funnel and washed with methylene chloride. The clear filtrate was evaporated to give a light yellowish solid, which was recrystallized from benzene/hexanes, giving 100 mg (67%) of pure **14**: mp 160–161 °C; IR (KBr) 1737 (C=O ester), 1728 (sh, C=O ester), 1608 (C=O dihydrothiopyrone) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.54 (s, 3 H, Me), 3.64 (s, 3 H, Me), 4.13 (d, 1 H, $J_{a,a}$ = 12 Hz, H-5 methine), 4.65 (d, 1 H, $J_{a,a}$ = 12 Hz, H-6 benzylic), 7.1–7.45 (m, 5 H, Ar H), 7.44 (br s, 5 H, Ar H). Anal. Calcd for $C_{21}H_{18}O_6S$: C, 66.0; H, 4.7; S, 8.4. Found: C, 65.6; H, 4.7; S, 8.5.

3,5-Bis(carbomethoxy)-2,6-diphenyl-4*H*-thiopyran-4-one (2). A mixture of 3.75 g (9.77 mmol) of diastereoisomers **5** and **6**, 67.5 g of active manganese dioxide,[16] and 400 mL of chloroform was azeotropically refluxed for 6 h (ca. 1.35 mL of water was collected). The reaction mixture was filtered over anhydrous magnesium sulfate, and the residue was washed with methylene chloride. The filtrate was evaporated to give 3.1 g of a solid, which was recrystallized from benzene/hexanes (1:2 v/v) to give 2 g (54%) of pure **2** as a white crystalline solid: mp 175–176 °C; IR (KBr) 1735 (C=O ester), 1729 (sh), 1605 (C=O thiopyrone) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.67 (s, 6 H, Me), 7.48 (s, 10 H, Ar H); mass spectrum, m/e 380 (M^+), 352 (M^+ – CO). Anal. Calcd for $C_{21}H_{16}O_5S$: C, 66.3; H, 4.2; S, 8.4. Found: C, 66.4; H, 4.4; S, 8.1.

The mother liquor was evaporated to give ca. 1 g of a yellow oil, from which one component was isolated by preparative TLC (CH_2Cl_2) and characterized as *trans*-methyl cinnamate:[19] mass spectrum, m/e 162 (M^+); ^1H NMR ($CDCl_3$) δ 3.8 (s, 3 H, Me), 6.4 (d, 1 H, J = 16 Hz), 7.65 (d, 1 H, J = 16 Hz), 7.15–7.6 (m, 5 H, Ar H).

Acknowledgment. We thank Frank M. Michaels of the Analytical Sciences Division of Kodak Research Laboratories for obtaining several key ^1H and ^{13}C NMR spectra on a Bruker WH-270 spectrometer.

Registry No. 2, 77461-74-6; **4**, 77461-75-7; **5**, 77461-76-8; **6**, 77461-77-9; **7**, 77461-78-0; **8**, 77461-79-1; **9**, 77461-80-4; **10**, 77461-81-5; **11**, 77461-82-6; **12**, 77519-43-8; **14**, 77461-83-7; *trans*-methyl cinnamate, 1754-62-7; dimethyl acetonedicarboxylate, 3298-40-6.

(19) The origin of *trans*-methyl cinnamate, which was formed only in small amounts from the active manganese dioxide oxidation of **5** and **6**, was not pursued further.

Absolute Configuration of 2,7-Diazaspiro[4.4]nonane. A Reassignment

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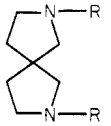
The absolute configuration of the axially dissymmetric spirane 2,7-diazaspiro[4.4]nonane (**1**) has been elucidated as (*R*)-(–),(*S*)-(+) in chloroform by synthesis of both enantiomers from the centrodissymmetric intermediate **5**; the configuration of (*R*)-(–)-**5** was correlated with that of (*S*)-α-ethyl-α-methylsuccinic acid through the substituted pyrrolidine **11**. The configuration thus established for the sulfonamide derivative **2** is opposite to that derived earlier. The source of the original error is shown to lie in the preparation of spiroimide **14**, which is accompanied by almost total racemization when carried out at high temperatures. A more direct, efficient synthesis of **1** is described followed by resolution with dinitrodiphenic acid to give the optically pure enantiomers. Lowe's rule is shown to predict correctly the absolute configurations of several derivatives of **1** but not of **1** itself.

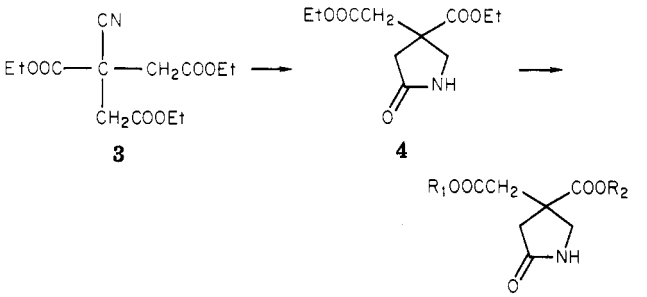
2,7-Diazaspiro[4.4]nonane (**1**), an axially dissymmetric molecule with C_2 symmetry, is similar to allenes and hindered biphenyls in possessing chirality without a formal chiral center. The determination of absolute configuration of molecules of this class has posed special problems because of the absence of an asymmetrically substituted carbon which might be related via chemical correlations to a standard of known configuration.[2] In 1968, in the first assignment of absolute configuration to a dissymmetric spiran, Krow and Hill[3] assigned the *S* configuration, according to the sequence rule of axial chirality, to the (–)-*N*,*N*-bis(*p*-toluenesulfonamide) (**2**) of **1** by synthesis



1, R = H
2, R = *p*-toluenesulfonyl

from a centrodissymmetric precursor. Reinvestigation of this synthesis has now shown that the assignment should be reversed. The details of the chemical correlation, the source of the initial misassignment, a new preparation of optically active **1**, and the corrected configurational assignment are presented in this paper.

Scheme I. Synthesis of Lactam 5



3 **4**

5, R_1 = H; R_2 = Et
6, R_1 = R_2 = H
7, R_1 = Et; R_2 = H
8, R_1 = CH_3; R_2 = Et

The key intermediate in the scheme to synthesize **1** from a centrodisymmetric precursor is lactam **5**; this is a chiral compound capable on the one hand of conversion to **1** without affecting the asymmetric center and, on the other hand, of chemical correlation with a configurational

(1) The portion of this work performed by Dr. Krow was carried out at Princeton University, Princeton, NJ.
(2) G. Krow, *Top. Stereochem.*, **5**, 31–68 (1970).
(3) G. Krow and R. K. Hill, *Chem. Commun.*, 430–431 (1968).

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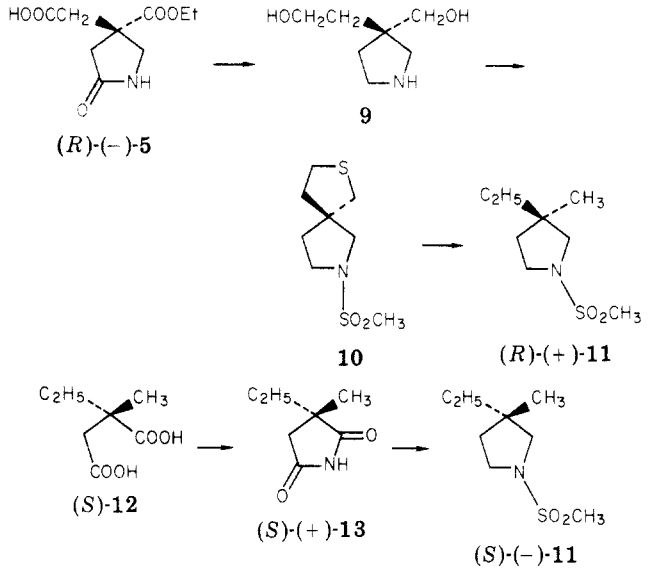
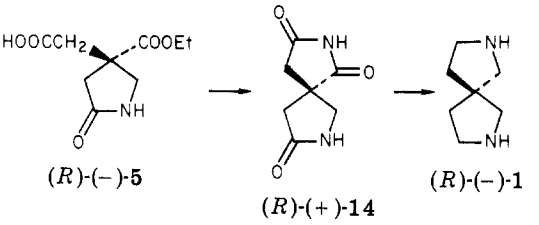
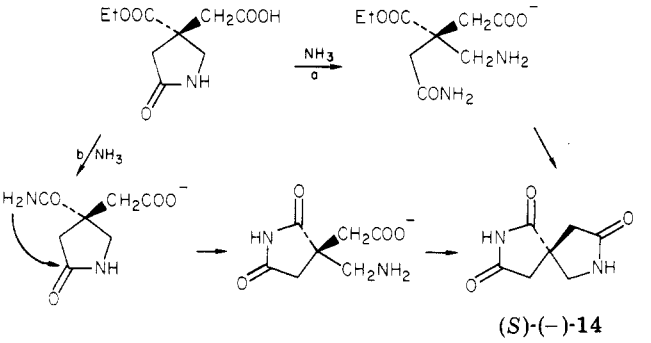
Scheme II. Correlation of Configuration of 5 with (S)-2-Ethyl-2-methylsuccinic Acid (12)



Scheme III. Synthesis of 1 from 5



Scheme IV. Inversion Pathways in Preparation of 14



standard. This approach may be divided into three phases: (i) preparation of optically pure 5; (ii) assignment of configuration to 5 by correlation with 2-ethyl-2-methylsuccinic acid; (iii) conversion of 5 to optically active 1.

