_2CO_3, filtered with charcoal and evaporated at reduced pressure. The residue (20·0 g) represents almost the theoretical yield of crude product. Recrystallization from acetone yielded 13·0 g pure substance, melting at 135—137°C. UV spectrum: λ_{max} 239·5 nm (log ε 3·74), 284 nm (3·61). IR spectrum: 752, 768, 844 (Ar—H), 1010 (CHOH in the ring), 3100 cm^{-1} (OH). For $C_{17}H_{21}NOS_2$ (319·5) calculated: 63·90% C, 6·63% H, 4·38% N, 20·08% S; found: 64·54% C, 6·80% H, 4·53% N, 19·80% S.

10-(3-Dimethylaminopropylidene)-5,10-dihydrothieno[3,2-*c*]-2-benzothiepin (*III*)

A slight excess of an ether solution of hydrogen chloride was added to a warm solution of 13·0 g *V* in 130 ml acetone and the mixture was refluxed for 30 min. On cooling, 13·7 g (99%) hydrochloride precipitated which, after recrystallization from a mixture of ethanol and ether, melts at 227—229°C and is chromatographically homogeneous. UV spectrum: λ_{max} 214 nm (log ε 4·35), infl. 266 nm (3·79), 313 nm (3·88). IR spectrum: 719, 759, 781, 835, 866 (Ar—H), 2440 and 2560 cm^{-1} (NH^+). NMR spectrum (CD_3SOCD_3): δ 7·66 (d, 1 H, 2-H), 7·00—7·60 (m, 4 H, protons of benzene ring), 6·78 (d, 1 H, 3-H), 6.07 (t, 1 H, CH=C), 4·24 (m, 2 H, CH_2S), 3·00—3·50 (m, 4 H, CH_2CH_2N), 2·75 and 2·64 (2 s, 6 H, CH_3NCH_3). For $C_{17}H_{20}ClNS_2$ (337·9) calculated: 60·42% C, 5·97% H, 10·49% Cl, 4·14% N, 18·98% S; found: 60·28% C, 5·98% H, 10·38% Cl, 4·01% N, 19·17% S.

2-(2-Bromo-3-thienylthiomethyl)benzoic Acid (*VII*)

A solution of 18 g bromine in 140 ml acetic acid was added dropwise under stirring over a period of 2·5 h to a solution of 28·2 g *VI* in 280 ml acetic acid. After standing overnight, the solution was filtered with charcoal and the filtrate poured into 1 500 ml water. The precipitated acid was filtered, washed with water and dried; 34 g (92%), m.p. 121—123°C. Analytical sample melts at 129—132°C (ethanol). NMR spectrum (CD_3SOCD_3): δ 7·75—8·05 (m, 1 H, 6-H), 7·67 (d, J = 3·0 Hz, 1 H, 5-H of thiophene), 7·10—7·55 (m, 3 H, remaining protons of benzene), 7·01 (d, J = 3·0 Hz, 1 H, 4-H of thiophene), 4·51 (s, 2 H, CH_2S). For $C_{12}H_9BrO_2S_2$ (329·3) calculated: 43·77% C, 2·76% H, 24·27% Br, 19·48% S; found: 43·84% C, 2·78% H, 24·42% Br, 19·56% S.

3-Bromothieno[3,4-*c*]-2-benzothiepin-10(5*H*)-one (*VIII*)

VII (22·8 g) was added to a mixture of 31 g P_2O_5 in 230 ml toluene and the mixture was refluxed for 4·5 h under stirring. The toluene solution was separated by decanting, the remainder was washed with toluene, the combined toluene solutions were washed with 10% NaOH, dried with K_2CO_3 and evaporated. The yield was 14·7 g residue which, after a single recrystallization from a mixture of benzene and light petroleum, had a m.p. of 100—102°C and a content of bromine of 8·33%. According to thin-layer chromatography on silica gel the product contains mainly ketone *IV* and a minor amount of another compound. A similar result was obtained in paper chromatography where, depending on the system used, the new compound appeared either more or less polar than ketone *IV*. Chromatography on a column of alumina (activity II) did not separate the two components; moreover, most of the substance remained adsorbed to the column even after

elution with a mixture of benzene and methanol. After recrystallization from benzene, the first fraction to crystallize is markedly enriched with the desired *VIII*. Repeated crystallization yielded a sample of homogeneous compound, melting at 165–167°C. UV spectrum: λ_{max} 269·5 nm (log ε 4·07). IR spectrum (KBr): 730, 763, 780, 854, 912 (Ar—H), 1 598 (Ar), 1 636 cm^{-1} (Ar_2CO). NMR spectrum: δ 8·49 (s, 1 H, 1-H), 7·10–7·85 (m, 4 H, protons of benzene), 4·01 (s, 2 H, SCH_2). For $C_{12}H_7BrOS_2$ (311·2) calculated: 46·30% C, 2·27% H, 25·68% Br, 20·61% S; found: 46·71% C, 2·22% H, 25·92% Br, 20·43% S.

Thieno[3,2-*b*]-1-benzothiopyran-9-one (*X*)

Heating of a mixture of 45 ml 85% H_3PO_4 and 67·5 g P_2O_5 to 120°C led to polyphosphoric acid. This was combined with 15·0 g 2-(3-thienylthio)benzoic acid *IX* (m.p. 194–195°C) (ref.[22]) and the mixture was heated under stirring for 3 h at 140°C. After cooling, it was decomposed with 250 ml water and the product was isolated by extraction with chloroform. The extract was washed with 10% NaOH, dried, filtered and evaporated. The residue (13 g) yielded on recrystallization from 50 ml benzene a total of 10·5 g (76%) pure compound, melting at 161–162°C. Ref.[24] reports a m.p. of 161·5°C for a product obtained by cyclization with the aid of sulfuric acid.

