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Registry No.—**1**, 5675-13-8; **5**, 1515-23-7; **6**, 1515-19-1; **8**, 50388-57-3; **9**, 50388-58-4; **10**, 50388-59-5; **11**, 50388-60-8; **12**, 50388-61-9; **13**, 50388-62-0; **14**, 26549-64-4; **15**, 38201-52-4; **19**, 50388-65-3; **20**, 41902-36-7; **21**, 17673-68-6; phthalic acid, 88-99-3.

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Nuclear Magnetic Resonance Studies of the Geometrical Isomers of α,α'-Disubstituted Succinosuccinic Esters

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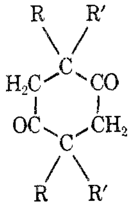
Investigation of the nmr spectra of a series of α,α'-disubstituted succinosuccinic esters, all except one existing as cis and trans isomers, has shown that every pair of these isomers gave nmr spectra which differed from each other in the spacings between the doublets for the four methylene protons in the cyclohexane ring. By association of the nmr spectral data with conformational analysis of the isomeric esters under investigation, it is possible to make plausible assignment of configuration to these isomers. This has found support from nmr spectroscopy of α,α'-dimethylsuccinosuccinic esters at very low temperatures and preliminary results from X-ray analysis of one of the isomers of di-*p*-bromobenzylsuccinosuccinic ester. The difference in the temperature effect on the nmr spectra of the geometrical isomers is discussed. Of the substituted succinosuccinic esters investigated in the present work, those which were previously unknown have been characterized.

While using nmr spectroscopy in the characterization of α,α'-disubstituted succinosuccinic esters, each existing as cis and trans isomers, it was found that, for each pair of such isomers, the nmr spectrum of the one differed from that of the other in the spacing between the doublets for the four methylene protons in the cyclohexane ring. This has led to the attempt at the feasibility of assigning the configurations of these isomers according to their nmr spectra.

The story began when the present authors were reinvestigating the reaction between disodiosuccinosuccinic ester and a benzyl halide, which was first investigated by Nef[1] more than 80 years ago. This latter author regarded the key products that resulted from the reaction as two isomers of diethyl 2,5-dibenzoxy-3,6-dihydroterephthalate, on account of their sluggishness to the action of carbonyl reagents, their resistance to ketonic cleavage by the action of dilute sulfuric acid, and their crystallographic resemblance to the product obtained by reducing diethyl 2,5-dibenzoxyterephthalate.[1] Being curious about the occurrence of the isomerism of the dienolic ethers, Chan[2] repeated Nef's experiment, and isolated exactly the same products as those obtained by Nef. She found, however, that they did react with hydroxylamine to give the corresponding dioximes, showing the presence of two carbonyl groups. Her investigation was not carried any further owing to the failure of the products to undergo ketonic cleavage. Nor did she seem to have obtained pure samples of the dioximes.

Following the discovery of the cleavage of β-keto esters by the action of metal iodides,[3] the present authors again made a study of the reaction between disodiosuccinosuccinic ester and benzyl iodide and of the isomeric products, with a view to elucidating their structure and, should they exist as geometrical isomers, determining their configuration. As those described by Nef, the two crystalline substances that resulted from the reaction melted at 140.5 (Ia) and 148.5° (Ib). Both of them reacted with hydroxylamine, giving the corresponding dioximes, mp 221° dec and 252° dec, respectively. On refluxing for 48 hr with dilute sulfuric acid, Ib was converted into a product of unknown structure, melting at 272°, which had the same percentage



I, R = COOEt; R′ = CH_2Ph

II, R = H; R′ = CH_2Ph

III, R = COOEt; R′ = CH_2COOEt

IV, R = COOEt; R′ = CH_3

V, R = H; R′ = CH_3

VI, R = COOEt; R′ = $CH_2C_6H_4Br$

VII, R = COOEt; R′ = $CHPh_2$

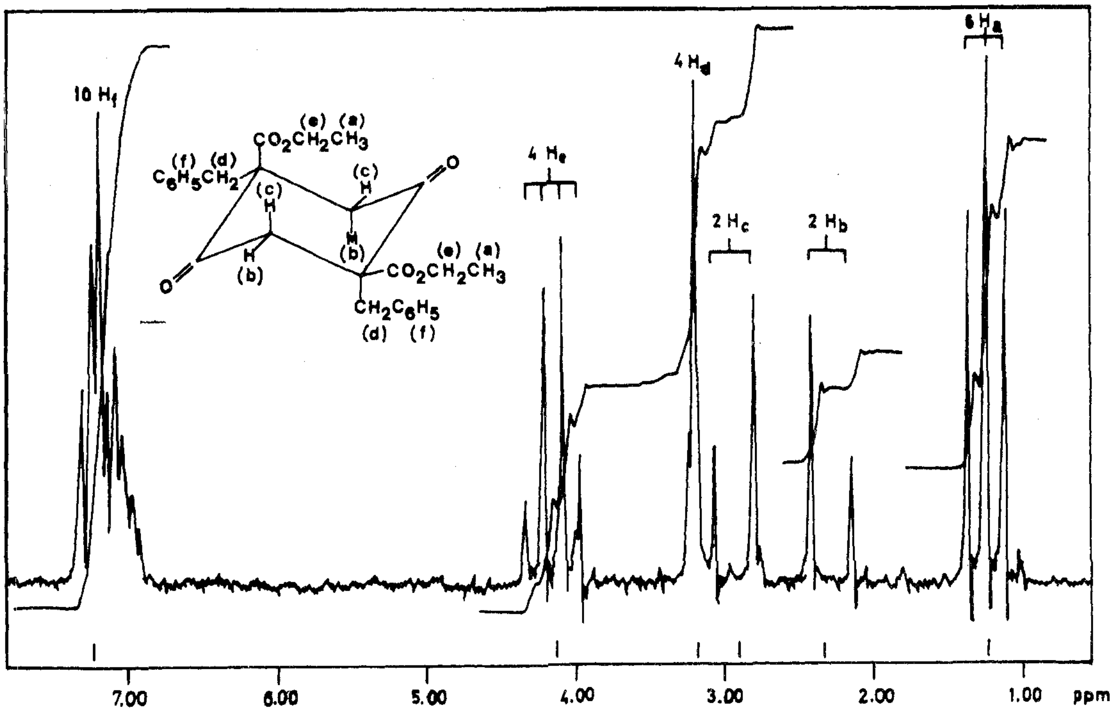


Figure 1. Nmr spectrum of *cis*-2,5-dibenzyl-2,5-dicarbethoxycyclohexane-1,4-dione.

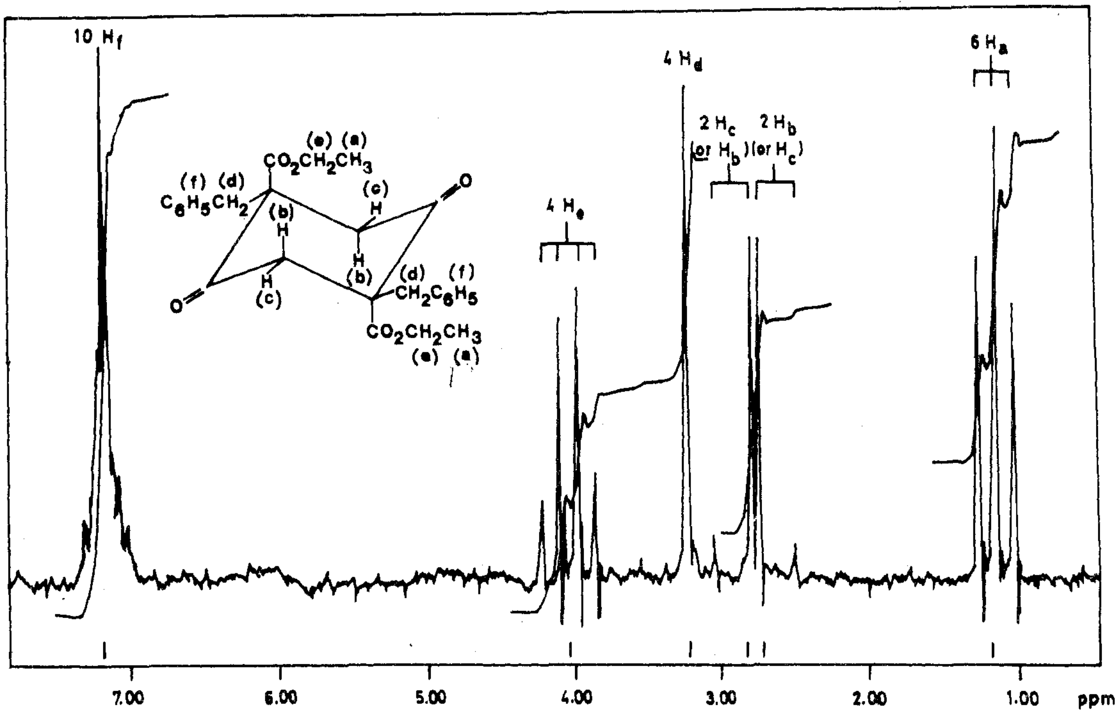
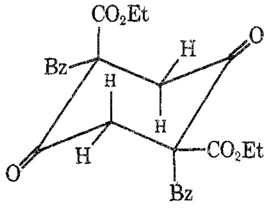


