Tetrahedron Vol. 44, No. 23, pp. 7181 to 7184, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00

CONVERSION OF 6α-PHENYL-7,7-DICHLORO-2,3-(2',3'-DIMETHOXYBENZO)-1-THIAOCTEM IN THE PRESENCE OF BASE[1]

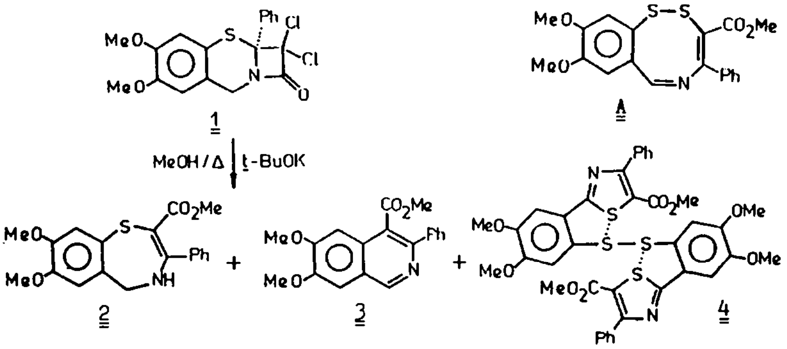
LAJOS FODOR[≠], JÁNOS SZABÓ[*o], GÁBOR BERNÁTH[o], PÁL SOHÁR[+], GYULA ARGAY[x], ALAJOS KÁLMÁN[x] and JÓZSEF TAMÁS[x]

[≠]Central Laboratory, County Hospital, H-5701 Gyula, POB 46;
[o]Institute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University, H-6701 Szeged, POB 121; [+]Spectroscopic Department, EGIS Pharmaceuticals, H-1475 Budapest, POB 100;
[x]Central Research Institute of Chemistry, Hungarian Academy of Sciences, H-1525 Budapest, POB 17, Hungary

(*Received in UK* 22 *September* 1988)

Abstract - Basic treatment in methanol of linearly condensed 1,3-benzothiazinedichloro-β-lactam 1 led to a 1,4-benzothiazepine 2, a tetrasubstituted isoquinoline 3, and a thiazole disulfide derivative 4 via a new ring transformation. The structure of the thiazole disulfide 4 was determined by X-ray diffraction.

It was reported earlier[2,3] that treatment of 6α-aryl-7α-chloro-2,3-(2',3'-dimethoxybenzo)-1-thiaoctems[4] in methanol in the presence of bases led in good yield to 3-aryl-2-carbomethoxy-7,8-dimethoxy-4,5-dihydrobenzothiazepines. As a continuation of these studies, in the present paper we report the identification of three products (2[2], 3[1], 4) isolated from the reaction of 6α-phenyl-7,7-dichloro-2,3-(2',3'-dimethoxybenzo)-1-thiaoctem (1) in methanol in the presence of t-BuOK.



Two of the isolated products (2 and 3) proved to be identical with known compounds.[1,2] The high sulfur content and the EI ms data the unknown third product suggested a disulfide structure with a molecular formula $C_{19}H_{17}NO_4S_2$. Structure A was first considered.

The ^1H nmr spectrum proved the existence of a conjugated phenyl group (downfield shift of the *ortho* proton signal, at about 7.85 ppm; multiplet of the *meta* and *para* hydrogens at about 7.45 ppm), and a third methoxy group besides the two methoxy groups on the substituted benzene ring (3 singlets, at 3.80, 3.81 and 3.82 ppm, each with 3H intensity). The intense ester bands appeared split in the ir spectrum (νC=O: 1722, 1693, ν_{as}C-O: 1261, 1213 and ν_sC-O: 1034, 1020 cm^{-1}. However, the azomethine signal was not identifiable in the ^1H nmr spectrum and DEPT measurements showed that, apart from the three methyl and seven aromatic CH carbons (five of the phenyl ring atoms and two of the tetrasubstituted benzene ring atoms), only quaternary carbons are present in the molecule (altogether nine, as expected). In order to elucidate the structure, X-ray diffraction measurements were carried out.

