Tetrahedron Vol. 44, No. 22, pp. 6875 to 6880, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00

PROPELLANES. XCVIII. THREADING OF ANTI,ANTI[20.3.3]PROPELLANE-24,27-DIOL BY SEBACIC ACID.**

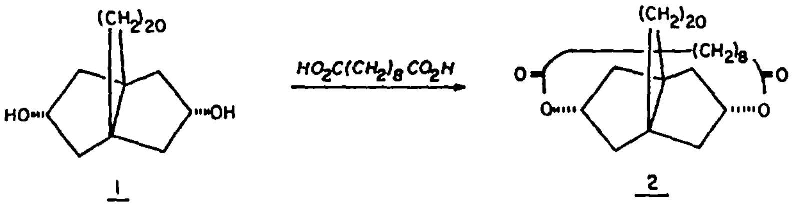
PNINA ASHKENAZI*, ARIE L. GUTMAN, and DAVID GINSBURG ✿

Department of Chemistry, Israel Institute of Technology, Haifa, Israel.

(*Received in UK* 20 *June* 1988)

Abstract. - A spherical cyclic diester has been prepared from the title components, separated from by-products, and purified by aid of double labelling of the components with ^3H and ^{14}C, respectively. The product may be viewed as a doubly-anchored rotaxane.

Introduction. - We mentioned our intention of using a suitable propellane for the potential threading of its large ring with a bifunctional aliphatic chain, eventually forming an intramolecular rotaxane, 2, (Scheme 1).



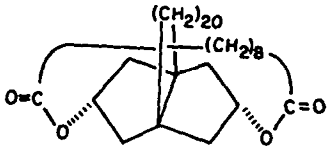
SCHEME 1

We chose to thread a diol of the type 1, n=20. The [20.3.3] dione 1 was triated (^3H) at the α-positions to the carbonyl groups and reduced to a mixture of the corresponding 24,27-diols.[2] We have found in the interim that coniguratіonal isomers of this type may be distinguished unambiguously. The anti,anti-isomer has a symmetrical NMR spectrum[3,4] and a strong MH^+ peak under isobutane-chemical ionization.[5] The syn,syn-isomer also has a symmetrical NMR spectrum, however, like the syn,anti-isomer, it fragments to give $[M-OH]^+$ and $[M-OH-H_2O]^+$ under chemical ionization.

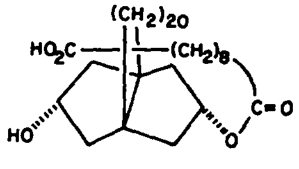
The isomer used for threading was the aa-diol (1, anti-anti-OH). We should have expected from a study of models that the aa-diol could perhaps just barely be thresed at all.[1,4] This is based on a concept stemming from the talmud called "Kal vachomer".[6] If a more difficult action may be accomplished, a simpler analogous one may certainly be done. Thus, although we have not threaded the syn,syn or syn,anti-isomers of the anti,anti-diol we used, if the latter be threaded so must surely the two former isomers as well.

** Part XCVII. P. Ashkenazi, M. Kapon, and D. Ginsburg, Tetrahedron, in press.

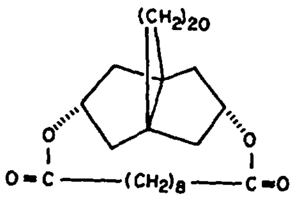
✿ Deceased March 9, 1988.



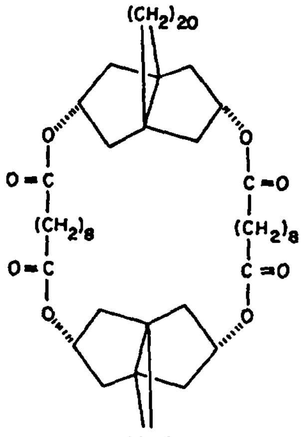
2a,a



4



3



e.g 5, also possible higher oligomer

While this work was in progress, a breakthrough occurred during the synthesis of catenanes via rotaxanes. Here too a P-TSOH equilibrium step was employed.[7] But in Schill's case hydrolysis of the rotaxane is easier than in ours. Once we have threaded our 22-membered ring under acidic conditions the acidic hydrolysis equilibrium is on the side of the half-ester 4 which then gives the rotaxane 2. In order to differentiate between 2 and 3, we undertook a saponification step (see below). It would be more difficult for the base to approach both ester groups and the kinetics show this when 3 disappears more readily and the desired 2 survives.