Figure 2. Nmr spectrum of *trans*-2,5-dibenzyl-2,5-dicarbethoxycyclohexane-1,4-dione.

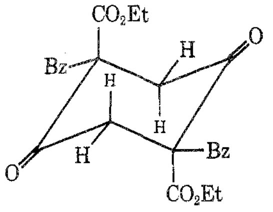
composition as Ib, while Ia remained unchanged. When heated with hydrated calcium iodide, both Ia and Ib were readily decarboxylated, each giving the same pair of isomers, mp 155 (IIa) and 196° (IIb), respectively. These latter products also formed the corresponding dioximes.

The reactions just outlined clearly indicate that the products Ia and Ib were in all probability geometrical isomers of 2,5-dibenzyl-2,5-dicarbethoxycyclohexane-1,4-dione, and IIa and IIb geometrical isomers of 2,5-dibenzylcyclohexane-1,4-dione. Further information in support of the proposed structures was provided by ir and nmr spectroscopy. It was the nmr spectra of Ia and Ib (Figures 1 and 2) that first attracted our attention to the different features existing in the part of the peaks for the methylene protons in the cyclohexane ring. In both spectra, the absorptions of four ring protons give rise to two doublets with equal coupling constants of 16 Hz. However, the spacings between the chemical shifts are different. In the spectrum of Ia, these chemical shifts lie at 2.33 and 2.90 ppm, while, in the spectrum of Ib, the corresponding shifts lie at 2.70 and 2.83 ppm. In the former case the doublets are separated by a spacing of 0.57 ppm and in the latter case the doublets are separated by a spacing of only 0.13 ppm.

Attempts have been made to correlate the difference in the spacing between the chemical shifts for ring protons with the configuration of the geometrical isomers on the basis of conformational analysis. On the evidence which will be given in a later section, Ia and Ib and the other disubstituted cyclohexane-1,4-diones should exist in the chair form. Inspection of the cis and trans configurations of I, both in the chair form, would make it clear that the

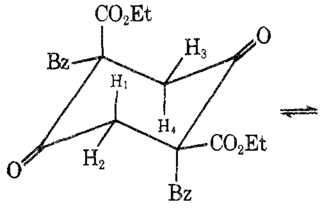


I (cis)

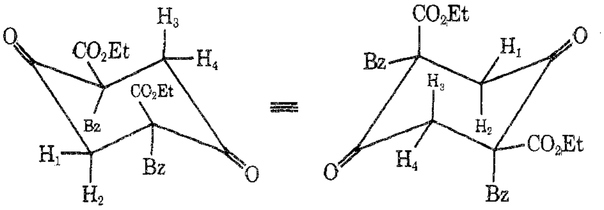


I (trans)

ring methylene protons are of three kinds in both cases. It follows that the absorption of these protons should give three doublets instead of two. To account for this discrepancy we have to take a closer look at these isomers. Let us consider first the cis isomer, Ia, and mark the four ring methylene protons with subscripts. The axial protons H_1 and H_4 lie in environments differing from each other, while the equatorial protons H_2 and H_3 lie in very similar environments. These latter protons may be treated as equivalent. Flipover of Ia gives Ia′, with a perfectly iden-



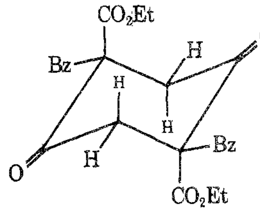
Ia



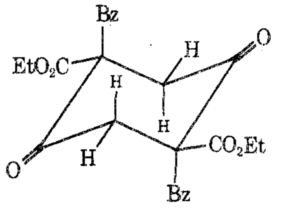
Ia′

tical conformation. After the conversion, H_3 in Ia′ assumes the same environment as H_1 in Ia, and H_4 in Ia′ assumes the same environment as H_2 in Ia. The actual form of the cis isomer may be regarded as consisting of half of Ia and half of Ia′, rapidly transforming one to the other at *ordinary temperatures*, similar to the interconversion of axial and equatorial hydrogen atoms in cyclohexane. Thus, in the cis isomer, the four ring methylene protons may be regarded as consisting of two kinds, those of the one kind lying in environments intermediate between H_1 and H_3, and those of the other lying in environments intermediate between H_2 and H_4. While proton H_1 is subject to the deshielding effects of the neighboring equatorial carbethoxyl group and the 3-axial carbethoxyl group, proton H_3 is subject to the deshielding effects of the neighboring oxo group and the 3-axial carbethoxyl group, and the shielding effect of the neighboring equatorial benzyl group. As to the protons H_2 and H_4, the former lies in a similar environment to that of H_3, and the latter is subject to the shielding effects of the neighboring equatorial benzyl group and the 3-axial benzyl group. By constructing models it can be shown that the distance between an axial proton and a neighboring equatorial group or a 3-axial group and that between an equatorial proton and a neighboring axial group or equatorial group are approximately equal. We may presume accordingly that the anisotropic effect of an axial substituent group on a neighboring equatorial proton or a 3-axial proton and that of the same group in an equatorial position on a neighboring axial or equatorial proton are nearly the same. On comparing the anisotropic effects of the substituent groups on the ring methylene protons, we see that the pairs of protons H_1–H_3 and H_2–H_4 differ from each other by the shielding effect of one benzyl group and the deshielding effect of one carbethoxyl group. For reasons which will be given in a later section, these two kinds of protons should give rise to two doublets considerably separated from each other.

As to the trans isomer, Ib, there are two conformations possible, as shown by Ib and Ib′. The equatorial protons



Ib



Ib′

in both forms lie in very similar environments and may be treated as equivalent, while the axial protons lie in different environments. However, for reasons given in the foregoing paragraph, the axial protons in Ib and Ib′ may be treated as nearly equivalent. It follows that in the trans isomer there are but two kinds of protons. However, as far as stability is concerned, Ib should be more stable, because strong dipole-dipole repulsion between carbethoxyl groups and oxo groups would cause the former to orient themselves as remote from the latter as possible. We presume that the trans isomer consists entirely of Ib. In this conformer, the ring methylene protons are also of two kinds: the axial protons and the equatorial ones. The former are subject to the deshielding effect of the 3-axial carbethoxyl group and the shielding effect of the neighboring equatorial benzyl group, and the latter are subject to the deshielding effects of the neighboring oxo group the σ electron of a C–C bond,[4] and the neighboring axial carbethoxyl group and the shielding effect of the neighboring equatorial benzyl group. These two kinds of protons differ by the deshielding effects of one oxo group and the σ electron of one C–C bond. As we shall see later, both of these effects are relatively small, and the two pairs of ring protons should give two more closely spaced doublets.

