TABLE III
PREPARATION OF BENZOPHENONE DERIVATIVES

Substituent	Reagents: Acylating	Aromatic	Condensing	M.p., °C. (cor.)	Lit. m.p., or b.p., °C.
3-NO_2	3-$NO_2C_6H_4COCl$	C_6H_6	$AlCl_3$	94.5–95.5	94–95[a]
2-NO_2	2-$NO_2C_6H_4COOH$	C_6H_6	CF_3CO_3H	103–104	103–104[b]
4-OCH_3	C_6H_5COCl	$C_6H_5OCH_3$	$AlCl_3$	62–63	61[c]
2-OH	4-$CH_3OC_6H_4COCl$	C_6H_6	$AlCl_3$	39–40	41[c]
4,4′-$(Cl)_2$					146.5–148.5[d]
4,4′-$(OCH_3)_2$					143.5–145[e]
3,3′-$(OCH_3)_2$[f]					144–145 (0.3)[f]
4-Cl-4′-OCH_3	4-ClC_6H_4COCl	$C_6H_5OCH_3$	I_2	125–127	124.5[g]
4-OCH_3-3′-NO_2	3-$NO_2C_6H_4COCl_3$	$C_6H_5OCH_3$	$AlCl_3$	92.5–95	95[h]

[a] R. Geigy and W. Koenigs, *Ber.*, **18**, 2400 (1885). [b] H. H. Szmant and C. M. Harmuth, THIS JOURNAL, **81**, 962 (1959). [c] F. Ullman and I. Goldberg, *Ber.*, **35**, 2811 (1902). [d] Eastman Org. Chem. P-1440. [e] *Ibid.*, 4395. [f] Graciously supplied by Professor L. H. Klemm and Dr. Emilios P. Antoniades; see L. H. Klemm, R. Mann and C. D. Lind, *J. Org. Chem.*, **23**, 349 (1958). [g] I. A. Kaye, H. C. Klein and W. J. Burlant, THIS JOURNAL, **75**, 745 (1953). [h] W. Blakey, W. I. Jones and H. A. Scarborough, *J. Chem. Soc.*, 2865 (1927).

3-nitro-4′-methoxybenzophenone at 1658 cm.$^{-1}$ lies closer to that of *p*-methoxybenzophenone (ν_{max} 1655 cm.$^{-1}$) than to that of *m*-nitrobenzophenone (ν_{max} 1668 cm.$^{-1}$), and the main aromatic vibration band of 3-nitro-4′-methoxybenzophenone is similar to that of *p*-methoxybenzophenone (see Tables I and II).

Experimental

Infrared Absorption Spectra.—The infrared spectra were determined on a Unicam SP 100 instrument, using a NaCl prism and a diffraction grating; concn. 3.5–4.5·10^{-2} moles/l., cell thickness 0.5 mm., CCl_4 solvent. Most of the data are listed in Tables I and II. Other data are: acetophenone, ν_{max} 1691(s) cm.$^{-1}$ (carbonyl band); *p*-methoxyacetophenone, ν_{max} 1681(s) cm.$^{-1}$ (carbonyl band); ν_{max} 1598(s) and ν_{max} 1571(w) cm.$^{-1}$ (aromatic vibration bands); *o*-hydroxyacetophenone, ν_{max} 1642(s) cm.$^{-1}$ (carbonyl band); ν_{max} 1613(m), ν_{max} 1592(vw) and ν_{max} 1576(m) cm.$^{-1}$ (aromatic vibration bands); salicylaldehyde, ν_{max} 1665(s) cm.$^{-1}$ (carbonyl band); ν_{max} 1643(s) cm.$^{-1}$ ν_{max} 1617 (m) and ν_{max} 1575(m) cm.$^{-1}$ (aromatic vibration bands); *o*-hydroxybenzophenone (concn., 0.2 mole/l.), ν_{max} 3031 cm.$^{-1}$ (aromatic C–H band) and no maximal absorption near 3600 cm.$^{-1}$.

Ultraviolet Absorption Spectra.—The ultraviolet absorption spectra were determined in 1-cm. cells using a Unicam SP 500 spectrophotometer calibrated against a didymium filter. For each compound at least two independent sets of observations were made. The accuracy of λ_{max} values is estimated to be ± 1 mμ, and the precision of ϵ_{max} values ±5% or better. Values were reproducible in most cases to ±2%. Most of the B-band data are listed in Tables I and II. Also, *o*-hydroxybenzophenone was found to exhibit C-band absorption in cyclohexane at λ_{max} 328 mμ, ε 3500, and at λ_{max} 334 mμ, ε 4,000. The same compound in alkaline media absorbed maximally at 236 mμ, ε 19,000.

