HETERODIENE SYNTHESIS—XI[1]

A STUDY OF THE ISOMERIZATION OF TETRAHYDROPYRAN[2',3':2,3] 2,3-DIHYDROPYRAN[6,5-c] PYRAZOLES

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Abstract—The stereoisomers (1–4) of the tetrahydropyran[2',3':2,3] 2,3-dihydropyran[6,5-c] pyrazole system equilibrate in deuterated trifluoroacetic acid at 35°.

The mechanism which causes incorporation of deuterium in the 4a-position is discussed.

The isomers distribution is rationalized in terms of steric and electronic interactions, and the energy values for the interaction between the phenyl group in 5 and the substituent in position 6 on the pyrazole ring are given.

In a preceding paper[1] we have shown that an α,β-unsaturated carbonyl system in a heterocyclic ring can undergo 1,4 cycloaddition with dihydropyran.

The remarkable nucleophilicity of this vinyl ether, compared with open-chain vinyl ethers, gives an increased character of nucleophilic attack to the cycloaddition. A discrete intermediate, probably of zwitterionic character, is sometimes indicated when the ring closure occurs as it gives rise to adducts with loss of the original *cis* configuration of the starting ether.
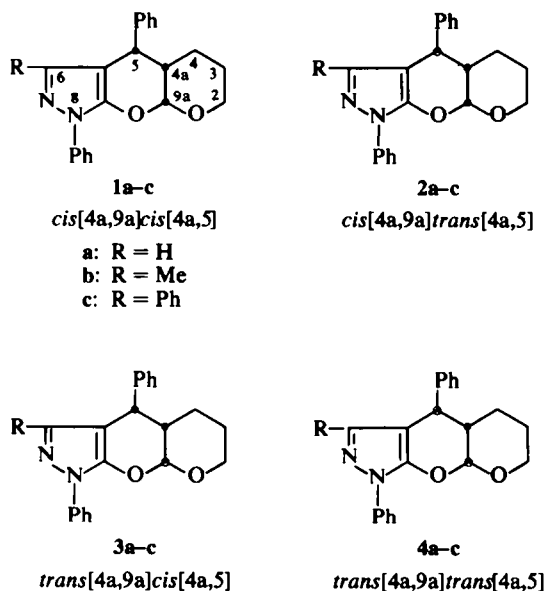
In order to support the "two-step" origin of these adducts, we have investigated the isomerization of the tetrahydropyran[2',3':2,3] 2,3-dihydropyran [6,5-c] pyrazoles and we now wish to report the results of this research.

Isomerization

No isomerization occurs upon heating at 140° in 2,3-dihydropyrane or xylene for 10 days, but this is achieved on refluxing with acetic acid. Each single pure isomer, under these conditions, is transformed into a mixture of the four possible isomers (Scheme 1).†

All *cis* 4a,9a products (1 and 2), and 3, are kinetically-controlled adducts of the above mentioned cycloaddition, but the other derivatives are new. The NMR spectra allow assignment of the configuration, and the main parameters of the previously known[1] and unknown products are reported in Table 1.

A *trans* [4a,9a] stereochemistry is always consistent with a value of 8·0–8·8 Hz, but J_{4a5} to be *trans* it must be axial/axial if H_{4a} is axial. The

1a–c

cis[4a,9a]*cis*[4a,5]

a: R = H
b: R = Me
c: R = Ph

2a–c

cis[4a,9a]*trans*[4a,5]

3a–c

trans[4a,9a]*cis*[4a,5]

4a–c

trans[4a,9a]*trans*[4a,5]

SCHEME 1

values found for 3 (5·0–6·0 Hz) are too small for this but are consistent with a *cis* coupling.[3] Therefore, the configuration already proposed for 3b is correct and a *trans* [4a,5] configuration has to be assigned to 4a–c where the J_{4a5} values are 9·5, 10·0 and 9·1 Hz respectively, as predicted for an all-axial configuration (Fig 1).

To investigate the mechanism of isomerization we had to find suitable conditions to follow the evolution of the isomers. This was achieved with deuterated trifluoroacetic acid (dTFA) which allowed the isomerization to operate at 35°. Thus, the evolution of the NMR spectrum was followed and this is illustrated in Fig 2 for 3c.

