Tetrahedron Letters No. 19, pp 1697 - 1700.
© Pergamon Press Ltd. 1979. Printed in Great Britain.

0040-4039/79/0501-1697$02.00/0

BICYCLO[3.3.0]OCTENOL AS AN EFFECTIVE TOOL FOR THE DETERMINATION OF ABSOLUTE CONFIGURATION OF CHIRAL ACIDS. THE ABSOLUTE CONFIGURATION OF ARYL-*t*-BUTYLACETIC ACID

Hiroko Kuritani, Seiichi Imajo, Keiji Shingu* and Masazumi Nakagawa
Department of Chemistry, Faculty of Science, Osaka University,
Toyonaka, Osaka, 560 Japan

Summary: (+)-*endo-cis*-Bicyclo[3.3.0]oct-7-en-2-ol gave good optical yields in the kinetic resolution of aryl-*t*-butylacetic anhydride, establishing the absolute configuration of *t*-butyl-α-naphthylacetic acid as (*S*) - (+).

Horeau's method has found the greatest use in the assignment of the absolute configuration of chiral secondary alcohols.1) Since this method is based on the kinetic resolution of a racemic acid anhydride by an optically active alcohol, the absolute configuration of a chiral acid can also be determined, in principle, by the use of an active alcohol of known configuration.2) This possibility has preliminarily been tested by Horeau1) using (-)-menthol (8) with some acids which have an asymmetric tertiary carbon atom attached by an alkyl and a phenyl group (1; R = methyl, ethyl, *n*-propyl and isopropyl).

One prerequisite for the success of this empirical method is the clearcut decision of the sequence of "size" of the substituents in the chiral acid. Hence, the kinetic resolution of *t*-butylphenylacetic acid (3) of known configuration3) seems interesting in testing the difference in "size" between a *t*-butyl and a phenyl group which cannot *a priori* be decided.

Another is the selection of effective alcohols which give satisfactory optical yields in the kinetic resolution. Recently, we have determined the absolute configuration of *endo-cis*-bicyclo[3.3.0]oct-7-en-2-ol (6) and its hydrogenation product 7 by chemical correlation.4) They are expected to be more effective than 8 for the chiral discrimination (consequently, for the assignment of the absolute configuration) of acids, since, because of their *endo-cis* structure, the differences in the steric requirement between the substituents around the hydroxy methylene carbon in them are larger than that in 8.

From these points of view, we examined the kinetic resolution of the anhydride of (±)-2-phenylbutanoic acid (2)5) and that of (±)-*t*-butylphenylacetic acid (3),6) by the use of the alcohols 6, 7 and 8. In addition, the anhydride of (±)-*t*-butyl-α-naphthylacetic acid (4)6) was examined as the application of this method to the configuration assignment of aryl-*t*-butylacetic acid. Each acid anhydride was prepared from the sodium salt of acid with oxalyl chloride.[1] Kinetic resolution was carried out according to Horeau's procedure,[1] using a small amount of the active alcohol and about double the molar quantity of the anhydride. The results are listed in the table.

In entries 1 ∿ 3 with 2-phenylbutanoic anhydride, all three alcohols, (+)-6, (+)-7 and (-)-8, gave the same enantiomer of residual acid, (+)-2 (5, R=ethyl). Therefore, it turned out that the steric arrangement around the hydroxy methylene group in (+)-6 and (+)-7 is the same as that in (-)-8 which has the configuration shown by 9,[1] where L (large) and M (medium) indicate the relative "size" of the substituent groups. This is consistent with the expectation from the established absolute configuration of (+)-6 and (+)-7.[7] In particular, (+)-6 gave extremely high optical yield, demonstrating its powerful ability in the determination of absolute configuration of chiral acids.

Furthermore, these experimental results make it reasonable to postulate that the configuration of the residual acid obtained by the reaction with the alcohol 9 is shown by 10, since the phenyl and ethyl groups in 5 (R=ethyl) are considered to be L and M, respectively.[8,9]

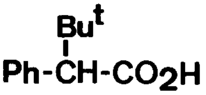
In entries 4, 5 and 6 the effect of an increase in "size" of the alkyl substituents in acids was examined by use of the anhydride of (±)-3 of known absolute configuration.[3] Both (+)-6 and (-)-8 gave the *dextro* residual acid 3


$\mathrm{Ph{-}\overset{R}{\overset{|}{C}}H{-}CO_2H}$

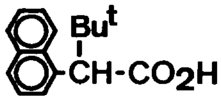
1


$\mathrm{Ph{-}\overset{Et}{\overset{|}{C}}H{-}CO_2H}$

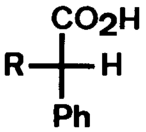
2


$\mathrm{Ph{-}\overset{Bu^t}{\overset{|}{C}}H{-}CO_2H}$

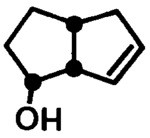
3



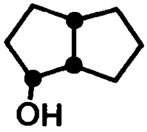
4



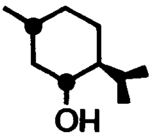
5



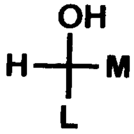
(+)-6



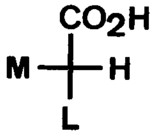
(+)-7



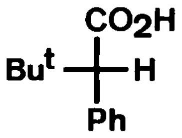
(-)-8



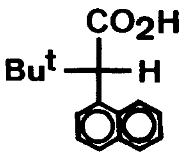
9



10



11



12

whose configuration is shown as **11**.[3] Since this residual acid also is expected to have the arrangement of **10**, the phenyl and *t*-butyl groups can be decided as L and M, respectively. This result is in harmony with the order of "size" of the groups found in benzylic alcohols by Horeau.[1,9]

However, the optical yield was very poor by the use of **8**, showing that **8** is unsuitable for the kinetic resolution of this type of acid, whilst **6** gave the relatively high optical yield. This indicates the great usefulness of **6** for the determination of the absolute configuration of aryl-*t*-butylacetic acid, which seems troublesome by means of chemical method.[10]

Table. Kinetic resolution of acid anhydrides with optically active alcohols.