Preparation of Compounds.—The substituted benzophenones were invariably prepared by a Friedel–Crafts reaction. Reagents and product m.p. data are summarized in Table III. Salicylaldehyde and the acetophenones were best-grade commercially available materials. These compounds were carefully redistilled until their boiling point and refractive indices agreed with the values reported in the literature and until further distillation did not cause any change in their spectral properties. Most of the compounds afforded the calculated C,H values on elemental analysis.

Acknowledgments.—The authors wish to thank Mr. John Barone and Mr. Eugene McInerney, and Mr. Thomas Doyle for the preparation of some of these compounds. They are also indebted to Miss Florence Jackman and Mr. D. L. Coffen for the careful determination of the ultraviolet data and infrared data, respectively. Financial assistance from the National Research Council of Canada, and (in part) from the Research Corporation, and the U. S. Public Health Service, National Cancer Institute C-3325(C2) is gratefully acknowledged.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF NORTHWESTERN UNIVERSITY, EVANSTON, ILL.]

Overlap Control of Organic Reactions. III. The Stereochemistry of the Darzens Reaction

BY HOWARD E. ZIMMERMAN[1] AND LEO AHRAMJIAN

RECEIVED MARCH 7, 1960

The Darzens condensation of benzaldehyde with ethyl α-chlorophenylacetate affords predominantly ethyl 2,3-*cis*-diphenyl-2,3-epoxypropionate. A carbene mechanism is excluded. The synthesis of two possible Darzens intermediates, the diastereomeric ethyl 2-chloro-3-hydroxy-2,3-diphenylpropionates, is described. Under Darzens reaction conditions each of these affords ethyl 2,3-*cis*-diphenyl-2,3-epoxypropionate. Evidence is presented that the initial aldolization step is rapidly reversible and that the reaction stereochemistry is overlap controlled in the subsequent cyclization step. For facile ring closure, the carbonyl group must be unhindered.

The present investigation stemmed from an earlier study[2a] in which configurations were assigned to the stereoisomeric 2,3-diphenyl-2,3-epoxypropionic acids which first had been described by Kohler.[3] It was shown[2a] that the 122° acid and its 58° ester are 2,3-*cis*-diphenyl-2,3-epoxypropionic acid and ethyl 2,3-*cis*-diphenyl-2,3-epoxypropionate

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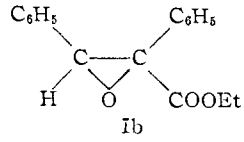
(2) (a) Paper I of this series: H. E. Zimmerman, L. Singer and B. S. Thyagarajan, THIS JOURNAL, **81**, 108 (1959); (b) paper II, H. E. Zimmerman and L. Ahramjian, *ibid.*, **81**, 2086 (1959).

(3) E. P. Kohler and F. W. Brown, *ibid.*, **55**, 4299 (1933).

(Ib), respectively. This configurational assignment was of particular interest, since the 58° ethyl ester Ib was known[4,5] to be the predominant product of the Darzens condensation of benzaldehyde with ethyl α-chloro- and α-bromophenylacetate. Elucidation of the intriguing stereoselective formation,

$$C_6H_5CHO + C_6H_5CHClCOOEt \xrightarrow{KO\text{-}t\text{-}Bu}$$

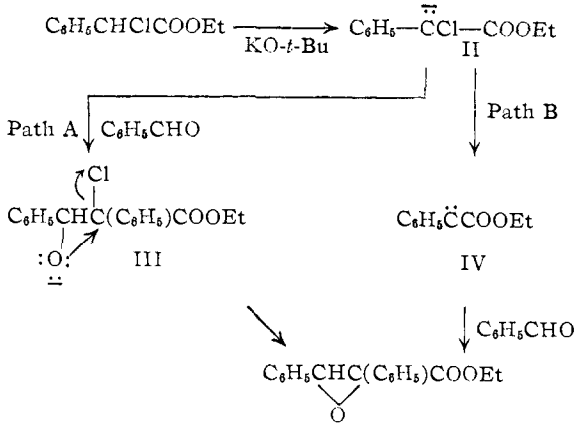


Ib

in the Darzens reaction, of the stereoisomer having the large phenyl groups *cis* was the goal of the presently described investigation.