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†The only by-product of the above reported isomerization is a red derivative, isolated from 1–4a in low yield, which we shall consider elsewhere.[2]

Table 1

Compd.	H_{9a} J_{4a9a}	H_{4a}	H_5 J_{4a5}	H_2	H_3–H_4	R	Aromatic protons
1a	D 5·78 1·5	M 2·1	D 4·40 5·5	M 3·8–4·1	M 1·0–1·9	Overlp. by arom.	M 7·1–8·0
1b	D 5·68 1·5	M 2·1	D 4·32 6·0	M 3·7–4·2	M 1·3–2·0	S 1·79	M 7·0–8·0
1c	D 5·80 1·5	M 2·2	D 4·66 6·1	M 3·6–4·3	M 0·9–1·8	Aromatics	M 6·9–8·1
2a	D 5·44 1·5	M 2·1	D 3·88 3·25	M 3·7–4·1	M 1·2–2·0	Overlp. by arom.	M 7·0–8·1
2b	D 5·43 1·5	M 2·0	D 3·77 2·25	M 3·7–4·2	M 1·5–2·0	S 1·92	M 7·0–8·0
2c	D 5·50 1·5	M 2·1	D 3·96 1·2	M 3·6–4·0	M 1·4–1·9	Aromatics	M 7·0–8·1
3a	D 5·09 8·8	M 2·2	D 3·97 5·8	M 3·6–4·0	M 1·3–1·8	Overlp. by arom.	M 7·1–8·0
3b	D 5·06 8·75	M 2·0	D 3·89 6·0	M 3·7–4·2	M 1·2–2·0	S 1·90	M 7·0–8·0
3c	D 5·11 8·7	M 2·2	D 4·08 5·5	M 3·8–4·0	M 1·5–2·0	Aromatics	M 7·0–8·2
4a	D 5·07 8·2	M 2·1	D 3·55 9·5	M 3·5–4·0	M 1·4–2·0	Overlp. by arom.	M 7·2–8·0
4b	D 4·95 8·0	M 2·0	D 3·40 10·0	M 3·8–4·3	M 1·5–2·0	S 1·57	M 7·0–8·0
4c	D 5·15 8·0	M 2·2	D 3·86 9·1	M 3·9–4·2	M 1·8–2·2	Aromatics	M 7·0–8·2
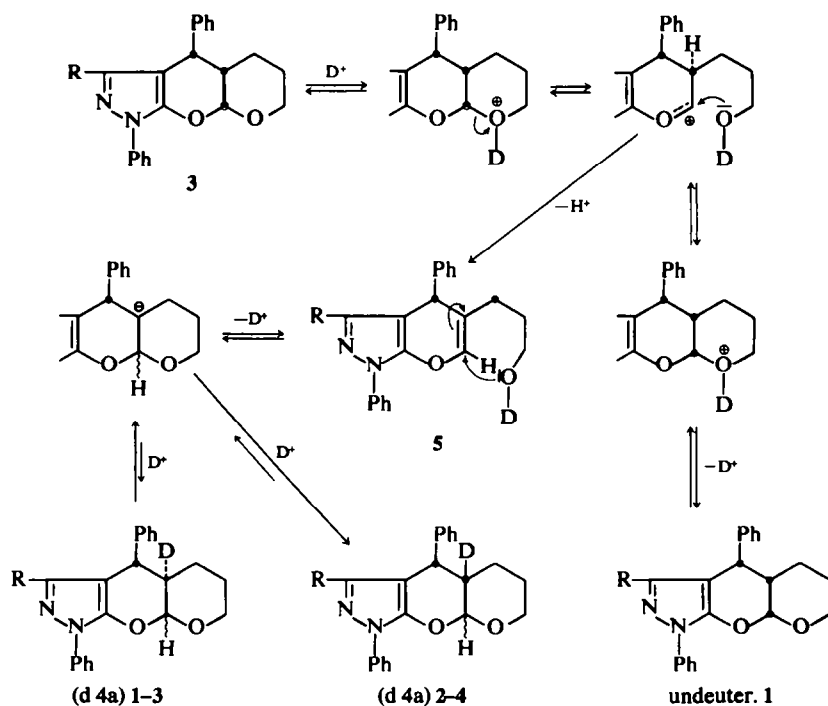
SCHEME 2

