B. By Deacetylation of IX.—The physical properties of the trisaccharide obtained follow: mp 185–186°; R_{lactose} 0.6; $[\alpha]^{23}\text{D}$ +30.7° (*c* 0.8, water).

Anal. Calcd for $C_{20}H_{35}NO_{16}\cdot{}^1/_2H_2O$: C, 43.32; H, 6.54. Found: C, 43.13; H, 6.68.

A sample of X obtained *via* VIII gave on acetylation a polyacetyl derivative identical in every respect with IX.

1,4,6-Tri-*O*-acetyl-2-*O*-benzoyl-3-*O*-[2,3,6-tri-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-β-D-galactopyranosyl]-α-D-glucopyranose (XIII).—The homogeneous material obtained after ring opening of XI (0.2 g) and column chromatography as described above was crystallized from ether and a few drops of hexane: yield 0.15 g (64.5%); mp 126–127°; $[\alpha]^{23}\text{D}$ +6.2°; tlc (ethyl acetate) R_{I} 1.3, R_{XI} 1.8, R_{VIII} 1.08. The nmr spectrum indicated a ratio of 30 acetyl to 5 phenyl protons.

Anal. Calcd for $C_{45}H_{57}NO_{26}$: C, 52.58; H, 5.59. Found: C, 52.75; H, 5.47.

2-Acetamido-2-deoxy-*O*-β-D-galactopyranosyl-(1→4)-*O*-β-D-galactopyranosyl-(1→3)-D-glucopyranose (XIV).—Catalytic deacylation of the preceding compound (0.1 g) was carried out as described for V and XI and afforded a substance which was crystallized from methanol–ether (2:1) to yield 50 mg (94%) of a white hygroscopic powder: mp 175–178°; $[\alpha]^{23}\text{D}$ +24.7° (*c* 0.9, water); tlc (benzene–methanol, 1:2) R_{lactose} 0.7, R_{X} 1.15.

Anal. Calcd for $C_{20}H_{35}NO_{16}H_2O$: C, 42.63; H, 6.62. Found: C, 42.85; H, 6.79.

Registry No.—V, 27537-64-0; VI, 27537-65-1; VIII, 27537-66-2; IX, 27537-67-3; X, 27537-68-4; XI, 27537-69-5; XIII, 27537-70-8; XIV, 27537-71-9.

An Attempted Assignment of Absolute Configuration to the *d*-Fecht Acid and Other 2,6-Disubstituted Spiro[3.3]heptane Derivatives

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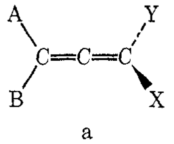
Optically active Fecht acid has been used for the preparation of a number of other optically active 2,6-disubstituted spiro[3.3]heptane derivatives. Application of Lowe's rule to the spiro[3.3]heptane system suggests the *R* configuration for the *d*-spiro[3.3]heptane-2,6-dicarboxylic acid. The optical purity of a few compounds could be determined. A discussion is given on the magnitude of the optical activity of 2,6-disubstituted spiro[3.3]heptanes, as compared to the optical activity of dissymmetrical allenes. The low optical activity of the 2,6-disubstituted spiro[3.3]heptane system gives rise to many exceptions to Lowe's rule, since other effects easily play a role in the optical activity. This is illustrated by carbonyl compounds, among which the Fecht acid (1), many of which show a sign of rotation opposite to the one expected on the basis of Lowe's rule.

In recent years several examples have been described in the literature of absolute configuration assignments to molecules of the allene and spiran type.[1-9] In most cases use was made of a chemical correlation of the configuration of the optically active allenes or spirans with centrodissymmetrical molecules of known configuration. From the results found for allenes, Lowe[10] pointed out that molecules of type a



a

are dextrorotatory at the sodium D line when A is more polarizable than B and X is more polarizable than Y. The Lowe rule is related to other models of optical activity, for example, Kirkwood's model[11] and Brewster's uniform conductor model,[12] and should be generally applicable to helical systems.[4,8] The results found in the alkylidenecycloalkane field seem to be in agreement with Lowe's rule.[4,5] Brewster and Privett, however, have pointed out that a deduction of an absolute configuration from the sign of the optical rotation in the region of the visible absorption spectrum is not without hazard when Cotton effects dominate this optical activity.[4]

Those spirans for which the absolute configuration has been determined owe their optical activity to the nature and the relative position of the rings constituting the spiran system.[13] Two calculations[14] have been reported on the absolute configuration of spirans.[15]

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(1) B. L. Crombie and P. A. Jenkins, *Chem. Commun.*, 870 (1967).

(2) R. J. D. Evans, S. R. Landor, and J. P. Regan, *ibid.*, 397 (1965).

(3) K. Shingu, S. Hagishita, and M. Nakagawa, *Tetrahedron Lett.*, 4371 (1967).

(4) J. H. Brewster and J. E. Privett, *J. Amer. Chem. Soc.*, **88**, 1419 (1966).

(5) H. Gerlach, *Helv. Chim. Acta*, **49**, 1291 (1966).

(6) G. G. Lyle and E. Tyminski Pelosi, *J. Amer. Chem. Soc.*, **88**, 5276 (1966).

(7) G. Krow and R. K. Hill, *Chem. Commun.*, 430 (1968).

(8) J. H. Brewster and R. S. Jones, *J. Org. Chem.*, **34**, 354 (1969).

(9) H. Gerlach, *Helv. Chim. Acta*, **51**, 1587 (1968).

(10) G. Lowe, *Chem. Commun.*, 411 (1965).

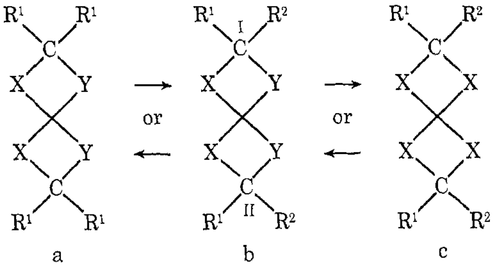
(11) J. G. Kirkwood, *J. Chem. Phys.*, **5**, 479 (1937); W. W. Wood, W. Fickett, and J. G. Kirkwood, *ibid.*, **20**, 561 (1952); H. Looyenga, Thesis, Leiden, 1955.

(12) J. H. Brewster in "Topics in Stereochemistry," Vol. 2, N. L. Allinger and E. L. Eliel, Ed., Interscience, New York, N. Y., 1967.

(13) An illustrative example is 2,7-diazaspiro[4.4]nonane.[7] In such a compound the spiro carbon atom will become an asymmetric carbon atom when one of the rings is made unlike the other one. 4,4'-Dimethoxy-1,1',3,3'-tetrahydrospiro[isoindole-2,2'-isoindolium] bromide[8] belongs to the same class of compounds.

(14) Two tentative determinations of the absolute configurations of spirans whose optical activity is due only to the substitution pattern have to be mentioned. W. Kuhn and K. Bein [*Z. Phys. Chem., Abt, B*, **24**, 335 (1934)], calculated the *S* configuration for *d*-dipyruvic erythritol, and T. M. Lowry and W. C. G. Baldwin [*Proc. Roy. Soc.*, **162**, 204 (1937)], assigned the *S* configuration to *l*-spiro[3.3]heptane-2,6-diamine (**16**).

(15) A *chemical* determination of the absolute configuration of compounds in this category, for instance of the Fecht acid, is more complicated than in the case discussed in ref 13. A general route is shown in the scheme below.



a b c

Molecule a represents a chiral spiran of the category discussed in ref 13 ($X \neq Y$). When the absolute configuration is known, and, in addition the absolute configuration at the carbon atoms C^{I} and C^{II} in molecule b ($R^1 \neq R^2$), the absolute configuration of c may be deduced.

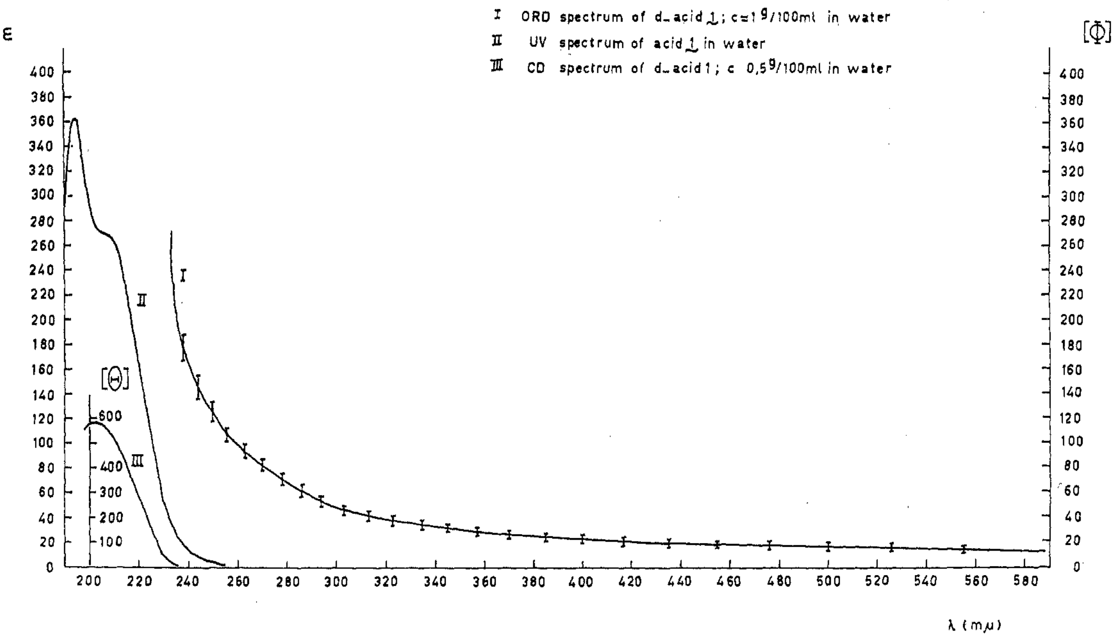
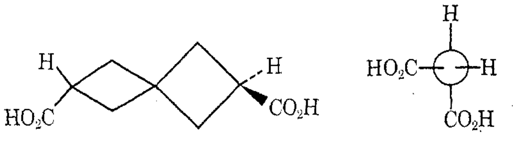


Figure 1.

