rection. When the corrections are small enough the standard errors are calculated and the constants a, b and k and their standard errors are punched on the output cards. The machine then takes in data from the cards for the next run and continues calculating. The program for a 70-point run usually takes 5 to 10 minutes machine time depending on the number of successive corrections (usually two to four) it must calculate. This compares with DeTar's estimate of 4 hours used by an experienced operator to calculate a single set of corrections and the standard errors for a 10 point run using a desk calculator. With the program used here *no* calculations are made by the operator. The method described by DeTar seemed to overcome almost all of the difficulties traditionally associated with the exact calculation of first-order rate constants. Its only drawback was the excessive time required. By the application of electronic computing machines this last difficulty is overcome.

Acknowledgment.—The author would like to thank Professor L. L. Merritt for his assistance in developing the computer program, and Professor Riley Schaeffer for his help in obtaining the n.m.r. data. The computations were done using the facilities of the Indiana University Research Computing Center. This work was supported in part by a Grant from the National Science Foundation.

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY, CORNELL UNIVERSITY, ITHACA, N. Y.]

The Stereochemistry of 1,1,5,5-Tetramethylcyclononane Derivatives[1,2]

BY A. T. BLOMQUIST AND GEORGE A. MILLER[3]

RECEIVED SEPTEMBER 19, 1960

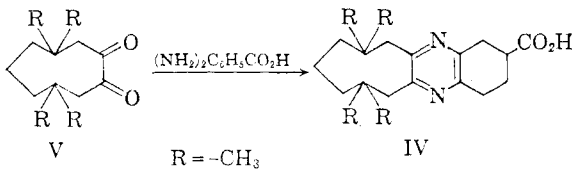
The purpose of this investigation was to discern the intrinsic molecular dissymmetry of a preferred conformation in a nine-membered carbon ring. To this end an azeloin was synthesized which possessed two *gem*-dimethyl groups attached to annular atoms, 4,4,8,8-tetramethylcyclononanol-2-one. Two different approaches were examined in an effort to resolve suitable derivatives of the highly substituted azeloin. The first of these studies was the attempted resolution of the quinoxaline derivative produced by reaction of 4,4,8,8-tetramethyl-1,2-cyclononanedione with 3,4-diaminobenzoic acid; the second study comprised chromic acid oxidation, at 0°, of pure optical antipodes of 3,3,7,7-tetramethylcyclononanol. Neither path led to a successful demonstration of our original purpose. Synthesis of the cyclic acyloin aforementioned and the several related tetramethylcyclononane derivatives, required for the study, was straightforward and involved only procedures described earlier by ourselves and others.

Molecular dissymmetry in certain derivatives of nine-membered carbon rings has been discussed in earlier reports.[2,4] Up to the present time there has been no success in efforts to construct cyclononane derivatives which possess sufficient restriction in single bond rotation to allow, at room temperature, their resolution into optical antipodes.

The present article describes efforts to discern hindered rotation about single carbon–carbon bonds in certain cyclononane derivatives which have two *gem*-dimethyl groups attached to annular atoms. The particular nine-membered ring compound selected as the starting point for the investigation is the substituted azeloin 4,4,8,8-tetramethylcyclononanol-2-one (I).

The intermediate δ-keto-β,β,β′,β′-tetramethylazelaic acid (II) was prepared by basic hydrolysis[5] of the ketene-dimer obtained upon dehydrochlorination[6] of γ-carbomethoxy-β,β-dimethylbutyryl chloride.[7] The keto-acid II was easily reduced (70%) to β,β,β′,β′-tetramethylazelaic acid (III) by the standard Hwang-Minlon[8] modification of the Wolff Kishner method.[9,10] Acyloin cyclization of the dimethyl ester of III by a standard procedure,[12] using solvent toluene, produced the cyclic acyloin I in excellent yield (84%).[13]

With the purpose of demonstrating dissymmetry in appropriate unsymmetrical derivatives of 1,1,5,5-tetramethylcyclononane, a study was made of the resolution of the quinoxaline derivative IV obtained by the condensation of 3,4-diaminobenzoic acid and 4,4,8,8-tetramethyl-1,2-cyclononanedione (V). In the 6-carboxyquinoxaline derivative IV the rigidity of the 2,3-heptamethylene part of the molecule is