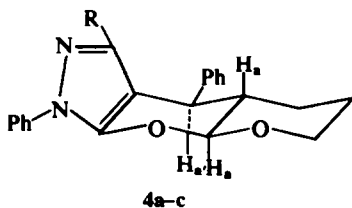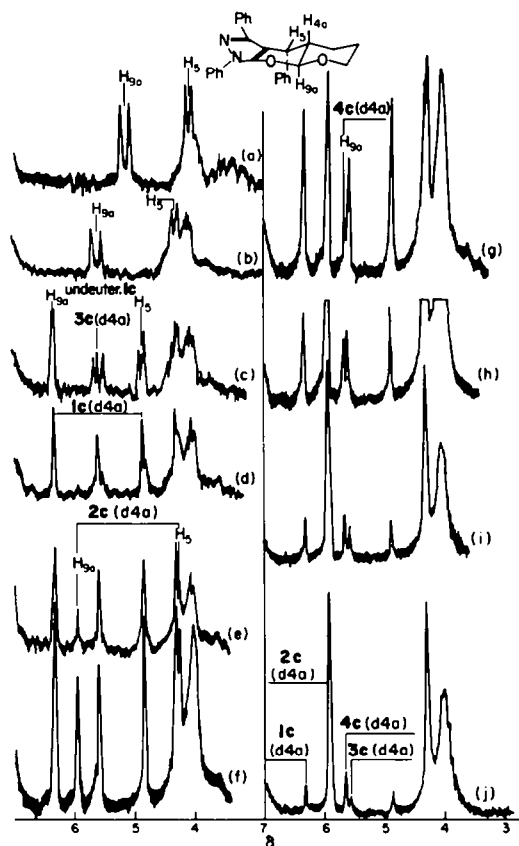Fig 1.

Fig 2. Evolution of the NMR spectrum of 3c, (a) CDCl₃ as solvent, (b–j) dissolved in deutero trifluoroacetic acid. (b) registered immediately, (c) after 15 min, (d) after 30 min, (e) after 45 min, (f) after 4 hr, (g) after 8 hr, (h) after 26 hr, (i) after 2 days, (j) after 30 days.

A reasonable pathway for the isomerization of 1–4 can be proposed involving deuteration of the tetrahydropyran-oxygen atom followed by ring opening. Scheme 2 shows the mechanism starting from the *trans* [4a,9a] *cis* [4a,5] configuration but, with suitable modifications for the starting configuration, this can be common to every equilibration.

Scheme 2 clearly shows that starting from 3, the first product formed is undeuterated 1, i.e. the product with inversion of configuration of the chiral centre at C_{9a}. Therefore, the faster reaction must be the nucleophilic attack of the alcoholic deuterated portion of the molecule on the carbonium ion at C_{9a} with both loss and retention of configuration.

The formation of undeuterated 1 is competitive with the loss of the proton at C_{4a} and the formation of an enolether-type intermediate (5). Ring closure of 5 by nucleophilic attack is followed by deuteration of the 4a-position. This deuteration occurs under conditions of "steric approach control" and 1 and 3 are formed due to the easier deuteration at C_{4a} from the side opposite to the C_5 phenyl group. However, these *cis* [4a,5] adducts are slowly transformed into the thermodynamically more stable *trans* [4a,5] adducts with consequent formation of an equilibrated mixture of the four d4a-isomers.

Sometimes during the equilibration, a singlet appears at $7·0 \, \delta$ and vanishes when equilibration is accomplished: this could be the vinylic proton of the intermediate 5 which becomes evident when a suitable concentration is reached.

Equilibria

The composition of the equilibrated mixtures at 35° is reported in Table 2 and their variation, starting from each pure isomer, was taken to represent the error.

The Maxwell-Boltzmann distribution law enables calculation of the free-energy differences of the levels related to that of the lowest, which in all cases is that of the isomer with *cis* [4a,9a] *trans* [4a,5] configuration. The relative scale for a temperature of 35° is shown in Fig 3.

