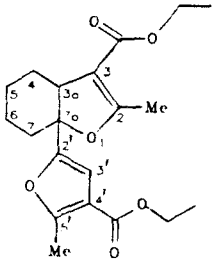
USE OF TWO-DIMENSIONAL SPECTROSCOPY FOR THE DETERMINATION OF THE STEREOCHEMICAL STRUCTURE OF 3-CARBETHOXY-2-METHYL-7*a*-(4-CARBETHOXY-5-METHYL-2-FURYL)-3*a*,4,5,6,7,7*a*-HEXAHYDROBENZOFURAN

V. A. Chertkov, G. G. Melikyan,
A. B. Sargsyan, and Sh. O. Badanyan

UDC 543.422.25:547.728

Homo- and heteronuclear two-dimensional correlation spectra, as well as J-resolved spectra with selective excitation, were used to analyze in detail the stereochemical structure of 3-carbethoxy-2-methyl-7a-(4-carbethoxy-5-methyl-2-furyl)-3a,4,5,6,7,7a-hexahydrobenzofuran, obtained by the reaction of cyclohexenylacetylene with acetoacetic ester in the presence of a manganese(III) salt. It was shown that the use of the long-range ^{13}C-^{1}H coupling constants is a very effective method for the determination of the conformation of the molecule. The stereochemical aspects of the reaction of cyclohexenylacetylene with acetoacetic ester is discussed.

The reaction of conjugated alkenynes and alkadienes with β-dicarbonyl compounds, initiated by manganese(III) acetate, gives 2,3,5-trisubstituted 4,5-dihydrobenzofurans and furans [1-3]. For 1,2-disubstituted 1-buten-3-yne (cyclohexenylacetylene) the products of the reaction are the corresponding hexahydrobenzofuran derivatives, formed as a result of consecutive cycloaddition of the carbonyl compounds to the triple and double bonds of the substrate [4]. Determination of the stereochemical structure of the latter was of interest because of the possibility of using this class of reaction for the stereoselective synthesis of condensed bicyclic systems, and also to determine the stereochemistry of cyclization of α-furylcyclohexyl radical-adducts, formed by the addition of α,α-dioxoalkyl radicals to a double bond of the cyclohexenyl ring [4]. It should be noted that the configuration of cyclic and condensed bicyclic compounds, obtained in reactions initiated by manganese(III) acetate [5], has been determined for products of the reaction of alkenes with acetic acid [6, 7], 1-methyl-1-phenylethene with malonic acid [8] and butadiene with acetone [9]. The stereochemistry of the binuclear system, containing a carbocycle condensed with a dihydrofuran ring, has not been reported in the literature.



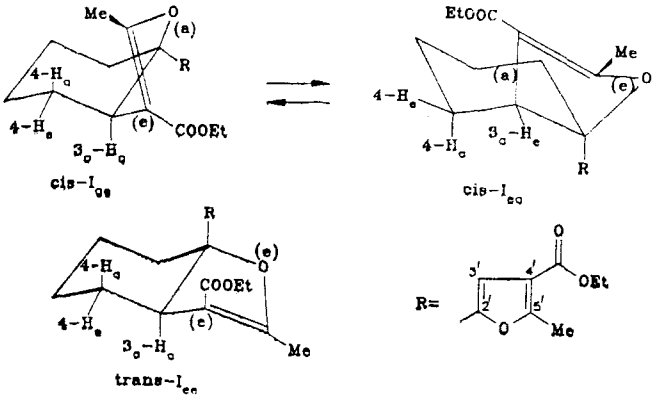
I

*cis-Configuration has an axial-equatorial arrangement of the $C_{(7a)}$—O and $C_{(3a)}$ bonds, trans-configuration has a diequatorial (diaxial) arrangements of these bonds.

M. V. Lomonosov Moscow State University. Institute of Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 167-171, February, 1991. Original article submitted May 3, 1989.

0009-3122/91/2702-0135$12.50

We chose to study the product of the reaction of cyclohexenylacetylene with acetoacetic ester — 3-carboethoxy-2-methyl-7*a*-(4-carbethoxy-5-methyl-2-furyl)-3*a*,4,5,6,7,7*a*-hexahydrobenzofuran (I) [4]. Construction of molecular models of the trinuclear substrate showed that both cis- and trans-couplings* of cyclohexane and dihydrofuran rings are possible; in the case of the cis-isomer both cis-I_{ae} and cis-I_{ea} conformers can be expected, while for the trans isomer only one conformation is possible (trans-I_{ee}), in which the $C_{(7a)}$—O and $C_{(3a)}$—$C_{(3)}$ bonds occupy equatorial positions in the cyclohexane ring. The alternative conformation, with a diaxial arrangement of these bonds, cannot occur because of steric hindrance.