V R = -CH3 IV

enhanced both by the two bulky *gem*-dimethyl groups and by fusion to the quinoxaline system.[2]

Cupric acetate oxidation of the acyloin I gave the α-diketone V in nearly quantitative yield; the latter afforded the quinoxaline IV smoothly (75%). Salts of the 6-carboxyquinoxaline IV with the active bases cinchonidine, strychnine, (+)-α-phenyl-

(1) This is the 22nd report in a series of articles on invetigations of many-membered carbon rings. For the preceding paper in the series see A. T. Blomquist and B. H. Smith, *J. Am. Chem. Soc.*, **82**, 2073 (1960).

(2) For closely related papers see (a) A. T. Blomquist, E. S. Wheeler and Y. Chu, *ibid.*, **77**, 6307 (1955); and (b) A. T. Blomquist and Y. C. Meinwald, *J. Org. Chem.*, **23**, 6 (1958).

(3) Supported by funds from du Pont Grant-in-Aid, Summer, 1958; Procter and Gamble Fellow, Summer, 1959; American Viscose Fellow, Summer, 1960; Procter and Gamble Fellow, 1960–1961.

(4) A. T. Blomquist, L. H. Liu and J. C. Bohrer, *J. Am. Chem. Soc.*, **74**, 3463 (1952).

(5) J. C. Sauer, *ibid.*, **69**, 2444 (1947).

(6) A. T. Blomquist, *et al.*, *ibid.*, **74**, 4203 (1952).

(7) J. Cason, G. Sumrell and R. S. Mitchell, *J. Org. Chem.*, **15**, 850 (1950).

(8) Hwang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(9) "Organic Reactions," Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 378.

(10) Application of the Barton modification for sterically hindered ketones proved to be hazardous. A violent explosion occurred when anhydrous hydrazine was distilled into the reaction vessel.[11]

(11) D. H. Barton, D. A. J. Ives and B. R. Thomas, *J. Chem. Soc.*, 2056 (1955).

(12) A. T. Blomquist, R. E. Burge and A. C. Sucsy, *J. Am. Chem. Soc.*, **74**, 3636 (1952).

(13) It is interesting to note here the effect of the presence of the two *gem*-dimethyl groups. Azelaic ester and 5,5-dimethylazelaic ester afford their respective acyloins in yields of 35–40% and 66–70%; see refs. 2a and 4.

ethylamine and quinine methohydroxide were prepared and carefully fractionated by recrystallization. Hydrolysis of the various fractions of the several salts to liberate the free acid IV failed to produce specimens of IV which showed optical activity, *i.e.*, no evidence was obtained for the resolution of IV by this procedure.

In view of the results described in the foregoing, a more elaborate study of nine-membered ring flexibility was made. To begin with, 3,3,7,7-tetramethylcyclononanone (VI) prepared (76%) by reduction of the acyloin I was reduced to 3,3,7,7-tetramethylcyclononanol (VII) by three different methods: (a) with lithium aluminum hydride, (b) catalytically with Adams catalyst, and (c) with sodium and ethanol. The same cyclononanol VII was isolated in all three instances. Thus, under the conditions of the experiments made, there was no evidence for the stable independent existence of quasi-axial and quasi-equatorial conformations of the cyclononanol VII.

With the alcohol VII at hand, a resolution study based on it was made. This study was similar in procedure to one used earlier in experiments on 5,5-dimethylcyclononanol.[2a] The 3-nitro acid phthalate derivative of VII was prepared and resolved *via* its cinchonidine salts into optically pure 3-nitro acid phthalate derivatives of VII: one isomer had m.p. 191–192°, $[\alpha]^{25}D$ +22.2 ± 1°; the other form had m.p. 187–188°, $[\alpha]^{25}D$ −23.4 ± 1°. Hydrolysis of these optically active 3-nitro acid phthalate derivatives gave, respectively, (+)-VII, m.p. 98.5–99.5° and $[\alpha]^{25}D$ + 12.6 ± 1°; and (−)-VII, m.p. 97.5–98.5° and $[\alpha]^{25}D$ −13.0 ± 1°. Chromic acid oxidation of each active alcohol VII produced only ketone VI whose rotation was indistinguishable from zero when examined in the polarimeter both with the 5893 Å. sodium line and the 4358 Å. mercury line.