Entry (No)	Anhydride of the Acid (mg)	Alcohol (mg)	Reaction Time (hr)	Recovered Alcohol (mg)	Esterification Yield (%)	Observed Rotation of the Residual Acid (degree)	Optical Yield (%)
	2						
1	160.4	(+)-**6** 34.5	4	–[b]	67[e]	+0.201[g]	69
2	162.4	(+)-**7** 34.1	4	–[b]	81[e]	+0.156[g]	45
3	167.2	(-)-**8**[a] 44.2	4	–[b]	81[e]	+0.145[g]	40
	3						
4	162.9	(+)-**6** 27.0	19	16.2[c]	40[f]	+0.068[h]	33
5	212.9	(+)-**6** 35.8	237	–[d]	100[f]	+0.215[h]	32
6	215.3	(-)-**8**[a] 45.7	236	–[d]	100[f]	+0.012[h]	2
	4						
7	253.3	(+)-**6** 35.0	237	7.9[c]	77[f]	+0.377[h]	22
8	193.5	(-)-**8**[a] 28.8	236	–[d]	100[f]	+0.045[h]	3

a) $[\alpha]_{589}$ -50.34° (*c* 4.07, ethanol)
b) not isolated
c) isolated by column chromatography on silica gel
d) alcohol was not detected by TLC on silica gel
e) calculated from the titrated volume according to Horeau's procedure[1]
f) calculated from the recovered alcohol
g) measured at 589 *nm* in benzene (10 *ml*, *l* = 1 *dm*)
h) measured at 405 *nm* in ethanol (10 *ml*, *l* = 1 *dm*)

Next, we undertook the determination of the hitherto unknown absolute configuration of *t*-butyl-α-naphthylacetic acid (**4**) (entry 7 and 8). (+)-**6** gave much higher optical yield than (-)-**8**, affording the *dextro* residual acid **4**. If naphthyl group is assumed to be "larger" than *t*-butyl group as is the case with phenyl group in **11**,[9] the absolute configuration of (+)-**4** is expected to be (*S*), that is, **12**. This was confirmed by its chemical correlation with (*S*)-(+)-**3**,[11] and bicycloalcohol **6** has proved to be useful for the kinetic resolution to determine the absolute configuration of aryl-*t*-butylacetic acid.

References and Notes

1) A. Horeau, "Stereochemistry, Fundamentals and Methods," vol. 3, edited by H. B. Kagan, Georg Thieme, Stuttgart, 1977.
2) *cf.*, H. Falk, K. Schlögl and W. Steyrer, *Monatsh. Chem.*, **97**, 1029 (1966); S. Hagishita and K. Kuriyama, *Tetrahedron*, **28**, 1435 (1972).
3) C. Aaron, D. Dull, J. L. Schmiegel, K. Jaeber, Y. Ohashi and H. S. Mosher, *J. Org. Chem.*, **32**, 2797 (1967); D. R. Clark and H. S. Mosher, *ibid.*, **35**, 1114 (1970).
4) (+)- **6** was correlated to (*S*)-(-)-3-oxocyclopentaneacetic acid, establishing its configuration as (1*R*, 2*R*, 5*R*); H. Kuritani, Y. Takaoka and K. Shingu, *J. Org. Chem.*, in press (1979). Camphanate ester of (1*R*, 2*R*, 5*R*)-(+)-**6** was hydrogenated over platinum to give (+)-camphanate ester of **7**, $[\alpha]_{589}$ +9.06° (*c* 1.017, ethanol), mp 87.2∿87.8°, which was hydrolyzed to afford (1*R*, 2*R*, 5*R*)-(+)-**7**, $[\alpha]_{589}$ +29.6° (*c* 1.094, ethanol).
5) 2-Phenylbutanoic acid (**2**), which is the standard acid for Horeau's method, is commercially available.
6) **3** and **4** (new compound) were synthesized according to Mosher's method.[3] Optical resolution with brucine gave (-)-**3**, $[\alpha]_{589}$ -48.2°, $[\alpha]_{405}$ -122° (*c* 2.315, ethanol), and (+)-**4**, $[\alpha]_{589}$ +119°, $[\alpha]_{405}$ +330° (*c* 0.295, ethanol), respectively.[11]
7) Bridged five membered rings correspond to L group and methylenes to M group.
8) In Horeau's method, the relative sizes of phenyl and alkyl groups in active secondary alcohols are established as L and M, respectively.
9) Horeau reported a striking illustration of the concept of steric size in alkylphenylcarbinols with 2-phenylbutanoic anhydride;[1] the phenyl group always appears to be the "largest" – even though alkyl group is *t*-butyl or triphenylmethyl.
10) The configurational assingment of 2-naphthylpropionic acid was achieved by the method of quasi-racemates; B. Sjöberg, *Arkiv Kemi*, **13**, 1 (1958).
11) Both (+)-**3** and (+)-**4** were converted to (+)-dimethyl *t*-butylsuccinate, $[\alpha]_{589}$ +12.4° (*c* 1.123, ethanol), *via* several steps; details will be reported elswhere.

(Received in Japan 2 February 1979)