Based on the foregoing discussion, it is plausible to assign the cis configuration to the isomer of melting point 140.5° (Ia) and the trans configuration to the isomer of melting point 148.5° (Ib). Such assignments are in accord with the close constancy of the values of the spacings for the trans isomers of most of the substituted succinosuccinic esters studied, and the wide range of the values for the corresponding cis isomers. This point will be elaborated in the next section.

The nmr studies have been extended to other α,α'-disubstituted succinosuccinic esters including 2,5-dibenzylcyclohexane-1,4-dione (II), dicarbethoxymethylsuccinosuccinic ester (III),[5] dimethylsuccinosuccinic ester (IV),[6] di-*p*-bromobenzylsuccinosuccinic ester (VI), and dibenzhydrylsuccinosuccinic ester (VII). Among these, II, VI, and VII were previously unknown. Each of these esters exists as cis and trans isomers with the exception of VII, of which only one isomer has been found. The formation of II has been mentioned previously. Of the isomers of the dimethylsuccinosuccinic ester, only the crystalline isomer had been known in its pure state, while the liquid isomer was purified in the authors' laboratory by chromatography.

Referring to Table I, it is seen that the pairs of isomers of III, IV, and VI gave nmr spectra with the spacings of

Table I
Assignment of Configuration to the Isomers of I, III, IV, VI, and VII According to the Chemical Shifts for Their Ring Methylene Protons

		Chemical shifts, ppm						Chemical shifts, ppm			
Isomer	Mp, °C	Upfield	Downfield	Spacing	Configuration	Isomer	Mp, °C	Upfield	Downfield	Spacing	Configuration
Ia	140.5	2.33	2.90	0.57	Cis	Ib	148.5	2.70	2.83	0.13	Trans
IIIa	60	2.81	3.30	0.49	Cis	IIIb	106.5	2.97	3.07	0.27	Trans
IVa	Liquid	2.67	3.43	0.76	Cis	IVb	73	2.87	3.13	0.26	Trans
VIa	151–152	2.27	2.87	0.60	Cis	VIb	216–217	3.60	2.91	0.31	Trans
VIIa	216–217	1.97	3.43	1.46	Cis						

the peaks for ring methylene protons differing from each other in much the same way as those in the nmr spectra of Ia and Ib. With the same reasoning as that given for the assignment of configurations of Ia and Ib, we may assign the cis and trans configuration to each of these isomers.

In isomers of II, and those of V, the presence of tertiary protons on α-carbon atoms imposes highly complicated coupling with the neighboring protons, rendering the analysis of the spectrum virtually impossible. The decarboxylation of Ia and Ib by the action of $CaI_2 \cdot 4D_2O$ gave the deuterated counterparts of IIa and IIb, with all the ring methylene protons replaced by deuterons. This will be discussed in the succeeding section. The only isomer of VII isolated is probably the cis isomer, because the peaks for ring methylene protons are widely spaced.

Results of nmr spectroscopy of the dimethylsuccinosuccinic esters (IVa and IVb) at temperatures ranging from 20 to −90° provide strong support to the foregoing accounts for the special features of the nmr spectra of the isomers of α,α'-disubstituted succinosuccinic esters. On the other hand, X-ray analysis of the isomers of di-*p*-bromosuccinosuccinic ester is being carried out, with a view to further justifying the assignment of configuration by nmr spectroscopic data as outlined above. Preliminary results unequivocally establish the configuration of one of the isomers of VI. All these will be discussed in the succeeding section.

Results and Discussion

The nmr spectra of the geometrical isomers of α,α'-disubstituted succinosuccinic esters need to be described in greater detail. As we have seen, the portion of the spectra that is relevant to the determination of configuration of the isomers consists of the peaks for the ring methylene protons. Table I gives the chemical shifts of the doublets for the ring protons in the nmr spectra of the isomers of I, III, IV, VI, and VII, together with the configuration assigned to each of them according to the considerations given in the preceding section.

Let us first focus our attention to the spectral assignments on which the assignment of configuration to the pairs of isomers of I, III, IV, and VI depends. In the compounds I, II, III, VI, and VII, there exists in each of the substituents [$CH_2C_6H_5$, $CH_2C_6H_5$, $CH_2COOC_2H_5$, $CH_2C_6H_4Br$, and $CH(C_6H_5)_2$] a pair of diastereotopic groups. The protons are potentially anisochronous. The best-known examples are the nonequivalence of benzylic protons in some, but not all, *N*-benzyl heterocyclic bases.[7]

Examination of the nmr spectra of the substituted succinosuccinic esters and some of their decarboxylation products investigated in the present study would show that none of the substituent groups mentioned above gave signals that seriously interfered with our spectral assignments. The benzylic protons in Ia and Ib give a singlet. In the deuterated IIa and IIb, in which all the ring protons have been replaced by deuterons (see Experimental Section), the benzylic protons give two doublets with J = 14.0 Hz, differing from the doublets for the ring protons with J = 16.0 Hz. In the spectrum of IIIa, the absorption of the methylene protons of the $CH_2COOC_2H_5$ group gives rise to a singlet at 3.22 ppm, and that of the ring protons to two doublets at 2.81 and 3.30 ppm, with J = 16.0 Hz. As to its isomer, IIIb, the methylene protons of the $CH_2COOC_2H_5$ group give two doublets at 3.13 and 3.32 ppm, with J = 14.4 Hz, differing from the doublets for the ring protons at 2.97 and 3.07 ppm, with J = 16.0 Hz. In the spectra of IVa and IVb, the protons of the methyl groups on α-carbon atoms give their signals quite remote from those of the ring protons. Among the isomers of VI, the cis isomer, VIa, gives a spectrum in which the absorption of the benzylic protons gives rise to two doublets more downfield than those for the ring protons, with J = 14.0 *vs.* 16.0 Hz. In the spectrum of the trans isomer, VIb, the absorption of the benzylic protons gives rise to a singlet. Finally, in the spectrum of VIIa, the doublets for the ring protons are easily characterized by proton counting and finding out the coupling constant. We may conclude that there is scarcely anything ambiguous in the assignments of the doublets to the ring methylene protons in all the pairs of isomers of I, III, IV, VI, and VII.

The interpretation of the spectral data as well as the reasoning on which to base the assignment of the configuration of cis and trans isomers can be provided by considering more specifically the anisotropic effects of the substituent groups on the ring methylene protons. In the spectra of Ia, IIIa, IVa, VIa, and VIIa, to which the cis configurations are assigned, the downfield doublet of the ring protons may be ascribed to the deshielding effect of carbethoxyl group, while the upfield one may be ascribed to the shielding effect of the substituent group $CH_2C_6H_5$, $CH_2COOC_2H_5$, CH_3, $CH_2C_6H_4Br$, or $CH(C_6H_5)_2$. It follows that the magnitudes of the downfield shifts should be close to one another, and those of the upfield shifts may be widely different, and, consequently, the spacings that separate each pair of doublets, or the chemical shift differences, for the doublets in the spectra of these isomers should differ widely. These turned out as expected. Referring to Table I, the downfield shifts lie within the range 2.87–3.43 ppm; the upfield shifts within the range 1.97–2.81 ppm; and the chemical shift differences extend from 0.49 to 1.47 ppm.

It should be noted that for cis isomers the deshielding effect of σ electrons on equatorial protons[4] does not influence the chemical shift differences, since the protons concerned undergo constant axial–equatorial interconversions. Additionally, the substituent groups that ultimately give rise to chemical shifts are capable of taking favorable orientations for exerting their anisotropic effects on neighboring protons.