In order to establish that no racemization had occurred in the hydrolysis of the active 3-nitro acid phthalate derivatives of the alcohol VII, pure (−)-VII was reconverted to its 3-nitro acid phthalate derivative. The ester of (−)-VII thus obtained was identical in all respects with the sample of the same derivative obtained earlier by resolution of the inactive 3-nitro acid phthalate of VII.

The investigation described in this report supports the views that (a) either "nine-membered ring dissymmetry" in bis-*gem*-dimethylcyclonane derivatives is absent at room temperature or (b) possibly the optical activity due to the intrinsic dissymmetry of the preferred conformation of the nine-membered ring is too small to be observed with the polarimetric equipment available.

Experimental Part

Materials.—β,β-Dimethylglutaric acid was obtained from dimedone[14] by hypohalite oxidation.[15] γ-Carbomethoxy-β,β-dimethylbutyryl chloride was prepared in 86% overall yield from the glutaric acid as described by Cason.[7]

δ-Keto-β,β,β′,β′-tetramethylazelaic Acid (II).—The procedure followed for the preparation of the ketene dimer was that of Blomquist, *et al.*[6] Hydrolysis was carried out using the method described by Sauer[5] for the preparation of 6-ketohendecane-1,11-dioic acid.

A solution of γ-carbomethoxy-β,β-dimethylbutyryl chloride (231 g., 1.2 moles) in 200 ml. of anhydrous ether was added rapidly to a cooled, well stirred solution of 173 g. (1.7 moles) of triethylamine in 1400 ml. of anhydrous ether, all under an atmosphere of purified nitrogen. The reaction mixture was stirred for 10 hr. at 0°, allowed to come to room temperature, and then stirred for an additional 14 hr. The precipitated triethylamine hydrochloride was removed by filtration, and the pale yellow filtrate washed twice each with 200-ml. portions of 5% hydrochloric acid, saturated sodium bicarbonate solution, and saturated aqueous sodium chloride. From the dried ether solution there was obtained 194 g. (95%) of crude ketene dimer.

Into a solution of 214 g. (3.25 moles) of 85% potassium hydroxide in 1000 ml. of absolute ethanol and 650 ml. of water was dissolved 194 g. (0.57 mole) of crude ketene dimer. The solution was refluxed for 41 hr., then 900 ml. of ethanol–water was removed by distillation. The remaining alkaline solution was cooled and extracted three times with 200-ml. portions of ether, and refluxed for 4 hr. with 2 g. of activated charcoal. After filtration, the solution was acidified to congo red litmus paper by adding slowly, with constant stirring, 560 ml. of a 50–50 concentrated hydrochloric acid–water solution. The keto-azelaic acid II precipitated and, after cooling, was collected. The yield of crude II was 106 g. (68.5% from γ-carbomethoxy-β,β-dimethylbutyryl chloride), m.p. 103–107°. On crystallization from ethanol–water the acid II had m.p. 107.5–109°.

Anal. Calcd. for $C_{13}H_{22}O_5$: C, 60.44; H, 8.59; neut. equiv., 129. Found: C, 60.61; H, 8.68; neut. equiv., 134.

The keto-diacid II showed strong carbonyl bands in the infrared at 5.80 and 5.90 μ. However, it formed no 2,4-dinitrophenylhydrazone derivative after standing with the hydrazine reagent for several weeks.[16]

The semicarbazone derivative of II, prepared in the usual way,[17] showed m.p. 159° dec. from ethanol–water.

Anal. Calcd. for $C_{14}H_{25}N_3O_5$: C, 53.30; H, 7.99; N, 13.33. Found: C, 53.28; H, 8.09; N, 13.43.

The di-*p*-bromophenacyl ester derivative of II, prepared using the procedure described by Shriner and Fuson,[18] was obtained from absolute ethanol as colorless needles, m.p. 86–87°.

Anal. Calcd. for $C_{29}H_{32}Br_2O_7$: C, 53.39; H, 4.94; Br, 24.49. Found: C, 53.61; H, 5.03; Br, 24.57.