A number of ways have been proposed for analyzing the conformation of cyclohexane derivatives based on NMR spectral parameters [10]. From general considerations it should be possible to determine conformation from the proton—proton coupling constants involving the 3*a*-H methine proton. Moreover, characteristic values for the coupling constant at 9-12 Hz should be observed for the $^3J_{3a\text{-}H_a,4\text{-}H_a}$ in the cis-I_{ae} and trans-I_{ee} forms with diaxial 3*a*-H and 4-H protons [11-13]; for diequatorial and equatorial-axial configurations, the coupling constant is from 2.5 to 4.5 Hz [11-13]. The experimental ^{1}H NMR spectrum of compound I contains a complex multiplet from the 4-H, 5-H, and 6-H methylene group protons at 1.25-1.82 ppm, a signal from the 7-H protons showing a weak-field shift due to the effect of the aromatic ring at 2.00 ppm (t, J = 6.3 Hz), and a 3*a*-H proton signal at 3.37 ppm (t, q: J_T = 6.3 Hz; J_K = 1.4 Hz). Quadruplet splitting of the latter is related to the long-range coupling constant $^5J_{3a\text{-}H,2\text{-}CH_3}$. From triplet splitting, the total magnitude of the vicinal coupling constants for the 3*a*-H proton with the 4-H_a and 4-H_e protons can be estimated ($^3J_{3a\text{-}Ha,4\text{-}H_a}$ + $^3J_{3a\text{-}H,4\text{-}H_e}$) = 12.2 Hz. Because of the extreme complexity of the multiplet structure of the 4-H_a and 4-H_e signals, the values of the coupling constant for each of these protons with the 3*a*-H proton, taken separately, could not be determined. From the literature data cited above it follows that the sum of the constants ($^3J_{3a\text{-}H,4\text{-}H_a}$ + $^3J_{3a\text{-}H,4\text{-}H_e}$) should be 11.5-16.5 Hz for the cis-I_{ae} and trans-I_{ee} isomers, while for the cis-I_{ea} isomers values of 5-9 Hz can be expected. The total magnitude of the vicinal coupling constants is 12.2 Hz, indicating that compound I is either in the trans-I_{ee} form or in the cis-form, in which the conformational equilibrium is displaced in the direction of the cis-I_{ae} conformer.

It is known that interconversions such as cis-I_{ee} ⇄ cis-I_{ea} take place more slowly at lower temperatures, while at temperatures close to −100°C signals are observed in the NMR spectra corresponding to individual conformations [10]. We recorded ^{13}C NMR spectra for compound I in CD_2Cl_2 over the range 20 to −95°C. In this series of experiments no significant broadening of any of the signals was observed, confirming the decrease in the rate of interchange of conformers. This agrees with the above conclusion, that there is no dynamic conformational equilibrium, from which it follows that compound I occurs either as the conformationally stable trans-isomer (trans-I_{ee}), or as one of the cis-isomer conformers.

Unambiguous information on the stereochemical structure of compound I was obtained by using the vicinal carbon—proton coupling constant $^3J_{C(2'),3a\text{-}H}$. In both cis-isomer conformers the 3*a*-H and $C_{(2')}$ of the ring are in the gauche-position relative to each other. A value of 0-3 Hz is typical for this type of constant [14, 15]. For the anti-arrangement of this ring, which occurs in the trans-I_{ee} isomer, considerably greater values of the corresponding constants, 4-8 Hz, are expected [14, 15].