Far different are the trans isomers in these respects. In the first place, the effect of the σ electrons of C–C bonds should be taken into consideration, although its magnitude may be very small (see below). Secondly, as mentioned earlier, the spacing that separates the chemical shifts for the ring protons depends on the deshielding effects of one oxo group and one C–C bond, and is practically independent of the effects of other substituent groups attached to the α-carbon atoms. Thirdly, the oxo group,

Table II
Effect of Temperature on the Peaks for Ring Methylene Protons in the Nmr Spectra of Isomeric α,α'-Dimethylsuccinosuccinic Esters in Deuteriochloroform

	Cis isomer, liquid, bp 130° (1 mm) (IVa)		Trans isomer, crystalline, mp 73° (IVb)	
Temp, °C	Apparent chemical shifts of ring protons, ppm	Spacing between the apparent shifts, ppm	Apparent chemical shifts of ring protons, ppm	Spacing between the apparent shift, ppm
20	2.67–3.43	0.76	2.87–3.13	0.26
−11	2.75–3.37	0.62	2.90–3.15	0.25
−38	2.83–3.30	0.47	2.87–3.13	0.26
−48	2.87–3.28	0.41	2.88–3.13	0.25
−58	2.93–3.20	0.27	2.88–3.13	0.25

which is held in a rigid system, should exert a rather small deshielding effect on the neighboring equatorial proton, which is barely embraced in its deshielding cone[8] and should give a small chemical shift. So is the deshielding effect of the C–C bond. All these are reflected in the chemical shifts for the ring protons and their differences for the isomers Ib, IIIb, IVb, and VIb, as listed in Table I. The chemical shift differences for the last three isomers lie within the range 0.26–0.31 ppm, and the lowest value, that for Ib, is 0.13 ppm. The close constancy of the chemical shift differences and their relatively small magnitudes are in good agreement with the deductions outlined above. It may also be inferred that, in our present case, neither the deshielding effect of the oxo group nor that of the C–C bond may produce a shift as much as 0.31 ppm.

While the foregoing considerations justify the assignment of configurations to the α,α'-disubstituted succinosuccinic esters, they do not exclude the possibility that these substances might exist in the boat form. It has been known that for certain derivatives of cyclohexanone, the twist-boat form is preferred.[9]

If we assume that the substituted succinosuccinic esters existed in the boat form, the spacings of the doublets for the ring protons could be correlated in a similar way with the anisotropic effects of the substituent groups on these protons, on the assumption that each isomer consisted of two enantiomeric twist forms, which could be represented by the regular boat form as the average state. However, deductions from such correlation would be contradictory to the experimental facts. For example, while the trans configuration (boat form) should be assigned to Ia, IIIa, IVa, and VIa in the same way as the cis configuration (chair form) had been assigned to them, the spacings of the doublets predicted in the way as previously described for the "trans isomers" (Ia, IIIa, IVa, and VIa) would be definitely smaller than the spacings for the corresponding "cis isomers" (Ib, IIIb, IVb, and VIb). Furthermore, if the cis configuration (boat form) should be assigned to Ib, IIIb, IVb, and VIb, the high flexibility of the molecules would obviate the need of taking some preferred conformation. As a result, all the ring protons would be nonequivalent.

Low-temperature nmr spectroscopy of dimethylsuccinosuccinic esters was carried out, with our original aim focused at testing whether some conformational isomers of the cis form of the ester could be "frozen" so that their chemical shifts could be identified and interpreted. The dimethyl derivatives were chosen as the model compounds on account of their ready solubility in most organic solvents. Solutions of the esters in deuteriochloroform at a concentration of approximately 50 mg/0.5 ml were first used. The effect of low temperatures on the absorptions of the ring methylene protons in IVa and IVb is summarized in Table II. It is seen that in the case of the cis isomer, lowering the temperature resulted in the decrease of the spacing between the doublets for the ring methylene protons, with the two chemical shifts apparently drawing nearer to each other from both directions, while, in the case of the trans isomer, practically no change occurred throughout the entire temperature range investigated. The effect of temperature on the peaks for the ring protons is also shown in Figure 3, which indicates that, while the temperature became lower, the peaks for the ring protons grew broader. At −58°, crystallization of the solute took place. In order that the experiment could be carried out at still lower temperatures, deuteriochloroform was replaced by deuteriomethanol as solvent. The concentration of the solution was also approximately 50 mg/0.5 ml. With these solutions, the nmr spectra showed that the chemical shifts of the doublets for the ring protons were generally more closely spaced as compared with those in the spectra using deuteriochloroform as solvent. At temperatures lower than −65°, the broadened peaks for the ring protons in the spectrum of IVa, instead of separating into more peaks as first expected, fused into a single band which grew flatter with decreasing temperature as shown in Figure 4a. For the isomer IVb, its solution in deuterated methanol at the concentration of approximately 50 mg/0.5 ml was used at first. When the temperature was decreased below −40°, crystallization took place, and the experiment could not be carried any further. A more dilute solution (approximately 10 mg/0.5 ml) was then used. At a temperature as low as −66°, when the solution had set to a jelly-like mass, there was still no change in the spacing between the shifts for the ring protons. In order that the spectra of IVa and IVb may be compared on equal bases, the data that resulted from the use of more concentrated solutions only are shown in Figures 4a and 4b.

The temperature effect on the peaks for the ring methylene protons can be satisfactorily interpreted by presuming the flipover of the cyclohexane ring of the cis isomers of the substituted succinosuccinic esters. The assignment of cis and trans configurations to the pairs of these isomeric esters can be made accordingly, as discussed earlier. Let us consider first the cis isomer of an α,α'-disubstituted succinosuccinic ester. Molecules of this isomer can flip over from one conformer to the other, requiring only a small amount of activation energy. At room temperature, the frequency of interconversion is high, and the two chair conformers, being more stable than the intermediate forms, constitute almost the entire population of the molecules. The chemical shifts of the two pairs of ring protons H_1–H_3 and H_2–H_4 (see foregoing part) are virtually the weighted averages of the chemical shifts of H_1 and H_3, and of those of H_2 and H_4, in the two conformers. As the temperature is reduced, the rate of interconversion between the two conformers is slowed down, chiefly owing to decreased thermal agitation and increased viscosity, and the spectrum becomes broader and changes gradually its overall character, until finally the broadened peaks fuse to a flattened band (Figures 3 and 4). On the other hand, since the spectrum of the trans isomer does not show similar temperature effect, we may presume that the trans isomer exists in the form of a *single, more stable* conformer. A precise interpretation of the temperature ef-

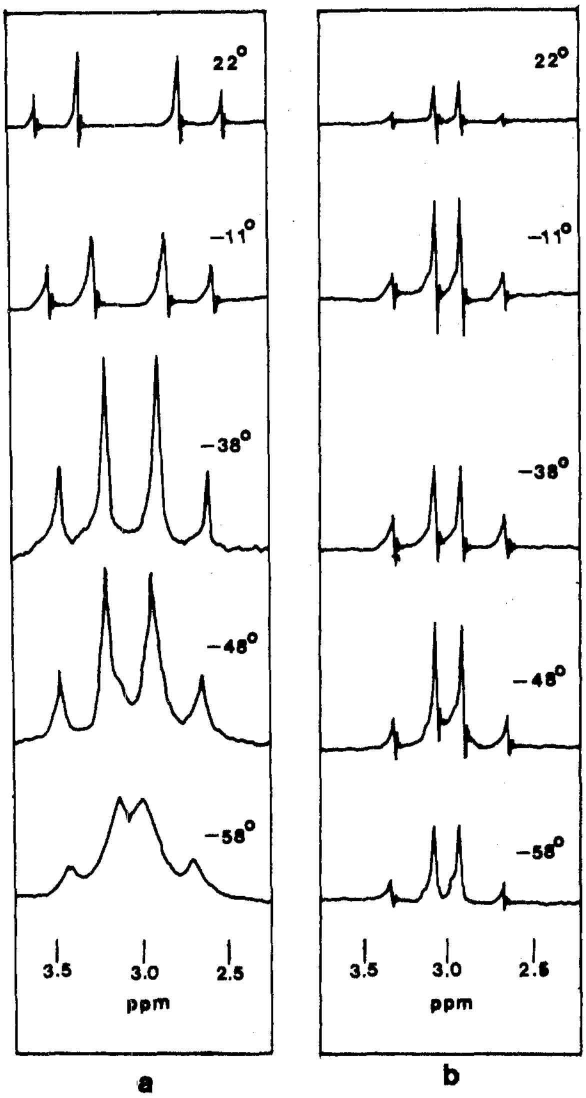


Figure 3. Parts of the nmr spectra of the isomers of dimethylsuccinosuccinic esters (IVa and IVb) embracing only the two doublets for the ring methylene protons, showing the effect of varying temperatures on the spacing that separates the doublets from each other. (a) The doublets for the ring methylene protons in the cis isomer (IVa) approach each other as temperature decreases. (b) Those for the ring methylene protons in the trans isomer (IVb) do not undergo any change in their spacing by decreasing temperature. Solvent used was $CDCl_3$.

fect on the peaks for the ring protons as described above would call for a total line shape analysis. For our present purpose, it is sufficient to demonstrate that the interconversion of the two conformer of the cis isomer of the dimethylsuccinosuccinic ester by flipping back and forth does take place, while the same thing does not occur in the trans isomer.