The dimethyl ester derivative of II was prepared using the diazomethane method[19]; b.p. 106–106.5° (0.2 mm.), $n^{25}D$ 1.4470 and $d^{25}_{25.5}$ 1.0365.

Anal. Calcd. for $C_{15}H_{25}O_5$: C, 62.92; H, 9.16; mol. wt., 286. Found: C, 62.97; H, 9.25; mol. wt., 277.

The diethyl ester derivative of II was prepared by the Fischer esterification method; b.p. 109° (0.11 mm.) and $n^{25}D$ 1.4450.

Anal. Calcd. for $C_{17}H_{30}O_5$: C, 64.94; H, 9.62; mol. wt., 314. Found: C, 65.09; H, 9.70; mol. wt., 307.

β,β,β′,β′-Tetramethylazelaic Acid (III).—The keto-acid II was reduced following the general method described by Hwang-Minlon.[8] In 940 ml. of diethylene glycol was dissolved by gentle heating with a flame 152 g. (2.4 moles) of 85% potassium hydroxide pellets. The solution was cooled and 106 g. (0.411 mole) of the acid II and 74 ml. (2.2 moles) of 95% hydrazine hydrate was added and dissolved. The solution was refluxed for 10 hr., then 115 ml. of excess hydrazine and water was removed by distillation. During the distillation the temperature of the liquid in the flask rose to 215°, and the reaction was allowed to reflux at that temperature for 18 hr. After reflux, 500 ml. of water was added to the *viscid* reaction mixture to make it more manageable; the aqueous solution was extracted twice with 300-ml. portions of ether and stirred overnight with 10 g. of activated charcoal. After filtration the solution was acidified to congo red litmus paper by the slow addition of 520 ml. of a 50–50 concentrated hydrochloric acid–water solution. The mixture was cooled, and the acid III which precipitated was collected. The crude diacid was then dissolved in 300 ml. of

(14) A. H. Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 200.

(15) R. S. Schreiber, *Org. Syntheses*, **31**, 40 (1951).

(16) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., p. 219.

(17) Ref. 16, p. 218.

(18) Reference 16, p. 200.

(19) Reference 14, p. 165.

benzene, and the benzene solution was separated from the diethylene glycol which settled to the bottom. On cooling the benzene solution, 70 g. (70%) of the acid III, m.p. 103–105°, was obtained, which on recrystallization from ethanol–water had m.p. 108–109°.

Anal. Calcd. for $C_{13}H_{24}O_4$: C, 63.90; H, 9.90; neut. equiv., 122. Found: C, 63.83; H, 9.85; neut. equiv., 129.

The reduced-diacid III showed a carbonyl band in the infrared at 5.90μ, with no observable splitting. Also, the melting point of the reduced-diacid III was depressed when mixed with starting keto-diacid.

The di-*p*-bromophenacyl ester derivative of III was prepared as described above[18] and showed m.p. 87–88°.

Anal. Calcd. for $C_{29}H_{34}Br_2O_6$: C, 54.55; H, 5.37; Br, 25.03. Found: C, 54.54; H, 5.28; Br, 25.21.

When the di-*p*-bromophenacyl esters of the acids II and III were mixed, the melting point of the mixture was depressed.

The dimethyl ester derivative of III was prepared as described previously[19] and also by the Fischer method; b.p. 94° (0.25 mm.), $n^{25}D$ 1.4413 and $d^{25}_{25.5}$ 0.9744.

Anal. Calcd. for $C_{15}H_{28}O_4$: C, 66.15; H, 10.36; mol. wt., 272. Found: C, 66.39; H, 10.46; mol. wt., 289.

4,4,8,8-Tetramethylcyclononanol-2-one (I).—The cyclic acyloin I was obtained in 84% yield from the dimethyl ester of III following a standard procedure.[12] Toluene was employed as solvent, and in a typical run 15 g. (0.055 mole) of diester in 100 ml. of toluene was added dropwise over a 12-hr. period to 1200 ml. of toluene containing 6.32 g. (0.275 mole) of dispersed sodium. The acyloin obtained (9.85 g., 84%) showed b.p. 92° (0.75 mm.), $n^{20}D$ 1.4784. The product I was extremely difficult to obtain colorless, as it turned yellow almost immediately when exposed to air.