Preparation of 2,6-disubstituted spiro[3.3]heptanes of known relative configuration should give information about the validity of Lowe's rule for this spiran system.

Using Backer and Schurink's method,[16] we prepared and resolved *dl*-spiro[3.3]heptane-2,6-dicarboxylic acid (**1**) (Fecht acid) and measured the ORD and the CD spectra of the *d* acid **1**, shown in Figure 1, together with the uv spectrum. The ORD spectrum shows a plain curve that could not be measured at a wavelength shorter than 230 mμ. The CD spectrum, however, shows a positive Cotton effect at 203 mμ, $[\theta]$ +570 ± 60. The sign of the Cotton effect is the same as the sign of the optical activity in the visible wavelength region; this makes an assignment of the *S* configuration, expected on basis of the Lowe rule, to the *d* acid **1** rather dubious.[17] In an attempt to clarify this assignment, the optical activities of a number of other 2,6-disubstituted spiro[3.3]heptane derivatives **3–17**, all prepared from optically active Fecht acid, were measured. The rotations of the compounds with the same chirality as the *d* acid **1** are summarized in Table I. The following situation makes reliable assignment of configuration difficult in general. In most compounds containing carbonyl groups, the Cotton effects dominate the optical activity even in the visible region. This means that a positive Cotton effect coupled with a positive rotation in the visible region tells us nothing about the chirality of the dissymmetric portion of the molecule. Only in those cases where (independent of solvent effects) clear sign reversal between the Cotton effect and the rotation in the visible wavelength region is observed can a configurational assignment be made on the basis of this long-wavelength rotation. For our configurational assignment, we have therefore utilized only those compounds (Table I) which show sign reversal independent of solvent effects.

Supporting this use of the sign reversal region for configurational assignment is the fact that compounds **15**, **16**, and **17** are levorotatory. These three compounds have no chromophore and these substituents (compounds **15–17**) cannot show conformational dissymmetry. In the compounds **13** and **14**, the substituents may occur in asymmetrical conformations, giving rise to an additional contribution to the optical activity. These compounds are levorotatory and do not show wavelength-dependent optical rotation sign reversal. Compounds **10**, **11**, and **12** possess substituents which likewise may show asymmetry due to the conformations, and further contain chromophores, which may give rise to Cotton effects. The CD spectra of **10** and **12**, however, do not show maxima or minima, and the compounds are again levorotatory; compound **11**, however, seems to constitute an exception. The behavior of compounds **10** and **12–17** is in accordance with Lowe's rule, suggesting for these levorotatory compounds, and by consequence for the *d*-spiro[3.3]heptane-2,6-dicarboxylic acid (**1**), the *R* configuration.[18]



(*R*)-spiro[3.3]heptane-2,6-dicarboxylic acid (**1**)

Agosta[19] and Gerlach[5] applied Lowe's rule to several spirans, other than Fecht's acid, successfully.

Our data indicate that the optical activity inherent

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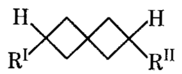
[16] H. J. Backer and H. B. J. Schurink, *Proc. Kon. Ned. Akad. Wetensch.*, **37**, 384 (1928); *Recl. Trav. Chim. Pays-Bas*, **50**, 921 (1931). The authors report the following values for the optical activity of the Fecht acid after resolution with brucine: $[\phi]_{589}$ +2.3°, $[\phi]_{546}$ +2.6°, $[\phi]_{436}$ +3.4° (*c* 6.0, water for the ammonium salt); and $[\phi]_{589}$ +1.9° (for the acid in ether solution).

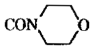
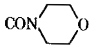
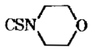
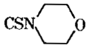
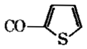
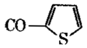
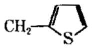
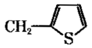
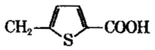
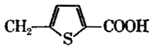
[17] An interpretation of the positive Cotton effect at 203 mμ should be possible and should give a decisive answer about the absolute configuration, according to the sector rule of Klyne for carboxylic acids [J. D. Renwick and P. M. Scopes, *J. Chem. Soc. C*, 1949 (1968)], if the conformational situation of the carboxylic groups could be clarified. This, however, is not the case.

[18] Lowry and Baldwin[14] assign the opposite configurations to spiro[3.3]-heptane-2,6-diamine, based on Born's theory; *cf.* T. M. Lowry, "Optical Rotatory Power," Longmans, Green and Co., London, 1935, p 391.

[19] W. C. Agosta, *J. Amer. Chem. Soc.*, **86**, 2638 (1964).

TABLE I
OPTICAL ACTIVITIES OF COMPOUNDS OF THE TYPE



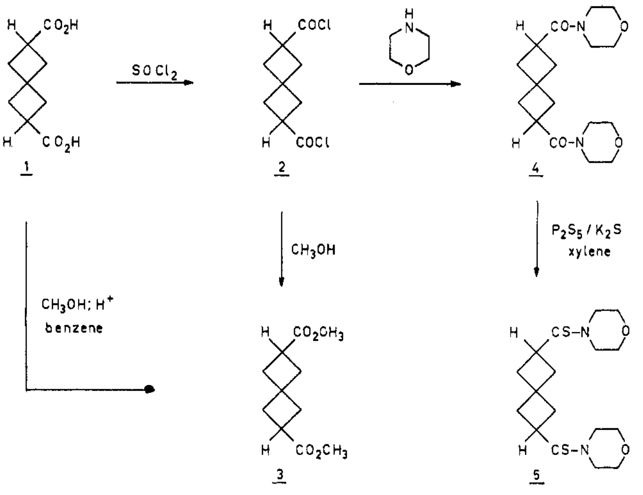
Compd	R^I	R^{II}	CD		ORD			Visible region optical activity					Concn	Solvent	Remarks
			λ_{max}, mμ	[θ]	λ_{peak}, mμ	λ_{trough}, mμ	Amplitude[h]	$[\phi]_{5FS}$	$[\phi]_{546}$	$[\phi]_{436}$	$[\phi]_{405}$	$[\phi]_{365}$	(g/100 ml)		
1	COOH	COOH	203	+570									0.5	Water	a
								+8.6	+9.6	+15.4	+18.2	+23.7	5.3	Acetone	b
								+2.7	+3.3	+4.5	+5.1	+5.4	5.1	Ethanol, 96%	b
								+3.1	+3.5	+5.6	+6.3	+7.7	5.3	Ammonia, 1 *N*	b
3	$COOCH_3$	$COOCH_3$	209	+540									1.5	*n*-Hexane	a
			207	+310									1.1	Ethanol, 96%	a
								+3.2	+3.8	+5.7	+6.5	+7.7	5.0	Acetone	b
								−2.0	−2.2	−4.3	−5.5	−7.8	7.6	*n*-Hexane	b
								+6.7	+7.5	+12.4	+14.7	+18.6	6.2	Ethanol, 96%	b
4								−43.0	−49.3	−86.8	−105.9	−142.9	4.1	Ethanol, 96%	b, d, g
5					357	389	−4.8	−184	−192	−246 ± 10	−238 ± 15	+132	0.3	Dioxane	c, d, f
6								−51.5	−58.7	−103.3	−124.2		8.0	Acetone	b, g
7	$COCH_3$	$COCH_3$						+1.9	+2.5	+11.5	+19.1	+45.1	4.0	Acetone	b, d, e
								−8.6	−11.5	+2.5	+17.6	+77.4	0.6	Cyclohexane	c, d, e
					312	263	+27.1						0.1	Cyclohexane	c, d, e
8	$COC(CH_3)_3$	$COC(CH_3)_3$						−22.8	−25.5	−38.9	−40.9	−33.6	2.0	Ethanol, 96%	b, d, f
					317	256	+19.1	−70	−81	−138	−162	−181	0.3	Cyclohexane	c, d, f
9	$COC(CH_3)_3$	$CONH_2$						−16.6	−18.9	−29.8	−34.4	−37.8	2.0	Ethanol, 96%	b, d,
10								−10.4	−12.2	−21.9	−26.7	−36.1	4.2	Cyclohexane	b
			i										0.03	*n*-Hexane	h
11									+8 ± 2				4.8	Sodium hydroxide, 3 *N*	b
12	$(CH_2)_5COOH$	$(CH_2)_5COOH$						−7.2	−8.1	−14.0			5.0	Acetone	b
			i												i
13	CH_2OH	CH_2OH						−6.2	−6.9	−11.5	−13.7		5.2	Chloroform	b, e
								−3.8	−4.2	−7.6	−8.9		5.0	Ethanol, 96%	b, e
14	CH_2Cl	CH_2Cl						−3.8	−4.4	−7.5	−8.9		11.2	Tetrahydrofuran	b, e
15	CH_3	CH_3						−5.8	−6.5	−10.4	−12.3	−16.6	1.8	Cyclohexane	c, e
16	NH_3Cl	NH_3Cl						−15.1	−17.6	−29.9	−36.0	−48.1	2.2	Water	b, e
17	$N(CH_3)_3I$	$N(CH_3)_3I$						−27.0	−27.0	−42.4	−49.4	−63.8	2.6	Water	b, d, f

[a] Measured at room temperature in a Roussel Jouan Dichrograph II provided with a 50-W deuterium lamp. [b] Measured at room temperature in a Zeiss Lichtelektrisches Präzisionspolarimeter 005 provided with a mercury lamp. [c] Measured at room temperature with a Bendix Ericsson Polarmatic 62 spectropolarimeter provided with a 150-W xenon lamp. [d] Actually the *l* enantiomer of the acid 1 was used in the synthesis of the concerning compounds. The values in Table I are optical activities that should have been found when *d* acid 1 should have been used. [e] The starting material, the acid 1, was optically impure. The values in Table I are corrected to the optical purity of the *d* acid 1. [f] The optical activity of these compounds is not corrected for optical purity of the starting acid 1; the acid used was optically impure. [g] On further crystallization these solid compounds showed a constant optical activity, given in Table I. [h] H. Ripperger, *Z. Chem.*, 6, 161 (1966), or P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, London, Amsterdam, 1965. [i] As was expected, no measurable circular dichroism effect was found.