X-ray structure determination. The crystal structure of this unknown compound (which proved to be **4**) is depicted in Fig. 1. The molecule is built up from two identical monomer units, linked by disulfide bridge which is almost perpendicular to the overlapping sheets of the monomers. The length of the -S-S- bridge is 2.071(1) Å. In each unit, one of the oxygen atoms of the methoxycarbonyl moiety forms an intramolecular S...O close contact, which is somewhat stronger in the monomer atoms denoted by primed numbers. Surprisingly, in this case the ether oxygen is the donor of the S...O interaction, while the weaker contact is formed by the oxo group. Their parameters: S(1')...O(8') = 2.798(3) Å, C(5')-S(1')...O(8') = 144.9(2)° vs S(1)...O(7) = 2.994(3) Å, C(5)-S(1)...O(7) = 141.3(2)°. However, both constants are shorter than the sum of the van der Waals radii of S and O atoms (3.25 Å). Each S(1) atom in the planar thiazole ring also participates in another non-bonding interaction with S in the disulfide bridge. Bot S...S close constants are considerably shorter than the sum of their van der Waals radii (3.7 Å): S(1)...S(22) = 3.117(2) and 3.110(1) Å, accompanied by quasi-linear bridgehead arrangements: C(2)-S(1)...S(22) = 165.4(2) and 160.6(2)°, respectively.

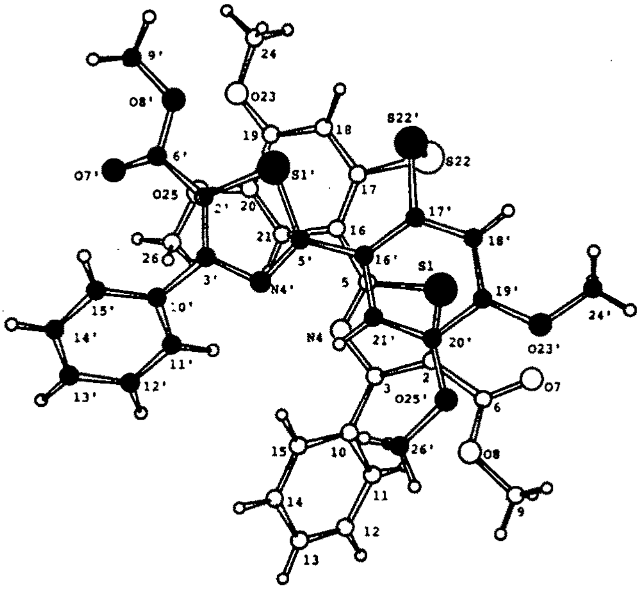


Fig. 1. A perspective view of the dimeric structure of **4**, almost perpendicular to the disulfide bridge. The atoms in the upper level of the sandwich are denoted by primed numbers. Numbers denote carbon atoms, unless indicated otherwise. The hydrogen atoms are shown, but not numbered.

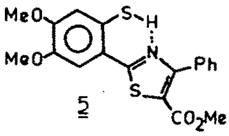
In the monomer units the corresponding bond lengths and angles agree well within experimental error. The best planes computed for the S-phenyl and thiazole rings make a dihedral angle of 8.6° and are separated by an average distance of 2.88 Å. Relative to this empty sandwich-like arrangement, the phenyl substituent of each thiazole ring is tilted by an angle of 51.6 and 47.2°, respectively. As noted above, the planar methoxycarbonyl moiety is oriented differently to the thiazole ring. The difference in the rotation about the C(2)-C(6) bond is 178.5°.

Table 1. Final fractional coordinates for non-hydrogen atoms, with e.s.d.'s in parentheses