(i) Preparation of Optically Pure Lactam 5. The synthetic route to 5 is shown in Scheme I. Cyano triester 3 was formed in good yield by dialkylation of ethyl cyanoacetate with ethyl bromoacetate. High-pressure hydrogenation of the cyano function over Raney nickel provided lactam 4. The less hindered ester group of 4 could be selectively hydrolyzed by alkali to afford monoacid 5. A small amount of diacid 6 was isolated as well, but none of the other monoester 7. Resolution of 5 was achieved by repeated recrystallization of the quinine salt, and both enantiomers, with equal but opposite rotations, were recovered from their quinine salts. It was also noted that by seeding the solution, the (-) isomer, mp 165–167 °C, could be collected by recrystallization of a partially enriched (-) acid, mp 147–155 °C, from ethyl acetate. Attempts were made to confirm the optical purity by using the chiral NMR shift reagent $Eu(TFC)_3$ on the methyl ester, but no specific information could be deduced from this experiment.

(ii) Configurational Correlation of 5 with 2-Ethyl-2-methylsuccinic Acid. For configurational correlation, both (-)-5 and (S)-2-ethyl-2-methylsuccinic acid were converted to a common intermediate, 3-ethyl-3-methylpyrrolidine methanesulfonamide (11). The reactions used are shown in Scheme II. A partially resolved sample of 5, $[\alpha]^{24}_D$ -22.3° (c 3.63, H_2O), was esterified with diazomethane to diester 8 and reduced with $LiAlH_4$ to give the pyrrolidinediol 9. Treatment with methanesulfonyl chloride afforded the *N,O,O*-trimesylate, which upon further reaction with sodium sulfide yielded the crystalline thioether 10. Raney nickel desulfurization provided the crystalline methanesulfonamide 11, $[\alpha]^{24}_D$ +3.06° ($CHCl_3$). Its ORD spectrum showed a plain positive curve between 600 and 320 nm.

Sulfonamide 11 was then synthesized independently from (S)-(-)-2-ethyl-2-methylsuccinic acid[4] (12), prepared by quinine resolution of its half methyl ester according to Ställberg-Stenhagen.[5] This acid is remarkable in changing signs with concentration in chloroform solution; concentrated solutions are levorotatory, but solutions more dilute than about 10% are dextrorotatory. The imide[6] (13) of the (S)-acid was reduced with $LiAlH_4$ and converted to sulfonamide 11, $[\alpha]^{23}_D$ -5.4° ($CHCl_3$). This material showed a plain negative ORD curve between 600 and 250 nm and is the enantiomer of the sulfonamide prepared from (-)-5. The S configuration assigned to (+)-imide 13 has subsequently been confirmed by Knabe and Plisch by correlation of (R)-(-)-13 with (S)-(+)-isovaline.[7]

Since the (-)-sulfonamide 11 prepared from (S)-12 has the S configuration, the (+)-sulfonamide is R and (-)-5 must also possess the R configuration.

(iii) Conversion of (-)-5 to 1 (Scheme III). In the original procedure,[3] acid 5 was treated with aqueous ammonia, concentrated to dryness, and the residue pyrolyzed at 190–230 °C to give spiroimide 14. The crystalline imide formed in this way from (-)-5 had essentially zero rotation at the sodium D line but showed small negative rotations below 300 nm. It could be reduced by lithium aluminum hydride to 1, isolated as the levorotatory bissulfonamide 2.

The low optical rotation observed for imide 14 led to suspicion that extensive racemization may have occurred during its pyrolytic preparation, and so an alternative route was devised to avoid such drastic experimental conditions. The levorotatory acid 5 was converted to the acid chloride with thionyl chloride, followed by treatment with ammonia, all operations being carried out below 40 °C. The imide prepared in this way in 50% yield was *dextrorotatory*, in contrast to the initial high-temperature preparation, and had a higher rotation and melting point than the first product. Application of the same mild procedure to (S)-(+)-5 gave an enantiomeric sample of 14, with an optical rotation of equal magnitude but opposite sign. In addition, when the (+)-imide was sublimed at 200–210 °C for 2 h, the product obtained was racemized.

Reduction of pure (+)-imide 14 gave (-)-1, $[\alpha]^{25}_D$ -3.68°, which furnished a dextrorotatory bis(*p*-toluenesulfon-

(4) For proof of absolute configuration, see M. R. Cox, G. A. Ellestad, J. Hannaford, I. R. Wallwork, W. B. Whalley, and B. Sjoberg, *J. Chem. Soc.*, 7257–7260 (1965).

(5) S. Ställberg-Stenhagen, *Arkiv. Kemi*, 3, 273–280 (1951).

(6) Imide 13 is the antiepileptic agent ethosuximide [A. Spinks and W. S. Waring, *Prog. Med. Chem.*, 3, 261–331 (1963)] and this preparation from (S)-12 constitutes a proof of its absolute configuration.

(7) J. Knabe and J. Plisch, *Tetrahedron Lett.*, 745–746 (1973).

Scheme V. Alternative Preparation of 1

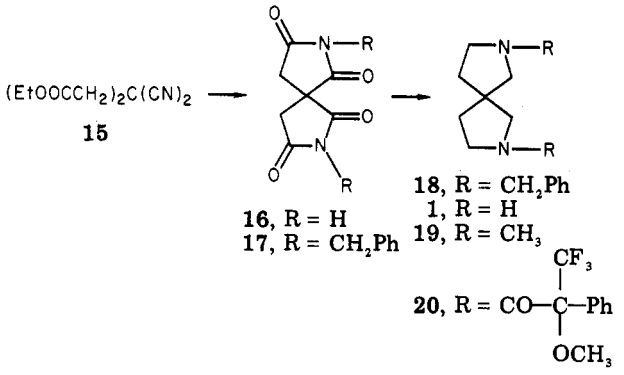


Table I. Optical Rotations, $[\alpha]^{25}_D$, of 1 and Its Derivatives

	by resolution	from (−)-5	from (+)-5
1	−3.21 ($CHCl_3$)	−3.68 ($CHCl_3$)	+3.67 ($CHCl_3$)
2	+8.65 ($CHCl_3$)	+8.60 ($CHCl_3$)	−8.43 ($CHCl_3$)
1·2HBr		+1.8 (CH_3OH)	−1.7 (CH_3OH)
19	+3.08 (EtOH)		

amide), while reduction of (−)-14 gave (+)-1, $[\alpha]^{25}_D$ +3.67°, which afforded a levorotatory bis(*p*-toluenesulfonamide).

These findings reveal that in the original preparation[3] of 14, not only sigtnificant racemization but also, unexpectedly, a slight degree of *inversion* at the asymmetric center occurred. Two reasonable suggestions for how this might have happened are shown in Scheme IV. In a, attack of ammonia at the lactam carbonyl in preference to the hindered ester would lead to overall inversion, while in b, cyclization of the initial amide nitrogen with the lactam carbonyl in preference to the carboxylate carbonyl also leads to inversion.

These correlations show that spiranes (−)-1 and (+)-2 should be assigned the *R* configuration, using the system of Cahn, Ingold, and Prelog for compounds which possess both central chirality and a C_2 axis.[8,9]

Alternative Synthesis of 1. For a more direct synthesis of optically active 1, an alternative route (Scheme V) was devised. Dialkylation of malononitrile with ethyl bromoacetate afforded diester 15, which could be cyclized to the spiroimide 16 in a refluxing mixture of sulfuric and acetic acids. The good yields (60% overall) and ease of operation make this route preferable to that previously described.[10] Attempts to reduce 16 to 1 with lithium aluminum hydride or sodium bis(2-methoxyethoxy)aluminum hydride gave yields too low to be useful, primarily because the acidic imide groups react immediately to form a salt which is relatively inert to reduction. To circumvent this problem the imide nitrogens were benzylated, and subsequent reduction of the substituted imide 17 proceeded smoothly to spiroamine 18. The benzyl groups were readily removed by catalytic hydrogenolysis, providing 1 in 60% overall yield from 16.