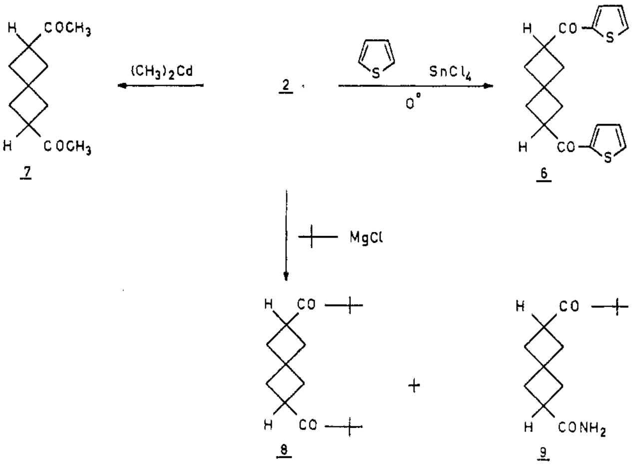
in the dissymmetrical 2,6-disubstituted spiro[3.3]heptane system is small[20] compared to allenes and 4-substituted alkylidenecycloalkanes,[21,22] while the influence of the Cotton effect in the visible wavelength region is much more important in the case of our spiro[3.3]heptane-2,6-dicarboxylic acid (**1**) than it is in the case of the allene acids.

Preparation and Optical Purity.—Starting with the acid chloride **2** of optically active acid **1**, the methyl ester **3** and the morpholide **4** could be prepared in optically active form. The ester **3**, in inactive form prepared by Backer and Kemper[23,24] could also be prepared in optically active form by direct esterification of the acid **1** with methanol. The values of the optical activity of the methyl ester **3**, prepared in these two ways, were approximately the same. The thioamide **5** was prepared in moderate yield from the amide **4** by the action of phosphorus pentasulfide and potassium sulfide in xylene at 70° according to Kindler.[25] These reactions are shown in Scheme I. *l*-2,6-Bis(2′-thenoyl)spiro[3.3]heptane (**6**) was prepared from the *d* acid *via* the acid chloride **2** under mild Friedel–Crafts conditions. The 2,6-diacetylspiro[3.3]heptane (**7**) was synthesized in low yield by reaction of **2** with dimethylcadmium. The reaction of excess **2** with *tert*-butylmagnesium chloride gave 2,6-dipivaloylspiro[3.3]heptane in low yield. During the work-up of the reaction mixture with an ammonium chloride solution, the amide **9** was formed (Scheme II). Clemmensen reduction of *l*-**6** gave a moderate yield of *l*-2,6-bis(2′-thenyl)spiro[3.3]heptane (**10**) while Wolff–Kishner reduction of optically active **6** gave as expected a good yield of racemized **10**. From **10** the diacid **11** could be prepared easily by a Vilsmeier–Haack formylation,[26] followed by oxidation of the aldehyde with silver oxide in alkaline medium to the acid **11**, as shown in Scheme III. The coupling constants for the protons at the 3 and 4 positions of the thiophene rings are 3.5 cps.[27]

Scheme I



Scheme II



Desulfurization of the acid **11** was accomplished in excellent yield by addition of nickel–aluminum alloy to a boiling solution of the acid in 3 *N* sodium hydroxide solution, according to the method of Papa, Schwenk, and Ginsberg.[28] The reduction of racemic dimethyl spiro[3.3]heptane-2,6-dicarboxylate (**3**) with

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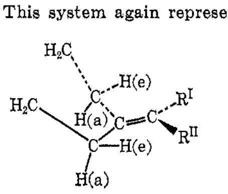
[20] For the optical activity, the following expression is deduced.[12]

$$[\phi]_\lambda = (144\,\pi^2 N_0/\lambda^2)(\beta + \gamma)f(n)$$

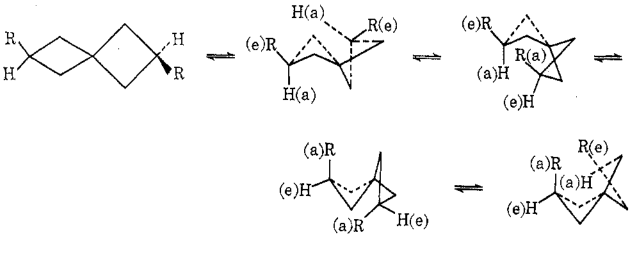
[21] The polarizability of the substituent in the 4 position is perhaps of less importance than the ability of this substituent to make one chair conformation of the cyclohexane ring more favorable than the other one. This has no influence on the sign of rotation in the reported instance,[4,5] if it is assumed that an equatorial position for the methyl group is preferred over an axial one and, secondly, that the sequence of polarizabilities between the methylene groups and axial hydrogen atoms at the 2 and 6 position in the cyclohexane ring is the same one, as the sequence of polarizabilities between methyl and hydrogen at the 4 position. The dissymmetric system is represented in structure b. This system again represents a better conductor



b

than a spiran system does, giving rise to high values of optical activity as compared to the spiran system. This is confirmed by the data of optical rotation for 4-substituted alkylidenecycloalkanes reported in the literature (ref 4 and 5, and cited references).

[22] It is clear from the C-2 symmetry of all (except one) of our spirans that conformational mobility of the spiran system itself can have no influence on the sign of the rotation but only on the magnitude. When the methyl groups in (*S*)-2,6-dimethylspiro[3.3]heptane (R = CH_3) are in the same position (both "equatorial" or both "axial"), the spiran system is in a chiral conformation giving rise to optical activity with the same sign to be expected as one should expect for the 2,6-disubstituted spiro[3.3]heptane system in which the cyclobutane rings are flat. If one substituent is in an "equatorial" and the other one in an "axial" position, the spiran system will give rise to optical activity of the opposite sign. Calculations suggest that these contributions are always smaller than the first ones and therefore are not able to dominate the optical activity.



[23] H. G. Kemper, Thesis, Groningen, 1937.

[24] (a) H. J. Backer and H. G. Kemper, *Recl. Trav. Chim. Pays-Bas*, **57**, 1249 (1938); (b) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, **26**, 54 (1961).

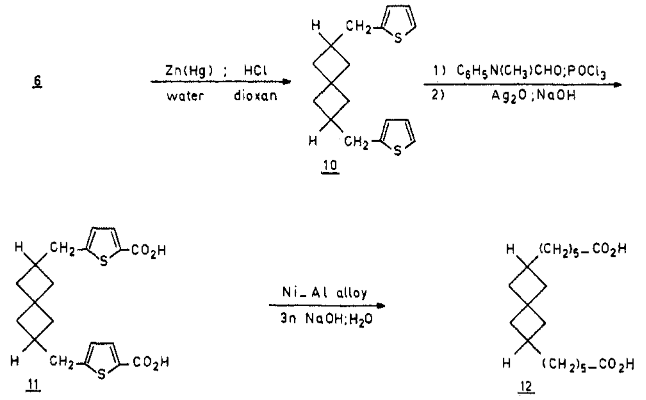
[25] K. Kindler, *Justus Liebigs Ann. Chem.*, **431**, 187 (1923); J. V. Burakevich and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 51 (1965).

[26] A. Vilsmeier and A. Haack, *Ber.*, **60B**, 119 (1927). For a general review, see G. A. Olah and S. J. Kuhn, "Friedel-Crafts and Related Reactions," Vol. III, part II, G. Olah, Ed., Interscience, New York, N. Y., 1964, p 1153.

[27] R. A. Hoffman and S. Gronowitz, *Ark. Kemi*, **16**, 563 (1960).

[28] D. Papa, E. Schwenk, and H. F. Ginsberg, *J. Org. Chem.*, **14**, 723 (1947); M. Sy, *Bull. Soc. Chim. Fr.*, 1175 (1955).

SCHEME III

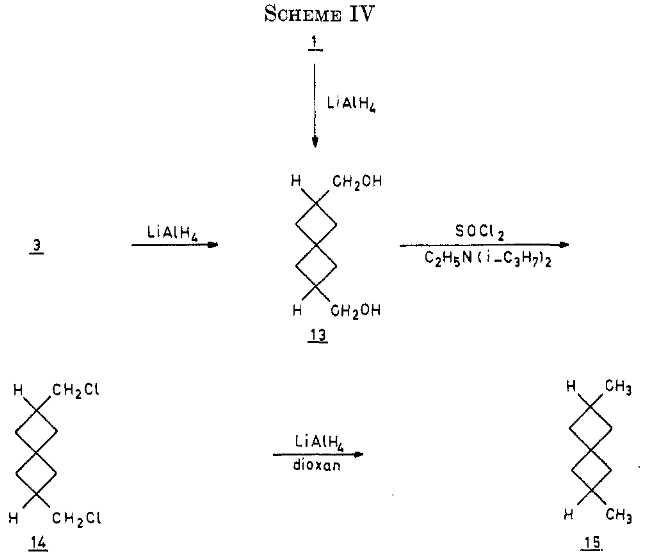


lithium aluminum hydride to yield *dl*-2,6-bis(hydroxymethyl)spiro[3.3]heptane (**13**) has been accomplished.[23,24b]

In the same way *l* diol **13** was prepared *via* the ester **3** from *d*-spiro[3.3]heptane-2,6-dicarboxylic acid (**1**). The *d* diol **13** was prepared in low yield by reduction of the *l* acid **1**.

Reaction of *l* diol **13** with thionyl chloride in ethyldiisopropylamine furnished in sufficient yield *l*-2,6-bis(chloromethyl)spiro[3.3]heptane (**14**), reduction of which with lithium aluminum hydride in boiling dioxane gave *l*-2,6-dimethylspiro[3.3]heptane (**15**) as shown in Scheme IV. Optically pure spiro[3.3]heptane-2,6-diammonium chloride (**16**) has been prepared by Janson and Pope[29] by resolution of the racemic amine with *d*- and *l*-camphorsulfonic acid.