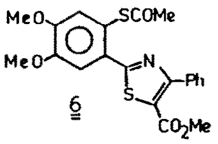
Atom	x/a	y/b	z/c
S(1)	0.3616(1)	0.2785(1)	0.0783(1)
C(2)	0.3478(2)	0.1431(2)	0.1264(1)
C(3)	0.2204(2)	0.1476(1)	0.1711(1)
N(4)	0.1361(1)	0.2559(1)	0.1671(1)
C(5)	0.1964(2)	0.3341(1)	0.1207(1)
C(6)	0.4684(2)	0.0456(2)	0.1200(2)
O(7)	0.5707(1)	0.0554(1)	0.0654(1)
O(8)	0.4490(1)	-0.0505(1)	0.1803(1)
C(9)	0.5511(3)	-0.1558(2)	0.1696(2)
C(10)	0.1658(2)	0.0511(1)	0.2240(2)
C(11)	0.1985(2)	-0.0420(2)	0.1803(2)
C(12)	0.1469(3)	-0.1311(2)	0.2352(2)
C(13)	0.0659(3)	-0.1297(2)	0.3309(3)
C(14)	0.0298(3)	-0.0366(2)	0.3721(2)
C(15)	0.0795(2)	0.0527(2)	0.3190(2)
C(16)	0.1212(2)	0.4570(1)	0.1065(1)
C(17)	0.1715(2)	0.5490(1)	0.0726(1)
C(18)	0.0874(2)	0.6614(1)	0.0614(1)
C(19)	-0.0440(2)	0.6839(1)	0.0843(1)
C(20)	-0.0956(2)	0.5925(1)	0.1196(1)
C(21)	-0.0134(2)	0.4815(1)	0.1293(1)
S(22)	0.3378(1)	0.5337(1)	0.0493(1)
O(23)	-0.1319(1)	0.7900(1)	0.0775(1)
C(24)	-0.0850(2)	0.8847(2)	0.0492(2)
O(25)	-0.2264(1)	0.6222(1)	0.1401(1)
C(26)	-0.2865(2)	0.5347(2)	0.1845(2)
S(1')	0.0741(1)	0.5695(1)	0.3295(1)
C(2')	-0.0793(1)	0.5578(1)	0.3795(1)
C(3')	-0.0747(1)	0.4447(1)	0.4080(1)
N(4')	0.0478(1)	0.3696(1)	0.3903(1)
C(5')	0.1361(1)	0.4236(1)	0.3476(1)
C(6')	-0.1916(2)	0.6618(1)	0.3734(1)
O(7')	-0.3006(1)	0.6660(1)	0.3876(1)
O(8')	-0.1532(1)	0.7542(1)	0.3450(1)
C(9')	-0.2525(2)	0.8636(2)	0.3342(2)
C(10')	-0.1838(2)	0.3967(1)	0.4510(1)
C(11')	-0.1782(2)	0.3069(2)	0.4139(2)
C(12')	-0.2795(2)	0.2611(2)	0.4511(2)
C(13')	-0.3858(2)	0.3026(2)	0.5259(3)
C(14')	-0.3910(2)	0.3897(2)	0.5629(2)
C(15')	-0.2915(2)	0.4371(2)	0.5258(2)
C(16')	0.2755(1)	0.3582(1)	0.3238(1)
C(17')	0.3757(1)	0.4026(1)	0.2607(1)
C(18')	0.5040(2)	0.3308(1)	0.2450(1)
C(19')	0.5338(2)	0.2156(1)	0.2879(1)
C(20')	0.4330(2)	0.1691(1)	0.3488(1)
C(21')	0.3073(2)	0.2398(1)	0.3668(1)
S(22')	0.3517(1)	0.5461(1)	0.1884(1)
O(23')	0.6549(1)	0.1400(1)	0.2762(1)
C(24')	0.7563(2)	0.1784(2)	0.2010(3)
O(25')	0.4707(1)	0.0540(1)	0.3845(1)
C(26')	0.3741(2)	0.0028(2)	0.4299(2)

Ir, nmr and ms evidence. Structure 4 explained the splitting of the ester ir bands, which is due to mechanical coupling of the corresponding stretching of the two identical ester groups. In accordance with structure 4, one of the two singlets of H-3 and H-6 (at 7.08 and 7.68 ppm) is downfield shifted due to anisotropy of the sp^2 nitrogen[5] in the thiazole ring. This fact suggests a rigid structure with coplanar and close H-3 and nitrogen atoms. All ^{13}C nmr lines of molecule 4 are observable in the expected intervals, as follows (ppm): C-1: 122.7, C-2,5': 126.0 and 128.8, C-3: 117.9, C-4,5: 150.1 and 150.6, C-6: 112.6, C-2': 161.9, C-4': 158.9, OCH_3: 55.95 and 55.99 (pos. 4 and 5), 52.0 (ester), C-1": 134.2, C-2",6": 130.0, C-3",5": 127.6, C-4": 128.9, C=O: 166.1. Due to the two-fold symmetry of the molecule, the analogous carbon pairs in the two halves of the disulfide are chemically equivalent and give common signals, of course.