9-(3-Dimethylaminopropyl)thieno[3,2-*b*]-1-benzothiopyran-9-ol (*XI*)

Like in the case of *V*, a Grignard reagent was prepared in a reaction of 10·8 g 3-dimethylaminopropyl chloride and 2·2 g Mg in 30 ml tetrahydrofuran. After cooling, this was combined with 13·0 g ketone *X* in 80 ml tetrahydrofuran and the mixture was stirred for 1·5 h at room temperature. After cooling, it was decomposed with a solution of 16 g NH_4Cl in 80 ml water and extracted with benzene. The extract was dried with K_2CO_3, filtered with charcoal and evaporated. A total of 18·1 g residue was obtained which, after recrystallization from a mixture of benzene and light petroleum, yielded 11·2 g (62%) pure compound, melting at 116–118°C. UV spectrum: λ_{max} 233·5 nm (log ε 3·96), 257·5 nm (3·82), 282 nm (3·74). IR spectrum: 710, 752, 766 (Ar—H), 1 100 (R_3C—OH), 1 567 (Ar), 2 700 and 2 780 cm^{-1} (N···HO). For $C_{16}H_{19}NOS_2$ (305·5) calculated: 62·91% C, 6·27% H, 4·59% N, 21·00% S; found: 63·19% C, 6·35% H, 4·72% N, 20·73% S.

The authors are indebted to Drs E. Svátek and J. Holubek for recording and interpretation of some of the spectra and to Mr M. Čech, Mr K. Havel, Mrs J. Komancová and Mrs V. Šmídová for carrying out the analyses.

REFERENCES

1. Protiva M., Rajšner M. (Spofa): Czech. 115 241 (Appl. 31. VIII. 1963); Brit. 1 037 019; Fr. P. 1 413 978; Ger. 1 239 704; U.S. 3 519 648; Neth. Appl. 64/10 097; Chem. Abstr. *63*, 2977 (1965); *64*, 5098, 17 608 (1966).
2. Protiva M., Rajšner M., Adlerová E., Seidlová V., Vejdělek Z. J.: This Journal *29*, 2161 (1964).
3. Rajšner M., Protiva M., Svátek E., Metyš J.: Czech. 146 688 (Appl. 19. IX. 1969); Chem. Abstr. *79*, 53 284 (1973).
4. Rajšner M., Svátek E., Metyš J., Protiva M.: This Journal *39*, 1366 (1974).
5. Metyš J., Metyšová J.: Acta Biol. Med. Ger. *15*, 871 (1965); Chem. Abstr. *64*, 16 478 (1966).
6. Metyš J., Metyšová J.: Česk. Farm. *20*, 251 (1971).
7. Melich H.: Čas. Lék. Čes. *112*, 899 (1973).

8. Jucker E., Ebnöther A., Rissi E. (Sandoz Ltd).: Neth. Appl. 64/14 153 (Swiss Appl. 10. XII. 1963); Czech 122 959; Fr. 1 430 923; Fr. 4 178 M; Ger. (GDR) 44 839; Chem. Abstr. *63*, 18 090 (1965).
9. Rajšner M., Protiva M. Metyš J.: Czech. 146 689 (Appl. 19. IX. 1969); Chem. Abstr. *79*, 53 283 (1973).
10. Rajšner M., Svátek E., Protiva M.: 3rd Symp. Chem. Heterocycl. Compounds, Brno, Sept. 24, 1969; Abstr. of papers, p. 111.
11. Gronowitz S.: Acta Chem. Scand. *13*, 1045 (1959).
12. Gronowitz S., Raznikiewicz T.: Org. Syn., Coll. Vol. *5*, 149 (1973).
13. Jakobsen G. I., Lavesson S. O.: *Sintezy Geterocikl. Soedin.* (A. L. Mndžojan, Ed.) *7*, 20 (1966).
14. Brandsma L., Bos H. J. T.: Rec. Trav. Chim. *88*, 732 (1969).
15. Hoffman R. A., Gronowitz S.: Arkiv Kemi *16*, 515 (1960); Chem. Abstr. *55*, 26 682 (1961).
16. Gardner J. H., Naylor C. A. jr: Org. Syn., Coll. Vol. *2*, 526 (1943).
17. Mukaiyama T., Hata T.: Bull. Chem. Soc. Jap. *34*, 99 (1961); Chem. Abstr. *55*, 18 548 (1961).
18. Hartough H. D., Kosak A. I.: J. Amer. Chem. Soc. *69*, 3093 (1947).
19. Gattermann L., Römer M.: Ber. *19*, 688 (1886).
20. Steinkopf W., Jacob H.: Justus Liebigs Ann. Chem. *515*, 282 (1935).
21. Jilek J. O., Rajšner M., Pomykáček J., Protiva M.: Česk. Farm. *14*, 294 (1965).
22. Schindler W., Zuest A. (J. R. Geigy A. G.): Neth. Appl. 68/6701 (Swiss Appl. 19. V. 1967); S. African 68/3189; Austrian 276 406; Chem. Abstr. *71*, 39 008 (1969).
23. Allen C. F. H., MacKay D. D.: Org. Syn., Coll. Vol. *2*, 580 (1943).
24. Steinkopf W., Schmitt H. F.: Justus Liebigs Ann. Chem. *533*, 264 (1938); Chem. Zentr. *1938*, I, 3044.
25. Janssen P. A. J., Niemegeers C. J. E., Schellekens K. H. L., Lenaerts F. M.: Arzneim.-Forsch. *17*, 841 (1967).

Translated by A. Kotyk.