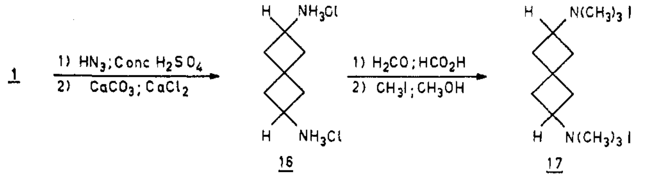
SCHEME IV



For the *l* salt **16** these authors found $[\phi]_{578}$ $-15.5°$, $[\phi]_{546}$ $-17.7°$, and $[\phi]_{436}$ $-30.5°$ (c 2.1, water). In our case *d* acid **1**, $[\phi]_{578}$ $+7.8°$, $[\phi]_{546}$ $+8.8°$, and $[\phi]_{405}$ $+17.0°$ (c 5.0, acetone), was used and the amine hydrochloride **16** prepared from *d* acid **1** showed the following rotations: $[\phi]_{578}$ $-13.7°$, $[\phi]_{546}$ $-16.0°$, and $[\phi]_{436}$ $-27.2°$ (c 2.2, water). This means that the optical purity of the acid **1** used is at least 90%. This value is in agreement with the maximal optical activity found by us for the Fecht acid **1**, $[\phi]_{578}$ $+8.6°$, $[\phi]_{546}$ $+9.6°$, and $[\phi]_{405}$ $+18.2°$ (c 5.3 in acetone), the resolution of the Fecht acid **1** with brucine according to Backer and Schurink being as efficient as the resolution of spiro[3.3]heptane-2,6-diamine with camphorsulfonic acid according to Janson and Pope.[29,30]

The Leuckart reaction (Eschweiler–Clark procedure)[31] applied to the *d* amine hydrochloride **16**, followed by methiodation of the tertiary amine, furnished *d*-spiro[3.3]heptane-2,6-bis(dimethylamine) dimethiodide (**17**) as shown in Scheme V. There is no reason to presume racemization during the preparation of the methiodide **17**. The rotations given in Table I are therefore the values for at least 75% optically pure methiodide **17**.

SCHEME V



The optical purity of the diol **13** was determined by oxidation of the *d* diol **13** with potassium permanganate in 1.5 *N* sulfuric acid at room temperature. The *l* acid **1** obtained in this way showed the same rotation within the error as the *l* acid **1** used for the preparation of *d* diol **13**. The *l* diol **13** prepared by reduction of the methyl ester of *d* acid **1** showed a rotation of the same magnitude as the *d* diol **13** did, proving the optical purity of the ester **3** and of the intermediate spiro[3.3]heptane-2,6-dicarbonyl chloride (**2**), used as the starting material in the preparation of compounds **3–9**.

The optical purity of 2,6-bis(chloromethyl)spiro[3.3]heptane (**14**) or 2,6-dimethylspiro[3.3]heptane (**15**) has not been determined.

Repeated crystallization of the morpholide **4** gave a sample, the rotation of which on continued crystallization showed no further change; this indicates that the compound is probably optically pure.[32] The same argument may be applied to 2,6-bis(2′-thenoyl)spiro[3.3]heptane (**6**). No data are available on the optical purity of the other compounds.

Experimental Section

Boiling points are uncorrected. Melting points were determined on a Mettler FP1 apparatus, at a warm-up rate of 0.2°/min unless otherwise stated.[33] Infrared spectra were recorded on a Unicam SP 200 infrared spectrophotometer. Ultraviolet spectra were obtained on a Zeiss PMQ II apparatus. Nmr spectra were recorded on a Varian A-60 instrument using tetramethylsilane as internal standard. Mass spectra were run on an AEI MS 902 mass spectrometer. Microanalyses were performed in the analytical section of our department under the supervision of Mr. W. M. Hazenberg.

Optical activity was measured on a Zeiss Lichtelektrisches Präzisionspolarimeter 005, using a 1-dm cell. Where this is mentioned, a Bendix Ericsson Polarmatic 62 is used, provided

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(29) S. E. Janson and W. J. Pope, *Proc. Roy. Soc., Ser. A*, **154**, 53 (1936).

(30) It means that the *d* acid **1** used was optically pure. This is of importance since there exists some doubt about the optical purity of the Fecht acid **1** resolved *via* the brucine salt; *cf.* E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 310.

(31) M. L. Moore, *Org. React.*, **5**, 301 (1949).

(32) This method of the determination of optical purity is only relatively reliable; *cf.* M. Raban and K. Mislow, ref 12, p 199.

(33) Occasionally we record melting points (one value) instead of melting ranges. These melting points are derived when no recorder is used.

with a 150-W Xenon lamp and a 0.1-dm cell. Concentrations are given as grams/100 ml. The measurements were taken at room temperature. Ellipticity was measured with a Roussel-Jouan Dichrograph II, provided with a deuterium lamp.

***dl*-Spiro[3.3]heptane-2,6-dicarboxylic acid** (1) was prepared according to Backer and Schurink[16] starting with 200 g (0.5 mol) of 1,3-dibromo-2,2-bis(bromomethyl)propane.[34] In contrast to the procedure of these authors, the spiro[3.3]heptane-2,2,6,6-tetracarboxylic acid was not isolated by ether extraction, but, after acidification of the solution of the potassium salt in water with 400 ml of concentrated hydrochloric acid, water was evaporated and the residue pyrolyzed at 190° for 1 hr under reduced pressure (30 mm). Extraction of the reaction product in a Soxhlet apparatus with ethyl acetate, evaporation of the solvent, and crystallization of the residue from water gave *dl*-spiro[3.3]-heptane-2,6-dicarboxylic acid (1) in yields varying from 65 to 75% (lit.[16,24] 75 to 80%).

***d*-Spiro[3.3]heptane-2,6-dicarboxylic Acid** (1).—The resolution of the *dl* acid 1 was accomplished according to Backer and Schurink[16] using 171 g (0.43 mol) of brucine, 40 g (0.22 mol) of *dl*-spiro[3.3]-heptane-2,6-dicarboxylic acid, and 3 l. of distilled water. The boiling solution was filtered and placed in a haybox. After cooling to room temperature the supernatant liquid was decanted and the residue was dissolved again. After five crystallizations the brücine salt was dissolved in water and 50 ml of concentrated ammonia was added. Brucine separated and after one night it was filtrated over a Büchner funnel. The filtrate was washed with chloroform, evaporated to a volume of 50 ml, and acidified with concentrated hydrochloric acid, and the precipitated acid was recrystallized from water, yielding 8–12 g (40–60%) of the *d* acid **1**: $[\phi]_{578}$ +8.7°, $[\phi]_{546}$ +9.9°, $[\phi]_{436}$ +15.9°, $[\phi]_{405}$ +18.8°, $[\phi]_{365}$ +23.9° (*c* 5.3, acetone); $[\phi]_{578}$ +2.7°, $[\phi]_{546}$ +3.3°, $[\phi]_{436}$ +4.5°, $[\phi]_{405}$ +5.1°, $[\phi]_{365}$ +5.4° (*c* 5.1, ethanol 96%); $[\phi]_{578}$ +3.1°, $[\phi]_{546}$ +3.5°, $[\phi]_{436}$ +5.6°, $[\phi]_{405}$ +6.3°, $[\phi]_{365}$ +7.7° (*c* 5.3, ammonia); $[\theta]_{203}$ +570 ± 60 in water (ref 16).

***l*-Spiro[3.3]heptane-2,6-dicarboxylic Acid** (1).—The mother liquor obtained after the first crystallization of the brucine salt of *dl*-spiro[3.3]heptane-2,6-dicarboxylic acid (**1**) was boiled in a beaker until the volume (originally 3 l.) was reduced to 2 l. A small amount of the salt separated on cooling. This was removed and the filtrate was concentrated again in the same way to 1 l. After separation and removal of a second crop of the salt, 40 ml of concentrated ammonia was added to the filtrate. The work-up, in the same way as described for the *d* acid **1** in the preceding section, gave 5–7 g (25–35%) of the *l* acid **1** with optical purity varying from 70 to 80% (related to the optical activity of the *d* acid **1**).

Spiro[3.3]heptane-2,6-dicarbonyl Chloride (2).—A mixture of 18.5 g (0.10 mol) of spiro[3.3]heptane-2,6-dicarboxylic acid (**1**) and 25 ml of thionyl chloride was stirred for 90 min at 50°. Excess of thionyl chloride was removed at reduced pressure and distillation furnished 20.4 g (0.092 mol or 92%) of acid chloride, bp 103–107° (0.5 mm) [lit.[24] bp 154° (15 mm)].

***d*-Dimethyl Spiro[3.3]heptane-2,6-dicarboxylate** (3) was prepared from *d*-spiro[3.3]heptane-2,6-dicarboxylic acid (**1**), $[\phi]_{578}$ +8.6° (*c* 5.0, acetone), *via* the acid chloride **2** and absolute methanol according to Backer and Kemper:[23,24] $n^{20}{}_{\mathrm{D}}$ 1.4626; $[\phi]_{578}$ +3.3°, $[\phi]_{546}$ +3.7°, $[\phi]_{436}$ +5.5°, $[\phi]_{405}$ +6.4° (*c* 4.8, acetone). After one distillation the optical activity remained unchanged: bp 164–167° (17 mm); $n^{20}{}_{\mathrm{D}}$ 1.4624; $[\phi]_{578}$ +3.2°, $[\phi]_{546}$ +3.8°, $[\phi]_{436}$ + 5.7°, $[\phi]_{405}$ +6.5°, $[\phi]_{365}$ +7.7° (*c* 5.0, acetone); $[\phi]_{578}$ −2.0°, $[\phi]_{546}$ −2.2°, $[\phi]_{436}$ −4.3°, $[\phi]_{405}$ −5.5°, $[\phi]_{365}$ −7.8° (*c* 7.6, *n*-hexane); $[\phi]_{578}$ +6.7°, $[\phi]_{546}$ +7.5°, $[\phi]_{436}$ +12.4°, $[\phi]_{405}$ +14.7°, $[\phi]_{365}$ +18.6° (*c* 6.2, ethanol 95%); $[\theta]_{209}$ +540 (*n*-hexane); $[\theta]_{207}$ +310 (ethanol 95%).

