Application of the Procedure of Pope and Peachey to the Resolution of Alcohols

By SAMUEL H. WILEN,* ROBERT DAVIDSON, ROBERT SPECTOR, and HARRY STEFFANOU

(*Department of Chemistry, The City College of the City University of New York, New York, N.Y.* 10031)

Summary The variant methods of Pope and Peachey and of Kantor and Hauser, individually or in combination, are applicable to the resolution of alkyl hydrogen phthalates and have advantages over classical resolutions.

RESOLUTIONS of alcohols modified by the Pope and Peachey procedure[1] are rarely used.[2] We demonstrate here that this resolution procedure is advantageous in classical resolutions of alkyl hydrogen phthalates. We suggest also its application in new resolutions and particularly those attended by difficulties.

Resolution of alkyl hydrogen phthalates

Alkyl hydrogen phthalate of	(1) Typical resolutions[a] $[\alpha]_D$[c]	Optical purity[d]	Yield[e]	(2) Pope–Peachey procedure[b] $[\alpha]_D$[c]	Optical purity[d]	Yield[e]
Butan-2-ol	+9·67°	24%	68%	+22·9°	58%	45%
Octan-2-ol	+31°; 33°	66%	61%	+32·4°	67%	60%
1-Phenylethanol	+13·5°	37%	69%	+15·3°	42%	58·5%

[a] Moles alkyl hydrogen phthalate : brucine = 1 : 2 (solvent, acetone); [b] Moles alkyl hydrogen phthalate : brucine : triethylamine = 2 : 1 : 1 (solvent, acetone); [c] Specific rotations of alkyl hydrogen phthalates measured in 100% ethanol (t = 25—28°); [d] Reported for optically pure 2-butyl hydrogen phthalate $[\alpha]_D^{20}$ + 39·5° (ethanol) (ref. 6); for optically pure 2-octyl hydrogen phthalate $[\alpha]_D^{18}$ + 48·4° (ethanol) (ref. 8); for optically pure 1-phenethyl hydrogen phthalate $[\alpha]_D^{25}$ + 36·5° (ethanol) (ref. 9); [e] Complete recovery of the alkyl hydrogen phthalate enantiomer shown corresponds to 100%.

Pope and Peachey have shown that resolutions which depend upon relatively small solubility differences between diastereomeric salts may be made more effective by incorporating in the resolution an optically inactive reagent (A) which competes with the optically active resolving agent (B) for the enantiomers (±C) in the racemic mixture being resolved.[1] In favourable cases the inactive reagent reacts completely with one enantiomer while the optically active resolving agent reacts completely with the other.

(1) Typical Resolution:

$$2\ (\pm)\mathrm{C} + 2\ \mathrm{B}_{\mathrm{active}} \rightarrow (+)\mathrm{C{\cdot}B} + (-)\mathrm{C{\cdot}B}$$

(2) Pope and Peachey Procedure:

$$2\ (\pm)\mathrm{C} + \mathrm{B}_{\mathrm{active}} + \mathrm{A}_{\mathrm{inactive}} \rightarrow \begin{array}{c} (+)\mathrm{C{\cdot}B} + (-)\mathrm{C{\cdot}A} \\ \text{or} \\ (-)\mathrm{C{\cdot}B} + (+)\mathrm{C{\cdot}A} \end{array}$$

In case (1), extent of resolution is dependent upon usually small solubility differences, often requiring many recrystallizations to effect complete separation of the diastereomeric products. In case (2), where (A) and (B) are both typically either acids or bases, the products are not diastereomers. While the extent of resolution also as a rule depends upon a solubility difference, a suitable choice of (A) should make such separation easier and complete with fewer, if any, recrystallizations than in case (1).[3] Bases, *e.g.* 2-methyltetrahydroquinoline, as well as acids, *e.g.* 3-bromocamphor-8-sulphonic acid, were resolved by Pope and his co-workers with this procedure.[1,4]

We have found that the Pope and Peachey procedure is applicable to the classical resolution of secondary alcohols *via* reaction of their alkyl hydrogen phthalates with brucine.[5] Resolution of 2-butyl hydrogen phthalate with brucine and triethylamine as the inactive base (molar ratio 1·9 : 1 : 2) in acetone yielded the less soluble brucine salt (56% after one recrystallization) which after base hydrolysis afforded butan-2-ol, $[\alpha]_D^{18}$ + 10·8° (neat), corresponding to an optical purity of 78%.[6] Similar resolution of 2-octyl hydrogen phthalate (molar ratio 2·7 : 1 : 1·8) yielded 80% of crude salt which was directly hydrolysed to octan-2-ol, $[\alpha]_D^{28}$ + 8·5° (neat), corresponding to an optical purity of 80%.[7] Thus, the optical purities of the isolated alcohols were found to be high even without carrying out any (one in the case of butan-2-ol) recrystallizations of the first precipitated salts.

