the intraperitoneal injection of Triton WR-1339 in a dose of 224 mg/kg, and endogenous hypolipidemia by the method generally adopted.

Pulicarin was used in a dose of 50 mg/kg. The preparation was injected into the intact animals in the course of 10 days. Under the conditions of hypercholesteremia, this was carried out twice: simultaneously with Triton WR-1339 and the generation of endogenous hypolipidemia and 2 h before the decapitation of the animals. The level of cholesterol in the blood serum was determined by the method of Abel et al. [11]. The results obtained were treated by the methods generally adopted.

LITERATURE CITED

1. K. E. Schulte, G. Rucker, and F. Muller, Arch. Pharm., 301, 115 (1968).
2. J. O. Pares, S. O. Oksuz, A. Ulubelen, and T. J. Mabry, Phytochemistry, 20, 2057 (1981).
3. I. El-Negoumy Sabry, M. A. Mansour Ragaa, and A. M. Salen Nabiel, Phytochemistry, 21, 953 (1982).
4. M. A. Yahya, A. M. Sayed, J. S. Mosso, J. F. Kozlowski, M. D. Antoun, M. Ferin, W. M. Baird, and J. M. Cassady, J. Nat. Prod., 51, 621 (1988).
5. A. S. Feliciano, M. Medarde, M. Gordaliza, E. Olmo, and J. M. Corral, Phytochemistry, 28, 2717 (1989).
6. Vascular Plants of the USSR [in Russian], Nauka, Leningrad (1981), p. 91.
7. M. R. Nurmukhamodova, Sh. Z. Kasymov, N. D. Abdullaev, G. P. Sidyakin, and M. R. Yagudaev, Khim. Prir. Soedin., 201 (1985).
8. J. H. Bowie and D. W. Cameron, Aust. J. Chem., 19, 1627 (1966).
9. F. J. Mabry, K. R. Markham, and M. B. Thomas, The Systematic Identification of Flavonoids, Springer, New York (1970).
10. M. T. Siddiqui and M. Siddiqui, Lipids, 11, 243 (1976).
11. L. L. Abel, B. B. Levy, and B. B. Bodie, J. Biol. Chem., 195, 357 (1952).

X-RAY STRUCTURAL INVESTIGATION OF GOSSYPOL AND ITS DERIVATIVES

XXII. STRUCTURE OF THE H-CLATHRATE OF GOSSYPOL WITH DIMETHYL SULFOXIDE

B. T. Ibragimov, S. A. Talipov, B. N. Dadabaev, and A. A. Abduvakhabov

UDC 547.737

In crystals obtained from solutions in DMSO, gossypol molecules are again present in the aldehyde tautomeric form. These crystals are H-clathrates with the channel type of structure which has much in common with the structure of the complexes of gossypol with methanol and with formic acid.

It is known that the gossypol molecule can theoretically exist in aldehyde, lactol, and quinoid tautomeric forms [1]. In all the clathrates (H-clathrates) and polymorphs of gossypol interpreted previously there is a single form – the aldehyde form [2-6]. In [7] on the basis of NMR studies it was reported that in samples obtained by recrystallization from benzene gossypol is present in the lactol form. However, the results of our x-ray structural investigations have refuted this statement [8]. In another paper [9], again on the basis of NMR investigations, it was established that in solutions of gossypol in DMSO there is a dynamic equilibrium between the lactol and aldehyde forms. The isolation of gossypol which, according to NMR results, existed in the form of the pure lactol tautomer has been reported relatively recently [10].

Institute of Bioorganic Chemistry, Uzbekistan Academy of Sciences, Tashkent.

Translated from Khimiya Prirodnykh Soedinenii, Nos. 3,4, pp. 330-334, May-August, 1992. Original article submitted July 9, 1991; revision submitted November 21, 1991.