Alternative Preparation of *d*-Dimethyl Spiro[3.3]heptane-2,6-dicarboxylate (3).—A mixture of 6.2 g (0.034 mol) of *d*-spiro[3.3]-heptane-2,6-dicarboxylic acid (**1**) {$[\phi]_{578}$ +7.3°, $[\phi]_{546}$ +8.2°, $[\phi]_{436}$ +13.5°, $[\phi]_{405}$ +16.0° (*c* 5.2, acetone)}, 80 ml of benzene, 33 ml of methanol, and 7 ml of concentrated sulfuric acid was refluxed over a period of 5 hr. The mixture was allowed to cool, poured onto melting ice, and worked up with ether, furnishing 6.9 g (0.033 mol or 96%) of diester **3**: $n^{20}{}_{\mathrm{D}}$ 1.4620; $[\phi]_{578}$ +3.2°, $[\phi]_{546}$ +3.5°, $[\phi]_{436}$ +4.9°, $[\phi]_{405}$ +5.6° (*c* 4.6, acetone).

***d*-2,6-Bis(morpholinocarbonyl)spiro[3.3]heptane** (4).—To a stirred and ice-cooled solution of 2.0 g (0.009 mol) of spiro[3.3]-heptane-2,6-dicarbonyl chloride (**2**), prepared from the *l* acid **1** {$[\phi]_{578}$ −6.8°, $[\phi]_{405}$ −15.6° (*c* 5.5, acetone)} in 20 ml of dioxane was added a solution of 4.0 g (0.046 mol of morpholine in 40 ml of dioxane over a period of 10 min. After a further 20 min the reaction mixture was filtered, and the solvent was removed by evaporation yielding 2.9 g of a solid residue. One crystallization from ethyl acetate gave 2.4 g of the compound, showing $[\phi]_{546}$ +37.6° (*c* 4.2, ethanol 96%). A constant optical activity of the product was observed after four crystallizations: mp 167–170°; ir (KBr) 1630 (C═O); yield 2.7 g (8.4 mol or 93%); $[\phi]_{578}$ +43.0, $[\phi]_{546}$ +49.3°, $[\phi]_{436}$ +86.3°, $[\phi]_{405}$ +105.9°, $[\phi]_{365}$ +142.9° (*c* 4.1, ethanol 96%).

Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.13; N, 8.69; mol wt, 322.41. Found: C, 63.3, 63.3; H, 8.2, 8.0; N, 8.8, 8.7.

***d*-2,6-Bis(morpholinothiocarbonyl)spiro[3.3]heptane** (5) was prepared according to Kindler's method[25] from a homogeneous mixture of 450 mg of potassium sulfide, 500 mg of phosphorus pentasulfide, and 300 mg (0.93 mmol) of *d*-2,6-bis(morpholinocarbonyl)spiro[3.3]heptane (**4**), $[\phi]_{546}$ +32.2° (*c* 4.0, ethanol 96%), in 4.0 ml of dry xylene. The mixture was stirred for 1.5 hr at room temperature and 1 hr at 70°. The xylene layer was removed and the solid was extracted six times with 4-ml portions of xylene at 70°. On cooling of the combined xylene solutions, a white solid separated. Three crystallizations from ethanol (96%) furnished an analytically pure sample: mp 201.4° (warm-up rate 10°/min); mass spectrum (70 eV) *m/e* (rel intensity) 354 (100), 338 (6), 321 (18), 268 (11), 236 (24), 224 (30), 209 (23), 196 (47), 182 (26), 164 (24), 157 (44), 130 (23), 86 (95), 71 (60); ir (KBr) showed no carbonyl absorption; uv max (dioxane) 364 mμ (ε 104) and 280 (26,700); yield 160 mg (0.45 mmol or 48%) of crude product; $[\phi]_{555}$ +189 ± 3°, $[\phi]_{500}$ +216 ± 2°, $[\phi]_{455}$ +250 ± 10°, $[\phi]_{408}$ +238 ± 12°, $[\phi]_{389}$ +290 ± 26°, $[\phi]_{371}$ 0°, $[\phi]_{357}$ −185 ± 12°, $[\phi]_{342}$ −113 ± 12°, $[\phi]_{333}$ −245 ± 12°, $[\phi]_{228}$ −800 ± 60° (*c* 0.33, dioxane; Bendix Ericsson Polarmatic 62).

Anal. Calcd for $C_{17}H_{26}N_2O_2S_2$: C, 57.59; H, 7.39; N, 7.90; S, 18.09; mol wt, 354.54. Found: C, 57.6, 57.5; H, 7.4, 7.4; N, 8.1, 8.1; S, 18.0, 18.0.

***dl*-2,6-Bis(2′-thenoyl)spiro[3.3]heptane** (6).—From 20.4 g (0.092 mol) of *dl*-spiro[3.3]heptane-2,6-dicarbonyl chloride (**2**) the diketone was prepared under the same conditions that Schuetz and Baldwin[35] used for the preparation of 1,4-bis(2′-thenoyl)-butane. To a solution of the acid chloride **2** in 34 ml of thiophene, 140 ml of benzene, and 14 ml of carbon disulfide, stirred at 0°, was added 60 g of stannic tetrachloride at such a rate that the temperature remained below 10°. The mixture was stirred at room temperature for another hour and then poured onto 1500 g of crushed ice and 700 ml of concentrated hydrochloric acid, and the product was worked up with ether. The crude product, 26.9 g (0.085 mol or 92%), melting at 83–86°, was crystallized three times from petroleum ether (60–80°), furnishing a pure fraction melting at 81.9–82.9°: ir (KBr) 1650 cm^{-1} (C═O); uv max (96% ethanol) 261 mμ (ε 21,400) and 284 (18,300); nmr (deuteriochloroform) δ 7.66 (d, 4, J = 5.0 cps), 7.06 (quartet, 2, J = 3.6 cps and 5.0 cps), 4.07–3.48 (quintet, 2), and 2.75–2.12 (m, 8).

Anal. Calcd for $C_{17}H_{16}O_2S_2$: C, 64.52; H, 5.10; S, 20.27; mol wt, 316.43. Found: C, 64.9, 64.6; H, 5.2, 5.2; S, 20.0, 20.1.

***l*-2,6-Bis(2′-thenoyl)spiro[3.3]heptane** (6).—From 7.1 g (0.039 mol) of *d*-spiro[3.3]heptane-2,6-dicarboxylic acid (**1**) {$[\phi]_{578}$ +8.7°, $[\phi]_{546}$ +9.9°, $[\phi]_{405}$ +18.8° (*c* 5.2, acetone)} *via* the acid chloride **2** the diketone **6** was prepared. The crude product (10.5 g) furnished on crystallization from petroleum ether a first fraction of 4.1 g: mp 96.0–97.0°; $[\phi]_{578}$ −51.5°, $[\phi]_{546}$ −58.7°, $[\phi]_{436}$ −103.3°, $[\phi]_{405}$ −124.2° (*c* 8.0, acetone). A subsequent fraction (2.5 g) showed $[\phi]_{578}$ −45.0°, $[\phi]_{436}$ −90.4° (*c* 7.9, acetone).

***l*-2,6-Diacetylspiro[3.3]heptane** (7).—Under the conditions used by Pinson and Friess for the synthesis of methyl cyclobutyl ketone,[36] *l*-2,6-diacetylspiro[3.3]heptane (**7**) was prepared from 6.0 g (0.027 mol) of spiro[3.3]heptane-2,6-dicarbonyl chloride (**2**) {from *l* acid; $[\phi]_{578}$ −6.8°, $[\phi]_{405}$ −15.6° (*c* 5.5, acetone)}. Distillation of the crude product gave 700 mg (3.9 mmol or 14%) of diketone **7**, bp 92–94° (0.6 mm). Analytically pure **7** was obtained after another distillation: $n^{20}{}_{\mathrm{D}}$ 1.4718; ir (neat)

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[34] H. L. Herzog, "Organic Syntheses," Collect. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, p 753.

[35] R. D. Schuetz and R. A. Baldwin, *J. Org. Chem.*, **27**, 2841 (1962).

[36] R. Pinson and S. L. Friess, *J. Amer. Chem. Soc.*, **72**, 5333 (1950).

1705 (C═O) and 1365 cm^{-1} ($COCH_3$); uv max (cyclohexane) 284 mμ (ε 64); nmr (deuteriochloroform) δ 3.38–2.84 (quintet, 2), 2.04 (s), and 2.37–2.00 (m, together 14 H); $[\phi]_{578}$ −1.5°, $[\phi]_{546}$ −2.0°, $[\phi]_{436}$ −9.2°, $[\phi]_{405}$ −15.3°, $[\phi]_{365}$ −36.0° (*c* 4.0, acetone); $[\phi]_{526}$ +9.2°, $[\phi]_{435}$ −1.6°, $[\phi]_{357}$ −78.5° (*c* 0.55, cyclohexane; Bendix Ericsson Polarmatic 62); $[\phi]_{323}$ −460°, $[\phi]_{312}$ −760°, $[\phi]_{303}$ −680°, $[\phi]_{293}$ 0°, $[\phi]_{270}$ +1320 ± 50°, $[\phi]_{263}$ +1390 ± 70°, $[\phi]_{245}$ +1300 ± 40°, $[\phi]_{233}$ +1340 ± 70°, $[\phi]_{222}$ +1490 ± 80° (*c* 0.11, cyclohexane; Bendix Ericsson Polarmatic 62).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95; mol wt, 180.25. Found: C, 73.2, 73.5; H, 9.0, 8.9.

d-**2,6-Dipivaloylspiro[3.3]heptane** (**8**).—To a solution of 4.8 g (0.022 mol) of spiro[3.3]heptane-2,6-dicarbonyl chloride (**2**) {prepared from *l* acid; $[\phi]_{578}$ −6.8°, $[\phi]_{405}$ −15.6° (*c* 5.5, acetone)} in 50 ml of dry ether was added over a period of 30 min 40 ml of a 0.65 *N* solution of *tert*-butylmagnesium chloride in ether.