Discussion. - Our use of double-labelled substrates proved to be a happy choice. Sufficient differences in the energy spectra of ^{3}H and ^{14}C, albeit both are β-emitters, enabled us to obtain separate estimates of the contents of both isotopes (remembering that due to low enrichment of isotopic label it is most unlikely that either [^{14}C]-sebacic acid or of [3H]-propellanediol have more than one labelled site (see experimental section for preparation of labelled sebacic acid).

^{3}H content is normally measured by reference to a ^{14}C label by determining the $^{3}H/^{14}C$ ratio. Constancy of this ratio from the start of the reaction through to the product (the cyclic diester) conclusively proves that the latter is indeed formed by a 1:1 coupling of the ^{3}H and ^{14}C labelled starting materials; unforeseen by-products are thus avoided.

From the workup of our doubly-labelled reaction we isolated several chromatographic fractions having the same ^{3}H:^{14}C ratio ("1:1"), as present in the mixture of the two labelled starting materials. These could be the desired 2, or the cyclic diester 3. Cyclic oligomers 5 obtained would also have a 1:1 ratio as well as the half-acid 4 intermediate *en route* to 2. The last is easily separable from neutral components 2, 3, and 5 by introducing an effective alkaline wash into the workup procedure before chromatographic separation of 2, 3 and 5. The oligomeric fraction 5 was easily separated chromatographically from 2 and 3 of lower molecular weight.

Kinetics of hydrolysis. - Since 2 and 3 may not be separable chromatographically, we had concocted a felicitous strategy to separate them. Alcoholysis with KOBu^t clearly appears able to nucleophilically attack the ester moiety of 3 without being able to reach this group within spherical 2 (steric repulsion). This method appeared to be successful, for when the cyclic oligomer 5 was thus treated with the same base, it readily underwent the desired nucleophilic fragmentation to afford the starting propellane diol and the aliphatic thread.

Kinetics showed rapid fragmentation of the apparently minor component but the 1:1 threaded component 2, by comparison, survived. We interpreted our kinetics (see below) as indicating purification of the desired (threaded) rotaxane 2 by destroying the accompanying 3 (scheme 2) in a fast reaction.

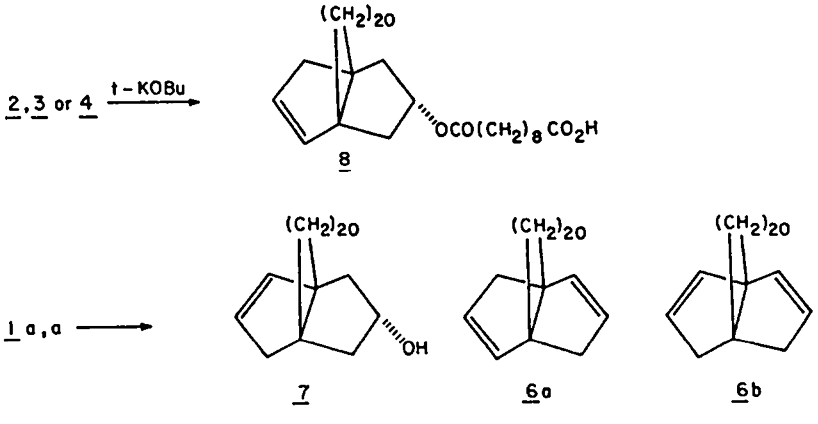
Hydrolysis was accomplished under pseudo-first order conditions with respect to the large quantity of base used, and first order with respect to the lactone mixture; the graph corresponding to the log [lactones]/time was a straight line. The graph recorded therein shows very well the break at about 40 hr hydrolysis when one lactone is finished hydrolyzing, analogously to the corresponding oligomers, and much slower rate begins for the stable threaded lactone. There does not seem to be a difference between the two lactones 2 and 3 in the ^{1}H- and ^{13}C-NMR spectra of the mixture. Mass spectra also appeared the same at different temperatures, mass peak for mixture, 586; IR($CHCl_3$): 1725 cm^{-1}.