Despite its acidity, spiroimide 16 could not be resolved with brucine. Diamine 18 could not be resolved with *d*-tartaric acid, *d*-camphor-10-sulfonic acid, or 2,3:4,6-di-*O*-isopropylidene-2-oxo-L-gulonic acid. However, direct resolution of 1 was accomplished with *l*-6,6′-dinitro-2,2′-diphenic acid. Seven recrystallizations of the salt gave optically pure 1, $[\alpha]^{25}_D$ −3.21° ($CHCl_3$). The rotations of 1 prepared by resolution and its bissulfonamide 2 are essentially identical with those of the enantiomers of 1 and 2 prepared from 5, as shown in Table I.

Table II. Melting Points of Mixtures of (+)- and (−)-2

% (*R*)-(+)	% (*S*)-(−)	mp, °C
100	0	167-168.5
75	25	142-155
67	33	140-147
50	50	137-139
33	67	139-147
25	75	142-154
0	100	167-168

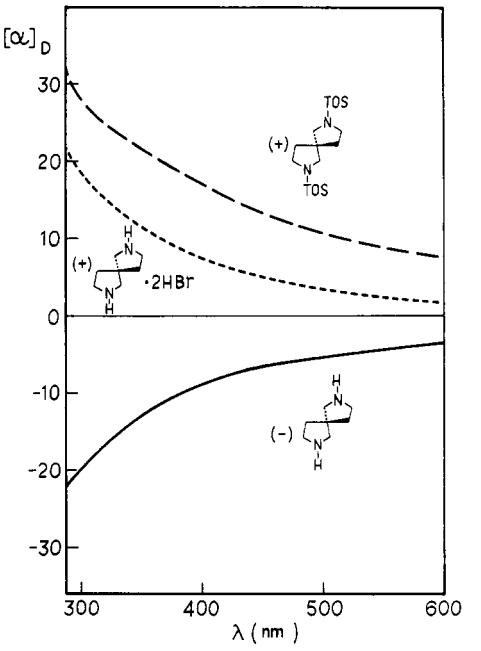


Figure 1. ORD spectra of (−)-1 and its derivatives.

As additional evidence of optical purity, the diastereomeric amides (20) formed from Mosher's reagent,[11] α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA), were examined by NMR. The spectra are complicated by the appearance of multiple peaks in the methoxy region between 3.55–3.80 ppm, due likely to the anisotropic phenyl ring current and to the presence of cisoid and transoid conformations about the amide bonds. Nevertheless, the spectra of the diastereomeric amides derived from (+)-1 and (−)-1 are distinctly different, while the spectrum of the amide from racemic 1 appeared to be the sum of those of the two diastereomers, lending support to the conclusion that the samples of 1 prepared in this study are essentially optically pure. Mixture melting points of mixtures of the enantiomeric bissulfonamides 2 follow the typical melting-point pattern of an enantiomeric mixture (Table II).

The ORD spectra of 1, its bishydrobromide, and the bissulfonamide 2 are shown in Figure 1; all show plain ORD curves. It is noteworthy that the sign of optical rotation changes in proceeding from either enantiomer of 1 to its salt, sulfonamide, or *N*-methyl derivative. The ORD and CD spectra of intermediate 14 are shown in Figure 2.

(8) R. S. Cahn, C. Ingold, and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, 5, 385-415 (1966); see especially example 31 on p 397.

(9) In the original assignment of ref 3, the configuration was based on the rules of axial chirality rather than central chirality. According to the sequence rules of axial chirality, the spiranes (−)-1 and (+)-2 could be designated as *S* configuration. For a detailed discussion, see D. W. Wang, Ph.D. Dissertation, The University of Michigan, Ann Arbor, MI, 1979.

(10) G. Casini, O. Cicchetti, and M. Ferappi, *Ann. Chim.*, 51, 366–374 (1961); *Chem. Abstr.*, 55, 27051 (1961).

(11) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.* 34, 2543–2549 (1969).

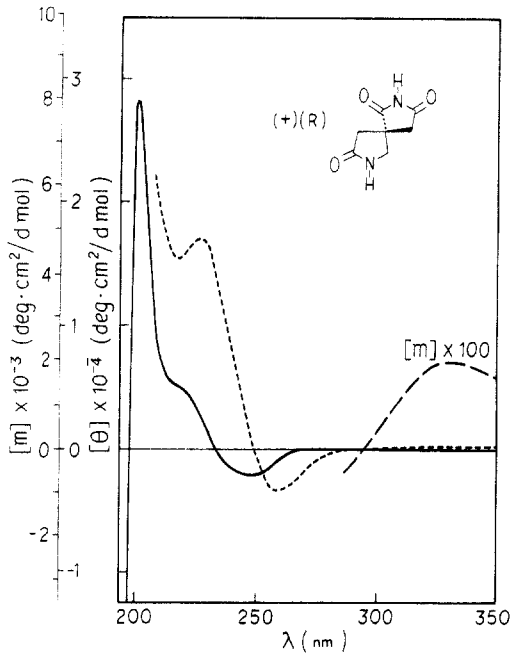
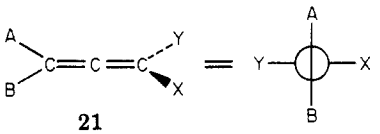


Figure 2. ORD (---) and CD (—) curves of **14** in water.

Discussion

In 1965, Lowe derived an empirical rule,[12] based on a screw pattern of polarizability of the substituents, to predict the absolute configuration of chiral allenes. Lowe's rule states that an allene **21** will be dextrorotatory at the sodium D line when A is more polarizable than B and X is more polarizable than Y.



21

It was suggested[12] that this rule might be extended to predict the absolute configuration of spiranes, alkylidenecycloalkanes, and other axially dissymmetric molecules. In the initial assignment[3] of absolute configuration to sulfonamide **2**, the result was not in agreement with Lowe's rule, and Brewster and Jones[13] subsequently suggested that dissymmetric orientations of the polarizable toluenesulfonamide groups might be swamping the contributions of the diazaspirane skeleton. With the corrected assignment, it is seen that the absolute configurations of sulfonamide **2**, the bishydrobromide of **1**, and the *N*-methyl derivative **19** are all *correctly* predicted by Lowe's rule. Curiously, the parent amine **1** remains an exception to the rule. Other exceptions among spiranes are now known,[14-16] and Brewster[15] has emphasized that Lowe's rule cannot be general.

Experimental Section

Melting points were measured with a Fisher-Johns melting-point apparatus, a Thomas-Hoover melting-point apparatus, or a Perkin-Elmer DSC-2 differential scanning calorimeter. Melting points and boiling points are uncorrected. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI, Galbraith Microanalytical Laboratory, Knoxville, TN, or George Robertson, Florham Park, NJ. Specific rotations of the sodium D line were measured on a Perkin-Elmer Model 141 or 241 MC polarimeter, with concentration expressed in g/100 mL. Infrared spectra were recorded on a Perkin-Elmer 137, 237B, or 257 spectrophotometer. ORD and CD spectra were recorded on JASCO ORD/UV-5 and J-40A spectropolarimeters, respectively, using a cell of 0.1–1.0 mm, or on a Cary 60 ORD instrument using a 1-cm silica cell. NMR spectra were taken on a Varian T-60, A-60A, or HA-100 spectrometer or on a JEOL PS-100 spectrometer using tetramethylsilane and DDS as internal standards.

Triethyl 2-Cyano-1,2,3-propanetricarboxylate (3). Under a nitrogen atmosphere, 250 g (2.21 mol) of ethyl cyanoacetate (Aldrich) was added slowly to a mechanically stirred suspension of 53 g (2.21 mol) of 99% sodium hydride (Ventron) in 1.2 L of dry benzene. A heat gun was used to initiate the reaction. After the addition was completed, the slurry was heated under reflux for 2 h. The mixture was cooled and 369 g (2.21 mol) of ethyl bromoacetate (Aldrich) was added slowly at 60 °C. After a 2.5-h reflux, the mixture was cooled again and 53 g of sodium hydride was added at 50 °C. The slurry was warmed slowly under reflux for 2.5 h. Ethyl bromoacetate (369 g) was added at 60°C, and the mixture was heated under reflux for another 6 h.

Water (700 mL) was added to the mixture and the organic layer was separated, washed twice with 500 mL of water, dried over $CaCl_2$, and concentrated under reduced pressure. The residue crystallized in the refrigerator overnight and was recrystallized from a benzene–petroleum ether (bp 30–60 °C) mixture, yielding 480 g (77%) of colorless crystals: mp 40–41 °C; IR (neat) 2940, 2360, 1750, 1200 cm^{-1}; NMR ($CDCl_3$) δ 1.2–1.5 (m, 9 H, CH_3), 3.10 (s, 4 H, CH_2CO), 4.06–4.55 (m, 6 H, OCH_2).

Anal. Calcd for $C_{13}H_{19}NO_6$: C, 54.70; H, 6.68; N, 4.91. Found: C, 54.82, 54.54; H, 6.72, 6.79; N, 4.99, 5.09.