The decarboxylation of the substituted succinosuccinic esters to give substituted cyclohexanediones deserves mentioning. As we have seen, the products that resulted from the decarboxylation of Ia or Ib and IVa or IVb gave highly complex nmr signals. Attempts were made to decarboxylate Ia or Ib with $CaI_2 \cdot 4D_2O$, with a view to obtaining IIa and IIb, with their α hydrogen replaced by deuterium. However, these resulted in a failure. The nmr spectra of the deuterated products of IIa and IIb show that all the ring hydrogen atoms have been replaced by deuterium. Unexpectedly, the absorptions for benzylic methylene protons, which give a singlet in the spectra of both Ia and Ib, give two doublets in the spectra of the deuterated counterparts IIa and IIb. The same situation of benzylic methylene protons is also observed in the spectrum of VIa. All these have been mentioned in the earlier part of this section. The question may arise, however, as to whether the ring methylene protons or the benzylic protons are replaced by deuterium when Ia or Ib is decarboxylated with $CaI_2 \cdot 4D_2O$, since it had been found that toluene can undergo deuterium exchange in a strongly alkaline medium, resulting in the replacement of side-chain hydrogen by deuterium.[10] This question is easily settled by referring to the mass spectra of deuterated IIa and IIb (see Experimental Section). In both of them the M^+ peak at m/e 298 reveals that 6 out of 14 hydrogen atoms have been replaced by deuterium, and an intense peak of $C_7H_7^+$ at m/e 91 reveals that ring hydrogen atoms, not the benzylic ones, have been replaced by deuterium. For, if the latter hydrogen atoms were replaced, an intense peak of $C_7H_5D_2^+$ should appear at m/e 93, but this was not the case. In the nmr spectra of deuterated Va and Vb, only the methyl protons appear as a singlet, and the doublet characteristic of C_6 ring protons is absent.

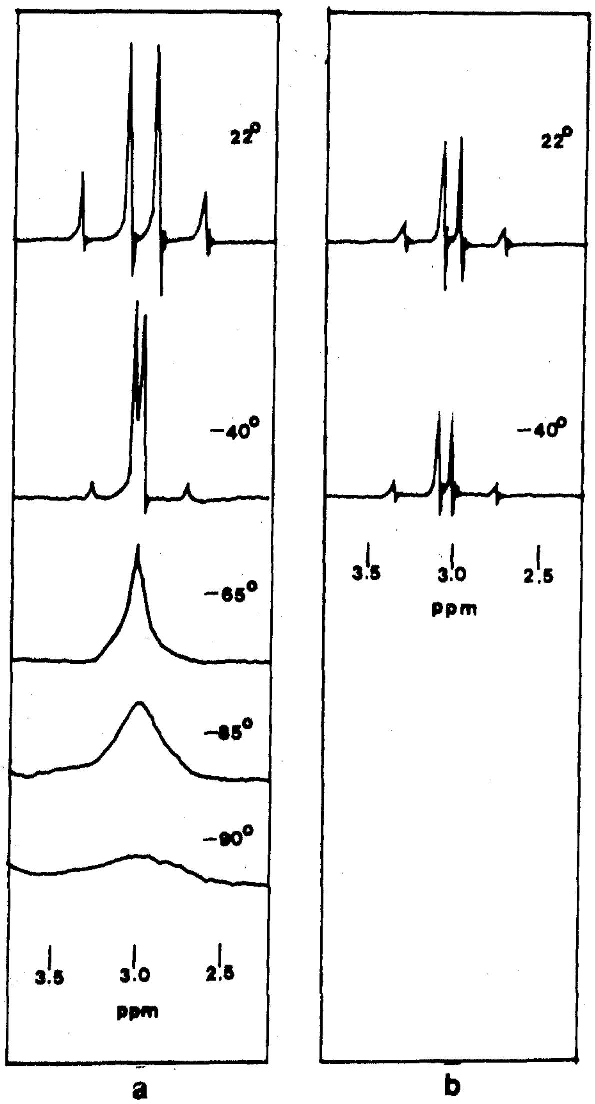


Figure 4. Similar to Figure 3, CD_3OD being used instead of $CDCl_3$ as solvent so as to permit the nmr spectra to be taken at still lower temperatures.

Incidentally, the present investigation firmly establishes the fact that the reaction between disodiosuccinosuccinic ester and benzyl iodide or chloride furnishes the α,α'-dibenzyl derivatives but not the enolic ethers as was regarded by Nef. It also affords examples illustrating the readiness with which β-keto esters, even those known to be resistant to hydrolysis, can be cleaved by the action of hydrated calcium iodide. The formulation of IIa and IIb from either Ia or Ib gives further support to the mechanism suggested by one of the present authors.[3] Equilibration experiments were carried out by the action of ethanolic sodium hydroxide as well as sodium ethoxide on IIa and IIb with a view to further strengthening the establishment of the geometrical isomerism of IIa and IIb. Unexpectedly, the attempt was unsuccessful. Both IIa and IIb were slowly oxidized to deeply colored material when heated in an alkaline medium. Later experiments were conducted in an atmosphere of nitrogen, but the reaction mixture, though only weakly discolored, did not give any crystalline material.

Among the substituted succinosuccinic esters studied in the present work, VIa, VIb, and VII, being previously unknown, were obtained from the reactions of *p*-bromobenzyl bromide and benzhydryl bromide, respectively, on disodiosuccinosuccinic ester. As mentioned earlier, only one isomer of VII, presumably the cis isomer, was isolated. The reason for the failure to obtain the trans isomer is not understood. It is also interesting to note that, while Ib gives a product of much higher melting point but with the same percentage composition on refluxing for a long time with dilute sulfuric acid, the *p*-bromobenzyl analog (VIb) remains unchanged when treated in the same way.

Finally, X-ray analysis of the isomeric di-*p*-bromobenzylsuccinocuccinic esters (VIa and VIb) is being carried out, with the dual purpose of verifying that the substituted succinosuccinic esters exist in the chair, but not in the boat form, and providing justification of the configurations assigned to these esters on the basis of their nmr spectra. Preliminary results from the X-ray analysis of VIb show that the molecule possesses a center of symmetry, indicating that VIb should exist in the chair form, and that it should be the trans isomer. Packing considerations strongly suggest that in this isomer the two bulky *p*-bromobenzyl groups should be in equatorial positions, in agreement with our postulate that in Ib (and IIb, IVb, and VIb) the carbethoxyl groups should take the axial positions for the avoidence of strong dipole–dipole repulsion.

Experimental Section

Reaction between disodiosuccinic Ester and Benzyl Iodide. The disodiosuccinosuccinic ester used was prepared by adding a slight excess of ethanolic sodium hydroxide to a hot ethanolic solution of diethyl succinosuccinate, with vigorous shaking. The magenta-colored disodium enolate was filtered, washed with ethanol, and dried in a vacuum drying oven at 60° until the weight became constant.