$$\underline{2} + \underline{3} \xrightarrow[80°C,\, C_6H_6]{t\text{-BuOK}} \underline{4} + \underline{1}\,a,a + HO_2C(CH_2)_8CO_2H$$

Scheme 2

Unfortunately, our purification protocol afforded us the doubly-anchored rotaxane 2, but only at the expense of destruction of its isomer 3. Nevertheless, our attack of the cyclic diester mixture permitted saving 2 at the expense of 3.

Scheme 2 shows that in a much slower reaction via an E1 mechanism (Scheme 3) 2 may also be destroyed, affording ^{3}H and ^{14}C labelled products. (See experimental section).



SCHEME 3

^{1}H permitted observation of the starting anti-diol, the two dienes resulting therefrom - as well as the ene-ol, all neutral materials with ^{14}C content fit this conclusion and helped in our interpretation.

There is an ancient Hebrew saying: "What I feared has come to pass".[8] Although Sukenik *et al*[4] succeeded in preparing crystals of anti,anti-1, n=10 and proving its configuration by X-ray analysis, we feared, as soon as we observed our waxy [20.3.3] propellane diols, that even X-rays in the Holy Land would be of insufficient avail. And indeed the "crystals" we submitted to our X-ray laboratory were shown to be plastic and incapable of analysis. We feared, of course, that a compound such as 3, and needless to say, a fatty sphere such as 2, n=22, would be even less prone to thus divulge their structures. This fear was indeed justified and we cannot present direct X-ray proof for the product we spent much time in preparation, 2, n=20. We hope, however, that under these objective circumstances, the evidence afforded has the internal logic required to strongly support our conclusion that we have indeed prepared a propellane having the composition of a doubly-anchored rotaxane.

We can only be certain that if we had a ring larger than C_{22} described above, i.e. 1, n=28,38 the hole to be threaded would be acceptable to all. Such compounds as 2, 3, n=28,38 might have NMR spectra of conformational interest.

We have therefore prepared these higher homologs of whose "plastic" crystals we correctly predicted.[9] Such compounds might be substrates capable of affording additional evidence of threading, perhaps through NMR conformational analysis.

Experimental. - *Reaction between 1 and sebacic acid*. Threading was conducted between [23,25,26,28-^{3}H] [20.3.3] propellane-24,27-anti,anti-diol (1.074g, 2.56 mmol, ca 1.3x10^{9} dpm) and [1,10-^{14}C]-sebacic acid (517mg, 2.56 mmol, ca 2.8x10^{8} dmp), by refluxing with p-toluenesulfonic acid (1.383 g, 7.27.mmol) in dry benzene (4.2 L) for 21 days. The starting ratio was ^{3}H/^{14}C = 4.67.

The evaporated benzene contained no ^{14}C but the count of 3x10^{7} dpm of ^{3}H (2%) indicated partial dehydration of the diol. (Such dehydration results in loss of ^{1}H, rather ^{3}H, because of a primary kinetic isotope effect. Hence loss of ^{3}H is significant and implies substantial dehydration to form en-ol and even diene; Cf. discussion in above text and below).