Ethyl 3-(Carboethoxy)-5-oxo-3-pyrrolidineacetate (4). A solution of 200 g (0.70 mol) of **3** in 700 mL of ethanol was sealed in a hydrogenation bomb with 12 g of T-1 Raney nickel[17] and hydrogenated at 1500 psi at 70 °C for 48 h.[18] After the catalyst and solvent had been removed, the residue was induced to crystallize by scratching. The solid was recrystallized from a benzene–petroleum ether (bp 30–60 °C) mixture to afford 160 g (94%) of colorless crystals: mp 63.5–64.5 °C; IR (KBr) 3250, 1740, 1710, 1200 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (t, 6 H, CH_3), 2.90 (s, 2 H, CH_2CO_2), 2.67 (AB pattern, 2 H, $\Delta\delta$ = 32.9 Hz, J = 17 Hz, CH_2CON), 3.68 (AB pattern, 2 H, $\Delta\delta$ = 29.3 Hz, J = 10 Hz, CH_2NCO), 4.03–4.46 (m, 4 H, OCH_2).

Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.27, 54.54; H, 7.05, 7.16; N, 5.74, 5.51.

3-(Carboethoxy)-5-oxo-3-pyrrolidineacetic Acid (5). A solution of 115 g (0.47 mol) of **4** in 250 mL of 7.5% aqueous NaOH was stirred at 30 °C for 20 h. Extraction with two 50-mL portions of $CHCl_3$ gave 18 g of recovered **4**. The aqueous layer was adjusted to pH 3.8 with concentrated HCl and the solution was extracted with five 100-mL portions of ethyl acetate. More HCl was added to the aqueous layer to bring the pH to 3.0, and the solution was again extracted with ethyl acetate (5 × 100 mL). The combined ethyl acetate extracts were dried over Na_2SO_4 and concentrated, and the residual solid was recrystallized from ethyl acetate to give 43 g (50% based on nonrecovered **4**) of colorless crystals: mp 128.5 °C; IR (KBr) 3280, 2550, 1735, 1714, 1648 cm^{-1}; NMR (D_2O) δ 1.33 (t, 3 H, CH_3), 2.73 (AB pattern, 2 H, $\Delta\delta$ = 25.9 Hz, J = 18 Hz, CH_2CON), 2.97 (s, 2 H, CH_2CO_2), 3.67 (AB pattern, 2 H, $\Delta\delta$ = 20.5 Hz, J = 10 Hz, CH_2NCO), 4.23 (q, 2 H, OCH_2).

Anal. Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.24, 50.07; H, 6.05, 6.14; N, 6.49, 6.57.

During recrystallization, 5.2 g of a white crystalline solid, insoluble in hot ethyl acetate, was collected by filtration and identified as diacid **6**, 3-carboxy-5-oxo-3-pyrrolidineacetic acid: mp 170 °C; IR (KBr) 3485, 1720, 1640 cm^{-1}; NMR (D_2O) 2.73 (AB pattern, 2 H, $\Delta\delta$ = 22.3 Hz, J = 17 Hz, CH_2CON), 3.00 (s, 2 H, CH_2CO_2), 3.67 (AB pattern, 2 H, $\Delta\delta$ = 22.5 Hz, J = 11 Hz, CH_2NCO).

(12) G. Lowe, *Chem. Commun.*, 411–413 (1965).
(13) J. H. Brewster and R. S. Jones, Jr., *J. Org. Chem.*, **34**, 354–358 (1969).
(14) H. Wynberg and J. P. M. Houbiers, *J. Org. Chem.*, **36**, 834–842 (1971).
(15) J. H. Brewster and R. T. Prudence, *J. Am. Chem. Soc.*, **95**, 1217–1229 (1973).
(16) R. K. Hill and D. A. Cullison, *J. Am. Chem. Soc.*, **95**, 1229–1239 (1973).
(17) X. A. Dominguez, I. C. Lopez, and R. Franco, *J. Org. Chem.*, **26**, 1625 (1961).
(18) We are indebted to Dr. B. R. Franko-Filipasic and Mr. W. J. McCarthy of the FMC Corporation for carrying out large-scale reductions.

Anal. Calcd for $C_7H_9NO_5$: C, 44.93; H, 4.85; N, 7.48. Found: C, 45.04; H, 4.84; N, 7.41.

Resolution of 3-(Carboethoxy)-5-oxo-3-pyrrolidineacetic Acid (5). A mixture of racemic **5** (210 g, 0.98 mol) and quinine (318 g, 0.98 mol) was dissolved in a warm mixture of 1.1 L of methanol and 1.14 L of acetone. After the mixture stood in the refrigerator for 2 days, 267 g of crystalline salt A was collected. Concentration of the filtrate gave 260 g of salt B.

Anal. Calcd for $C_{29}H_{37}N_3O_7$ (salt A): C, 64.55; H, 6.91; N, 7.79. Found: C, 64.41; H, 6.96; N, 7.72.

Salt A was recrystallized six times from 1:1 methanol–acetone. The final recrystallization concentration was 6% (w/v) and gave 70 g of the salt as white needles, $[\alpha]^{25}_D$ −129° (*c* 0.6, CH_3OH); further recrystallization did not change the optical rotation. Another 53 g of the pure salt was collected by recrystallization of fractions from mother liquors.

The salt (63 g) was treated with 169 mL of 1.5 N HCl and extracted with five 200-mL portions of ethyl acetate. Sodium sulfate (12 g) was added to the aqueous solution, which was again extracted with ethyl acetate (5 × 200 mL) and finally subjected to continuous extraction with ethyl acetate. The combined extracts were dried over Na_2SO_4 and concentrated at reduced pressure. The solid residue was recrystallized from ethyl acetate to give 20.1 g of (*R*)-(−)-(**5**): mp 165–167 °C; $[\alpha]^{21}_D$ −28.3° (*c* 3.0, H_2O); $[\alpha]^{21}_D$ −23.2° (*c* 3.04, CH_3OH).

Quinine salt B was recrystallized six times from 1:1 methanol–acetone; each time the enriched salt of the (+)-acid was recovered from the filtrate. The final recrystallization, at a concentration of 30% w/v, gave 84.5 g of salt, $[\alpha]^{25}_D$ −110° (*c* 0.6, CH_3OH); the rotation remained constant on further recrystallization. Another 52 g of this salt was obtained by recrystallization of fractions rich in the quinine–(+)-acid salt. Decomposition of the salt with HCl, as described above, gave the (*S*)-(+)-acid **5**: mp 164–165 °C; $[\alpha]^{21}_D$ +23.5° (*c* 3.09, CH_3OH). The IR and NMR spectra of the individual enantiomers were identical with those of the racemate.

(±)-3-(β-Hydroxyethyl)-3-(hydroxymethyl)pyrrolidine (9). A solution of 19.6 g of **4** in 100 mL of THF was added dropwise to a stirred slurry of lithium aluminum hydride (6.0 g) under reflux in 150 mL of THF. After 2 days of vigorous reflux the excess hydride was destroyed with a saturated solution of Na_2SO_4. The solid salts were filtered and washed with THF. The combined filtrates were dried over $MgSO_4$ and concentrated at reduced pressure to yield 6.2 g of the liquid diol **9**; IR (neat) 3300, 1050 cm^{-1}.

The Reinecke salt was prepared and recrystallized from ethanol, mp 215–218 °C.

Anal. Calcd for $C_{11}H_{22}N_7O_2S_4Cr$: C, 28.42; H, 4.74; N, 21.18. Found: C, 28.64; H, 4.83; N, 21.18.

2-Thia-7-azaspiro[4.4]nonane Methanesulfonamide (10). (a) To a solution of 23 g of methanesulfonyl chloride in 45 mL of benzene was slowly added a solution of 6.2 g of (±)-**9** in 20 mL of pyridine, and the mixture was stirred at room temperature for 4 days. The mixture was partitioned between ice–water and ether, and the water layer was extracted with three 50-mL portions of ether. The combined organic layers were washed successively with water, dilute HCl, and water, dried over Na_2SO_4, and concentrated at reduced pressure. The crude residue (6.3 g, 39%) had IR absorption at 1350, 1330, 1175, and 1150 cm^{-1}, characteristic of sulfonate and sulfonamide groups.

The crude *N,O,O*-trimethanesulfonyl derivative was heated on a steam bath for 10 h with a mixture of sodium sulfide hydride (6.5 g) and 30 mL of ethanol. After cooling, the mixture was partitioned between $CHCl_3$ and water, and the water layer was extracted with several portions of $CHCl_3$. The combined extracts were washed successively with water, dilute HCl, saturated Na_2CO_3, and water, dried over $MgSO_4$, and concentrated to leave 2.0 g of oily residue. Chromatography over Florisil, eluting with benzene–petroleum ether, gave a solid which was recrystallized from ethanol to afford 1.5 g (16% from **9**) of colorless crystals of (±)-**10**: mp 60–62 °C; IR ($CHCl_3$) 1330, 1150 cm^{-1}; NMR ($CDCl_3$) δ 2.04 (m, 4 H), 2.81 (s, 2 H), 2.88 (s, 3 H), 3.0–3.2 (m, 2 H), 3.2–3.8 (m, 4 H).