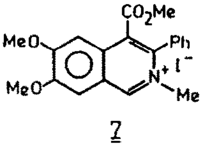
The fast atom bombardment (FAB) mass spectrum of 4 was measured, too. The FAB spectrum exhibits abundant peaks at m/z 773 $(M+H^+)$, 795 $([M+Na]^+)$ and 386 $(M/2^+)$, in accordance with the symmetrical "dimer" structure. The main fragments appearing in the mass spectrum can be deduced from the structural formula expected for 4. For their origin, see the Experimental.



5



6



7

Preparative evidence. The disulfide structure of compound 4 was proved by its Zn/H^+ reduction, which yielded the corresponding thiophenol derivative 5. Compound 5 and its S-acetyl derivative 6 were identified via their ir and nmr spectra. As a characteristic derivative, the methoiodide 7 was prepared from 3 with methyl iodide.

EXPERIMENTAL

Ir spectra were measured in KBr discs with an Aspect 2000 computer-controlled Bruker IFS-113v vacuum optic FT instrument. ^1H and ^{13}C nmr spectra were recorded on Bruker WM-250 and WP-80 SY FT spectrometers controlled by an Aspect 2000 computer at 250 and 20 MHz in $CDCl_3$ solution at room temperature, using TMS as internal standard and the ^2H signal of the solvent as the lock. The FAB and EI mass spectra were recorded with an AEI-MS 902 mass spectrometer. Melting points are uncorrected.

Preparation of 2-carbomethoxy-7,8-dimethoxy-3-phenyl-4,5-dihydro-1,4-benzothiazepine (2), 4-carbomethoxy-6,7-dimethoxy-3-phenylisoquinoline (3) and 4,4',5,5'-tetramethoxy-[2,2'-di-(5"-carbomethoxy-4"-phenyl-2"-thiazolyl)],-diphenyl disulfide (4)

Compound 1 (1.98 g, 5 mmol) was dissolved in methanol (20 ml), and t-BuOK (1.12 g, 10 mmol) was added. The solution was stirred under reflux. After 3 h the reaction mixture was diluted with chloroform (150 ml) and extracted with water. The organic layer was dried (Na_2SO_4) and evaporated to dryness, the residue was dissolved in the minimum amount of chloroform, and the solution was chromatographed on a silica column. The column was developed with a 1% solution of MeOH in $CHCl_3$. The first compound to be eluted was 4 (0.46 g, 24%), mp 188-189 °C, orange crystals from benzene. (Found; C, 59.25; H, 4.29; N, 3.69; S, 16.11. $C_{38}H_{32}N_2O_8S_4$ requires: C, 59.05; H, 4.17; N, 3.63; S, 16.59%.) FAB-ms of 4 (Ar, 6 kV, matrix: $3-NO_2-C_6H_4CH_2-OH+NaCl$) m/z(%): 795(16), $[M+Na]^+$; 773(18), $[M+H]^+$; 386(100) $[M/2]^+$.

Crystal structure and crystal data on compound 4

$(C_{19}H_{16}NO_4S_2)$, M = 772.94, triclinic, a = 11.490(1), b = 12.965(1), c = 14.040(1) Å, α = 71.32(1), β = 70.72(1), γ = 67.78(1)°, U = 1781.3(2) $Å^3$, Z = 2, D_c = 1.444 $g.cm^{-3}$, F(000) = 804, μ = 2.87 mm^{-1} for Cu-K_α radiation (λ = 1.54184 Å). Space group $P\bar{1}$.