During this period and 1 hr thereafter the reaction mixture was stirred at −30°. After stirring for another 4 hr at room temperature, 100 ml of a solution of ammonium chloride in water was added and the reaction mixture was worked up in the normal way. The crude product was dissolved in cyclohexane. Concentration furnished a residue which crystallized from a mixture of equal volume of water and ethanol, to give 800 mg (0.003 mol or 14%) of **8**. After three crystallizations from ethanol with 10% water, an analytically pure sample was obtained: mp 92.8° (warm-up rate 10°/min); ir (Nujol) 1690 cm^{-1} (C═O); uv max (cyclohexane) 296 mμ (ε 67); nmr (carbon tetrachloride) δ 3.71–3.15 (quintet, 2), 2.51–1.87 (m, 8), 1.07 (s, 18); $[\phi]_{578}$ +22.8°, $[\phi]_{546}$ +25.5°, $[\phi]_{436}$ +38.9°, $[\phi]_{405}$ +40.9°, $[\phi]_{365}$ +33.6° (*c* 2.0, ethanol 96%); $[\phi]_{526}$ +86.6 ± 3.5°, $[\phi]_{400}$ +165.4 ± 3.2°, $[\phi]_{370}$ +184.0 ± 5.6°, $[\phi]_{435}$ +170.7 ± 11.1°, $[\phi]_{328}$ 0°, $[\phi]_{318}$ −175.5 ± 21.6°, $[\phi]_{307}$ 0°, $[\phi]_{286}$ +1190 ± 10°, $[\phi]_{270}$ +1620 ± 12°, $[\phi]_{250}$ +1800 ± 25°, $[\phi]_{238}$ +2120 ± 30° (*c* 0.33, cyclohexane; Bendix Ericsson Polarmatic 62).

Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67; mol wt, 264.41. Found: C, 77.4, 77.0; H, 10.7, 10.7.

d-**6-Pivaloylspiro[3.3]heptane-2-carboxamide** (**9**).—As stated above the crude reaction product from **8** was dissolved in cyclohexane. White crystals separated from the mixture. The compound was isolated and recrystallized from acetone to give an analytically pure sample melting at 184.3° (warm-up rate 10°/min): ir (KBr) 3370 and 3200 (NH_2), 1655 and 1630 ($CONH_2$), 1300 cm^{-1} ($COC(CH_3)_3$); nmr (deuteriochloroform) δ 6.38–5.48 (broad s, 2), 3.81–3.25 (quintet, 1), 3.07–2.50 (quintet, 1), 2.50–1.40 (m, 8), 1.09 (s, 9); mass spectrum (70 eV) *m/e* (rel intensity) 223 (20), 166 (100), 138 (16), 121 (13), 95 (68), 93 (38), 79 (13), 77 (12), 72 (22), 67 (25), and 57 (68); $[\phi]_{578}$ +16.6°, $[\phi]_{546}$ +18.9°, $[\phi]_{436}$ +29.8°, $[\phi]_{405}$ +34.4°, $[\phi]_{365}$ +37.8° (*c* 2.0, ethanol 96%).

Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27; ml wt, 223.32. Found: C, 70.2, 70.2; H, 9.6, 9.4; N, 6.2, 6.2.

dl-**2,6-Bis(2′-thenyl)spiro[3.3]heptane** (**10**).—A mixture of 8.0 g (0.025 mol) of *dl*-2,6-bis(2′-thenoyl)spiro[3.3]heptane (**6**), 25 ml of 100% hydrazine hydrate, and 125 ml of diethylene glycol was kept at 150° during 4 hr and allowed to cool to room temperature. This mixture was added dropwise over a period of 45 min to a stirred solution of 20 g of potassium hydroxide in 300 ml of diethylene glycol. During the addition and for 1 hr after it the temperature was kept at 230–240° by distilling off water and excess hydrazine. The reaction mixture was cooled and then poured onto crushed ice and 100 ml of hydrochloric acid. The organic layer was taken up into ether yielding, after work-up in the normal way, removal of the solvent, and column chromatography over neutral alumina (Merck, Aktivitätsstufe 1) with cyclohexane as eluent, 5.5 g (0.019 mol or 76%), of *dl*-**10**: bp 158–160° (0.3 mm); $n^{20}{}_{\mathrm{D}}$ 1.5704; uv max (ethanol 96%) 235 mμ (ε 16,800); nmr (carbon tetrachloride) δ 7.00–6.50 (m, 6), 2.78 (d, 4), 2.66–1.42 (m, 10).

Anal. Calcd for $C_{17}H_{20}S_2$: C, 70.78; H, 6.99; S, 22.23; mol wt, 288.46. Found: C, 70.9, 70.8; H, 7.0, 7.1; S, 22.3, 22.0.

l-**2,6-Bis(2′-thenyl)spiro[3.3]heptane** (**10**).—Amalgamated zinc was prepared from 200 g of zinc wool in a 2-l. three-necked round-bottomed flask. The amalgam was covered with 300 ml of 6 *N* hydrochloric acid, followed by a solution of 15.0 g (0.047 mol) of *l*-2,6-bis(2′-thenoyl)spiro[3.3]heptane {$[\phi]_{578}$ −51.5°, $[\phi]_{436}$ −103.3° (*c* 8.0, acetone)} in 350 ml of dioxane. In the boiling and stirred mixture gaseous hydrogen chloride was introduced, until after about 5 hr most of the zinc had disappeared. The reaction mixture was cooled to room temperature and then poured out into 1 l. of water and the product was taken up in ether. The ether solution was washed with bicarbonate solution and water and then dried over magnesium sulfate; ether was removed.

Column chromatography over neutral alumina (Merck Aktivitätsstufe 1) with cyclohexane as eluent yielded, after evaporation of the solvent, 6.9 g (0.024 mol or 51%) of pure 2,6-bis(2′-thenyl)spiro[3.3]heptane (**10**) as a colorless liquid, $n^{20}{}_{\mathrm{D}}$ 1.5711. The infrared spectrum is identical with that of the racemic compound: $[\phi]_{578}$ −10.4°, $[\phi]_{546}$ −12.2°, $[\phi]_{436}$ −21.9°, $[\phi]_{405}$ −26.7°, $[\phi]_{365}$ −36.1° (*c* 4.2, cyclohexane).

No maximum or minimum between 200 and 400 mμ could be detected in the circular dichroism spectrum of a solution of 7.5 mg of the *l* compound {$[\phi]_{578}$ −5.8°, $[\phi]_{436}$ −12.4° (*c* 5.0, cyclohexane)} in 25 ml of *n*-hexane (Merck, Uvasol).

l-**2,6-Bis(hydroxymethyl)spiro[3.3]heptane** (**13**).—According to the procedure followed by Rice and Grogan,[24] 6.9 g (0.033 mol) of *d*-dimethyl spiro[3.3]heptane-2,6-dicarboxylate (**3**) {$[\phi]_{578}$ +3.2°, $[\phi]_{405}$ +5.6° (*c* 4.6, acetone)} was reduced with lithium aluminum hydride, yielding 4.1 g (26 mmol or 80%) of diol **13**, $[\phi]_{578}$ −5.4°, $[\phi]_{546}$ −6.0°, $[\phi]_{436}$ −10.0°, $[\phi]_{405}$ −12.0° (*c* 5.2: chloroform); $[\phi]_{578}$ −3.3°, $[\phi]_{546}$ −3.7°, $[\phi]_{436}$ −6.6°, $[\phi]_{405}$ −7.8° (*c* 5.0, ethanol 96%).

d-**2,6-Bis(hydroxymethyl)spiro[3.3]heptane** (**13**).—*l*-Spiro[3.3]heptane-2,6-dicarboxylic acid (**1**) (2.6 g, 0.0014 mol) {$[\phi]_{578}$ −7.7°, $[\phi]_{546}$ −8.7°, $[\phi]_{436}$ −14.2°, $[\phi]_{405}$ −17.3°, $[\phi]_{365}$ −22.5° (*c* 5.0, acetone)}, was reduced with 3.5 g of lithium aluminum hydride in 100 ml of diethyl ether. During 8 hr the reaction mixture was refluxed and kept at room temperature for 3 days. The excess lithium aluminum hydride was decomposed by addition of water. Work-up furnished 300 mg (0.002 mol or 13%) of diol **13**: $[\phi]_{578}$ +3.2°, $[\phi]_{546}$ +3.8°, $[\phi]_{436}$ +6.4°, $[\phi]_{405}$ +7.5° (*c* 5.4, ethanol 96%).

Optical Purity Control of 2,6-Bis(hydroxymethyl)spiro[3.3]heptane (**13**).—To an emulsion of 270 mg of *d*-2,6-bis(hydroxymethyl)spiro[3.3]heptane (**13**) {$[\phi]_{578}$ +3.2°, $[\phi]_{436}$ +6.4° (*c* 5.4, ethanol 96%)} in 50 ml of 1.5 *N* sulfuric acid, stirred at room temperature, was added powdered potassium permanganate until the color disappeared slowly. The reaction mixture was filtered over a glass funnel, the residue was washed with water, and the combined filtrates were saturated with sodium sulfate and extracted with ethyl acetate. After removal of the solvent, the residue was recrystallized twice from water, furnishing 46 mg (0.25 mmol or 14%) of *l*-spiro[3.3]heptane-2,6-dicarboxylic acid (**1**), showing an infrared spectrum identical with that of the starting *l* acid **1**: $[\phi]_{578}$ −8.8°, $[\phi]_{546}$ −10.4°, $[\phi]_{436}$ −16.0°, $[\phi]_{405}$ −18.6° (*c* 4.6, acetone).

dl-**2,6-Bis(chloromethyl)spiro[3.3]heptane** (**14**).—Thionyl chloride (10 ml) was added dropwise in 30 min to a mixture of 2.75 g (0.018 mol) of *dl*-2,6-bis(hydroxymethyl)spiro[3.3]heptane (**13**) and 0.3 ml of dry pyridine. The reaction mixture was cooled in an ice–salt bath in order to keep the temperature below +10°. The mixture was allowed to stand at room temperature for one night, refluxed for 3 hr on a water bath, and cooled to 0°. Water was added and the organic layer was taken up into ether and worked up in the normal way. After removal of the ether, the residue was chromatographed over neutral alumina (Merck, Aktivitätsstufe 1) with *n*-pentane as an eluent. The eluate furnished, after removal of *n*-pentane, 1.8 g (9.33 mmol or 53%) of 2,6-bis(chloromethyl)spiro[3.3]heptane (**14**), bp 130–132° (17 mm).