Anal. Calcd for $C_8H_{15}NO_2S_2$: C, 43.33; H, 6.83; N, 6.33. Found: C, 43.32; H, 6.83; N, 6.05.

(b) For the preparation of (+)-**10**, a solution of 10.1 g of (*R*)-(−)-**5**, $[\alpha]^{24}_D$ −22.3° (*c* 3.63, H_2O), in methanol was esterified with ethereal diazomethane. Distillation of the solvents left 10.7 g of diester **8**. Reduction with lithium aluminum hydride was carried out as described for **4** to give 5.05 g (74%) of (*R*)-**9**. This was converted to the *N,O,O*-trimethanesulfonyl derivative as described for (±)-**9** to give 12.6 g (96%) of crude product. Treatment of a 6.6-g sample with sodium sulfide hydrate as described in part a afforded 1.4 g (36%) of (*R*)-(+)-**10**: mp 60–62 °C after recrystallization from methanol; ORD [*c* 6.57; $CHCl_3$ $[\alpha]^{23}$ (nm)] +0.61 ± 0.07° (589), +2.28° (360), 0° (330), −18.8° (270). The IR and NMR spectra were identical with those of racemic **10**.

(*S*)-2-Ethyl-2-methylsuccinic Acid (12). 3-(Carbomethoxy)-3-methylpentanoic acid was prepared by partial hydrolysis of the dimethyl ester of 2-ethyl-2-methylsuccinic acid and resolved with quinine following the procedure of Ställberg-Stenhagen.[5] The quinine salt, mp 93–95 °C, obtained after four recrystallizations was acidified with 1 N HCl and extracted with ether to give the levorotatory half ester: bp 103–104 °C (1.1 mm) [lit.[5] bp 88 °C (0.5 mm)]; α^{24}_D −10.42° (neat, 1 dm) [lit.[5] α^{23}_D −12.55° (neat)]. Esterification with ethereal diazomethane gave the dimethyl ester: bp 65 °C (1.25 mm) [lit.[5] bp 71–72 °C (3.0 mm)]; α^{23}_D −7.87° (neat, 1 dm) [lit.[5] α^{23}_D −8.87° (neat)].

Hydrolysis of the resolved half-ester with 10% KOH (overnight reflux) afforded diacid **12**; after recrystallization from benzene–petroleum ether it had mp 71–73 °C (lit.[5] mp 64.6–65.4 °C for optically pure diacid); $[\alpha]^{24}_D$ −9.45° (*c* 7.93, C_2H_5OH) [lit.[5] $[\alpha]^{23}_D$ −5.9° (*c* 7.45, $CHCl_3$).

The rotation of **12** in $CHCl_3$ solution was observed to vary with concentration; some representative values for $[\alpha]^{24}_D$ (*c*) are as follows: −4.98° (16.5), −3.03° (13.2), −0.56° (10.6), +1.66° (8.45), +4.3° (6.75), +6.1° (5.4), +18.9° (2.17), +29.6° (1.08), +40.8° (0.27). The ORD spectrum showed a plain positive curve at concentrations of 10.8 and 16.5 g/100 mL in $CHCl_3$.

2-Ethyl-2-methylsuccinimide (13). (a) A stream of ammonia was bubbled into a mixture of 9.45 g of (±)-2-ethyl-2-methylsuccinic acid and 15 mL of water until the acid dissolved. While the ammonia flow was maintained, the flask was immersed in a metal bath at 110 °C. The water was evaporated and the bath temperature slowly raised to 130–140 °C until a solid remained. The ammonia flow was stopped and the bath temperature was raised to 220–240 °C for 1 h, until ammonia evolution ceased. Distillation of the residue at 114–130 °C (0.4 mm) gave a colorless liquid (3.7 g, 44%) which solidified on standing. Redistillation of 100–103 °C (0.20 mm), followed by several recrystallizations from chloroform–petroleum ether, gave colorless crystals: mp 48.5–50.5 °C (lit.[19] mp 45–46 °C); IR ($CHCl_3$) 1787, 1725 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (t, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 1.5–1.9 (m, 2 H, CH_2C), 2.56 (AB pattern, 2 H, CH_2CO). The melting point could be raised to 50–51 °C by sublimation at 25 °C (25 mm).

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.55; H, 7.87; N, 9.92. Found: C, 59.27; H, 8.01; N, 9.67.

(b) Repetition of procedure a with 4.6 g of (*S*)-**12**, $[\alpha]^{24}_D$ −9.45° (C_2H_5OH), and purification of the imide by sublimation at 75 °C (13 mm) gave 2.5 g (62%) of colorless crystals of (*S*)-(+)-**13**: mp 69–71 °C; $[\alpha]^{23}_D$ +32.0° (*c* 2.28, $CHCl_3$). The IR and NMR spectra were identical with those of the racemic imide. The ORD spectrum in ethanol showed a plain positive curve from 600–215 nm.

3-Ethyl-3-methylpyrrolidine Methanesulfonamide (11). (a) A solution of 400 mg of (±)-**10** in 20 mL of ethanol was heated under reflux with 5 g of T-1 Raney nickel for 12 h. After the mixture cooled, the catalyst was filtered and washed with several portions of ethanol. The combined filtrate and washings were concentrated and the oily residue was recrystallized several times from petroleum ether (bp 30–60 °C) at −78 °C. The colorless sulfonamide had mp 29–30 °C: IR ($CHCl_3$) 1335, 1161 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (t, 3 H, CH_3), 1.10 (s, 3 H, CH_3), 1.3–1.9 (m, 4 H, CH_2), 2.83 (s, 3 H, CH_3SO_2), 3.09 (s, 2 H, CH_2N), 3.42 (t, 2 H, CH_2N).

(b) A 500-mg sample of (*R*)-(+)-**10** was desulfurized with Raney nickel as described in part a, affording (*R*)-(+)-**11**: mp 26.5–27.5

(19) C. Klinke, *Chem. Abstr.*, **63**, 15267 (1965).

°C; ORD [c 1.04, $CHCl_3$; $[\alpha]^{24}$ (nm)] +3.06° (589), +7.87° (400), +11.3° (350), +14.2° (320). The IR and NMR spectra were identical with those of racemic 11.

(c) A solution of 3.7 g of the racemic imide **13** in 60 mL of THF was heated under reflux overnight with 1.0 g of lithium aluminum hydride. IR examination of the product showed incomplete reduction, so the product was heated under reflux with 1.0 g of lithium aluminum hydride in 50 mL of THF for another 48 h. Following the workup procedure described for (±)-**9**, (±) 3-ethyl-3-methylpyrrolidine was distilled at 55–58 °C (12 mm).

The **picrate**, after recrystallization from ethanol, had mp 140–140.5 °C.

Anal. Calcd for $C_{13}H_{18}N_4O_7$: C, 45.61; H, 5.30; N, 16.37. Found: C, 45.50; H, 5.34; N, 16.38.

The **methanesulfonamide** 11 was recrystallized from petroleum ether at −78 °C to yield a colorless solid, mp 29–30 °C.

Anal. Calcd for $C_8H_{17}NO_2S$: C, 50.24; H, 8.96; N, 7.33. Found: C, 50.00; H, 9.10; N, 7.50.

(d) The (+)-imide **13** was reduced with lithium aluminum hydride in THF as described in part c to give 3-ethyl-3-methylpyrrolidine, bp 120–125 °C (0.3 mm). Upon treatment with methanesulfonyl chloride in $CHCl_3$ and 10 aqueous NaOH, it formed an oily sulfonamide which was crystallized from petroleum ether at −78 °C to give colorless 11: mp 33.5–35 °C; $[\alpha]^{23}_D$ −5.4° (c 12.5, $CHCl_3$). The IR and NMR spectra were identical with those of the products of parts a–c. The ORD spectrum ($CHCl_3$) showed a plain negative curve between 600 and 250 nm.

2,7-Diazaspiro[4.4]nonane-1,3,8-trione (14). (a) Ammonia was bubbled into a suspension of (±)-**5** (10.0 g) in 20 mL of water until the solid dissolved. While the ammonia flow was maintained, the flask was immersed in a Woods metal bath at 125–135 °C to remove the water. The ammonia flow was discontinued and the flask was heated at 220–230 °C for 1 h under reduced pressure (20 mm). After cooling, the glassy residue was crystallized from water to give 4.35 g (56%) of (±)-**14**, mp 204–208 °C. Recrystallization from methanol–water raised the melting point to 206–208 °C: IR (KBr) 3300, 2770, 1760, 1710, 1680 cm^{-1}; NMR (D_2O) δ 2.73 (AB pattern, 2 H, Δδ = 14.0 Hz, J = 17 Hz, CH_2CON), 3.00 (s, 2 H, CH_2CONCO), 3.65 (AB pattern, 2 H, Δδ = 14.3 Hz, J = 11 Hz, CH_2NCO).