The intensities of 7345 unique reflections were collected on an Enraf-Nonius CAD-4 diffractometer, in the range $1.5<\theta<50.0°$, by an $\omega-2\theta$ scan, using graphite monochromated Cu-K_α radiation. Cell constants were determined by least squares refinement of 25 reflections. Three standard reflections were monitored every hour and showed no significant decrease during the exposure. After data reduction, 5947 reflections with $I>3.0\sigma(I)$ were taken as observed. The phase problems were solved by direct methods, using the MULTAN 82 program.[6] In the course of the isotropic least squares refinement of the positional parameters of non-H atoms (R = 0.15), an empirical absorption correction was calculated with the DIFABS program,[7] which reduced R to 0.103. The minimum and maximum absorption corrections were 0.737 and 1.991. The fractional coordinates of H atoms were generated from assumed geometries and were only included in the structure factor calculations with isotropic temperature factors ($B_{iH} = B_{iC} + 1$ Å^2). Final R = 0.046, wR = 0.060, S = 5.22. The highest peak in the final difference map was 0.18 e.Å^{-3} ($\Delta/\sigma = 0.008$). Scattering factors were taken from standard tables.[8] All calculations were performed on a PDP-11/34 minicomputer with use of the SDP system of Enraf-Nonius with local modifications.

The second compound eluted from the column was **2** (0.28 g, 16%), mp 170–171 °C, yellow crystals from methanol. It was identical in every respect with an authentic sample.[2]

The third compound eluted from the column was **3** (0.29 g, 21%), mp 185–186 °C, colourless crystals from methanol. It was identical in every respect with an authentic sample.[1]

2-(5'-Carbomethoxy-4'-phenyl-2'-thiazolyl)-4,5-dimethoxy-thiophenol (5)

Compound **4** (0.39 g, 0.5 mmol) was dissolved in methylene chloride (50 ml), the solution was stirred, and 1 g of zinc dust and 20 ml of 10% hydrochloric acid were added. After 5 minutes, the reaction mixture was filtered and the organic layer was dried (Na_2SO_4) and evaporated. The residue was crystallized from methanol to give orange-yellow crystals (0.35 g, 90%), mp 151–153 °C. (Found: C, 58.57; H, 4.66; N, 3.45; S, 16.80 $C_{19}H_{17}NO_4S$ requires: C, 58.89; H, 4.42; N, 3.62; S, 16.55%.) Ir (cm^{-1}): νSH: 2360–2380, νC=O: 1724, νC=N: 1684, νC–O=: 1261. ^{1}H nmr (ppm): OCH_3: 3.84, 3.91, 3.92, 3xs (3x3H), SH: 6.47 broadened s (1H), H-6: 6.87 s (1H), H-3: 7.36 s (1H), $ArH^{m,p}$(Ph): 7.4–7.5 m (3H), ArH^{o}(Ph): 7.88 dd (2H). ^{13}C nmr (ppm): OCH_3 (ester): 51.9, OCH_3(4,5): 55.9, 56.1, C-3,6: 113.4, 114.9, C-1,5': 122.7, 125.1, C^{o}(Ph): 127.6, C-2: 128.7, C^{p}(Ph): 129.0, C^{m}(Ph): 129.8, C^{i}(Ph): 133.9, C-4: 147.5, C-5: 150.9, C-4': 159.2, C-2': 161.7, C=O: 168.7.

S-Acetyl-2-(5'-carbomethoxy-4'-phenyl-2'-thiazolyl)-4,5-dimethoxy-thiophenol (6)