Anal. Calcd. for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. Found: C, 73.58; H, 11.49.

The *p*-nitrobenzoate derivative of I was prepared as described by Shriner and Fuson[20] and was obtained from ethanol with m.p. 108–109°.

Anal. Calcd. for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.87. Found: C, 66.55; H, 7.59; N, 4.11.

The semicarbazone derivative of I, also prepared as described by Shriner and Fuson,[17] showed m.p. 185–186° (sl. dec.) after recrystallization from ethanol–water.

Anal. Calcd. for $C_{14}H_{25}N_3O_2$: C, 62.87; H, 9.42; N, 15.71. Found: C, 62.78; H, 9.62; N, 15.95.

4,4,8,8-Tetramethyl-1,2-cyclonanedione (V).—The cyclic acyloin I was oxidized by cupric acetate using a standard procedure described earlier[4] to give the diketone (85–90%) which after sublimation had m.p. 61–62°.

Anal. Calcd. for $C_{13}H_{22}O$: C, 74.24; H, 10.55. Found: C, 74.22; H, 10.36.

The 6-carboxyquinoxaline derivative of diketone V (IV) was prepared in 75% yield using the procedure described earlier.[2b] It was recrystallized from absolute ethanol, m.p. 269° (sl. dec.). The ultraviolet absorption spectrum of this quinoxaline IV showed maxima at 332, 319 and 247 mμ, with log ϵ values of 3.94, 3.88 and 4.59, respectively.

Anal. Calcd. for $C_{20}H_{25}N_3O_2$: C, 73.59; H, 8.03; N, 8.59. Found: C, 73.83; H, 8.19; N, 8.79.

The simple, unsubstituted quinoxaline was also prepared; m.p. 112–113°. The ultraviolet absorption spectrum of this quinoxaline was similar to that of IV except that the absorption maxima were shifted to shorter wave lengths. In this case the maxima occurred at 324, 311 and 238 mμ, with log ϵ values of 3.98, 3.88 and 4.49, respectively.

Anal. Calcd. for $C_{19}H_{26}N_2$: C, 80.81; H, 9.28; N, 9.92; mol. wt., 282. Found: C, 81.08; H, 9.53; N, 9.81; mol. wt., 278.

Attempted Resolution of Quinoxaline IV. A.—The resolution procedure followed was similar to that employed by Blomquist and Meinwald on 2,3-heptamethylenequinoxaline-6-carboxylic acid.[2b] An equimolar mixture of IV and the optically active base was gently refluxed in sufficient acetone to give a clear solution. On cooling, the first crop of crystals was received, and on evaporation of the mother liquor additional fractions were obtained. When it was possible, each salt fraction was crystallized to constant melting point and optical rotation. No crystalline salt was obtained using the bases brucine or quinine.

The cinchonidine salt of IV was obtained in five fractions, all of which after recrystallization from acetone showed m.p. 204–205° and $[\alpha]^{25}D$ 44.0 ± 2° (*c* 2.5, in chloroform).

Anal. Calcd. for $C_{39}H_{48}N_4O_3$: C, 75.45; H, 7.79; N, 9.03. Found: C, 75.58; H, 7.93; N, 8.83.

The strychnine salt of IV was obtained in four fractions, all having decomposition ranges between 210–230°. The salt resisted recrystallization from various solvents.

The (+)-α-phenylethylamine salt of IV crystallized in four crops, two of which showed m.p. 164–165°. The remaining two fractions had very wide melting ranges, 163–250°. The salt hydrolyzed very easily and an attempted recrystallization gave only the starting quinoxaline IV.

Four crops of a **quinine methohydroxide salt of IV** were obtained from 1,4-dioxane solvent. All fractions showed decomposition ranges between 156–200° and could not be purified by crystallization.

The various fractions of the different salts were decomposed by shaking a chloroform solution of the salt with 5% hydrochloric acid solution. On evaporation of the chloroform an acid was obtained in all cases which had zero optical rotation and showed m.p. 269–270° dec. which was not depressed on admixture with authentic IV.