Anal. Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.97, 50.04; H, 4.80, 4.95; N, 16.07, 16.42.

(b) Procedure a was repeated with 6.0 g of (*R*)-(−)-**5**, $[\alpha]^{24}_D$ −22.3°, to give 1.25 g of (−)-**14**: mp 205–208 °C; ORD [c 7.23, H_2O; $[\alpha]^{24}$ (nm)] −0.55° (600), −1.38° (350), −3.48° (300), −7.6° (270), −27.2° (260), −49.3° (250).

(c) A solution of 10.0 g (0.046 mol) of (*R*)-(−)-**5**, $[\alpha]^{21}_D$ −28.3° (c 3.0, H_2O), in 30 mL of purified thionyl chloride was treated with a small amount of anhydrous zinc chloride and stirred at 40 °C for 2 h. The excess thionyl chloride was removed under reduced pressure and the residue was taken up in ether. Ammonia gas was passed into the resulting dispersion for 30 min and the mixture was stirred at room temperature for 2.5 h; during this period the ring closure was monitored by NMR. The solvent was evaporated finally at 40–50 °C, and the residue was continuously extracted with 500 mL of dry THF for 2 days in a Soxhlet thimble. After the solvent had been removed, the residue was again continuously extracted with THF for 24 h to remove a trace amount of ammonium chloride. The product was recrystallized from 1:1 methanol–water to give colorless crystals of (*R*)-(+)-**14**: 3.9 g (50%); mp 234–237 °C; $[\alpha]^{25}_D$ +2.05° (c 7.30, H_2O); ORD [c 7.30, H_2O; [*M*] (nm)] +3.44 (589), +19.6 (328), 0 (295), −919 (257), 0 (249), +4720 (225), +4370 (217); CD [c 1.22 × 10^{-4} mol/L, H_2O; [θ] (nm)] 0 (270), −2210 (249), 0 (233), +4750 (220), +28000 (201), 0 (196). The ORD and CD spectra are shown in Figure 2. The IR and NMR spectra were identical with those of the racemic imide from part a.

Anal. Found: C. 49.90; H, 4.78; N, 16.61.

(d) Procedure c was repeated with (*S*)-(+)-**5** to give (*S*)-(−)-**14**: mp 235–237 °C; $[\alpha]^{25}_D$ −2.19° (c 7.30, H_2O); ORD [c 7.30, H_2O; [*M*] (nm)] −3.68 (589), −19.8 (328), 0 (295), +897 (257), 0 (249), −4700 (225), −4500 (217).

Anal. Found: C, 50.09; H, 4.94; N, 16.62.

2,7-Diazaspiro[4.4]nonane (1). (i) By $LiAlH_4$ Reduction of 14. (a) A Soxhlet extraction apparatus was assembled with 4.5 g of lithium aluminum hydride and 600 mL of dry THF in a 1-L round-bottom flask and 4.0 g of imide **13** in the thimble. The mixture was heated under reflux for 72 h and then cooled in ice, and the excess hydride was decomposed by the successive addition of 4.5 mL of water, 4.5 mL of 15% KOH, and 13.5 mL of water. The precipitate was filtered and washed with three 80-mL portions of THF. The combined filtrate and washings were dried over calcium oxide and concentrated at reduced pressure. Vacuum distillation of the residue gave 1.4 g (47%) of colorless amine: bp 80–82 °C (2.2 mmHg); NMR ($CDCl_3$) δ 1.67 (t, 4 H, J = 7 Hz, CH_2C), 2.85 (s, 4 H, CH_2N), 3.05 (t, 4 H, CH_2N); the amine protons were observed as a sharp singlet in the region of δ 2.0–3.2. The amine solidified at room temperature, but since it was very hydroscopic the melting point was not determined (lit.[20] mp 38–40 °C).

The **dipicrate** melted at 236–238 °C after recrystallization from ethanol.

Anal. Calcd for $C_{19}H_{20}N_8O_{14}$: C, 39.06; H, 3.45; N, 19.16. Found: C, 39.29; H, 3.69; N, 19.23.

The **bishydrobromide** was prepared by treating a solution of 1.4 g of 1 in 100 mL of chloroform with HBr gas and recrystallizing the crude salt from 95% ethanol: yield 2.8 g (90%); mp 262 °C dec (DSC, 20 °C/min); NMR (D_2O) δ 2.15 (t, 4 H, CH_2C), 3.43 (s, 4 H, CH_2N), 3.47 (t, 4 H, CH_2N).

Anal. Calcd for $C_7H_{16}N_2Br_2$: C, 29.19; H, 5.60; N, 9.72. Found: C, 29.22; H, 5.68; N, 9.70.

The **bis(*p*-toluenesulfonamide), (±)-2**, was prepared by using *p*-toluenesulfonyl chloride in pyridine and recrystallized from ethanol; mp 136.5–137 °C.

Anal. Calcd for $C_{21}H_{26}N_2O_4S_2$: C, 58.40; H, 6.06; N, 6.49. Found: C, 58.13; H, 6.15; N, 6.48.

(b) Reduction of (*R*)-(+)-**14**, $[\alpha]_D$ +2.05°, in the same way gave (*R*)-(−)-1 in 56% yield: bp 80–82 °C (2.2 mm); $[\alpha]^{25}_D$ −3.68° (c 16.0, $CHCl_3$); ORD [c 2.67, $CHCl_3$; $[\alpha]^{24}$ (nm)] −3.37° (600), 3.57° (589), −4.12° (500), −8.99° (400), −19.5° (300), −22.5° (290).

The **bishydrobromide** had mp 312 °C dec (DSC, 20 °C/min); ORD [c 2.0, CH_3OH; $[\alpha]^{24}$ (nm)] +1.8° (600), +3.6° (500), +7.2° (400), +18° (300), +34° (250).

Anal. Found: C, 29.44; H, 5.83; N, 9.70.

The **bis(*p*-toluenesulfonamide) (2)** was prepared in 50% yield by stirring 64 mg of (−)-1 with 0.70 g of *p*-toluenesulfonyl chloride in 6 mL of chloroform and 5 mL of 15% KOH at room temperature overnight. The product was extracted with chloroform, washed with 1 N HCl and water, dried over $MgSO_4$, concentrated, and recrystallized from 95% ethanol to afford 110 mg of (+)-**2**: mp 167–168.5 °C; $[\alpha]^{24}_D$ +8.60° (c 5.40, $CHCl_3$); $[\alpha]^{25}_D$ +6.2° (c 0.37, $CHCl_3$); ORD [c 4.10, $CHCl_3$; $[\alpha]^{24}$ (nm)] +7.80° (600), +8.24° (589), +10.9° (500), +17.5° (400), +21.4° (350), +27.0° (300), +39.6° (280); IR (KBr) 1595, 1345, 1170 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (t, 4 H, J = 7 Hz, CH_2C), 2.40 (s, 6 H, CH_3), 2.94 (s, 4 H, CH_2N), 3.25 (t, 4 H, J = 7 Hz, CH_2N), 7.45 (AB pattern, 8 H, aromatic).

Anal. Found: C, 57.99; H, 6.22; N, 6.25.

(c) Similar hydride reduction of (*S*)-**14**, $[\alpha]^{25}_D$ −2.19°, gave (*S*)-(+)-**1** in 54% yield: bp 80–82 °C (2.2 mm); ORD [c 23.7; $CHCl_3$) $[\alpha]^{25}$ (nm)] +3.54° (600), +3.67° (589), +4.17° (500), +6.58° (400), +19.7° (300), +22.7° (290).

The **bishydrobromide** had mp 313 °C dec (DSC, 20 °C/min); $[\alpha]^{24}_D$ −1.7° (c 2.0, CH_3OH).

Anal. Found: C, 29.05; H, 5.57; N, 9.57.

The **bis(*p*-toluenesulfonamide)**, prepared as described above, had mp 167–168 °C; $[\alpha]^{24}_D$ −8.43° (c 4.14, $CHCl_3$).

Anal. Found: C, 58.30; H, 6.18; N, 6.40.

(ii) By Hydrogenolysis of 18. A solution of 45.7 g of (±)-**18** in 50 mL of glacial acetic acid was hydrogenated with 0.1 g of 10% palladium on charcoal in a Parr shaker for 24 h at 40 °C at an initial pressure of 50 psi. After removal of the catalyst, the solution was made alkaline by the addition of 15% KOH and extracted four times with chloroform. The extracts were dried over calcium oxide, concentrated at 25 °C under reduced pressure, and distilled. The amine was collected at 50–52 °C (0.50 mm), 17.5 g (92%); it solidified in the ice-cooled receiver but melted on warming above 30 °C. The IR and NMR spectra were identical with those of the product from part ia.

(20) M. Kojima, T. Kawakita, and K. Kudo, *Yakugaku Zasshi*, **92**, 465–470 (1972); *Chem. Abstr.*, **77**, 34230 (1972).