0009-3130/92/0304-0288$12.50

© 1992 Plenum Publishing Corporation

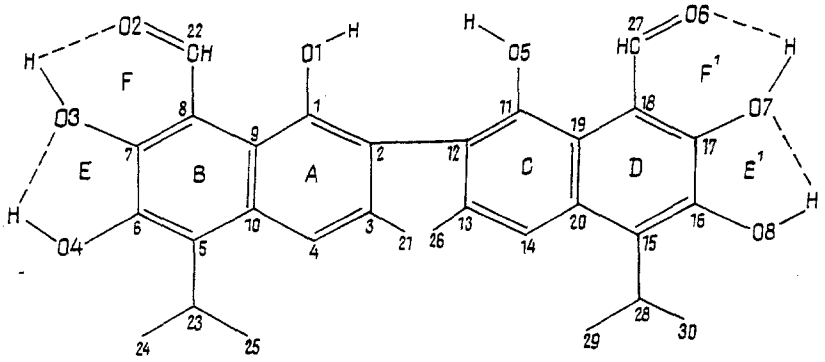

Fig. 1

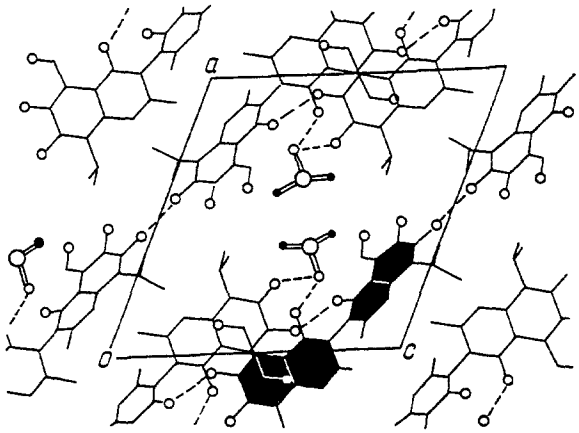

Fig. 2

Fig. 1. Gossypol molecule.

Fig. 2. Crystal structure of the H-clathrate of gossypol with DMSO.

TABLE 1. Geometry of the Intermolecular H-Bonds

Bond	Distance, Å			O–H...O angle
	O...O	O–H	H...O	
O5–H...O3^{i}	3,032	0,67	2,49	148
O8–H...O8$^{'i}$	2,663	0,50	2,54	169
O1–H...O(DMSO)	2,719	0,69	2,07	163
O4-H...O(DMSO)^{i}	2,955	0,51	2,87	165

Symmetry codes: (i) −x, −y, 1 − z; (ii) 1 − x, 1 − y, 2 − z.

In order to determine the tautomeric form of gossypol in crystals obtained by recrystallization from DMSO and to determine the type and structure of the next gossypol clathrate we have made a complete x-ray structural investigation.

With gossypol, DMSO forms a H-clathrate with the channel type of structure and the composition gossypol:DMSO = 1:1. In it, the gossypol molecules are again present in the aldehyde tautomeric form (Fig. 1). The dihedral angle between the naphthyl nuclei of the gossypol molecule amounts to 73.1°. The conformation of the molecule (the orientation of the isopropyl groups, the coplanarity of the atoms of the naphthyl nuclei, and the intramolecular H-bonds) do not differ from its conformation in the H-clathrates with methanol and with formic acid [11].

TABLE 2. Crystallographic Parameters of the Isostructural H-Clathrates of the "DMSO Group"

Parameters	DMSO	MF	MA
a, Å	15,132 (2)	14,174 (2)	14,945 (9)
b, Å	7,207 (1)	7,080 (1)	6,976 (4)
c, Å	14,726 (2)	14,651 (2)	14,727 (6)
α, deg	90,90 (1)	93,08 (1)	91,70 (4)
β, deg	66,94 (1)	85,91 (1)	87,07 (4)
γ, deg	96,15 (1)	97,70 (1)	108,78 (4)
V, Å^3	1469	1450	1452
ρ, g/cm^3	1,35	1,32	1,35

TABLE 3. Coordinates ($\times 10^{-4}$) and Equivalent Isotropic Thermal Parameters ($\times 10^{-3}$) of the Atoms in the H-Clathrate of Gossypol with DMSO

Atom	x/a	y/b	z/c	U_{iso}^{eq}
C1	4325(11)	2803(6)	8275(6)	43(3)
C2	2811(11)	2924(5)	8953(5)	38(3)
C3	1227(11)	3457(5)	8959(5)	40(3)
C4	1257(10)	3907(5)	8313(5)	43(3)
C5	2793(12)	4361(6)	6988(5)	53(4)
C6	4288(12)	4199(6)	6312(6)	58(4)
C7	5772(12)	3539(6)	6187(6)	61(4)
C8	5932(11)	3061(6)	6822(5)	47(4)
C9	4386(11)	3224(6)	7573(5)	42(4)
C10	2818(11)	3832(5)	7640(6)	42(3)
C11	2611(9)	1534(6)	9533(5)	37(3)
C12	2931(10)	2518(5)	9722(5)	41(3)
C13	3319(10)	3161(6)	10655(5)	42(3)
C14	3300(10)	2807(6)	11365(5)	45(3)
C15	2777(11)	1480(6)	11992(6)	46(3)
C16	2572(11)	0495(6)	11780(5)	51(3)
C17	2494(10)	−0199(6)	10827(6)	43(4)
C18	2470(10)	0082(5)	10045(6)	39(3)
C19	2668(10)	1130(5)	10250(5)	37(3)
C20	2919(11)	1818(6)	11201(5)	40(3)
C21	−0491(10)	3521(6)	9630(5)	62(3)
C22	7585(12)	2471(7)	0670(7)	82(4)
C23	1272(10)	5120(5)	7128(6)	59(3)
C24	1937(14)	6143(6)	7604(8)	110(5)
C25	0506(16)	5015(7)	6211(8)	140(6)
C26	3833(11)	4219(5)	10872(5)	63(3)
C27	2330(11)	−0690(5)	19106(5)	59(3)
C28	2845(13)	2209(6)	13029(5)	72(4)
C29	1086(14)	2249(7)	13673(6)	107(4)
C30	4609(15)	2074(8)	13433(6)	113(5)
O1	5861(6)	2246(3)	8239(3)	61(2)
O2	8762(9)	2303(5)	5956(4)	104(3)
O3	7050(7)	3402(4)	5431(4)	82(2)
O4	4419(9)	4654(4)	5671(4)	96(3)
O5	2213(7)	0904(3)	8643(3)	59(2)
O6	2228(8)	−1568(4)	8986(4)	72(2)
O7	2397(7)	−1152(3)	10711(3)	61(2)
O8	2466(8)	0117(4)	12482(3)	76(2)
S1′	0374(4)	0542(2)	6229(2)	74(1)
O1′	0486(9)	1204(4)	7264(4)	72(3)
C1′	2667(16)	1158(8)	5700(7)	97(5)
C2′	2624(19)	−0354(9)	6216(9)	138(7)