B.—A 0.5-molar quantity of the optically active base was mixed with the derivative IV, and the mixture dissolved in just sufficient acetone. The salt fractions were treated as before.

Crystalline salts were obtained with cinchonidine and strychnine. Both appeared to be identical to their respective counterparts obtained previously and on hydrolysis, as done before, yielded only inactive IV.

4,4,8,8-Tetramethylcyclononanone (VI).—The zinc dust (90%) reduction procedure described for the preparation of cyclononanone[4] was followed with the acyloin I (9.1 g., 0.043 mole) except that strict temperature regulation was required. Allowing 15 min. stirring between additions, three 16-ml. portions of concentrated hydrochloric acid were added, each in 5 min., to the stirred reaction mixture at 50–55°, 40–45° and 35–40°, respectively. In this manner 6.75 g. (76%) of the ketone VI was obtained, b.p. 88° (1.6 mm.), $n^{20}D$ 1.4698. The ketone crystallized in the refrigerator at 0°; m.p. 22.5–23.5°.

Anal. Calcd. for $C_{13}H_{24}O$: C, 79.53; H, 12.32; mol. wt., 196. Found: C, 79.61; H, 12.09; mol. wt., 209.

The semicarbazone derivative of VI was prepared in the usual manner[17]; m.p. 196–197°.

Anal. Calcd. for $C_{14}H_{27}N_3O$: C, 66.34; H, 10.74; N, 16.59. Found: C, 66.33; H, 10.43; N, 16.88.

The oxime derivative of VI was prepared using the vigorous conditions described by Shriner and Fuson[21] for cyclic ketones; m.p. 122–123.5°.

Anal. Calcd. for $C_{13}H_{25}NO$: C, 73.88; H, 11.93; N, 6.63. Found: C, 73.78; H, 11.93; N, 6.74.

4,4,8,8-Tetramethylcyclononanol (VII). A.—The ketone VI (4.38 g., 0.0223 mole) in 60 ml. of anhydrous ether was reduced with excess lithium aluminum hydride in the usual manner. The complex was decomposed by adding water, and the product was isolated following the usual procedure. On sublimation, 3.97 g. (90%) of VII, m.p. 80.5–81°, was obtained. Infrared and near infrared absorption spectra of this VII showed maxima at 2.80 (sharp) and 2.95 μ (broad), as well as 1.413 (sharp) and 1.720 μ (broad).

Anal. Calcd. for $C_{13}H_{25}O$: C, 78.72; H, 13.22; mol. wt., 198. Found: C, 78.88; H, 13.26; mol. wt., 215.

B.—One gram of the ketone VI was reduced catalytically at room temperature and atmospheric pressure, using glacial acetic acid solvent and platinum dioxide catalyst, to yield, after 24 hr., 0.89 g. (89%) of VII, m.p. 80–81.5°. The infrared and near infrared absorption spectra of this VII were identical to those of the sample of VII obtained by lithium aluminum hydride reduction.

C.—A sodium–alcohol reduction procedure similar to that described by Whitmore and Otterbacher[22] for the reduction of methyl *n*-amyl ketone was followed. To 1 g. (5.1 mmoles) of VI dissolved in 25 ml. of absolute ethanol at room temperature was added 1 g. (43.5 mmole) of small

(20) Reference 16, p. 212.

(21) Reference 16, p. 255.

(22) Reference 14, p. 317.

sodium pieces. After stirring the reaction mixture for 1 hr., the product was isolated and purified in the usual manner. The yield of VII was 0.350 g. (35%), m.p. 80–81°. The infrared and near infrared absorption spectra of this VII were identical to those of the specimens of VII obtained by the previous two reduction procedures.

Anal. Found: C, 78.87; H, 13.37; mol. wt., 201.

Samples of the alcohol VII obtained from chemical and catalytic reductions were mixed and sublimed together. No depression of melting point was observed.

4,4,8,8-Tetramethylcyclononanol 3-Nitro Acid Phthalate.—The alcohol VII (11 g., 0.056 mole) and 11.6 g. (0.06 mole) of 3-nitrophthalic anhydride were heated in 110 ml. of anhydrous toluene until all the anhydride dissolved, then refluxed for 0.5 hr. On cooling, 15 g. of solid was precipitated which, after crystallization from benzene, gave 10.2 g. of the pure 3-nitro acid phthalate derivative of VII which had m.p. 198° dec., and 2.65 g. which showed m.p. 188–192° dec. (58% total).