A crystalline hydrochloride was prepared by passing HCl gas into a methanol solution of the amine but was too hygroscopic to be useful for characterization.

The **bis(*p*-toluenesulfonamide) (2)**, after recrystallization from ethanol, had mp 138–139 °C.

Anal. Found: C, 57.84; H, 5.99; N, 6.37.

Resolution of 2,7-Diazaspiro[4.4]nonane (1). To a hot solution of 5.0 g of diamine 1 in 150 mL of 1:1 ethanol–water was added with stirring 13.15 g of *l*-6,6′-dinitro-2,2′-diphenic acid in 150 mL of hot 1:1 ethanol–water. The salt that precipitated after standing overnight was filtered, washed with cold ethanol, and dried, yielding 14.2 g. Six subsequent recrystallizations from 9:1 water–ethanol gave 3.0 g of a highly crystalline yellow salt. After treatment with dilute aqueous potassium hydroxide, the liberated amine was extracted with chloroform and, after removal of solvent at room temperature, was distilled at reduced pressure. In this way, 0.79 g of (−)-2,7-diazaspiro[4.4]nonane was obtained with $[\alpha]^{25}_D$ −3.21° (*c* 6.29, $CHCl_3$). The ORD spectrum ($CHCl_3$) showed a plain negative curve.

The (+)-bis(*p*-toluenesulfonamide) was prepared as described above: mp 168–169 °C; $[\alpha]^{25}_D$ +8.65° (*c* 5.34, $CHCl_3$).

Treatment of the (−)-amine with anydrous HCl gave the hydrochloride, $[\alpha]^{25}_D$ +3.45° (*c* 2.51, C_2H_5OH), showing a plain positive ORD curve in ethanol.

2,7-Dimethyl-2,7-diazaspiro[4.4]nonane (19). To 1.0 g (0.008 mol) of (±)-1 was added 1.84 g (0.040 mol) of formic acid and 0.528 g (0.0176 mole) of formaldehyde with cooling. The mixture was stirred at 25 °C for 30 min, then gradually heated to 100 °C, and maintained at that temperature overnight. After it was cooled, dilute HCl was added to adjust the pH to 1. Then the mixture was concentrated to dryness at reduced pressure. The residue was made alkaline and extracted with chloroform, and the extracts were dried over calcium oxide and concentrated at reduced pressure. Distillation at 1.0 mm (bath temperature 75 °C) gave (±)-**19**: IR 2940, 2790 cm^{-1}; NMR ($CDCl_3$) δ 1.6–2.0 (m, 4 H, CH_2C), 2.30 (s, 6 H, CH_3), 2.4–2.7 (m, 8 H, CH_2N).

The same procedure was used to convert (−)-**1**, $[\alpha]^{25}_D$ −3.21° ($CHCl_3$), to (+)-**19**, $[\alpha]^{25}_D$ +3.08° (*c* 1.94, C_2H_5OH); this amine showed a plain positive ORD curve in ethanol.

2,7-Bis(α-methoxy-α-(trifluoromethyl)phenylacetyl)-2,7-diazaspiro[4.4]nonane (20). (a) By Mosher's procedure,[11] 1.0 g of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (Aldrich) was stirred with 15 mL of thionyl chloride at 50 °C for 48 h. The acid chloride was collected at 55–56 °C (1 mm). A mixture of 100 mg of (±)-1 in 2 mL of pyridine and 10 mL of carbon tetrachloride was treated with 430 mg of the *R* acid chloride and stirred overnight. The mixture was washed with 0.5 N HCl, 10% NaOH, and water and concentrated, and the crude product recrystallized from a 5:1 mixture of *n*-pentane/benzene to give the diastereomeric amide mixture: mp 160–180 °C; $[\alpha]^{24}_D$ +86° (*c* 0.10, CH_3OH).

Anal. Calcd for $C_{27}H_{28}N_2O_4F_6$: C, 58.06; H, 5.05; N, 5.02. Found: C, 57.91; H, 5.06; N, 4.91.

(b) By the same procedure, (*S*)-(+)-1 gave a sample of bisamide **20**: mp 179–180 °C; $[\alpha]^{24}_D$ +40° (*c* 0.082, CH_3OH).

Anal. Found: C, 57.85; H, 5.17; N, 4.87.

(c) Similarly, (*R*)-(−)-1 afforded a bisamide: mp 203–204 °C; $[\alpha]^{24}_D$ +126° (*c* 0.085, CH_3OH).

Anal. Found: C, 57.92; H, 4.96; N, 4.95.

(d) The sample of (−)-1 prepared by resolution of (±)-1 gave a bisamide whose NMR spectrum was identical with that of the product of part c.

Diethyl 3,3-Dicyanoglutarate (15). To a mechanically stirred suspension of 64 g of a 57% dispersion of sodium hydride in mineral oil (1.5 mol of NaH) in 750 mL of dry benzene and 250 mL of dimethylformamide was slowly added 100 g (1.5 mol) of malononitrile. The addition rate was controlled so as to maintain the temperature below 40 °C, requiring an addition time of 5 h, and the mixture was maintained under an atmosphere of dry nitrogen. After evolution of hydrogen ceased, 252 g (1.5 mol) of ethyl bromoacetate was added slowly at 45–50 °C. After completion of the addition, stirring was continued at 40–50 °C for 10 h.

The mixture was cooled and filtered through a sintered glass funnel to remove sodium bromide. The filtrate was washed with two 500-mL portions of water and then with saturated brine and dried over magnesium sulfate. On concentration, the product crystallized; it was filtered and recrystallized from benzene–petroleum ether to give 229 g of **15** (65%, based on ethyl bromoacetate): mp 120–122 °C; NMR ($CDCl_3$) δ 1.23 (t, 6 H, CH_3), 3.22 (s, 4 H, CH_2CO), 4.12 (q, 4 H, OCH_2); IR (KBr) 2250, 1730 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.88; N, 11.76. Found: C, 55.26; H, 5.29; N, 11.83.

2,7-Diazaspiro[4.4]nonane-1,3,6,8-tetraone (16). A solution of 80 g of **15** in 20 mL of concentrated H_2SO_4 and 200 mL of glacial acetic acid was heated under reflux for 30 min. After cooling, the white crystals were collected and washed with ice–water, affording 56.5 g (93%) of **16**: mp 288–290 °C (lit.[10] mp 286–287 °C); IR (KBr) 1785, 1700 cm^{-1}; NMR (NaOD–D_2O) δ 2.95 (AB pattern, 4 H, Δδ = 15.9 Hz, *J* = 18 Hz).

Anal. Calcd for $C_7H_6N_2O_4$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.19; H, 3.31; N, 15.30.

2,7-Dibenzyl-2,7-diazaspiro[4.4]nonane-1,3,6,8-tetraone (17). (a) To a mixture of finely powdered anhydrous potassium carbonate (8.3 g, 0.06 mol) and diimide **16** (7.5 g, 0.041 mol) in a 250-mL round-bottom flask was added 28 g (0.20 mol) of benzyl chloride. The mixture was heated for 3 h at 190 °C in an oil bath with stirring, then 50 mL of water was added, and the excess benzyl chloride was removed by steam distillation. After the mixture was cooled, the solid residue was filtered and washed with several portions of water. The residue was recrystallized from 95% ethanol to afford 11.0 g (74.2%) of **17**, mp 133–135 °C. An analytical sample was obtained by recrystallization from ethanol: IR (KBr) 1790, 1710 cm^{-1}; NMR ($CDCl_3$) δ 2.83 (AB pattern, Δδ = 37.3 Hz, *J* = 18 Hz, 4 H, CH_2CO_2), 4.60 (s, 4 H, CH_2Ph), 7.20 (s, 10 H, aromatic).

Anal. Calcd for $C_{21}H_{18}O_4N_2$: C, 69.60; H, 5.00; N, 7.73. Found: C, 69.24; H, 4.99; N, 7.62.

(b) A solution of sodium hydroxide (24.2 g, 0.606 mol) in 350 mL of absolute alcohol was added slowly to a suspension of 55.0 g (0.303 mol) of **16** in 200 mL of ethanol. The mixture was stirred at room temperature for 2 h and kept in a refrigerator overnight. The precipitate was collected, washed with cold ethanol, and dried. The white powder was then mixed with 70.8 g (0.560 mol) of benzyl chloride in 480 mL of DMF and heated at 80–90 °C for 24 h. After cooling, the mixture was poured into 1600 mL of ice–water. The precipitate was collected and recrystallized from 95% ethanol to afford 72.5 g (79%) of product, mp 132–133 °C.

Anal. Found: C, 69.59; H, 4.89; N, 7.63.