At first glance one can see that some figures are independent (within the limit of the experimental error) of the nature of R: the energy difference between 4 and 1 is always about 0·25 Kcal and that

Table 2

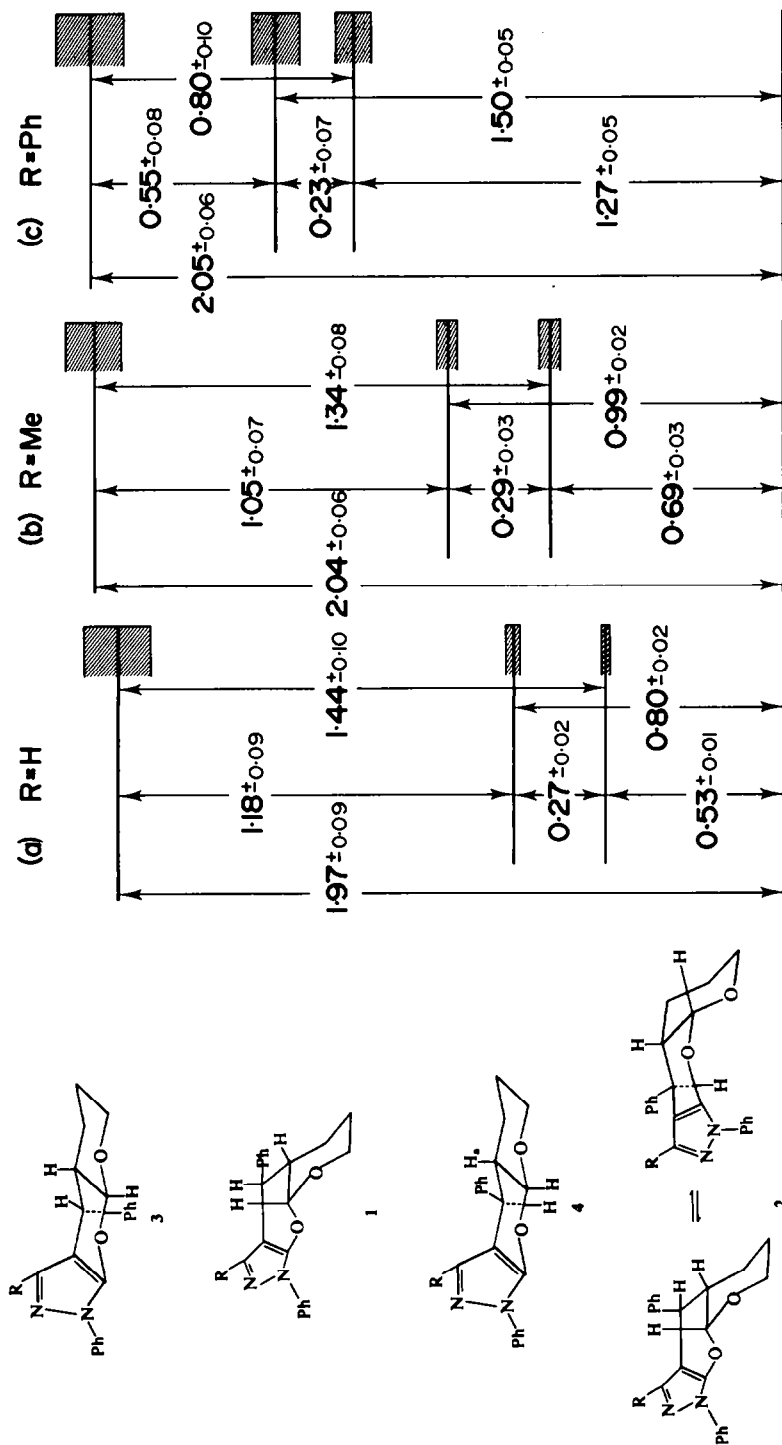| R	1 *cis* [4a,9a] *cis* [4a,5]	2 *cis* [4a,9a] *trans* [4a,5]	3 *trans* [4a,9a] *cis* [4a,5]	4 *trans* [4a,9a] *trans* [4a,5]
(a) H	15·7 ± 0·3	57·7 ± 0·3	2·3 ± 0·3	24·3 ± 0·3
(b) Me	12·8 ± 0·2	64·2 ± 0·5	2·3 ± 0·2	20·7 ± 0·6
(c) Ph	6·9 ± 0·4	80·3 ± 0·8	2·8 ± 0·2	10·0 ± 0·6

Fig 3.   Relative energies of tetrahydropyran[2':3':2.3]2,3-dihydropyran[6,5-c] pyrazoles.

between 2 and 3 always about 2·0 Kcal, whereas some are R-dependent.