Compound **5** (0.39 g, 1 mmol) was dissolved in benzene (20 ml) and, with continuous stirring, TEA (0.15 ml) and then acetyl chloride (0.07 ml, 1 mmol) were added. After 30 minutes, the reaction mixture was extracted with water, and the organic layer was dried (Na_2SO_4) and evaporated. The residue was crystallized from methanol to give pale-yellow needles (0.32 g, 74%), mp 158–159 °C. (Found: C, 58.94; H, 4.59; N, 3.53; S, 15.16. $C_{21}H_{19}NO_5S_2$ requires: C, 58.72; H, 4.46; N, 3.26; S, 14.93%.) Ir (cm^{-1}): νC=O: 1730 (ester), 1709 (thioester), νC–O: 1244. ^{1}H nmr (ppm): CH_3(Ac): 2.48 s (3H), OCH_3(ester): 3.83 s (3H), OCH_3(4,5): 3.84, 3.98 2xs (2x3H), H-6: 6.99 s (1H), ArH (Ph): ~7.5 m (3H), ArH^{o}(Ph): 7.88 dd (2H), H-3: 7.94 s (1H). ^{13}C nmr (ppm): CH_3(Ac): 30.1, OCH_3(ester): 51.9, OCH_3(4,5): 56.1 (two overlapping lines), C-3: 113.4, C-1: 118.4, C-6: 119.9, C-5': 123.0, C^{o}(Ph): 127.6, C^{p}(Ph): 128.9, C^{m}(Ph): 129.8, C-2: 130.1, C^{i}(Ph): 134.2, C-4,5: 150.6, 150.7, C-4': 159.1, C-2': 162.0, C=O (ester): 166.2, SC=O: 193.1.

4-Carbomethoxy-6,7-dimethoxy-2-methyl-3-phenylisoquinolinium iodide (7)

Compound **3** (0.32 g, 1 mmol) was dissolved in CH_3CN (5 ml). CH_3I (0.5 ml) was added and the mixture was refluxed for 1 h. On cooling, crystals of **7** separated out (0.38 g, 87%). Recrystallization from CH_3CN gave a product with mp 202–203 °C (dec.). (Found: C, 54.43; H, 4.73; N, 2.71. $C_{20}H_{20}INO_4$ requires: C, 54.68; H, 4.89; N, 2.45%.) Ir (cm^{-1}): νC=O: 1734, νC–O: 1254, 1165. ^{1}H nmr (ppm): OCH_3(ester): 3.58 s (3H), OCH_3(6,7): 4.12, 4.13 2xs (2x3H), N^+CH_3: 4.28 s (3H), H-8: 7.22 s (1H), ArH^{o}(Ph): ≅7.5 dd (2H), $ArH^{m,p}$(Ph): ~7.62 m (3H), H-5: 8.31 s (1H), H-1: 10.96 s (1H). ^{13}C nmr (ppm): NCH_3: 47.1, OCH_3(ester): 52.7, OCH_3(6,7): 56.8, 57.0, C-5: 102.3, C-8: 108.3, C-4,4a,8a and $C^{i,p}$(Ph): 123.8, 127.9, 129.8, 130.6, 132.4, $C^{o,m}$(Ph): 128.8, 129.3, C-3: 142.3, C-6,7: 147.9, 152.7, C-1: 159.0, C=O: 164.4.

REFERENCES

1. Part 4 of the series: Ring transformations of 1,3-benzothiazine derivatives. Part 3: L. Fodor, D. M. MacLean, Can. J. Chem., 65, 18 (1987). This paper is also regarded as Part 143 of the series "Saturated Heterocycles". Part 142: A. Pricken, F. Fülöp, P. Pflegel, G. Bernáth, Pharmazie, 42, 739 (1987).
2. L. Fodor, J. Szabó, G. Bernáth, L. Párkányi, P. Sohár, Tetrahedron Lett., 22, 5077 (1981).
3. L. Fodor, J. Szabó, E. Szűcs, G. Bernáth, P. Sohár, J. Tamás, Tetrahedron, 40, 4089 (1984).
4. The nomenclature follows that reported by A. K. Bose, J. Heterocyclic Chem., 13, 93 (1976).
5. P. Sohár: Nuclear Magnetic Resonance Spectroscopy, CRC Press, Boca Raton, Florida, 1983. Vol. 2, p. 89.
6. P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J.-P. Declercq, M. M. Woolfson, MULTAN 82. A System of Computer Programs for Automatic Solution of Crystal Structures from X-ray Diffraction Data. Univ.s of York, England and Louvain, Belgium, 1982 (adapted for use on a PDP-11/34 minicomputer).
7. N. Walker, D. Stuart, Acta Cryst., A39, 158 (1983).
8. D. T. Cromer, J. T. Waber, International Tables for X-ray Crystallography, Vol. 4, Table 2.2B, Kynoch Press, Birmingham, 1974.