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ASYMMETRIC CONTROL IN ESTERIFICATION REACTIONS

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Abstract—The partial esterification of racemic alcohols in the presence of an optically active base, which results in the formation of optically active esters, is discussed in terms of the preferred conformation of the intermediate acylammonium cation.

THE outstanding difference between syntheses performed in Nature and their laboratory counterparts is the high degree of asymmetric control exercised in the former. Much endeavour[1] has been devoted to attempts to emulate this high stereospecificity, particularly in the synthesis of acyclic compounds. In general attention has been focussed on reactions leading to the formation of a new asymmetric centre under the influence of an old one. This type is fairly common in the reactions of steroids, terpenes, alkaloids and carbohydrates, and the rationalization of these was the raison d'être of conformational analysis.[2] The application of these principles to asymmetric synthesis in acyclic molecules was initially investigated by Prelog[3] and Cram[4] with their respective collaborators.

A somewhat different type of what may be loosely termed asymmetric synthesis depends on the differing rates of reaction of optical isomers with an asymmetric molecule. A number of reactions of this type have been recorded, including several examples[5] of replacement reactions between optically active bases and organic halides. The much disputed Marckwald[6] synthesis may also belong to this class. However, the majority of reported examples of the above type relate to esterification reactions and it is the purpose of this paper to show how these results may be rationalized.

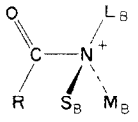
The mechanism of ester formation has been the subject of much investigation[7] and is now acknowledged to generally proceed via addition to the carbonyl group in a rate-determining step with formation of a tetrahedral intermediate.[8]

The approach employed is probably best illustrated by a consideration of the general case of acylation of an alcohol, $S_AM_AL_ACOH$, in the presence of an optically active base, conveniently designated $S_BM_BL_BN$. The letters S, M and L have their usual connotations, that is small, medium and large with reference to the respective effective bulk of the groups. The acylating agent is the acylammonium cation[9,10] whose preferred conformation can be depicted as in I or II (for one stereoisomer

[1] H. Freudenberg, *Stereochemie*. Leipzig and Vienna, Deuticke (1933); P. D. Ritchie, *Asymmetric Synthesis and Asymmetric Induction*. Humphrey Milford, London (1933); *Adv. in Enzymol.* **7**, 65 (1947).
[2] D. H. R. Barton and R. C. Cookson, *Quart. Rev.* **10**, 44 (1956).
[3] V. Prelog, *Helv. Chim. Acta* **36**, 308 (1953) and subsequent papers.
[4] D. J. Cram and F. A. A. Elhafez, *J. Amer. Chem. Soc.* **74**, 5828 (1952).
[5] H. J. Lucas and C. W. Gould, *J. Amer. Soc.* **64**, 601 (1942); F. Hawthorne and D. J. Cram, *Ibid.* **74**, 5859, (1952).
[6] F. J. Keyon and W. A. Ross, *J. Chem. Soc.* 2307 (1952).
[7] C. J. Ingold, *Structure and Mechanism in Organic Chemistry* p. 752. Bell, London (1953).
[8] M. R. Bender, *J. Amer. Chem. Soc.* **73**, 162 (1951).
[9] V. Gold and E. G. Jefferson, *J. Chem. Soc.* 1409, 1416 (1953).
[10] It has recently been shown that esterification with acid chlorides proceeds in some cases via ketene formation by Pracejus, *Liebigs. Ann.* **622**, 10 (1960).

of the amine) depending on the relative sizes of the carbonyl oxygen and R. The prime consideration being that *all non-bonded interactions in the acylammonium cation should be minimized.* Thus when R is larger than the carbonyl oxygen conformation I will be preferred, and vice versa.

The subsequent addition of an alcohol molecule to the carbonyl group of the acylammonium cation will also be governed by the principle of minimization of



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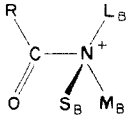

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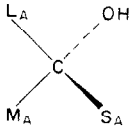

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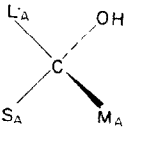

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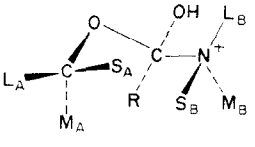

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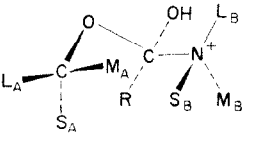

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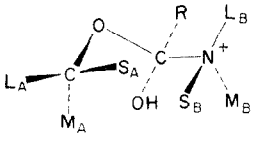

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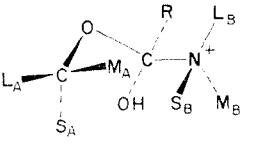
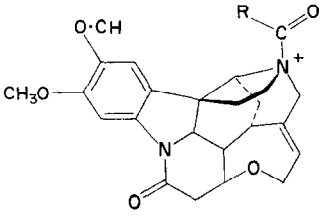


VIII

repulsive non-bonded interactions, so that addition will occur preferentially from the least hindered side. In the case of I or II this will be the frontside. Furthermore the alcohol stereoisomers will encounter differing amounts of steric hindrance to addition. For example the addition of alcohol III to I leading to the intermediate V will be less sterically hindered than that of IV to I giving rise to VI. Thus alcohol III will be more rapidly esterified than alcohol IV. Of course reaction may take place through several different conformations according to their energy but the one chosen should have the lowest energy and consequently be the preferred route. In the case of conformation II the addition of alcohol IV will be less hindered than that of III as can be seen from a consideration of the respective intermediates VII and VIII.