Inspection of molecular models shows that the *trans* [4a,9a] isomers (3 and 4), where a *trans* junction between two fused rings requires a rigid structure, are not the only isomers which are conformationally rigid. The isomers with a *cis* [4a, 9a] *cis* [4a, 5] configuration (1) also have a frozen conformation as the 5-phenyl group in the *pseudo*-axial position causes severe 1,3-steric interactions. Therefore, isomers 1 and 4 have the 5-phenyl group in the *pseudo*-equatorial position while 3 can be regarded as a rigid model with the phenyl group in the *pseudo*-axial position.

As the introduction of bulky groups in the 6-position on the pyrazole ring destabilizes the *pseudo*-equatorial position of the 5-phenyl group, the values for these interactions, related to Ph_{eq}/H_6 considered = 0, can be obtained from the following relations:

$$Ph_{eq}/Me_6 = 4a/3a{-}4b/3b = 1·44{-}1·34 = 0·10 \text{ Kcal}$$
$$= 1a/3a{-}1b/3b = 1·18{-}1·05 = 0·13 \text{ Kcal}$$
$$Ph_{eq}/Ph_6 = 4a/3a{-}4c/3c = 1·44{-}0·80 = 0·64 \text{ Kcal}$$
$$= 1a/3a{-}1c/3c = 1·18{-}0·55 = 0·63 \text{ Kcal}$$

These values seem useful inasmuch as these interactions, together with the anomeric effect, are the forces which govern the conformational equilibrium of condensed dihydropyrans.[7]

From the above reported considerations, the diagram in Fig 3 can be regarded as the superimposition of the substituent's contribution to the R = H part. We believe this is the rationalization of the R-dependent energy values.

It seems much more difficult to rationalize the relative stability scale of 1–4, but a few observations can be made.

If free rotation is not possible with the 5-phenyl group in the *pseudo*-equatorial position in 1 and 4, because the steric interactions between the *o*-hydrogen atoms and the 6-substituent (even if H) prevent coplanarity, the same perpendicular conformation just be adopted in both cases. The destablizing effects in 4 and 1 are therefore:

4	1
2 anomeric interactions† = 2·10 Kcal	1 anomeric interaction = 1·05 Kcal
	2 *gauche* propylether interactions[6] = 1·40 Kcal

The agreement between calculated and experimental ΔG° values (0·35 against 0·26 Kcal) seems satisfactory.

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†1·05 Kcal is the sum of 0·50 Kcal (A value for methoxy-cyclohexane — solvent independent) and 0·55 Kcal found in 2-methoxy-6-methyloxane for a solvent of comparable dielectric constant.[5]

The energy difference between 4 and 3 is 1·44 Kcal. This is far from the A value (2·6–3·1 Kcal) found for phenylcyclohexane[7] but one must remember that the axial contribution in cyclohexene is greater than in cyclohexane, due to diminished 1,3-interactions,[8] and furthermore ΔG° Ph is decreased if free rotation ot the phenyl group is forbidden.[9]

Finally we have to explain the reasons for the greater stability of 2 over the other isomers. The absence of one anomeric interaction alone cannot rationalize this; we believe the main reason is the high degree of freedom the molecule has. Both conformations are conceivable (for R = H, Me and Ph, J_{4a5} has a different contribution for ax/ax and eq/eq character) and in the axial position the phenyl group also has good possibilities for free rotation. Therefore, in the free energy expression the entropy factor should be negligible for 2, but not for 1, 3 and 4 because of their conformational rigidity.

EXPERIMENTAL

All m.ps are uncorrected. Microanalyses were performed by Dr. L. Dacrema Maggi. NMR spectra were obtained on a Perkin Elmer R-12 spectrometer and solvent (unless otherwise stated) was $CDCl_3$; TMS was the internal standard and chemical shifts are reported in ppm on the δ scale.