An understanding of the reaction stereochemistry required knowledge whether the reaction proceeds by the aldolization mechanism (path A) generally accepted for the Darzens reaction or instead by the carbene mechanism (path B) indicated in Chart I.

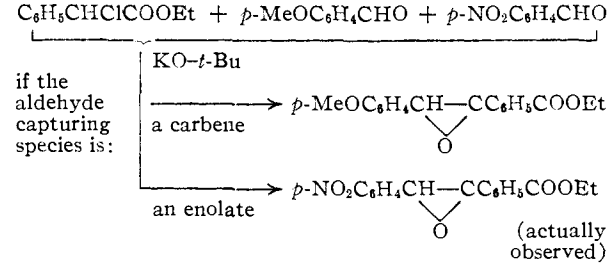
CHART I



While strongly persuasive evidence had been advanced by Ballester and Bartlett[6] in favor of the aldolization mechanism, the reactions on which these arguments were based did not include examples with phenyl substitution on the chloroester α-carbon atom. *A priori*, it was not impossible that ethyl α-chlorophenylacetate could afford a carbene with sufficiently greater facility than usual to allow operation of the carbene mechanism.

It appeared that one experiment would decisively settle this question, this experiment being based on the different predilections of enolate and carbene intermediates. One mole of ethyl α-chlorophenylacetate was treated with one mole each of *p*-nitrobenzaldehyde and *p*-methoxybenzaldehyde in the presence of the usual potassium *t*-butoxide catalyst. The electrophilic nature of carbene species was well known[7]; and, if phenylcarbethoxycarbene (IV) were actually the species attacking the aldehyde carbonyl group, it seemed certain to prefer the relatively electron-rich carbonyl group of *p*-methoxybenzaldehyde. Conversely, if the attacking species were the nucleophilic enolate II, the more electron-deficient *p*-nitrobenzaldehyde carbonyl group would be preferentially attacked.[8]

CHART II



This experiment was carried out with the result depicted in Chart II; there was isolated ethyl 2-phenyl-3-*p*-nitrophenyl-2,3-epoxypropionate in 87% yield with no indication of a second glycidic ester product, hence supporting the aldolization mechanism.

Since it was therefore apparent that at least one of the diastereomeric ethyl 2-chloro-3-hydroxy-2,3-diphenylpropionates (Va and Vb) was necessarily a reaction intermediate, being formed in the initial aldolization step, a synthesis of these diastereomers and a study of their behavior under Darzens reaction conditions seemed likely to cast light on the mechanistic details underlying the reaction stereochemistry. A successful synthesis of Va and Vb was realized from the condensation of benzaldehyde with ethyl α-chlorophenylacetate using diisopropylaminomagnesium bromide as a base according to the general method of Munch-Peterson.[9] Chromatography on silica gel of the crude reaction mixture afforded both an oily diastereomer as well as a solid isomer, m.p. 65°, of ethyl 2-chloro-3-hydroxy-2,3-diphenylpropionate. That these stereoisomers were discrete entities was evident from the transparency in the infrared spectrum of each of the isomers at wave lengths where the other possessed strong absorption bands.

Interestingly, each of the diastereomeric ethyl 2-chloro-3-hydroxy-2,3-diphenylpropionates, when treated individually with potassium *t*-butoxide in *t*-butyl alcohol under Darzens reaction conditions, afforded as the only isolable product ethyl 2,3-*cis*-diphenyl-2,3-epoxypropionate (Ib), the same stereoisomer obtained from the Darzens reaction itself.

(4) F. Blicke, J. Faust and H. Raffelson, THIS JOURNAL, **76**, 3161 (1954).

(5) H. Morris, R. Young, C. Hess and T. Sottery, *ibid.*, **79**, 411 (1957).

(6) (a) M. Ballester and P. D. Bartlett, *ibid.*, **76**, 2042 (1953); (b) M. Ballester, *Chem. Revs.*, **55**, 283 (1955); (c) M. Ballester and D. Perez-Blanco, *J. Org. Chem.*, **23**, 652 (1958).

(7) P. S. Skell and R. M. Ritter, *Chemistry & Industry*, 624 (1958).