The residue in benzene was washed with saturated aq Na_2CO_3 (9x100 ml) to remove acidic material, be it unreacted sebacic acid or any monoesters resulting therefrom. Counting of an aliquot of the combined carbonate washings revealed a content of 0.7x10^{8} dpm of ^{3}H (ca 5% of the total) and 1.1x10^{8} dpm ^{14}C (ca 40% (!) of total). Not surprisingly, in keeping with these results the ^{3}H:^{14}C ratio in the organic residue rose to 9.85 (1.300 mg, 1.2x10^{9} dpm ^{3}H and 1.2x10^{8} dpm ^{14}C). This crude mixture (TLC showed 9 spots) was subjected to silica gel chromatography with elution by solvents of gradually increasing polarity from hexane, through benzene to ethyl acetate. Analytically pure components were obtained by purifying each fraction on prep. silica gel plates.

The first four fractions, of lower polarity (366 mg) contained virtually no ^{14}C but 1.75x10^{8} dpm ^{3}H (15% of total ^{3}H), attributed (400 MHz NMR) to dienes 6 and ene-ol 7.

The following turned out to be the main cyclic fraction (400 mg, 3.1x10^{8} dpm ^{3}H and 0.6x10^{8} dpm ^{14}C, *i.e.* 25% of ^{3}H total and 50% of ^{14}C total, ^{3}H:^{14}C = 5.16). Further purification on silica gel plates gave ^{3}H:^{14}C = 4.55.

Further increase of eluent polarity eluted unreacted diol - (163 mg, 2x10^{8} dpm ^{3}H, 17% of total ^{3}H), followed by the highly polar oligomers 4 and residual materials such as half-acids (257 mg, 1.4x10^{8} dpm ^{3}H, 0.3x10^{8} dpm ^{14}C, 12% of total ^{3}H and 25% of total ^{14}C respectively).

The 4.55 ^{3}H:^{14}C ratio of the purified cyclic diester fraction indicated this was indeed the 1:1 addition product of the starting materials. NMR Bruker 400 MHz spectrometer ($CDCl_3$), ^{1}H: δ 5.11 (tt, 2H, CHOCO, J=8.3, J=4.2), 2.29 (t, 4H, CH_2CO_2, J=6.6), 2.01 (ddd, 8H, CH_2, J=14.5, J=8.6, J=4.6), 1.62 (t, 4H, $CH_2CH_2CO_2$, J=6.0), 1.26 (s, 48H, CH_2). ^{13}C: 173.55, 75.24, 54.98, 43.33, 34.51, 34.17, 29.75, 28.69, 28.35, 28.16, 28.06, 27.68, 27.62, 27.50, 24.89.

Reaction of 2 and 3 with t-BuOK.- Pure cyclic diester fraction (82 mg, $16x10^6$ dpm ^{14}C, $^3H/^{14}C$ = 4.55) was heated under reflux for 40 hr with freshly sublimed t-BuOK in benzene under Ar. (This is one example of 3 such nucleophilic runs). Treatment of the reaction with HCl (1N, 2ml) and extraction with saturated aq Na_2CO_3 solution (5x20 ml), left after evaporation of solvent an organic residue (59 mg).

Reflux was continued for another 6 days, affording upon similar workup organic residue (58 mg), $6.5x10^6$ dpm ^{14}C, $^3H:^{14}C$ = 5.9 (Only 40% ^{14}C was retained in the organic residue). Additional reflux under the above conditions for 5 days, then 4 more days did not result in substantial change on ^{14}C counting of organic residue (53 mg, $6.4x10^6$ ^{14}C, $^3H:^{14}C$ = 5.57 and 45 mg, $6.4x10^6$ dpm ^{14}C, $^3H:^{14}C$ = 5.4, respectively).

Final purification of the last residue on silica gel plates gave the unreacted cyclic diester (31 mg, $5.4x10^6$ dpm ^{14}C, $^3H:^{14}C$ = 4.60). This is the desired threaded product - (see text discussion). NMR ^1H: 5.11 (tt, 2H, C<u>H</u>OCO, J=8.5, J=4.3), 2.29 (t, 4H, C<u>H</u>$_2$CO$_2$, J=6.6), 2.01 (ddd, 8H, CH_2, J=14.5, J=8.6, J=4.6), 1.62 (t, 4H, C<u>H</u>$_2$CH$_2$CO$_2$, J=6.2), 1.26 (s, 48H, CH_2). ^{13}C: 173.70, 75.36, 55.11, 43.48, 34.69, 34.32, 29.90, 28.84, 28.47, 28.29, 28.20, 27.84, 27.72, 27.65, 24.99. Solvent shifts, lanthanides, COSY and NOESY could resolve only the first two sets of protones of the C_8- ester chain. The other protons are hidden under the massive C_{22}-chain.