The ^{13}C—H constants were measured using the technique of two-dimensional J-resolved spectroscopy with selective excitations [16], which unambiguously links the desired constant to the assigned pair and avoids possible ambiguities to the interpretation of proton-linked ^{13}C NMR spectra. To determine the values of $^3J_{C(2'),3a\text{-}H}$, two

TABLE 1. ^1H NMR Spectra for Compound I (AM-360, 360 MHz, $CDCl_3$, 30°C)

Protons	δ, ppm	Protons	δ, ppm
3a-H	3,37 t,q*1	2-CH_3	2,16*1
4-H_a; 4-H_e	1,67 м; 1,78 м	5'-CH_3	2,51s
5-H_a; 5-H_e	1,33 м; 1,46 м	3-COOCH_AH_BCH_3	4,10 м; 4,16 м*2
6-H_a; 6-H_e	1,42 м; 1,51 м	3-COOCH_2CH_3	1,24 t*2
7-H_a; 7-H_e	2,00 t*3	4'-COOCH_2CH_3	4,22 q*4
3'-H	6,51 s	4'-COOCH_2CH_3	1,29 t*4

*1 $(^3J_{3a\text{-H},4\text{-H}_e} + {}^3J_{3a\text{-H},4\text{-H}_a})$ = 12.2 Hz, $^5J_{3a\text{-H},2\text{-CH}_3}$ = 1.4 Hz.
*2 Spin system ABX_3: $J_{AX} = J_{BX}$ = 7.1 Hz; J_{AB} = 10.8 Hz.
*3 J = 6.3 Hz.
*4 $^3J_{CH_2,CH_3}$ = 7.2 Hz.

TABLE 2. ^{13}C NMR Spectra for Compound I (AM-360, 90 MHz, $CDCl_3$, 30°C): Chemical Shifts for Carbon Atoms [δ(X), ppm] and Long-Range Cooling Constants with 3a-H Proton ($J_{X,3a\text{-H}}$, Hz)

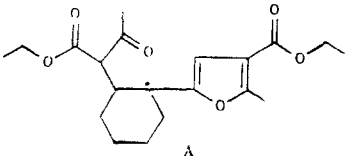
X	δ(X)	$J_{X,3a\text{-H}}$	X	δ(X)	$J_{X,3a\text{-H}}$
$C_{(2)}$	166,98	4,0	$C_{(5')}$	159,09	≤0,8
$C_{(3)}$	107,10	5,9	2-CH_3	14,60	0,8
$C_{(3a)}$	44,33	—	3-COOEt		
$C_{(4)}$	25,10	3,5	CO	166,00	1,2
$C_{(5)}$	19,15	<=3,0	CH_2	59,40	≤1,0
$C_{(6)}$	18,92	<=3,0	CH_3	14,43	≤0,5
$C_{(7)}$	29,97	2,6	4'-COOEt		
$C_{(7a)}$	85,52	3,0	CO	163,89	0,5
$C_{(2')}$	154,02	5,9	CH_2	60,13	≤1,0
$C_{(3')}$	107,22	<=1,0	CH_3	14,43	≤0,5
$C_{(4')}$	114,09	<=0,8	5'-CH_3	13,89	≤0,5

J-resolved spectra were recorded with selective excitation of the 3'-H and 3a-H protons. An experiment involving the excitation of the aromatic 3'-H proton should make it possible to unambiguously assign the ^{13}C signal at 154-167 ppm, a region where signals from the $C_{(2)}$, $C_{(2')}$, and $C_{(5')}$, and both the carbonyl groups are observed. Moreover, signals from the $C_{(2')}$ and $C_{(5')}$ furan-ring carbon atoms were identified from the values of long-range coupling constants ^{13}C–H: $^3J_{C(5'),3'\text{-H}}$ = 6.4 Hz, $^3J_{C(2'),3'\text{-H}}$ = 9.1 Hz [15, 17]. Having obtained reliable values by this method for the $C_{(2')}$ signal, we carried out a decisive experiment with excitation of the 3a-H methine proton. The desired $^3J_{C(2'),3a\text{-H}}$ was found to be 5.9 Hz, unambiguously confirming the trans-coupling of the cyclohexane and dihydrofuran ring. The value of the vicinal constant $^3J_{C(5),3a\text{-H}} \leq 3.0$ Hz and $^3J_{C(7),3a\text{-H}}$ = 2.6 Hz (see [14, 15]) also confirms the conclusion that the 3a-H proton is in the axial position.

Using homo- and heteronuclear correlative two-dimensional spectroscopy [18, 19], we conducted a complete assignment of signals in the ^1H and ^{13}C NMR spectra (see Tables 1 and 2).

The reaction of cyclohexenylacetylene with acetoacetic ester is a one-stage method for the stereoselective synthesis of a trans-linked condensed bicyclic system. This route should be useful in organic chemistry for the synthesis of natural products.