(8) This should be true regardless whether aldolization or cyclization is rate controlling. In the former event, in proceeding from ground state to transition state, the carbonyl π-orbital is partially destroyed with consequent diminution of the stabilizing interaction of this orbital with the methoxyl unshared electrons, an interaction which operates to a full extent in the ground state (*i.e.*, in the original aldehyde). On the other hand, should cyclization be rate controlling, the transition state follows intermediate III; and the carbonyl group is completely destroyed with loss of all the methoxyl–carbonyl interaction energy by the time this transition state is reached.

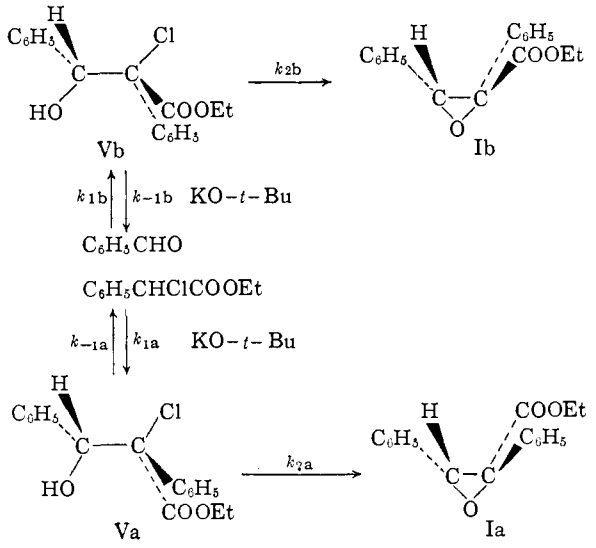
Comparable interaction is not found between the nitro and carbonyl groups in the *p*-nitrobenzaldehyde reactant, and hence no comparable delocalization energy is lost in the activation process. Rather, there is actually a gain in the nitro–phenyl interaction which is somewhat inhibited in the ground state by the *p*-carboxaldehyde group.

(9) J. Munch-Peterson, *Acta Chem. Scand.*, **7**, 1041 (1953).

The simplest interpretation, that Ib resulted from direct cyclization of each of the two conjugate bases derived from Va and Vb, was rejected. Ring closure involves nucleophilic attack of the β-alkoxide anion on the α-carbon atom with loss of chloride ion, and this would mean that, while one of the two diastereomers (Vb) could lead with Walden inversion at the α-carbon atom to the observed ethyl 2,3-*cis*-diphenyl-2,3-epoxypropionate, the second diastereomer (Va) would have to cyclize with front-side attack and retention of configuration, an unlikely possibility.[10]

A more reasonable possibility was a rapidly reversible aldolization—dealdolization preequilibrium followed by a rate-limiting cyclization. This mechanism is depicted in Chart III. As a test of

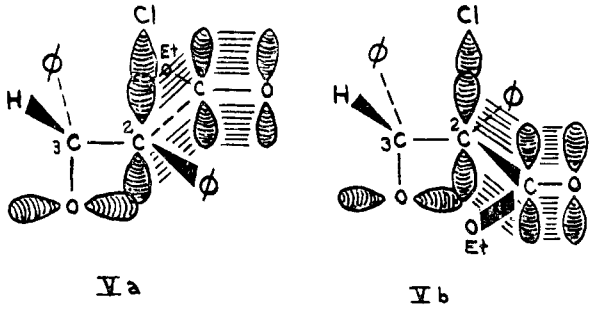
CHART III



this mechanism, the reaction of the solid diastereomer of ethyl 2-chloro-3-hydroxy-2,3-diphenylpropionate with potassium *t*-butoxide was repeated, however in the presence of an excess of *m*-nitrobenzaldehyde. There was isolated in 72% yield as the only glycidic ester product ethyl 2-phenyl-3-*m*-nitrophenyl-2,3-epoxypropionate, a product which could reasonably arise only by dealdolization of the ethyl 2-chloro-3-hydroxy-2,3-diphenylpropionate reactant followed by capture of the resulting ethyl α-chlorophenylacetate fragment by the reactive *m*-nitrobenzaldehyde. Further evidence for the reversibility of the aldolization step was found in experiments in which each of the diastereomeric ethyl 2-chloro-3-hydroxy-2,3-diphenylpropionates (Va and Vb) was treated with potassium *t*-butoxide in *t*-butyl alcohol for shorter times and at greater dilution than usual. Under these conditions poor yields of the glycidic ester resulted; also isolated were products resulting from dealdolization: benzaldehyde, ethyl α-chlorophenylacetate and the latter's hydrolysis product, mandelic acid.[11]