Isomerization of 5,8-diphenyltetrahydropyran[2′,3′:2,3] 2,3-dihydropyran[6,5-c] pyrazoles

1a (1·0 g) was dissolved in AcOH (6·0 ml) and the soln was refluxed over an oil bath at 120° for 50 min. After evaporation to dryness, the orange residue was chromatographed over a silicagel column with cyclohexane/AcOEt 9:1 as eluant. The first fraction was 1a (0·60g), followed by 2a (0·10 g). Both isomers, crystallized from diisopropyl ether (dIPE), were identical with previously described samples.[1] The second fraction gave 3a as small white crystals (0·15 g) m.p. 150–1° (dIPE). (Found: C, 76·02; H, 6·13; N, 8·56. Calc for $C_{21}H_{20}N_2O_2$: C, 75·88; H, 6·07; N, 8·43%). The third fraction gave small white needles of 4a (0·05 g) m.p. 165–6° (dIPE). (Found: C, 76·05; H, 6·10; N, 8·56. Calc for $C_{21}H_{20}N_2O_2$: C, 75·88; H, 6·07; N, 8·43%).

Table 3

Starting compounds	Equilibrated mixtures			
	1	2	3	4
1a	15·4	57·7	2·3	24·6
2a	15·9	57·8	2·2	24·1
3a	15·8	57·8	2·6	24·2
4a	15·7	57·7	2·3	24·3
1b	12·6	63·8	2·2	21·3
2b	13·0	64·2	2·3	20·6
3b	12·7	64·3	2·2	20·8
4b	12·8	64·2	2·5	20·4
1c	6·6	80·2	3·0	10·2
2c	7·2	80·4	2·6	9·8
3c	7·1	79·5	2·8	10·6
4c	6·5	81·0	3·0	9·5

A longer reflux causes the formation of small amounts of tar materials in this as well in all other isomerizations.

A comparable result, but with different yields, was obtained starting from 2a.

Isomerization of 5,8-diphenyl-6-methyltetrahydropyran [2',3':2,3] 2,3-dihydropyran[6,5-c] pyrazoles

1b (0·8 g) was dissolved in AcOH (7·0 ml) and the soln was refluxed at 120° for 1 hr. The dried residue was chromatographed over silicagel and eluted with cyclohexane/AcOEt 9:1. The first fraction was a mixture of 1 and 2b (0·50 g–63%; ratio 1b/2b 2:1) which were separated by fractional crystallization. The second fraction gave 3b (0·16 g–20%) and all these isomers were identical with previously described samples.[1] Finally, pure 4b (0·08 g–10%) was eluted and crystallization from EtOH gave white needles m.p. 156–7°. (Found: C, 75·93; H, 6·54; N, 7·96. Calc for $C_{22}H_{22}N_2O_2$: C, 76·27; H, 6·40; N, 8·09%).

A comparable results, but with different yields, was obtained starting from 2 and 3b.

Isomerization of 5,6,8-triphenyltetrahydropyran[2',3': 2,3] 2,3-dihydropyran[6,5-c] pyrazoles

1c (1·0 g) dissolved in AcOH (10·0 ml) was refluxed over an oil bath at 120° for 4 hr. The dried residue was chromatographed over silicagel using cyclohexane/ benzene 1:1 as eluant. 1c and 2c (0·7 g–ratio 1c/2c 4:1) were separated and found to be identical with previously described samples.[1] 3c was eluted (0·15 g) and, after crystallization from dIPE, gave small white crystals m.p. 175–6°. (Found: C, 79·70; H, 5·96; N, 6·92. Calc for $C_{27}H_{24}N_2O_2$: C, 79·38; H, 5·92; N, 6·86%). Finally, 4c was separated (0·12 g) as colourless needles m.p. 182–3° (EtOH). (Found: C, 79·73; H, 5·94; N, 6·96. Calc for $C_{27}H_{24}N_2O_2$: C, 79·38; H, 5·92; N, 6·86%).

A similar result, but with different yields, was obtained from 2c.

Equilibration of 1–4z–c in dTFA

0·3 Mmoles of a suitable derivative were introduced into an NMR tube, 0·4 ml of d-trifluoroacetic acid (CIBA) and a trace of TMS were added. The solid immediately dissolved and the NMR spectrum registered. The sealed tube was warmed at 35° and the spectra run until the mixture was equilibrated. The composition of the mixture was calculated from the anomeric proton signal areas, as measured on three runs, with a planimeter. Values starting from each pure isomer, are reported in Table 3.

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