The compound appeared, however, to be not analytically pure. To obtain a pure sample the substance was dissolved in *n*-pentane and this solution was shaken with concentrated sulfuric acid in a separatory funnel eight times. Pentane was evaporated under reduced pressure and **14** distilled *in vacuo* at bp 122–126° (15 mm): $n^{20}{}_{\mathrm{D}}$ 1.4916; mass spectrum (70 eV) *m/e* (rel intensity) 196 (0.1), 194 (0.6), 192 (0.9), 156 (13), 1.44 (1.7), 142 (5.2), 116 (48), 108 (39), 80 (100); nmr (carbon tetrachloride) δ 3.41 (d, 4), 2.76-1.55 (m, 10).

Anal. Calcd for $C_9H_{14}Cl_2$: C, 55.97; H, 7.31; Cl, 36.72; mol wt, 193.13. Found: C, 56.1, 56.0; H, 7.4, 7.2; Cl, 36.9, 37.1.

l-**2,6-Bis(chloromethyl)spiro[3.3]heptane** (**14**).—Purified thionyl chloride[37] (10 g) was added to an ice–salt bath cooled solution

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[37] L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 1158.

of 3.5 g (0.021 mol) of *l*-2,6-bis(hydroxymethyl)spiro[3.3]heptane (**13**) {$[\phi]_{578}$ −5.4°, $[\phi]_{436}$ −10.0° (*c* 5.2, chloroform)} in 7 ml of ethyldiisopropylamine. After the mixture was stirred for 4 hr at 90°, it was cooled and poured into cold 4 *N* hydrochloric acid. The organic layer was taken up into ether and worked up in the usual way. Removal of the solvent furnished a dark, crude product from which after distillation 3.1 g (0.016 mol or 75%) of *l*-2,6-bis(chloromethyl)spiro[3.3]heptane (**14**) was obtained: bp 116–120° (12 mm); $[\phi]_{578}$ −3.3°, $[\phi]_{546}$ −3.8°, $[\phi]_{436}$ −6.4°, $[\phi]_{405}$ −7.6° (*c* 11.0, tetrahydrofuran).

l-**2,6-Dimethylspiro[3.3]heptane** (**15**).—To a refluxing suspension of 2.5 g (0.066 mol) of lithium aluminum hydride in 20 ml of dry tetrahydrofuran was added a solution of 3.0 g (0.016 mol) of *l*-2,6-bis(chloromethyl)spiro[3.3]heptane (**14**) {$[\phi]_{578}$ −3.3°, $[\phi]_{405}$ −7.6° (*c* 11.0, tetrahydrofuran)} in 20 ml of tetrahydrofuran over a period of 20 min. After the mixture was refluxed for 16 hr, excess hydride was decomposed by adding a mixture of equal volume of water and tetrahydrofuran, and the reaction mixture was poured into cold 4 *N* hydrochloric acid. The organic material was taken up in pentane. The solution was dried over magnesium sulfate and pentane was removed by distillation at atmospheric pressure. The residue was purified by gas–liquid chromatography (F & M 775 chromatograph, 2 cm × 2 m stainless-steel column packed with 20% silicon rubber SE-30 on 60–80 mesh Chromosorb AN, oven 60°), yielding 0.9 g (7.2 mmol or 46%) of 2,6-dimethylspiro[3.3]heptane (**15**): nmr (carbon tetrachloride) δ 2.54–1.19 (m, 10), 1.01 (d, 6); mass spectrum (70 eV) *m/e* (rel intensity) 124 (1, parent peak), 109 (17), 96 (20), 95 (19), 82 (54), 81 (66), 68 (16), 67 (100), 54 (30), 41 (27), and 39 (24); $[\phi]_{578}$ −4.8° ± 0.4°, $[\phi]_{526}$ −6.1° ± 0.4°, $[\phi]_{476}$ −7.9° ± 0.3°, $[\phi]_{435}$ −9.4° ± 0.6°, $[\phi]_{400}$ −11.5° ± 0.6°, $[\phi]_{370}$ −14.1 ± 0.5°, $[\phi]_{323}$ −19.5° ± 1.1°, $[\phi]_{270}$ −29.5 ± 0.7°, $[\phi]_{250}$ −37.2° ± 0.9°, $[\phi]_{232}$ −43.9° ± 1.3° (*c* 1.8, cyclohexane; Bendix Ericsson Polarmatic 62).

Anal. Calcd for C_9H_{16}: C, 87.02; H, 12.98; mol wt, 124.23. Found: C, 86.8, 86.5; H, 12.8, 12.8.

dl-**2,6-Bis(5′-carboxy-2′-thenyl)spiro[3.3]heptane** (**11**).—*dl*-2,6-Bis(2′-thenyl)spiro[3.3]heptane (**10**) (98 g, 0.34 mol) was formylated according to Vilsmeier and Haack[26] with 142 g of *N*-methylformanilide and 128 g of phosphorus oxychloride in 500 ml of dry benzene at 35° during 2 hr. After the mixture was stirred for 1 night at room temperature, water was added and the reaction mixture was worked up in the normal way. The crude product, after solidification on standing at −20°, was washed with cold ether and recrystallized from petroleum ether (bp 40–60°), yielding 92 g (0.261 mol or 77%) of impure dialdehyde melting at 63–64°.

dl-2,6-Bis(5′-formyl-2′-thenyl)spiro[3.3]heptane (65 g, 0.189 mol) was dissolved in 1 l. of ethanol. Immediately after the addition of a solution of 60 g of sodium hydroxide in 0.5 l. of water to a stirred solution of 130 g of silver nitrate in 0.5 l. of water, the solution of the dialdehyde was added at once to the reagent. After stirring for 6 hr at 40°, solid was separated by filtration using a Büchner funnel. The residue was washed with distilled water. The filtrate was distilled at normal pressure to remove ethanol. The residue furnished, after acidification with 20 ml of concentrated hydrochloric acid and filtration, 70 g (0.186 mol or 76%, calculated on 2,6-bis(2′-thenyl)spiro[3.3]heptane (**10**)) of *dl*-2,6-bis(5′-carboxy-2′-thenyl)spiro[3.3]heptane (**11**) melting with decomposition from 250°, after crystallization from dioxane: ir (KBr) 3700–2300 (COOH), 1670 cm^{-1} (CO); nmr (DMSO-d_6) δ 7.56 (d, 2, *J* = 3.5 cps), 6.84 (d, 2, *J* = 3.5 cps), 2.87 (d, 4, *J* = 5.5 cps), 2.45–1.43 (m, 10).

Anal. Calcd for $C_{19}H_{20}O_4S_2$: C, 60.61; H, 5.36; S, 17.03; mol wt, 376.50. Found: C, 60.7, 60.8; H, 5.4, 5.5; S, 16.9, 16.8.

d-**2,6-Bis(5′-carboxy-2′-thenyl)spiro[3.3]heptane** (**11**).—*l*-2,6-Bis(2′-thenyl)spiro[3.3]heptane (**10**) (6.5 g, 0.023 mol) {$[\phi]_{578}$ −5.8°, $[\phi]_{405}$ −12.4° (*c* 5.0, cyclohexane)} was formylated and oxidized in the way described for the racemic compound, yielding 2.9 g (0.008 mol or 30%) of the diacid **11**. The infrared spectrum (KBr) was identical with that of the racemic compound; the optical activity was $[\phi]_{546}$ +8 ± 2° (*c* 4.8, 3 *N* sodium hydroxide solution).

dl-**2,6-Bis(5′-carboxy-1′-pentyl)spiro[3.3]heptane** (**12**).—*dl*-2,6-Bis(5′-carboxy-2′-thenyl)spiro[3.3]heptane (**11**) (8.0 g, 0.021 mol) was desulfurized according to the method of Papa, Schwenk, and Ginsberg,[28] in a solution of 110 g of sodium hydroxide in 1 l. of distilled water. The refluxing solution was stirred with a Herschberg stirrer, and 100 g of Raney nickel alloy was added in small portions. Foaming of the reaction mixture was reduced by adding small amounts of amyl alcohol.

After the mixture was stirred for another 2 hr at reflux temperature, the water layer was decanted and the residue was washed with 1 l. of boiling 1 *N* sodium hydroxide solution. After cooling, the combined water layers were washed with ether and acidified with 1.5 l. of concentrated hydrochloric acid. The dicarboxylic acid **12** was dissolved in ether. The ether solution was washed with water, dried on magnesium sulfate, and evaporated, yielding 6.1 g (0.019 mol or 88%) of diacid **12**, mp 96–97° after three crystallizations from petroleum ether (bp 80–100°).

Anal. Calcd for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94; mol wt, 324.47. Found: C, 70.4, 70.6; H, 9.9, 10.0.

l-**2,6-Bis(5′-carboxy-1′-pentyl)spiro[3.3]heptane** (**12**).—From 9.6 g (0.028 mol) of *l*-2,6-bis(2′-thenyl)spiro[3.3]heptane (**10**) {$[\phi]_{578}$ −11.1°, $[\phi]_{405}$ −28.2° (*c* 3.6, cyclohexane)} in the same way *l*-2,6-bis(5′-carboxy-1′-pentyl)spiro[3.3]heptane (**12**) was prepared in an overall yield of 71% (6.5 g or 0.020 mol): mp 94.9–95.4° after two crystallizations from petroleum ether (bp 80–100°); $[\phi]_{578}$ −7.2°, $[\phi]_{546}$ −8.1°, $[\phi]_{436}$ −14.0° (*c* 5.0, acetone). The CD spectrum between 200 and 400 mμ of a solution of 1.275 g in 100 ml of ethanol 95% (Merck, Uvasol) in a 0.1-cm cuvette showed no maxima or minima.

l-**2,6-Spiro[3.3]heptanediammonium Chloride** (**16**).—To a solution of 8.0 g (0.044 mol) of *d*-spiro[3.3]heptane-2,6-dicarboxylic acid (**1**) {$[\phi]_{578}$ +7.8°, $[\phi]_{546}$ +8.8°, $[\phi]_{405}$ +17.0° (*c* 5.0, acetone)} in 80 ml of concentrated sulfuric acid, stirred at a temperature of 45°, was added over a period of 15 min, a solution of hydrazoic acid,[38] prepared from 18.3 g sodium azide in 40 ml of chloroform according to Janson and Pope's procedure for the racemic compound **16**.[29] After the reaction mixture was stirred for 1 hr more, it was poured onto 500 g of crushed ice. The chloroform layer was removed and sulfuric acid in the water layer was neutralized by calcium carbonate. The suspension was filtered and the residue was washed with water, and to the combined filtrates calcium chloride was added. Calcium sulfate was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue furnished after two crystallizations from ethanol 7.6 g (0.038 mol or 87%) of *l*-2,6-spiro[3.3]heptanediammonium chloride (**16**).