Anal. Calcd. for $C_{21}H_{29}NO_6$: C, 64.42; H, 7.47; N, 3.58; mol. wt., 391. Found: C, 64.68; H, 7.41; N, 3.85; mol. wt., 379.

The **methyl ester derivative of the above acid phthalate** was prepared using the diazomethane method[19]; m.p. 129–134° from hexane.

Anal. Calcd. for $C_{22}H_{31}NO_6$: C, 65.15; H, 7.71; N, 3.46; mol. wt., 405. Found: C, 65.27; H, 7.57; N, 3.73; mol. wt., 385.

Resolution of the 3-Nitro Acid Phthalate Derivative of VII.[2a]—In 1700 ml. of acetone there was dissolved, by gentle refluxing, 10.15 g. (0.026 mole) of the nitro acid phthalate of VII and 7.65 g. (0.026 mole) of cinchonidine. On cooling and evaporation of the solvent 16.69 g. of salt was obtained. The residue was hydrolyzed with 5% hydrochloric acid solution to yield after three recrystallizations from benzene 0.54 g. of solid, m.p. 188–189° dec., with softening at 175°, $[\alpha]^{25}D$ + 23.5 ± 1° (*c* 5, in acetone).

Fractional crystallization of the salt from acetone until the least soluble fractions showed no further change in m.p. or optical rotation gave 6.11 g. of (−)-acid-(−)-base salt, m.p. 199° (sl. dec.), $[\alpha]^{25}D$ −90.8 ± 1° (*c* 2.5, in chloroform).

Anal. Calcd. for $C_{40}H_{51}N_3O_7$: C, 70.05; H, 7.50; N, 6.13. Found: C, 70.10; H, 7.74; N, 6.14.

A solution of 6.11 g. of (−)-acid-(−)-base salt in 50 ml. of chloroform was shaken three times in succession with 50-ml. portions of 5% hydrochloric acid solution. On evaporation of the chloroform 2.44 g. (48%) of the (−)-3-nitro acid phthalate of VII was obtained; m.p. 187–188° dec. with softening at 180°, $[\alpha]^{25}D$ −23.4 ± 1° (*c* 5, in acetone), constant rotation on recrystallization from benzene.

Anal. Calcd. for $C_{21}H_{29}NO_6$: C, 64.42; H, 7.47; N, 3.58; mol. wt., 391. Found: C, 64.69; H, 7.38; N, 3.86; mol. wt., 390.

The more soluble salt (5.10 g.), m.p. 165–168°, $[\alpha]^{25}D$ −108.8 ± 1° (*c* 2.5, in chloroform), was obtained in a reasonably pure state on further fractional crystallization. This salt was decomposed as described above to give the crude (+)-3-nitro acid phthalate of VII, m.p. 180–187°, $[\alpha]^{25}D$ + 16.8° (*c* 5, in acetone). On recrystallization of this crude phthalate from benzene–hexane the racemate, m.p. 198–199° dec., was obtained as insoluble material. The benzene–hexane solution deposited, on cooling, 1.1 g. of optically pure (+)-3-nitro acid phthalate; m.p. 191–192° dec., $[\alpha]^{25}D$ + 22.2 ± 1° (*c* 5, in acetone). The total yield of (+)-3-nitro acid phthalate of VII was 1.64 g. (32%).

Anal. Calcd. for $C_{21}H_{29}NO_5$: C, 64.42; H, 7.47; N, 3.58. Found: C, 64.61; H, 7.71; N, 3.67.

(+)- and (−)-Alcohol VII.—The (+)-3-nitro acid phthalate of VII (1.1 g., 2.82 mmoles) was hydrolyzed following a procedure described previously[2a] to yield 0.55 g. (90%) of (+)-VII, which after sublimation at 35° (0.07 mm.), showed constant m.p. 98.5–99.5° and $[\alpha]^{25}D$ + 12.6 ± 1° (*c* 5, in chloroform). After 3 weeks at room temperature, the material was unchanged; m.p. 99–100°, $[\alpha]^{25}D$ +12.0 ± 1° (*c* 5, in chloroform).