Fifteen grams (0.05 mol) of the disodium enolate and 23 g (0.11 mol) of benzyl iodide were placed in a round bottom flask fitted with a reflux condenser, and heated in an oil bath at 140° until the color of the disodium enolate disappeared; 0.5 hr was required. The reaction mixture was extracted with hot benzene and filtered. The filtrate, after removal of benzene, gave pale yellow crystals which on recrystallization from ethanol gave 14.5 g (66%) of colorless needles melting at 128°. This product consisted of a mixture of two components. It was repeatedly recrystallized from ethanol until the less soluble component (Ib) that separated melted at 148.5° (6 g). The combined mother liquor from the recrystallization was evaporated to a small volume. The crystals of the more soluble component (Ia) that separated were recrystallized several times from ethanol. The purified product (5.5 g) melted at 140.5°. On the evidence presented in the foregoing sections, and the the analytical data that follow, the substances Ia and Ib were characterized as *cis-* and *trans*-2,5-dibenzyl-2,5-dicarbethoxycyclohexane-1,4-dione, respectively.

***cis*-2,5-Dibenzyl-2,5-dicarbethoxycyclohexane-1,4-dione (Ia)** was obtained as colorless crystals: mp 140.5°; ir (KBr) 1715 cm^{-1} (ketonic C=O) and absorption maximum characteristic of phenyl group; nmr CDCl$_3$) 7.20 (m, 10, C_6H_5), 4.15 (q, 4, J = 7.0 Hz, CH_2CH_3), 3.20 (s, 4, $CH_2C_6H_5$), 2.90 (d, 2, J = 16.0 Hz, C_6 ring methylene H), 2.33 (d, 2, J = 16.0 Hz, C_6 ring methylene H), and 1.25 ppm (t, 6, J = 7.0 Hz, CH_2CH_3).

Anal. Calcd for $C_{26}H_{28}O_6$: C, 71.48; H, 6.47. Found: C, 71.28, 71.22; H, 6.22, 6.72.

***trans*-2,5-Dibenzyl-2,5-dicarbethoxycyclohexane-1,4-dione (Ib)** was obtained as colorless crystals: mp 148.5°; ir (KBr) 1715 (ketonic C=O), 1745 cm^{-1} (ester C=O), and absorption maximum characteristic of phenyl group; nmr (CDCl$_3$) 7.31 (m, 10, C_6H_5), 4.05 (q, 4, J = 7.0 Hz, CH_2CH_3), 3.23 (s, 4, $CH_2C_6H_5$), 2.83 (d, 1, J = 16.0 Hz, C_6 ring methylene H), 2.70 (d, 2, J = 16.0 Hz, C_6 ring methylene H), and 1.25 ppm (t, 6, J = 7.0 Hz, CH_2CH_3).

Anal. Calcd for $C_{26}H_{28}O_6$: C, 71.48; H, 6.47. Found: C, 71.41, 71.29; H, 6.71, 6.58.

Attempt to Hydrolyze Ia and Ib. A 0.5-g portion of the sample (Ia or Ib) was finely pulverized, dissolved in 2 ml of concentrated sulfuric acid, and then diluted with 20 ml of water. The mixture was refluxed for 48 hr. During the heating, a stream of nitrogen was led through the reaction flask and allowed to pass through a solution of barium hydroxide. No precipitation of barium carbonate was observed. When Ia was used, there was no apparent reaction, and almost all of the starting material was recovered. When Ib was used, a substance of unknown structure was obtained. The latter was purified by recrystallizing from ethanol. Oxidation of this substance with potassium permenganate did not give benzoic acid. The nature of the substance as well as its oxidation product remains to be investigated.

Product of unknown structure was obtained as crystals: mp 272°; ir (KBr) 1690 (ketonic C=O), 1740 cm^{-1} (ester C=O), absorption maximum characteristic of phenyl group absent, broad band at 3390–5590 cm^{-1} probably due to the presence of OH group.

Anal. Calcd for $(C_{26}H_{18}O_6)_n$: C, 71.48; H, 6.47. Found: C, 71.26, 71.27; H, 6.81, 6.57.

Preparation of *cis-* and *trans*-2,5-Dioximino-1,4-dicarbethoxy-1,4-dibenzylcyclohexane. The substances Ia and Ib were converted into the corresponding dioximes by the pyridine method. The crude products were purified by recrystallizing from ethanol.

Dioxime of Ia was obtained as colorless crystals, mp 221° dec.

Anal. Calcd for $C_{26}H_{30}O_6N_2$: C, 67.00; H, 6.44; N, 6.00. Found: C, 66.82, 67.04; H, 6.52, 6.81; N, 6.27, 6.29.

Dioxime of Ib was obtained as colorless crystals, mp 252° dec.

Anal. Calcd for $C_{26}H_{30}O_6N_2$: C, 67.00; H, 6.44; N, 6.00. Found: C, 67.08, 67.08; H, 6.56, 6.58; N, 6.00, 6.02.

Cleavage of Ia and Ib by the Action of Hydrated Calcium Iodide. A mixture of 2.2 g (0.005 mol) of Ia and 8.1 g (0.024 mol) of calcium iodide tetrahydrate was placed in a flat-bottomed flask provided with an outlet tube leading to a downward condenser. The flask was immersed in an oil bath over the hot plate of a magnetic stirrer, and heated with stirring at 170° for 2 hr. The ethyl iodide that distilled over was collected in a strongly cooled receiver, and the carbon dioxide evolved was absorbed in an absorption bottle filled with 40% potassium hydroxide and previously weighed. After the reaction was complete, the reaction mixture was allowed to cool and treated with dilute hydrochloric acid to dissolve unreacted calcium iodide and calcium carbonate formed during the reaction, the carbon dioxide formed being absorbed in a previously weighed absorption bottle. From the weights of carbon dioxide and ethyl iodide produced, it was estimated that at least 78% of the ester was decarboxylated.

The acidified mixture was extracted with chloroform. The chloroform extract on evaporation gave a crystalline material melting at 165°. The latter consisted of two isomers, IIa (mp 155°) and IIb (mp 196°), which were separated by taking advantage of the fact that IIb is less soluble in ether than IIa. The mixture of IIa and IIb was repeatedly crystallized from ether until the less soluble component (IIb) that crystallized melted at 196°. Its homogeneity was confirmed by thin layer chromatography.

The combined mother liquor was evaporated on a hot plate to remove most of the ether. On cooling, IIa crystallized. It was recrystallized several times from ethanol. The melting point of the purified product was 155°. Its homogeneity was also confirmed by thin layer chromatography.

***cis*(?)-2,5-Dibenzylcyclohexane-1,4-dione (IIa)** was obtained as needles, mp 155°, ir (KBr) 1710 cm^{-1} (ketonic C=O) and absorption maximum characteristic of phenyl group.

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.16; H, 6.89. Found: C, 81.90, 81.96; H, 7.01, 7.02.

***trans*(?)-2,5-Dibenzylcyclohexane-1,4-dione (IIb)** was obtained as long needles, mp 196°, ir (KBr) 1701, 1712 cm^{-1} (C=O), and absorption maximum characteristic of phenyl group.

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.16; H, 6.89. Found: C, 81.95, 82.08; H, 7.02, 6.96.

The cleavage of Ib was carried out in exactly the same way as described above for the cleavage of Ia. The same pairs of geometrical isomers IIa and IIb were obtained. The identity of IIa and IIb from the cleavage of Ib with those from the cleavage of Ia was confirmed by thin layer chromatography and ir spectroscopy.

Preparation of *cis*- and *trans*-2,5-Dioximino-1,4-dibenzylcyclohexane. Both IIa and IIb were converted into the corresponding dioximes by the pyridine method. These dioximes were purified by recrystallizing from ethanol.

***cis*(?)-2,5-Dioximino-1,4-dibenzylcyclohexane** was obtained as colorless crystals, mp 220°.

Anal. Calcd for $C_{20}H_{22}O_2N_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.68, 74.12; H, 6.90, 6.92; N, 8.57, 8.64.

***trans*(?)-2,5-Dioximino-1,4-dibenzylcyclohexane** was obtained as colorless crystals, mp 252°.

Anal. Calcd for $C_{20}H_{22}O_2N_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.50, 74.28; H, 6.94, 6.94; N, 8.84, 8.67.