2,7-Dibenzyl-2,7-diazaspiro[4.4]nonane (18). A solution of imide **17** (42 g, 0.12 mol) in 200 mL of dry THF was added slowly to a magnetically stirred suspension of lithium aluminum hydride (23 g, 0.62 mol) in 600 mL of THF at 50 °C. After the addition was completed, the mixture was heated under reflux for 36 h. The excess lithium aluminum hydride was decomposed by the successive addition of 23 mL of water, 23 mL of 15% potassium hydroxide, and 69 mL of water. The precipitate was removed by filtration and the organic layer was dried over $MgSO_4$. After the solvent was removed, the residue was distilled at 220 °C (0.75 mm). The colorless liquid weighed 29 g (83%); NMR ($CDCl_3$) δ 1.6–1.9 (m, 4 H, CH_2C), 2.3–2.7 (m, 8 H, CH_2N), 3.50 (s, 4 H, CH_2Ph), 7.20 (s, 10 H, aromatic).

Anal. Calcd for $C_{21}H_{26}N_2$: C, 82.31; H, 8.55; N, 9.14. Found: C, 82.26; H, 8.46; N, 9.21.

The **dipicrate** was prepared in ethanol and recrystallized from 95% ethanol to give yellow crystals, mp 190–195 °C.

Anal. Calcd for $C_{33}H_{32}O_{14}N_8$: C, 51.84; H, 4.22; N, 14.65. Found: C, 51.68; H, 4.19; N, 14.67.

Attempted Resolution of 2,7-Dibenzyl-2,7-diazaspiro[4.4]nonane. The amine formed a 1:2 salt with *d*-10-camphorsulfonic acid, mp 247–249 °C dec.

Anal. Calcd for $C_{41}H_{58}N_2O_8S_2$: C, 63.90; H, 7.53; N, 3.64. Found: C, 63.68; H, 7.45; N, 3.66.

The salt was repeatedly recrystallized from methanol/acetone and ethanol/ethyl acetate solvent systems but no resolution of the amine was observed.

The amine does not form a crystalline salt with *d*-tartaric acid or with 2,3:4,6-di-*O*-isopropylidene-2-oxo-L-gulonic acid.

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Registry No. (±)-1, 77415-53-3; (±)-1 dipicrate, 77415-54-4; (±)-1·2HBr, 77415-55-5; (*R*)-(−)-1, 77480-26-3; (*R*)-(−)-1·2HBr, 77480-27-4; (*S*)-(+)-1, 77480-28-5; (*S*)-(+)-1·2HBr, 77480-29-6; (±)-2, 77480-30-9; (*R*)-(+)-2, 77415-56-6; (*S*)-(−)-2, 20088-86-2; 3, 20822-61-1; (±)-4, 77415-57-7; (±)-5, 77480-31-0; (*R*)-(−)-5, 20088-81-7; (*R*)-(−)-5 quinine, 77415-58-8; (*S*)-(−)-5, 77415-59-9; (*S*)-(+)-5 quinine, 77415-60-2; (±)-6, 77415-61-3; (*R*)-8, 77415-62-4; (±)-9, 77415-63-5; (±)-9 reineckate, 77415-64-6; (±)-9 *N,O,O*-trimethanesulfenyl derivative, 77415-65-7; (*R*)-9, 77480-32-1; (*R*)-9 *N,O,O*-trimethanesulfonyl derivative, 77480-33-2; (±)-10, 77415-66-8; (*R*)-(+)-10, 20088-82-8; (±)-11, 77415-67-9; (*R*)-(+)-11, 20088-83-9; (*S*)-(−)-12, 40710-02-9; (±)-12 monomethyl ester, 43010-65-7; (*S*)-12 monomethyl ester quinine, 77481-54-0; (*S*)-12 monomethyl ester, 77480-34-3; (*S*)-12 dimethyl ester, 4727-78-0; (±)-13, 39122-18-4; (*S*)-(+)-13, 39122-19-5; (±)-14, 77415-68-0; (*S*)-(−)-14, 20088-85-1; (*R*)-(+)-14, 77480-35-4; 15, 77415-69-1; 16, 77415-70-4; 17, 77415-71-5; (±)-18, 77415-72-6; (±)-18 dipicrate, 77415-73-7; (±)-19, 77415-74-8; (*R*)-(+)-19, 77480-36-5; 20 (isomer 1), 77415-75-9; 20 (isomer 2), 77480-37-6; ethyl cyanoacetate, 105-56-6; ethyl bromoacetate, 105-36-2; (±)-dimethyl 2-ethyl-2-methylsuccinate, 77480-38-7; (±)-2-ethyl-2-methylsuccinic acid, 77480-39-8; (±)-3-ethyl-3-methylpyrrolidine, 77415-76-0; (±)-3-ethyl-3-methylpyrrolidine picrate, 77415-77-1; (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, 20445-31-2; (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetoxyl chloride, 20445-33-4; malononitrile, 109-77-3; (*S*)-(−)-11, 20088-84-0.

A Study of the Structure of Hydrazones of Indole-2,3-dione and 1-Methylindole-2,3-dione with Nuclear Magnetic Resonance Spectroscopy

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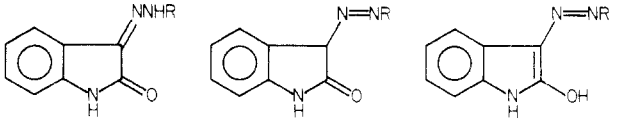
Nuclear magnetic resonance was used to determine the structure of mono- and disubstituted hydrazones of indole-2,3-dione and 1-methlindole-2,3-dione. The assignment of the hydrazone form to all of the monosubstituted derivatives is supported by infrared data. The ^{15}N isotopomer of indole-2,3-dione 3-phenylhydrazone confirms the hydrazone structure. These compounds all show strong intramolecular hydrogen bonding. The disubstituted hydrazones are found to exist as geometric isomers. No tautomeric forms involving the ring NH were detected.

Introduction

Although azo compounds derived from indol-2-one and the comparable hydrazones of indole-2,3-dione have been known for many years,[1] no definitive studies have been reported on the structure of these compounds. In an earlier paper,[2] we had reported that the 1-methyl-2-(phenylazo)indol-2-one probably existed in chloroform as a hydrazone. This assignment was based upon a low-field singlet in the NMR spectrum falling within a 2-ppm range of the shift of similar hydrazone heterocyclics.

The monosubstituted hydrazones of isatin (indole-2,3-dione) can exist in at least three tautomeric forms, 1–3.



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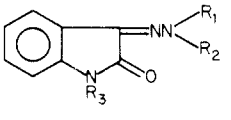
The possibility of tautomers involving the ring NH can be eliminated by studying the monosubstituted derivatives of *N*-methylisatin. On the other hand, the disubstituted hydrazones can exist only in the hydrazone form (4).



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Results and Discussion

NMR Spectra of Monosubstituted Hydrazones of Isatin and *N*-Methylisatin. The NMR spectrum of isatin 3-phenylhydrazone (see Table I) in Me_2SO shows two low-field singlets at 10.91 and 12.71 ppm and in dioxane at 9.27 and 12.75 ppm. The ^{15}N isotopomer of the 3-phenylhydrazone (where the ^{15}N is adjacent to the phenyl group) in Me_2SO contains a doublet centered at 12.75 ppm (J = 97 Hz) and a singlet at 10.95 ppm. The presence of this doublet and the magnitude of the coupling constant provide firm evidence for attachment of the proton to the ^{15}N nitrogen. Consequently, the compound exists in the hydrazone form (1). The higher field resonance can be assigned to the NH proton of the ring. The spectra of isatin 3-methylhydrazone (**5b**) also indicate a hydrazone structure. In both Me_2SO and $CDCl_3$ the methyl peak occurs as a doublet centered at 3.30 (J = 4.1 Hz) and 3.53 ppm (J = 3.9 Hz), respectively, while the lower field peak in Me_2SO occurs as a quarter centered at 10.87 ppm (J = 4.0 Hz) and a very broad signal at 10.98 ppm in $CDCl_3$. The proton of the ring NH appears as a singlet in Me_2SO at 10.61 and 8.71 ppm in $CDCl_3$. Decoupling experiments demonstrated that the doublet and quartet are a result of mutual coupling and therefore the doublet almost surely can be assigned to the NCH_3 group and the quartet to the NH proton of structure 1.

Comparable results are found with isatin 3-benzylhydrazone (**5c**) in Me_2SO. This NMR spectrum contains a lower field triplet centered at 11.32 ppm (J = 4.6 Hz) and a doublet centered at 4.78 ppm (J = 4.6 Hz) due to the methylene protons. Decoupling experiments again reveal the interaction of these protons.

The NMR spectra of *N*-methylisatin 3-phenylhydrazone (**5d**) in Me_2SO and $CDCl_3$ contain only one low-field signal at 12.78 and 12.72 ppm, respectively. The NMR spectra of *N*-methylisatin 3-methylhydrazone (**5e**) also contain only one low-field signal, a quartet centered at 10.83 ppm in Me_2SO and a very broad signal at 10.87 ppm in $CDCl_3$. The methyl peaks in both solvents are doublets (Table I)

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(2) F. A. Snavely and C. H. Yoder, *J. Org. Chem.*, **33**, 513 (1968).

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