Anal. Calcd for $C_7H_{16}Cl_2N_2$: C, 42.22; H, 8.10; Cl, 35.61; mol wt, 199.14. Found: C, 42.2, 42.2; H, 8.1, 8.2; Cl, 35.4, 35.4.

dl-**Spiro[3.3]heptane-2,6-bis(dimethylamine) Dimethiodide** (**17**).—From 18.4 g (0.10 mol) of *dl*-spiro[3.3]heptane-2,6-dicarboxylic acid (**1**), *dl*-spiro[3.3]heptane-2,6-diamine (**16**) was prepared according to Janson and Pope's method.[29]

After neutralization of excess sulfuric acid with calcium carbonate, removal of excess calcium carbonate and calcium sulfate by filtration over a Büchner funnel, and washing of the residue on the filter with water, the combined filtrates were evaporated to a volume of about 25 ml. To this solution were added 15 ml of a 32% sodium hydroxide solution in water, 60 g of formic acid, and 42 g of a 35% formaldehyde solution in water.

The mixture was kept for one night at 100°, allowed to cool, poured into 25 ml of 6 *N* hydrochloric acid, and evaporated under reduced pressure. A solution of 30 g of sodium hydroxide in 90 ml of water was added. The solution was saturated with potassium carbonate and the organic layer diluted with ether. The crude tertiary amine, obtained by removal of the ether, was dissolved in 100 ml of methanol, and 100 g of methyl iodide was added. After the mixture stood for 0.5 hr, crystals appeared. After five crystallizations from methanol, colorless crystals were obtained: yield (after one crystallization) 19.4 g (0.042 mol or 42% overall); nmr spectrum (in deuterium oxide, water signal δ 5.30 used as internal reference) δ 5.20–4.61 (quintet, 1.74, *J* = 8.5 cps), 3.81 (s, 18), 3.36–3.22 (d, 8, *J* = 8.5 cps).

Anal. Calcd for $C_{13}H_{28}I_2N_2$: C, 33.49; H, 6.05; mol wt, 466.19. Found: C, 33.2, 33.3; H, 6.4, 6.4.

d-**Spiro[3.3]heptane-2,6-bis(dimethylamine) Dimethiodide** (**17**).—From 9.2 g (0.05 mol) of *l*-spiro[3.3]heptane-2,6-dicarboxylic acid (**1**), $[\phi]_{546}$ −7.5° (*c* 5.1, acetone), spiro[3.3]heptane-2,6-bis(dimethylamine) dimethiodide (**17**) was prepared in the way described, in a yield of 64% with respect to the acid **1**. The dimethiodide **17** was recrystallized three times from methanol: $[\phi]_{578}$ +27.0°, $[\phi]_{436}$ +42.4°, $[\phi]_{405}$ +49.4°, $[\phi]_{365}$ +63.8° (*c* 2.6, water).

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[38] H. Wolff, *Org. React.*, **3**, 307 (1964).

Registry No.—*d*-**1**, 27259-78-5; *d*-**3**, 27259-79-6; *d*-**4**, 27317-55-1; *d*-**5**, 27317-56-2; *dl*-**6**, 27259-80-9; *l*-**6**, 27259-81-0; *l*-**7**, 27259-82-1; *d*-**8**, 27259-83-2; *d*-**9**, 27259-84-3; *dl*-**10**, 27259-85-4; *l*-**10**, 27259-86-5; *dl*-**11**, 27259-88-7; *dl*-**12**, 27259-87-6; *l*-**12**, 27259-89-8; *d*-**13**, 27259-90-1; *l*-**13**, 27259-91-2; *dl*-**14**, 27259-92-3; *l*-**14**, 27259-93-4; *l*-**15**, 27259-94-5; *l*-**16**, 27259-95-6; *dl*-**17**, 27259-96-7; *d*-**17**, 27259-97-8.

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Notes

Preparation of Guanine Pentofuranosyl Nucleosides Using a Friedel–Crafts Catalyst[1]

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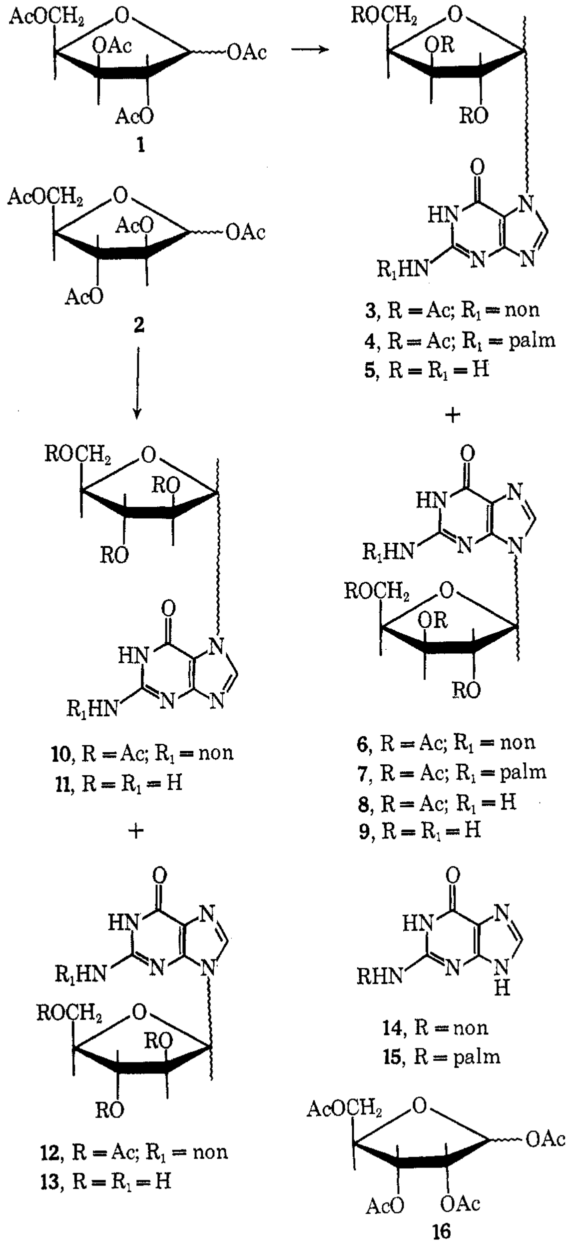
Furukawa and Honjo[2] described recently a novel and simple method of purine ribonucleoside preparation which employs Friedel–Crafts catalysts as condensing agents for the appropriate *N*-acylpurines and 2,3,5-tri-*O*-acyl-1-*O*-acetyl-D-ribofuranoses. The method gave only β-nucleosides and provided an especially useful method for the synthesis of guanosine. Because guanine nucleosides are less directly accessible by other routes[2,3] and because of our needs for considerable quantities of the guanine nucleoside (β-**9**),[4] we have applied this technique using 1,2,3,5-tetra-*O*-acetyl-D-xylofuranose (**1**) as the sugar. The results were of sufficient interest to warrant some experiments with 1,2,3,5-tetra-*O*-acetyl-D-arabinofuranose (**2**). Our findings are reported in this manuscript.



1

2

3, R = Ac; R_1 = non
4, R = Ac; R_1 = palm
5, R = R_1 = H

6, R = Ac; R_1 = non
7, R = Ac; R_1 = palm
8, R = Ac; R_1 = H
9, R = R_1 = H

10, R = Ac; R_1 = non
11, R = R_1 = H

12, R = Ac; R_1 = non
13, R = R_1 = H

14, R = non
15, R = palm

16

[non = $CH_3(CH_2)_7CO$–; palm = $CH_3(CH_2)_{14}CO$–]

The reaction was carried out as described by Furukawa and Honjo[2] with **1** and either N^2-nonanoylguanine (**14**) or N^2-palmitoylguanine[2] (**15**) using chlorobenzene and aluminum chloride (see Table I). N^2-Nonanoylguanine (**14**) reacted faster; thus, after 2 hr at reflux, the reaction of **1** with **14** was complete, while that with **15** had progressed only to a small extent, according to tlc data. N^2-Nonanoylguanine also gave a higher ratio of 7- to 9-substituted nucleoside than **15**. Surprisingly, the α anomer was formed in large amounts with the α:β anomer ratio being about 1:1 for both acylguanines and for both 7 and 9 isomers. A substantial improve-

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(2) Y. Furukawa and M. Honjo, *Chem. Pharm. Bull.*, **16**, 1076 (1968). These authors noted a trace amount of 7-ribofuranosylguanine in their preparation of guanosine.

(3) G. L. Tong, K. J. Ryan, W. W. Lee, E. M. Acton, and L. Goodman, *J. Org. Chem.*, **32**, 859 (1967), and references there.

(4) (a) S. Susaki, A. Yamazaki, A. Kamimura, K. Mitsugi, and I. Kumashiro, *Chem. Pharm. Bull.*, **18**, 176 (1970); (b) A. P. Martinez, *et al.*, manuscript in preparation describing the synthesis of β-**9** *via* the mercury derivative[4c] of 2-acetamido-6-chloropurine; (c) R. H. Iwamoto, E. M. Acton, and L. Goodman, *J. Med. Chem.*, **6**, 684 (1963).