Cleavage of I and II by the Action of Calcium Iodide·4D$_2$O. In a 150-ml flat-bottomed flask was placed 8.1 g (0.024 mol) of calcium iodide tetrahydrate. The flask was fitted with a cork bearing an inlet tube connected to a hydrogen cylinder, and an outlet tube connected to a downward condenser for distillation. A steady stream of hydrogen was allowed to pass over the surface of the salt, and the flask was strongly heated in a sand bath until no more water passed over. The heat source was removed, the flask was allowed to cool to room temperature, and then the stream of hydrogen was cut off. The cork was replaced by another one carrying a dropping funnel, from which 1.92 g (0.096 mol) of deuterium oxide was added into the flask, with vigorous shaking. To the calcium iodide·4D$_2$O thus formed was added 2.2 g (0.005 mol) of Ia or Ib. The flask was fitted with a cork carrying an upright condenser with a drying tube on its top, placed in an oil bath, and heated at 170° with stirring on a magnetic stirrer for 2 hr. The reaction mixture was allowed to cool, and then treated with a solution of deuterated acetic acid (CH_3COOD) in deuterium oxide, to dissolve unreacted calcium iodide and calcium carbonate formed during the reaction. The acidified mixture was extracted with chloroform. The chloroform extract on evaporation gave a mixture of IIa′ and IIb′, deuterated counterparts of IIa and IIb, respectively. They were separated by extraction with ether, in which only IIa′ was soluble. The ether extract on evaporation gave crystals of IIa′, which were purified by crystallization from carbon tetrachloride. The residue insoluble in ether was also purified by recrystallization from carbon tetrachloride to give IIb′.

Deuterated *cis*(?)-2,5-Dibenzylcyclohexane-1,4-dione (IIa′) was obtained as colorless crystals: mp 155°; nmr ($CDCl_3$) 7.22 (m, 10, C_6H_5), 3.19 (d, 2, J = 14.0 Hz, $C_6H_5CH_2$), 2.58 ppm (d, 2, J = 14 Hz, $C_6H_5CH_2$); mass spectrum M$^+$ at m/e 298 ($C_{20}H_{14}D_6O_2$), intense peak at m/e 91 ($C_7H_7^+$).

Deuterated *trans*(?)-2,5-Dibenzylcyclohexane-1,4-dione (IIb′) was obtained as colorless crystals: mp 196°; nmr ($CDCl_3$) 7.26 (m, 10, C_5H_5), 3.17 (d, 2, J = 14.0 Hz, $C_6H_5CH_2$), 2.68 ppm (d, 2, J = 14.0 Hz, $C_6H_5CH_2$); mass spectrum M$^+$ at m/e 298 ($C_{20}H_{14}D_6O_2$), intense peak at m/e 91 ($C_7H_7^+$).

Reaction between Disodiosuccinosuccinic Ester and Methyl Iodide. A mixture of 15 g (0.05 mol) of dried disodiosuccinosuccinic ester and 25.5 g (0.2 mol) of methyl iodide was placed in a round-bottom flask and heated on an oil bath under a reflux condenser until the magenta-colored suspended solid changed to dirty gray. During heating, additional amounts of methyl iodide were introduced into the flask to compensate for its loss by evaporation. When the reaction was complete, the contents of the flask was extracted with hot benzene and filtered. The filtrate was cooled when a crystalline product separated, which on recrystallization from ethanol gave crystals melting at 73°. This was the trans isomer of α,α'-dimethylsuccinosuccinic ester (IVb) which was first isolated by von Baeyer. Further cooling of the benzene mother liquor gave a second crop of IVb. The overall yield of the purified product amounted to 2 g. The mother liquor was evaporated to remove most of the benzene, and the residue was distilled under vacuum. Under 1 mm, a light yellow oil boiling at 130° was collected (10 g). Thin layer chromatography of the oil indicated that it consisted of two major components and one minor component. The former included IVb. To separate the components, about 2 g of the oil was dissolved in a small amount of benzene, and the benzene solution was cautiously introduced to a column packed with silica gel consisting of 15% of Camag DFO and 58% of Merck's Kieselguhr (0.2–0.5 mm). The chromatogram was developed by benzene containing 1% of ethanol and was clearly visible when irradiated with a uv lamp, the more strongly adsorbed material being intensely violet while the less strongly adsorbed one was bluish violet. The components in each zone was eluted out by the same solvent. The eluents of the less strongly adsorbed material still consisted of a mixture of unknown composition. The latter part of the eluents of the more strongly adsorbed material was concentrated by evaporation, and the residue was distilled under vacuum, the fraction boiling at 130° (1 mm) being collected. The product thus obtained consisted of a homogeneous substance, as verified by thin layer chromatography. Its nmr data indicated that it should be IVa.

***cis*-2,5-Dimethyl-2,5-dicarbethoxycyclohexane-1,4-dione (IVa)** was obtained as an oily liquid: bp 130° (1 mm); d^{25} 1.1530; $n^{25}{}_D$ 1.4659; ir (CCl_4) 1735 (ketonic C=O), 1720 cm^{-1} (ester C=O); nmr ($CDCl_3$) 4.21 (q, 4, J = 7.0 Hz, CH_2CH_3), 3.41 (d, 2, J = 16.0 Hz, C_6 ring methylene H), 2.67 (d, 2, J = 16.0 Hz, C_6 ring methylene H), 1.38 (s, 6, CH_3), 1.22 ppm (t, 6, J = 7.0 Hz, CH_2CH_3).

Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.15; H, 7.04. Found: C, 59.02, 58.86; H, 7.28, 7.34.

***trans*-2,5-Dimethyl-2,5-dicarbethoxycyclohexane-1,4-dione (IVb)** was obtained as colorless crystals: mp 73°; ir (KBr) 1728 (ketonic C=O) and 1700 cm^{-1} (ester C=O); nmr ($CDCl_3$) 4.18 (q, 4, J = 7.0 Hz, CH_2CH_3), 3.08 (d, 2, J = 16 Hz, C_6 ring methylene H), 2.85 (d, 2, J = 16.0 Hz, C_6 ring methylene H), 1.40 (s, 6, CH_3), 1.20 ppm (t, 6, J = 7.0 Hz, CH_2CH_3).

Decarboxylation of IV by the Action of CaI$_2$·4D$_2$O. A 1.4-g portion of IVa or IVb was heated with CaI$_2$·4D$_2$O prepared from 8.1 g (0.024 mol) of CaI$_2$·4H$_2$O. The reaction was carried out in exactly the same way as that described for the decarboxylation of Ia or Ib by the action of CaI$_2$·4D$_2$O. After completion of the reaction, the reaction mixture was acidified with CH_3COOD in D_2O. The solution was saturated with NaCl and extracted with chloroform. The crystalline residue that resulted from the evaporation of the dried chloroform extract was fractionally crystallized from ethanol to get two crystalline substances. The one more soluble in ethanol and melting at 87–88° was probably the cis isomer of the deuterated 2,5-dimethylcyclohexane-1,4-dione (IVa) and the other, less soluble in ethanol and melting at 120–121°, was probably the trans isomer (IVb). In the nmr spectra of these substances the only absorption of the α-methyl protons appears as a singlet around 1.40 ppm.

Decarboxylation of IV with D$_2$SO$_4$ in D$_2$O. A 1.4-g portion of IVa or IVb was refluxed with 20 ml of 6 N D_2SO_4 in D_2O until complete solution occurred. The reaction mixture was cooled and then extracted with chloroform. The chloroform extract after drying was evaporated to dryness. The crystalline mass that resulted was fractionally crystallized from ethanol to give deuterated IVa and IVb as described in the foregoing paragraph. The nmr spectra of these substances also showed that all the ring methylene protons had been replaced by deuterons.