* $U_{iso}^{eq} = 1/3 \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$.

In the crystal structure, the gossypol molecules are united through O5–H...O3 H-bonds into centrosymmetrical dimers. The C1–C10 naphthyl nuclei of the gossypol molecules bound in such dimers are arranged in parallel in the direction of the y axis at a distance of ~b/2 and form stacks (Fig. 2). In the direction of the [10$\bar{1}$] diagonal, the stacks are joined into layers parallel to the one-dimensional plane by means of O8–H...O8 H-bonds (Table 1). In the channels formed by the packing of such layers in the crystal there are two DMSO molecules. The H-bonds of the guest molecules with the O1–H and O4–H groups of the host molecule intensify the binding of the gossypol molecules into layers. In the channels, the DMSO molecules are in contact by their methyl groups.

The H-bound two-dimensional associate has both monolayer and bilayer sections. The hydrophobic-hydrophilic separation in the interlayer regions is not so ideal as is usually the case in the majority of crystalline forms of gossypol.

There is a definite link between the structure of the H-clathrates of gossypol with methanol and formic acid [2] and those with DMSO. This can also be seen from a comparison of their crystallographic parameters (Table 2). Thus, the structure of the H-clathrates described in the present communication may be considered as one obtained from the H-clathrates mentioned as the result of a slight rearrangement. In actual fact, the DMSO molecule is not accommodated in the pockets described in [11] because of its peculiar shape and size. For them to be located in the channels, the stacks must diverge considerably in the [$\bar{1}$0$\bar{1}$] direction, which leads to a broadening of the channels and an increase in the parameters a and c (Table 2). This divergence takes place until an O(8)–H...O(8) bond stabilizing the structure is formed (Fig. 2).

With gossypol, methyl formate (MF) and methyl acetate (MA) form complexes isostructural with the H-clathrate with DMSO (Table 2). The latter is stable up to melting point, while the two preceding H-clathrates decompose under the ordinary conditions. The existence of a definite link between the H-clathrates of the "methanol group" [11] and of the "DMSO group" (Table 2) or the "almost isostructuralness" of the complexes of these two groups is also confirmed by the fact that, on desolvation of the individual representatives, one and the same polymorph is formed. Usually, clathrates (H-clathrates) belonging to different groups of isostructural complexes of gossypol give different polymorphic modifications on decomposition, and this will be considered in a following communication.

Thus, in crystals obtained from solutions in DMSO the gossypol molecules are again present in the aldehyde tautomeric form. The centrosymmetric dimers typical for the overwhelming majority of crystalline forms of gossypol cannot be formed if the gossypol has the lactol form. Apparently, on the combined crystallization of DMSO and gossypol an energy minimum is reached when the gossypol molecules are combined into dimers (are present in the aldehyde form). This leads to the situation that from a solution in which two tautomeric forms exist in dynamic equilibrium only the gossypol in the aldehyde form passes into the solid phase.

EXPERIMENTAL

Single crystals of the H-clathrate of gossypol with DMSO were grown from its solution in DMSO with slow evaporation and the addition of 2-3 drops of water (to 5 ml of solution). The determination and refinement of the crystallographic parameters and the collection of experimental results (integral intensities of the reflections) were carried out on a Syntex $P2_1$ automatic diffractometer. Cu Kα radiation monochromatized by deflection from a graphite crystal was used. The $\theta/2\theta$ method was employed at rates of scanning of 3.91-11.2 deg/min up to angles of $2\theta < 120°$. No correction for absorption was introduced. After the correction of the experimental group for Lorentz and polarization factors, the number of reflections with $F > 2\sigma(F)$ was 2040.