Anal. Found: C, 78.75; H, 13.21; mol. wt., 218.

The (−)-3-nitro acid phthalate of VII (1.52 g., 3.89 mmoles) was hydrolyzed in a similar manner to yield 0.72 g. (94%) of (−)-VII, which after sublimation at 35° (0.07 mm.) showed constant m.p. 97.5–98.5° and $[\alpha]^{25}D$ −13.0 ± 1° (*c* 5, in chloroform).

Anal. Found: C, 78.87; H, 13.40; mol. wt., 199.

(−)-VII 3-Nitro Acid Phthalate from (−)-VII.—Compound (−)-VII (0.2 g., 1.01 mmoles) and 3-nitrophthalic anhydride (0.2 g., 1.04 mmoles) were dissolved in 5 ml. of anhydrous toluene and refluxed for 20 min. On cooling, 0.09 g. of unreacted anhydride was obtained. The solvent was removed and the residue sublimed to yield trace amounts of unreacted alcohol. The sublimation residue was crystallized from hexane to give 0.055 g. (14%) of the (−)-3-nitro acid phthalate of VII, m.p. 188.5–189° dec. with softening at 178°, $[\alpha]^{25}D$ −23.0 ± 1° (*c* 5, in acetone). A high melting material (m.p. > 220°) interfered with the hexane crystallization and caused the poor yield.

Chromic Acid Oxidation of (+) and (−)-VII.—The chromic acid oxidation procedure described in an earlier article in this series,[2a] but done at 0°, was followed. Thus, from 0.140 g. (0.715 mmoles) of (+)-VII there was obtained 0.134 g. (97%) of VI, $[\alpha]^{25}D$ 0° (*c* 13, in chloroform), $[\alpha]^{25}D$ 0° (*c* 13, in hexane), $[\alpha]^{25}_{4358}$ 0° (*c* 13, in chloroform) and $[\alpha]^{25}_{4358}$ 0° (*c* 13, in hexane). After molecular distillation the ketone VI showed $n^{20}D$ 1.4686. The infrared absorption spectrum of this VI was identical to that of the original ketone VI.

Anal. Found: C, 79.20; H, 12.58.

Similarly, from 0.50 g. (2.52 mmoles) of (−)-VII there was obtained 0.48 g. (96%) of VI, $[\alpha]^{25}D$ 0° (neat), $[\alpha]^{25}D$ 0° (*c* 3, in hexane), $[\alpha]^{25}D$ 0° (*c* 2.4, in chloroform), $[\alpha]^{25}_{4358}$ 0° (*c* 2.4, in chloroform). This ketone VI showed b.p. 46–47° (0.075 mm.) and $n^{20}D$ 1.4700. The infrared absorption spectrum of this VI was identical to that of the original ketone VI, as well as to that of the ketone VI obtained from (+)-VII.

Anal. Found: C, 79.43; H, 12.55.

COMMUNICATIONS TO THE EDITOR

NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY. LONG-RANGE SPIN–SPIN COUPLINGS IN SATURATED MOLECULES[1]

Sir:

It is usually assumed that spin–spin couplings except those involving fluorine–fluorine interactions[2] are negligibly small over more than three bonds in saturated systems.[3] At this time, we should like to report four examples of H–H and H–F spin–spin couplings that involve more than three consecutive single bonds. Each of these systems is characterized by having either fixed or at least reasonably favored geometrical conformations.

(1) Supported in part by the Office of Naval Research.

(2) See, for example, (a) A. Saika and H. S. Gutowsky, *J. Am. Chem. Soc.*, **78**, 4818 (1956); (b) N. Muller, P. C. Lauterbur and G. F. Svatos, *ibid.*, **79**, 1807 (1957).

(3) (a) J. D. Roberts, "Nuclear Magnetic Resonance," McGraw-Hill Book Co., New York, N. Y., 1959, Chap. 3; (b) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, Chap. 6; (c) M. Karplus, *J. Am. Chem. Soc.*, **82**, 4431 (1960).