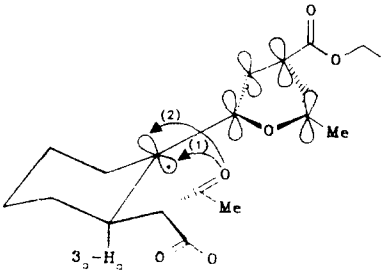
Based on the configuration of compound I, some conclusions can be made about the stereochemistry of cyclization of the radical-adduct A



A

which is formed by the addition of acetoacetic ester to the carbocyclic double bond of 3-carbethoxy-2-methyl-5-(1-cyclohexenyl)furan [4].

It is known that cyclohexyl radicals undergo fast interconversion of "chair" type conformers with an essentially planar structure of the radical center [20]. The presence in the radical-adduct A of the furyl group at the carbon atom carrying the unpaired electron is the electronic factor that gives stability to the planar structure, which supplies the coplanarity of the double bond of the furan ring with the p-orbital of the radical center. In the trans-isomer of compound I, the $C_{(3a)}$—$C_{(3)}$ bond is in the equatorial position of the cyclohexane ring. Based on the principle of "least disturbance of nonreacting groups" [21, 22], it is expected that this bond is also in the same place in the radical-adduct A. This supposition agrees with the data in [23], according to which, in substituted cyclohexane, the most thermodynamically stable conformer containing the bulky substituent is in the equatorial position of the ring [23]. Thus, the radical-adduct A should have the conformation



The cyclization stage can take place by one of two routes (1) and (2). The first of these can be regarded as a pseudoequatorial attack of the oxygen atom of the acetyl group on the radical center, the stereochemical result of which is a trans-configurational reaction product I with an equatorial arrangement of the $C_{(7a)}$—O bond. The second route involves a pseudoaxial attack and formation of the reaction product I with a cis-configuration (cis-I_{ae}) and an equatorial arrangement of the desired $C_{(7a)}$—O bond. The stereoselective cyclization process leading to the formation of the trans-I_{ee} confirms that only route (1) occurs, and that the oxygen atom of the carbonyl group attacks exclusively at the pseudoequatorial position of the cyclohexyl ring.

LITERATURE CITED

1. G. G. Melikyan, D. A. Mkrtchyan, and Sh. O. Badanyan, *Khim. Geterotsikl. Soedin.*, No. 7, 884 (1980).
2. G. G. Melikyan, D. A. Mkrtchyan, and Sh. O. Badanyan, *Khim. Geterotsikl. Soedin.*, No. 1, 19 (1982).
3. G. G. Melikyan, D. A. Mkrtchyan, V. M. Mkrtchyan, and Sh. O. Badanyan, *Khim. Geterotsikl. Soedin.*, No. 3, 308 (1985).
4. G. G. Melikyan, A. B. Sargsyan, V. S. Giri, R. T. Grigoryan, and Sh. O. Badanyan, *Khim. Geterotsikl. Soedin.*, No. 3, 317 (1988).
5. Sh. O. Badanyan, G. G. Melikyan, and D. A. Mkrtchyan, *Usp. Khim.*, **58**, 475 (1989).
6. W. E. Fristad and J. R. Peterson, *J. Org. Chem.*, **51**, 10 (1985).
7. K. Witkiewicz and Z. Chahudzinski, *Roczn. Chem.*, **51**, 2155 (1977).
8. N. Ito, H. Nishino, and K. Kurosawa, *Bull. Chem. Soc. Jpn.*, **56**, 3527 (1983).
9. M. G. Vinogradov, M. S. Pogosyan, A. Ya. Shteinshneider, and G. I. Nikishin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 4, 842 (1983).
10. N. M. Sergeev and O. A. Subbotin, *Usp. Khim.*, **47**, 477 (1978).
11. E. W. Garbish and M. C. Griffith, *J. Am. Chem. Soc.*, **90**, 6543 (1968).
12. V. R. Haddon and L. M. Jackman, *Org. Magn. Reson.*, **5**, 333 (1973).
13. D. Hoffner, S. Lesko, and G. Binsch, *Org. Magn. Reson.*, **11**, 179 (1978).
14. V. A. Chertkov and N. M. Sergeyev, *J. Am. Chem. Soc.*, **99**, 6750 (1977).
15. P. E. Hansen, *Progress in NMR Spectroscopy*, Vol. 14 (1981), p. 175.
16. A. Bax and R. Freeman, *J. Am. Chem. Soc.*, **104**, 1099 (1982).
17. M. Hansen, R. S. Hansen, and H. J. Jacobsen, *J. Magn. Reson.*, **13**, 386 (1974).
18. A. Bax, *Two-Dimensional NMR in Liquids*, Delft Univ. Press, Dordrecht (1984).
19. R. R. Ernst, G. Bodenhausen, and A. Wokaun, *Principles of NMR in One and Two Dimensions*, Clarendon Press, Oxford (1987).
20. D. Nonkhibel and Dz. Yolton, *Chemistry of Free Radicals* [Russian translation], Mir, Moscow (1977).