A comparative study of case (1) and case (2) resolutions was carried out, again with triethylamine as the inactive base. To simplify the comparison, the precipitated brucine salts were isolated and directly hydrolysed to the alkyl hydrogen phthalates without recrystallization. The phthalates were identified by m.p. and/or i.r. spectroscopy and directly assessed for optical activity and optical purity. The results (Table) show that the procedure of Pope and Peachey in these resolutions is at least as satisfactory as the typical resolutions both in optical purity of product and in recovery of the enantiomer having the less soluble brucine salt. In some cases, the procedure gives directly a higher optical yield. An additional advantage is that only half as much of the relatively expensive resolving agent is required. In cases where the optical purity of the less soluble salt is high, the second enantiomer may be obtained in moderate optical purity without further recrystallization of salt recovered from the resolution mother-liquor or without separate resolution of the phthalate recovered from this salt.

In 1953, Kantor and Hauser modified the typical resolution [case (1)] of 2-butyl hydrogen phthalate by using an insufficient amount of solvent for the reactants.[10] Prolonged heating under reflux effectively recrystallized the initially formed diastereomeric salts repeatedly prior to their isolation thus leading in one step to a higher optical yield than is normally obtained. The brucine salt of 2-butyl hydrogen phthalate was isolated from the reaction mixture in 82% optical purity (50% yield). While this procedure would seem to be generally applicable, as suggested in the original paper, it does not appear to have been used for resolutions other than those of butan-2-ol.

Using the conditions employed for the resolutions summarized in the Table, we have found that application of the Kantor–Hauser procedure to the typical resolution of 2-octyl hydrogen phthalate furnishes 49% of ester having $[\alpha]_D + 39{\cdot}2°$ (ethanol; 81% optically pure)[8] after 5 days at reflux. Application of the Kantor–Hauser procedure to case (2) resolutions (equivalent to combination of the two resolution variants) leads, for 2-octyl and 1-phenethyl hydrogen phthalates, to optical purities of 77% (55% yield) and 69% (38% yield), respectively.

It is evident that resolutions using the Kantor-Hauser procedure and our conditions lead to products of higher optical purity than resolutions described in the Table, albeit at the cost of a reduction in yield of product. The Pope–Peachey and Kantor–Hauser procedures combined do at least as well as the conventional Kantor–Hauser procedure does alone.

This investigation was supported by the National Science Foundation through its Undergraduate Research Participation Program.

(*Received, March 25th*, 1969; *Com.* 426.)

---

[1] W. J. Pope and S. J. Peachey, *J. Chem. Soc.*, 1899, **75**, 1066.

[2] See for example the statement in E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, 1962, p. 61.

[3] T. M. Lowry ("Optical Rotatory Power," Longmans, Green and Co., London, 1935, p. 53) considered the Pope and Peachey procedure an improvement over classical (or typical) resolutions since much larger differences in solubility were to be expected.

[4] W. J. Pope and C. S. Gibson, *J. Chem. Soc.*, 1910, **97**, 2207.

[5] A. W. Ingersoll, *Org. Reactions*, 1944, **2**, 376.

[6] C. E. Wood, J. E. Such, and F. Scarf, *J. Chem. Soc.*, 1926, 1935, reported $[\alpha]_D^{20} + 13{\cdot}89°$ (neat) for optically pure butan-2-ol.

[7] N. Kornblum, N. N. Lichtin, J. T. Patton, and D. C. Iffland, *J. Amer. Chem. Soc.*, 1947, **69**, 309, reported $[\alpha]_D^{25} - 10{\cdot}6°$ (neat for optically pure octan-2-ol.

[8] J. Kenyon, *Org. Synth., Coll. Vol. I*, 2nd edn., 1941, p. 418.

[9] E. Downer and J. Kenyon, *J. Chem. Soc.*, 1939, 1156.

[10] S. W. Kantor and C. R. Hauser, *J. Amer. Chem. Soc.*, 1953, **75**, 1744.