Reaction between Disodiosuccinosuccinic Ester and *p*-Bromobenzyl Bromide. Fifty grams (0.2 mol) of *p*-bromobenzyl bromide and a magnetic stirring bar were placed in a flat-bottomed, 250-ml flask fitted with a reflux condenser, and heated in an oil bath over a magnetic stirrer to 130–140°. Thirty grams (0.1 mol) of carefully dried disodiosuccinosuccinic ester was added, while the stirrer was on, in about ten portions. The addition took about 30 min. The reaction was vigorous. At the end of the reaction, the contents of the flask consisted of a brown, crystalline paste containing small granules of unreacted sodium enolate. Thirty milliliters of dry toluene was added, and the mixture was heated for 30 min longer with stirring and then filtered by suction. The filtrate crystallized readily into a crystalline paste. The solid residue on the filter was extracted first with hot chloroform, then with boiling toluene, and finally the residue, consisting mainly of sodium bromide, was treated with water to isolate small amounts of organic crystalline product. The crystalline paste that constituted the main portion of the product was filtered. The crystals collected amounted to 40 g, which on recrystallization twice from toluene melted at 151–152° (32 g). This product was characterized as *cis*-2,5-di-*p*-bromobenzyl-2,5-dicarbethoxycyclohexane-1,4-dione (VIa). The crystals from the chloroform extract, those from the toluene extract, and those obtained by treating the residue with water consisted of one and the same substance. They were combined and the total amount weighed 10 g. The crude product was recrystallized first from toluene, then from chloroform. The pure product (7 g), melting at 216–217°, was characterized as *trans*-di-*p*-bromobenzylcyclohexane-1,4-dione (VIb). The overall yield of the pure isomeric esters was 67%.

cis-**2,5-Di-*p*-bromobenzyl-2,5-dicarbethoxycyclohexane-1,4-dione (VIa)** was obtained as colorless crystals, very soluble in hot toluene and sparingly soluble in the cold. Single crystals for X-ray diffraction were obtainable by crystallization from chloroform: mp 151-152°; ir (KBr) 1710 cm^{-1} (ketonic and ester C=O); nmr ($CDCl_3$) 7.42 (d, 4, J = 9.0 Hz, C_6H_4Br), 6.93 (d, 4, J = 9.0 Hz, C_6H_4Br), 4.17 (q, 4, J = 7.0 Hz, CH_2CH_3), 3.23 (d, 2, J = 14.0 Hz, $CH_2C_6H_4$), 3.11 (d, 2, J = 14.0 Hz, $CH_2C_6H_4Br$), 2.90 (d, 2, J = 16 Hz, C_6 ring methylene H), 2.26 (d, 2, J = 16.0 Hz, C_6 ring methylene H), 1.28 ppm (t, 6, J = 7.0 Hz, CH_2CH_3) ppm.

Anal. Calcd for $C_{26}H_{26}O_6Br_2$: C, 52.53; H, 4.37; Br, 26.90. Found: C, 52.78, 52.78; H, 5.63, 4.60; Br, 26.92.

trans-**2,5-Di-*p*-bromobenzyl-2,5-dicarbethoxycyclohexane-1,4-dione (VIb)** was obtained as colorless crystals slightly soluble in chloroform and acetone and very sparingly soluble in cold benzene and toluene. Single crystals were obtainable by crystallization from 1:1 acetone-benzene: mp 216-217°; ir (KBr) 1710 cm^{-1} (ketonic and ester C=O); nmr ($CDCl_3$) 7.45 (d, 4, J = 9.0 Hz, C_6H_4Br), 7.03 (d, 4, J = 9.0 Hz, C_6H_4Br), 4.07 (q, 4, J = 7.0 Hz, CH_2CH_3), 3.20 (s, 4, $CH_2C_6H_4Br$), 2.83 (d, 2, J = 16.0 Hz, C_6 ring methylene H), 2.66 (d, 2, J = 16.0 Hz, C_6 ring methylene H), 1.13 ppm (t, 6, J = 7.0 Hz, CH_2CH_3).

Anal. Calcd for $C_{26}H_{26}O_6Br_2$: C, 52.53; H, 4.37; B, 26.92. Found: C, 52.66, 52.55; H, 4.62, 4.64; Br, 26.74.

Reaction between Disodiosuccinosuccinic Ester and Benzhydryl Bromide. A mixture of 30 g (0.1 mol) of carefully dried disodiosuccinosuccinic ester and 54.3 g (0.22 mol) of freshly distilled benzhydryl bromide free from HBr was placed in a round-bottom flask fitted with a reflux condenser. Dry toluene was added into the flask in an amount just sufficient to wet the solid mixture. The flask was heated in an oil bath under reflux for 3 hr. The color of the mixture changed from magenta to dirty green. More dry toluene was added into the flask, and the mixture was boiled for a few minutes and then filtered by suction. The filtrate partially crystallized on standing. On filtration, it gave the first crop of crystals, amounting to 23 g. By cooling the mother liquor, a second crop of crystals (10 g) was obtained which was slightly yellow owing to contamination of succinosuccinic ester. This latter can be removed from the main constituent by recrystallization from ligroin (bp 80-100°). The combined crude product free from succinosuccinic ester was crystallized from benzene. The crystals that separated were 'recrystallized several times from benzene. The purified product melted at 213-215° and was characterized as 2,5-dibenzhydryl-2,5-dicarbethoxycyclohexane-1,4-dione, probably having the cis configuration (VIIa). The trans isomer, which should have a higher melting point, did not seem to have been formed.

cis-**2,5-Dibenzhydryl-2,5-dicarbethoxycyclohexane-1,4-dione (VIIa)** was obtained as crystals: mp 213-215°; soluble in benzene, sparingly soluble in cold ethanol; ir (KBr) 1730 (ketonic C=O) and 1750 cm^{-1} (ester C=O), and absorption maximum characteristic of phenyl group; nmr ($CDCl_3$) 7.20 (m, 20, C_6H_5), 5.55 (s, 2, CH), 3.85 (q, r, J = 7.0 Hz, CH_2CH_3), 3.43 (d, 2, J = 16.0 Hz, C_6 ring methylene H), 1.97 (d, 2, J = 16.0 Hz, C_6 ring methylene H), 0.83 ppm (t, 6, J = 7.0 Hz, CH_2CH_3).

Anal. Calcd for $C_{38}H_{36}O_6$: C, 77.72; H, 6.11. Found: C, 77.53, 77.81; H, 6.31, 6.15.

Registry No.—Ia, 50378-31-9; Ia dioxime, 50378-32-0; Ib, 50378-33-1; Ib dioxime, 50378-34-2; IIa, 50378-35-3; IIa dioxime, 50378-36-4; IIa′, 50378-37-5; IIb, 50378-38-6; IIb dioxime, 50378-39-7; IIb′, 50378-40-0; IIIa, 50378-41-1; IIIb, 50378-42-2; IVa, 50378-43-3; IVb, 50378-44-4; VIa, 50378-45-5; VIb, 50378-46-6; VIIa, 50378-47-7.

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Nucleophilic Substitution at Phosphorus. Phosphorothioates[1]

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Cis and trans isomers of 2-substituted 5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinans were used as substrates to determine the stereochemical course of substitution at a thiophosphoryl center. Retention was found to increase with the basicity of the nucleophile while inversion increased with added salts. A mechanism is suggested.

The preparation of an optically active triester of phosphoric acid has not until very recently[2] been accomplished. Thus a definitive study of the stereochemical consequences of nucleophilic substitution at phosphorus in trialkylphosphates has been hindered by the lack of a suitable substrate. This deficiency has, at least to some extent, been overcome by the discovery[3,4] that 2-substituted 5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinans can be prepared in separable cis and trans forms. Fortunately, the geometrical isomers, owing to constraints put on the system by the large preference of groups at phosphorus to be either axial or equatorial, are for all practical purposes conformationally immobile. We have now extended the system to the 2-thio analogs and have studied, as was done previously with their 2-oxo counterparts, the influence of nucleophiles, leaving groups, and salts upon the stereochemistry of nucleophilic substitution at phosphorus.

The stereochemistry of nucleophilic substitutions at thiophosphoryl centers has been the subject of systematic investigations. Most studies which have employed optically active pyrophosphonothioates, phosphonothioic acids, and phosphonochloridothioates have concluded that substitution at thiophosphoryl centers occurs almost exclusively by inversion.[5] Optically active thiophosphates, owing to difficulties in their preparation, have not been investigated.

We have been successful in preparing, and in some cases purifying, a number of 2-substituted 5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinans. In all cases only a single conformer of each isomer was detected, which is in accordance with that reported for similar sys-