21. O. S. Ten, *J. Am. Chem. Soc.*, **91**, 144 (1969).
22. J. Hine, *J. Am. Chem. Soc.*, **88**, 5525 (1966).
23. E. Eliel, H. Allindzher, S. Enzhial, and G. Morrison, *Conformational Analysis* [Russian translation], Mir, Moscow (1969).

SYNTHESIS OF 3,3-DISUBSTITUTED 2-THIOPHTHALIDES

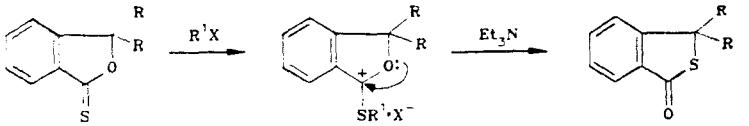
D. A. Oparin and A. S. Kuznetsova

UDC 547.588.21.07

The alkylation of 1-thiophthalides followed by treatment of the reaction mixture with triethylamine constitutes a convenient method of preparing 3,3-disubstituted 2-thiophthalides.

2-Thiophthalides are used as starting materials in the preparation of a number of useful thiophthalane derivatives, some of which are used as antidepressants [1], dyes [2, 3], and analytical reagents [4]. A general synthetic route to 2-thiophthalides is the mercuric acetate oxidation of the corresponding 1,2-dithiophthalides [5]. However, the starting dithiophthalides, especially the 3,3-disubstituted ones, are not easily available. Other reported methods for the preparation of 2-thiophthalides lack specificity and have only limited applicability [6-9]. The isomerization of the unsubstituted 1-thiophthalide in the presence of amines under relatively harsh reaction conditions (high temperature and pressure) has been reported [10, 11]. Since 3,3-disubstituted 1-thiophthalides are easily available, we investigated their isomerization in more detail in order to broaden the synthetic scope of this reaction.

As a starting material, we used 1-thiophthalides I, containing aromatic or aliphatic substituents at the 3-position of the heterocycle. We found that the recyclization of the phthalane ring with the formation of the isomeric 2-thiophthalides III can be carried out under relatively mild conditions by alkylation of the 1-thiophthalides I, followed by treatment of the reaction mixture with triethylamine:



Ia, b IIa, b IIIa, b

I—III a R=Ph; b R=Me, R'X=MeI, Me_2SO_4, $Et_3O^+ \cdot BF_4^-$, $2\text{-}O_2NC_6H_4SO_3Me$

As alkylating reagents we used successfully methyl iodide, triethyloxonium tetrafluoroborate, a mixture of triethyl orthoformate and boron trifluoride etherate, dimethyl sulfate, and methyl o-nitrobenzenesulfonate. The yields of the target compounds were in the range 60-80% and were practically independent of both the alkylating reagent used and the $C_{(3)}$ substituents in the starting 1-thiophthalides.

Solutions of 1-thiophthalides I in polar and high-boiling solvents (chloroform, acetonitrile, toluene, o-dichlorobenzene) are stable to prolonged heating in the absence of alkylating reagents. The addition of triethylamine to these solutions also does not result in the isomerization of these compounds. The formation of 1-alkyl-thio-substituted phthalilium salts II is therefore a necessary condition for the recyclization of 1-thiophthalides.

The salts II proved to be unstable and we were not able to isolate any of them. This instability is probably due to a low basicity of the thiocarbonyl function of II, similar to that reported for phthalilium and thiophthalilium salts with alkoxy groups [12]. The formation of phthalilium salts is indicated by the precipitation of phthalilium-tetrafluoroborates upon addition of dry ether to the reaction mixtures, but these salts proved to be very hygroscopic

Institute of Biochemistry, Academy of Sciences of the Belorussian SSR, Grodno 230009. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 172-174, February, 1991. Original article submitted July 17, 1989; revision submitted February 16, 1990.

0009-3122/91/2702-0139$12.50