The foregoing treatment appears to be fully justified by the experimental data available. Esterification in the presence of either brucine or strychnine, whose full absolute stereochemistries are known,[11] leads expectedly to the same results.[12] Examination of catalin models indicates that the preferred conformation of the acyl ammonium cation will be as depicted in Figure IX, in which the non-bonded interactions will be at a minimum. Frontal addition of the alcohol will then occur and



IX

preferentially by the stereoisomer corresponding to III. This deduction is borne out by the data assembled in the Table. A number of these examples are new and some others previously reported have been checked and the original result, where necessary, amended. Full details are recorded in the Experimental section. The absolute configurations have been taken mainly from two fairly recent summaries.[13] However, in one or two cases chemical correlation of compounds with higher alkyl groups has not been reported. In these cases correlation between individual members of the series has been achieved by comparison of molecular rotations. These conclusions are further supported by application of the concept of "screw pattern of electron polarizability".[14]

In all the examples involving benzoylation, the S alcohol stereoisomer is esterified the faster, and similar results are observed for acetylation except in the case of the benzyl alkyl carbinols. For acetylation where R (= CH_3) and the carbonyl oxygen atom are not so markedly different in size, the alcohol may prefer to react with the conformation corresponding to II depending on the relative steric hindrance involved. Thus the faster acetylation of the R isomer in this case is not so surprising. The apparent lack of optical activation in the acetylation of hexan-3-ol is explicable in terms of the similar steric size of the ethyl and propyl groups, resulting in practically identical steric hindrance to addition of either diastereoisomer to the acylammonium cation.

Although the discussion so far has been limited to asymmetrically substituted nitrogen atoms a similar role can obviously be filled by an adjacent asymmetric carbon atom. A particularly appropriate example is esterification in the presence of the acetylated cinchona alkaloids,[15] whose full absolute stereochemistries are known.[16] The intermediate acylammonium cations will then assume the conformations depicted as X for cinchonine and as XI for cinchonidine and quinine, in which the non-bonded

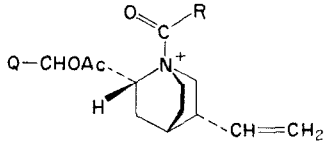
[11] A. F. Peerdeman, *Acta Cryst.* **9**, 824 (1956).
[12] R. Wegler, *Liebigs. Ann.* **506**, 77 (1933).
[13] W. Klyne, *Determination of Organic Structures by Physical Methods* p. 73. Academic Press, New York (1955); J. A. Mills and W. Klyne, *Progress in Stereochemistry* Vol. I, p. 182. Butterworths, London (1954).
[14] J. H. Brewster, *J. Amer. Chem. Soc.* **81**, 5475 (1959).
[15] R. Wegler and A. Ruber, *Ber. Dtsch. Chem. Ges.* **68**, 1055 (1935).
[16] V. Prelog and O. Häfliger, *Helv. Chim. Acta* **33**, 2021 (1950).

PARTIAL ESTERIFICATION OF SECONDARY ALCOHOLS*

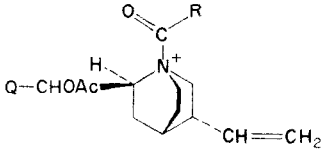
Alcohol	Esterifying agent		Absolute configuration of alcohol preferentially esterified	
L_AM_ACHOH	L_A	M_A	Acetic anhydride and brucine	Benzoyl chloride and brucine or strychnine
Butan-2-ol	C_2H_5	CH_3	S†	S
Pentan-2-ol	C_3H_7	CH_3	S†	S
3-Methylbutan-2-ol	$(CH_3)_2CH$	CH_3	S†	S
Hexan-2-ol	C_4H_9	CH_3	S†	S
Hexan-3-ol	C_3H_7	C_2H_5	No activation	S
Heptan-3-ol	C_4H_9	C_2H_5	—	S
1-Phenylethanol	C_6H_5	CH_3	S	S
1-Phenylpropanol	C_6H_5	C_2H_5	S	S
2-Methylphenylpropanol	C_6H_5	$(CH_3)_2CH$	S	S
1-Phenylpentanol	C_6H_5	C_4H_9	S	S
Phenylpropan-2-ol	$C_6H_5.CH_2$	CH_3	R†	S
Phenylbutan-2-ol	$C_6H_5.CH_2$	C_2H_5	—	S
3-Methylphenylbutan-2-ol	$C_6H_5.CH_2$	$(CH_3)_2CH$	R	S
1-Cyclohexylethanol	C_6H_{11}	CH_3	S	S
1-Cyclohexylpropanol	C_6H_{11}	C_2H_5	S	S
1-Cyclohexylbutanol	C_6H_{11}	C_3H_7	S	S
dl-Erythro-3-bromobutan-2-ol	$CH_3.CHBr$	CH_3	2S:3R‡	—
dl-Erythro-3-chlorobutan-2-ol	$CH_3.CHCl$	CH_3	2S:3R‡	—