The structure was interpreted by the direct method using the SHELXS86 program [12]. Refinement was carried out by the programs of the SHELX76 package [13], first in the isotropic and then in the anisotropic approximation. Hydrogen atoms were localized in difference Fourier syntheses. The final R factor was 0.057. The coordinates of the atoms and their equivalent isotropic thermal factors are given in Table 3.

LITERATURE CITED

1. R. Adams, T. A. Geissman, and I. D. Edwards, Chem. Rev., 60, 555-574 (1960).

2. S. A. Talipov, B. T. Ibragimov, G. N. Tishchenko, T. F. Aripov, G. B. Nazarov, B. V. Strokopytov, and K. M. Polyakov, Kristallografiya, 33, No. 2, 384-389 (1988).
3. S. A. Talipov, B. T. Ibragimov, G. N. Tishchenko, and T. F. Aripov, Kristallografiya, 34, No. 2, 327-332 (1989).
4. B. T. Ibragimov, S. A. Talipov, T. F. Aripov, and A. S. Sadykov, J. Inclusion Phen. Mol. Recognition., 8, 323-332 (1990).
5. B. T. Ibragimov, M. Gdaniec, and B. N. Dadabaev, J. Inclusion Phen. Mol. Recognition, 8, 333-348 (1990).
6. B. T. Ibragimov, S. A. Talipov, and M. Gdaniec, J. Inclusion Phen. Mol. Recognition, 8, 409-421 (1990).
7. R. D. Stepanovich, A. A. Bell, and C. R. Howell, J. Am. Oil. Chem. Soc., 50, 462-463 (1973).
8. M. Gdaniec, B. T. Ibragimov, and S. A. Talipov, J. Inclusion Phen. Mol. Recognition, 9, 231-242 (1990).
9. F. G. Kamaev, N. I. Baram, A. I. Ismailov, V. B. Leont'ev, and A. S. Sadykov, Izv. Akad. Nauk, Ser. Khim., 1003-1010 (1979).
10. I. Reyes, S. D. Wyrick, L. Borriero, and D. I. Benas, Biophys. Biochim. Acta, No. 863, 101-109 (1986).
11. B. T. Ibragimov, S. A. Talipov, B. N. Dadabaev, and A. A. Abdubakhabov, Khim. Prir. Soedin., No. 2, 191 (1992).
12. G. M. Sheldrick, SHELXS-86, Gottingen (1986).
13. G. M. Sheldrick, SHELX-76. Program for Crystal Structure Determination, University of Cambridge, UK (1976).

IMPROVED METHOD OF OBTAINING PIPERITONE

V. V. Bazyl'chik and T. N. Overchuk

UDC 542.941/942+547.596.7

A new convenient variant of the reduction of thymol methyl ether by lithium and isopropanol in the presence of ethylenediamine at 80-85°C and a molar equivalent ratio of ether to alcohol to amine to metal of 1:(8-12):(2.5-3):(4-6) has been developed. The proposed method permits the yield of piperitone to be doubled in comparison with known methods.

One of the main components of essential oils from medicinal raw material is p-menth-1-en-3-one (piperitone) (I) [1], which is also used in fine organic synthesis [2].

In natural sources, piperitone is present in admixture with terpene alcohols and its isolation is associated with considerable experimental difficulties. Of synthetic methods, the most convenient are the reduction of thymol ethers with alkali metals in liquid ammonia and ethanol [3] and with calcium hexaammoniate in the presence of isopropanol and isobutanol [4] followed by isomerization and acid hydrolysis of the dihydro derivatives obtain A disadvantage of these methods is the use of large amounts of carefully purified liqu m-monia and of a pyrophoric metal ammoniate. The reduction of thymol ethers with alka tals and alkaline-earth metals and a mixture of amines requires large amounts of the latt p to 47 moles per mole of the ether) [5-7], and in all the cases described the yield o iperitone does not exceed 23%.

We have recently established that on the reduction of anisole and its methyl-substituted derivatives with lithium and isopropanol in the presence of 0.25-1.0 mole of ethylenediamine the yield of 1,4-dihydro derivatives reaches 70-72% [8].

I. N. Ul'yanov Chuvash State University, Cheboksary. Translated from Khimiya Prirodnykh Soedinenii, Nos. 3,4, pp. 335-338, May-August, 1992. Original article submitted December 14, 1990; revision submitted July 18, 1991.

 0009-3130/92/0304-0292$12.50 © 1992 Plenum Publishing Corporation