Synthesis of sebacic acid. - Four experiments with inactive ^{12}C) potassium cyanide were carried out in order to determine the optimal conditions for the preparation of the dinitrile and its subsequent hydrolysis.[10]

It turned out that when 20% excess of KCN was used (as recommended in the literature) the dibromide was fully converted into the dinitrile at room temperature in DMF within 10 days. However, without excess of KCN, the conversion did not rise above 90% even after 30 days. (In the radioactive experiment it is unwise to use an excess of KCN, as this, and not the dibromide, is the more costly compound. Nevertheless, it is necessary to achieve complete conversion to assure absence in the product of Br-$(CH_2)_8$-CN. Therefore, initially less than one equiv. of $K^{14}CN$ was mixed with the dibromide in DMF for 10 days to ensure that all the $K^{14}CN$ is converted into -CH_2-^{14}CN. Then, an excess of radioinactive KCN was added to complete the conversion of the dibromide into the dinitrile). Thus, quantitative radioactive (based on $K^{14}CN$) may be achieved as well as quantitative chemical yield based on Br-$(CH_2)_8$-Br.

Conversion of 1,8-dibromooctane into 1,8-dicyanooctane was monitored by NMR ($CDCl_3$): the -CH_2-C<u>H</u>$_2$-Br protons give a triplet at 3.25 (J=6 Hz), while the -CH_2-CH_2-CN protons give a tripelt at 2.22 (J=22 (J=6 Hz).

Hydrolysis of the dinitrile was conducted by the published procedure. It turned out to be a rather sensitive one: when the reflux of the dinitrile with $Ac_2O/H_2O/H_2SO_4$ was carried out in an oil bath heated to 140-150°C and the level of the reaction solution in the flask was on the same level as the oil in the bath (overheating!); carbonization occurred and the isolated yield of sebacic acid was less than 40%. However, when the temperature of the oil was kept at 125-130°C, with most of the solution in the flask above the bath oil level, no carbonisation occurred and the isolated yield of sebacic acid was about 90%.

Preparation of the [^{14}C]1,8-dinitrile. - The potassium [^{14}C]cyanide, 2mCi (Amersham, > 50 cmCi/mmol) was transferred from the commercial ampoule by repeated washings with distilled water (20 ml in all) into a 50 ml r.b. flask containing 1.20 g of radioinactive potassium cyanide. The resultant solution was freeze-dried to constant weight of 1.25 g (18 mmol). The flask was equipped with a stirring bar and a drying tube. Dry DMF (15 ml) was added followed by 1,8-dibromooctane (1.8 ml, 2.72 g, 10 mmol) (Fluka). The slurry was stirred at room temperature for 10 days. Radioinactive potassium cyanide (0.65 g, 10 mmol) was added to the mixed slurry and stirring continued for another 10 days at room temperature. Water (60 ml) was added and the mixture extracted with dichloromethane (5x50 ml), dried over Na_2SO_4 and evaporated at reduced pressure. Most of the remaining DMF was removed by bulb-to-bulb distillation (100°C, 32 mm) to afford a yellow oily liquid, 2.44 g, ca 1.6 mCi. Its NMR spectrum indicated that it contained some DMF, but all of the dibromide was converted into the dinitrile.