* Except where otherwise noted the results are taken from Ref. 12.
† This paper.
‡ Ref. 17.

interactions will be at a minimum. The preferred side of addition to the carbonyl group obviously depends on the configuration at C8, and for X will be the frontside



X



XI

and for XI the rearside. For the reaction of l-phenylethanol, as II and IV ($L_A = C_6H_5$, $M_A = CH_3$, $S_A = H$, with X and XI it is readily deduced that IV would react faster with X and III faster with XI.)

Experimentally it is observed that (−)-l-phenylethanol is acetylated and benzoylated faster than the (+)-isomer in the presence of cinchonine acetate and the (+)-isomer faster than the (−)-isomer in the presence of quinine and cinchonidine acetates.

Thus IV must represent (−)-l-phenylethanol which will have the S configuration and III represents R-(+)-l-phenylethanol. These conclusions are in full agreement with the accepted configurations.

Other asymmetric tertiary bases such as exo- and endo-dimethylbornylamine, nicotine and dimethyl-l-phenylethylamine have also been analogously employed but, due to the greater conformational mobilities of these bases, unambiguous allotment of conformations to the derived acylammonium cations is not at present feasible.

Conversely the preceding considerations may be employed to predict the absolute configuration of either the alcohol or the base. This may be briefly illustrated by reference to two alcohols whose absolute configurations were unestablished. 2-Methylheptan-3-ol is partially esterified with benzoyl chloride in the presence of brucine or strychnine to give a dextrorotatory benzoate and unreacted laevorotatory alcohol. On the basis of the above discussion the dextrorotatory isomer will be represented by IV (L_A = isopropyl, M_A = n-butyl, S_A = H) which is the S configuration. DL-Threo-3-chloro (or bromo) butan-2-ol on partial acetylation[17] in the presence of brucine gives a laevorotatory alcohol and a laevorotatory acetate. In this case $L_A = CH_3.CHCl$, $M_A = CH_3$ and S_A = H and we can thus assign the configuration (2 S:3 S) to (+)-threo-3-chloro-(or bromo)-butan-2-ol.

Other partial esterification reactions such as those involving the partial esterification of a racemic acid with a non-asymmetric alcohol in the presence of an optically active base[18] are obviously capable of analysis in similar terms.

EXPERIMENTAL

Partial esterifications. The conditions used were similar to those of Wegler.[12] The racemic alcohol (0·05 mole) and brucine (5 g) were dissolved in carbon tetrachloride (50 ml). Acetic anhydride (2·5 ml) or the equivalent amount of benzoyl chloride, was added dropwise to the gently refluxing solution and refluxed for 3 hr (18 hr for benzoylation). The cooled solution was washed thoroughly with 2N sulphuric acid, water, sodium bicarbonate solution and water. The carbon tetrachloride extract was dried over sodium sulphate, the solvent then distilled off and the residue fractionally distilled to give the ester. In the case of phenylpropan-2-ol the alcohol and acetate were separated by chromatography on alumina using petroleum ether-diethyl ether mixtures.

The following alcohols were partially esterified in this way:

Butan-2-ol gave but-2-yl acetate, $[\alpha]_D^{19}$ 0·79°.
Pentan-2-ol gave pent-2-yl acetate, $[\alpha]_D^{19}$ 0·59°.
Hexan-2-ol gave hex-2-yl acetate, $[\alpha]_D^{19}$ 0·62°.
Hexan-3-ol gave hex-3-yl acetate with no detectable optical rotation.
Phenylpropan-2-ol gave phenylprop-2-yl acetate, $[\alpha]_D^{18}$ −0·21°, and phenylpropan-2-ol, $[\alpha]_D^{18}$ 0·35°.
Pentan-2-ol gave pent-2-yl benzoate, $[\alpha]_D^{19}$ 0·76°.

All compounds had boiling points and refractive indices in agreement with literature values.

[17] H. J. Lucas and S. Winstein, *J. Amer. Chem. Soc.* **61**, 2845 (1939); H. J. Lucas and C. W. Gould, *Ibid.* **63**, 2541 (1941).
[18] R. Wegler, *Liebigs Ann.* **510**, 72 (1934); G. Pracejus, *Ibid.* **622**, 10 (1959).