Counting of the aqueous layer revealed that it contained an activity of ca 400 µ Ci, 20% of the total activity introduced into the reaction. Additional extraction of the aqueous layer with various organic solvents resulted in no signifiucant transfer of radioactivity. Evidently the device of adding a second portion of radioinactive KCN resulted in an equilibrium:

$N^{14}C\text{-}(CH_2)_8\text{-}^{14}CN + KCN \rightleftharpoons N^{14}C\text{-}(CH_2)_8\text{-}^{12}CN = K^{14}CN.$

Hydrolysis of the dinitrile. - The foregoing dinitrile (containing some DMF) (1.6 g, ca 1.1 mCi) was added to a mixture consisting of sulfuric acid (96%; 2.5 ml), water (2 ml) and acetic anhydride (8 ml) and the whole was heated under reflux for 15 hr. The top of the reflux condenser was connected by a tube to a solution of NaOH so that any $^{14}CO_2$ that may have been produced as a result of partial decarboxylation would be trapped in the solution. Counting of an aliquot of this solution revealed that it contained ca 3 µCi of activity, which would indicate less than 0.3% of decarboxylation. The activity trapped by the NaOH solution could, perhaps, be attributed to $H^{14}CN$ which may have been produced during reflux from some residual $K^{14}CN$ under acidic conditions.

The reaction mixture was cooled and diluted with water (30 ml) to afford a crystalline precipitate which was removed by filtration and crystallized twice to give colorless crystals of sebacic acid (870 mg), ca 500 µCi, m.p. 134.5°C (ethyl acetate). The mother liquors were evaporated to give a gray solid, ca 300 µCi, which consisted mainly of sebacic acid. The aqueous filtrate contained ca 300 µCi of activity. It was extracted with dichloromethane (5x30 ml), dried (Na_2SO_4) and evaporated to a yellow oil (sebacid acid + DMF, carried over from the first step). Counting revealed, that it contained ca 300 µCi of ^{14}C-radioactivity, while the radioactivity of the remaining aqueous layer was negligible. This, as well as the mother liquors from crystallisation mainly contain impure [^{14}C]-sebacic acid. It may be purified by repeated crystallisation from ethyl acetate or benzene.

Acknowledgments. - We thank Dr. J. Sanders of the University Chemical Laboratory in Cambridge for certain help with NMR spectra and Prof. Y. Oref for help with the kinetics.

References

1. P. Ashkenazi, J. Kettenring, S. Migdal, A.L. Gutman, and D. Ginsburg, Helv. Chim. Acta, 68, 2033 (1985).
2. P. Ashkenazi, O. Weinberg, A. Zlota, and D. Ginsburg, and D. Ginsburg, Recl. Trav. Chim. Pays-Bas, 105, 254 (1986). The diol 2 assigned the SS configuration should be corrected to 4, the anti,anti isomer. The order of elution from a silica column in aa, sa, and ss, respectively.
3. a) S. Bhanumati, P. Ashkenazi, S. Migdal, and D. Ginsburg, Helv. Chim. Acta, 66, 2703 (1984). b) M. Kapon, P. Ashkenazi, and D. Ginsburg, Tetrahedron, 42, 2555 (1986).
4. A. Natrajan, J.D. Ferrara, W.J. Youngs, and C.N. Sukenik, J. Am. Chem. Soc., 109, 7477 (1987).
5. a) P. Ashkenazi, W. Blum, B. Domon, A.L. Gutman, A. Mandelbaum, D. Muller, W.J. Richter, and D. Ginsburg, J. Am. Chem. Soc., 109, 7325 (1987). b) Y. Klopstock, P. Ashkenazi, A. Mandelbaum, D. Muller, W.J. Richter, and D. Ginsburg, Tetrahedron, in press.
6. "Kal vechomer", this means here (and in general), that if an isomer more difficult to thread will be threaded those are easier to thread will be threaded.
7. G. Schikk, W. Breckmann, N. Schweikert, and H. Fritz, Chem Ber. 119, 2647 (1986).
8. Job, 3, 25.
9. R. Rienacker, P. Ashkenazi, S. Migdal, and D. Ginsburg, to be published.
10. Cf. K. Saotomo, H. Komoto, and T. Yamazaki, Bull. Chem. Soc. Jpn., 39, 480 (1966).