Thus the evidence indicates that $k_{-1} > k_2$ and that $k_{-1} > k_1$[12a] for both routes of Chart III. In addition, since ethyl 2,3-*cis*-diphenyl-2,3-epoxypropionate (Ib) is formed to the exclusion of its stereoisomer Ia, it may be concluded that the over-all rate $k_b = k_{2b}(k_{1b}/k_{-1b})$ of formation of Ib is greater than the over-all rate $k_a = k_{2a}(k_{1a}/k_{-1a})$ of Ia[12b] and that the free energy of cyclization transition state Tb is lower than that of Ta. These facts may be recorded conveniently in a free energy diagram (*cf.* Fig. 1).[12c]

Having considered evidence that the observed stereoselectivity derives from the lower free energy of transition state Vb relative to Va, one may turn his attention to the factors which influence the free energy of the transition states and lead to the lower energy of Vb. Va and Vb are depicted.



(10) It is true that examples of *acid-catalyzed* epoxide ring *opening* with retention of configuration are known (J. H. Brewster, THIS JOURNAL, **78**, 4061 (1956); D. Y. Curtin, A. Bradley and Y. G. Hendrickson, *ibid.*, **78**, 4064 (1956)). These appear to proceed by way of a species having a carbon atom which is electron deficient due to the departing group leaving before nucleophilic bonding is extensive. In the contrasting case of displacement of chloride by alkoxide anion, nucleophilic attack is synchronous with loss of chloride so that the orbital lobe involved in bonding carbon to chlorine is not available for bonding with a nucleophile.

(11) The effect of the greater dilution is to inhibit further condensation of molecules of benzaldehyde and chloroester formed by dealdolization. Since dealdolization is second order over-all (first order in base and first order in chlorohydrin ester V) whereas aldolization is third order over-all (first order each in base, chloroester and benzaldehyde), at greater dilution aldolization is slowed down to a greater extent than dealdolization.

(12) (a) The formation of only ethyl 2-phenyl-3-*m*-nitrophenyl-2,3-epoxypropionate in the experiment run with *m*-nitrobenzaldehyde present shows that dealdolization, at least for the solid diastereomer, is more rapid than cyclization. The isolation of dealdolization products from the runs of both diastereomers under mild conditions shows that dealdolization is at least competitive with cyclization. The isolation of only dealdolization and cyclization products, but no ethyl 2-chloro-3-hydroxy-2,3-diphenylpropionate diastereomers, in the mild runs suggests that the aldolization process has an unfavorable equilibrium constant; that is, $k_{-1} > k_1$. This is true where potassium is the cation; it is no longer true, as the Munch-Peterson synthesis of the diastereomers shows, when magnesium is the cation.

(b) The over-all rate of product formation is given by

$$d(I)/dt = k_2(V)(base)$$

where $(k_1/k_{-1}) = (V)/(C_6H_5CHO)(C_6H_5CHClCOOEt)$. Hence

$$d(I)/dt = k_2(k_1/k_{-1})(base)(C_6H_5CHO)(C_6H_5CHClCOOEt)$$

and the over-all rate constant is as given above. This constant may thus be seen to be a composite of the preequilibrium constant for formation of intermediate V and of the rate of cyclization of V.

(c) Since no direct information is available concerning the relative free energies of the two diastereomeric intermediates Va and Vb, these are arbitrarily drawn as having the same free energies. While on a theoretical basis one might predict Vb to be of lower energy than Va, since Vb has a low energy conformation with largest groups *s-trans* and medium groups also *s-trans*, nevertheless this is of no consequence. The free energies of the relatively unstable pre-equilibrium species Va and Vb do not affect the over-all rate constants: a change in the energy of one of these (*e.g.*, Va) will affect k_2 and the pre-equilibrium constant (k_1/k_{-1}) inversely, therefore with no change in k.

That T_b has a lower free energy than T_a (*i.e.*, that $F_a^* - F_b^* > 0$) can be stated since two transition states derive from a common ground state (*i.e.*, $\Delta F_a^* - \Delta F_b^* = F_a^* - F_b^*$). This is clear from consideration of the absolute rate expressions for k_a and k_b. Thus $(k_b/k_a) = e^{(\Delta F_a^* - \Delta F_b^*)} = e^{(F_a^* - F_b^*)} > 1$.

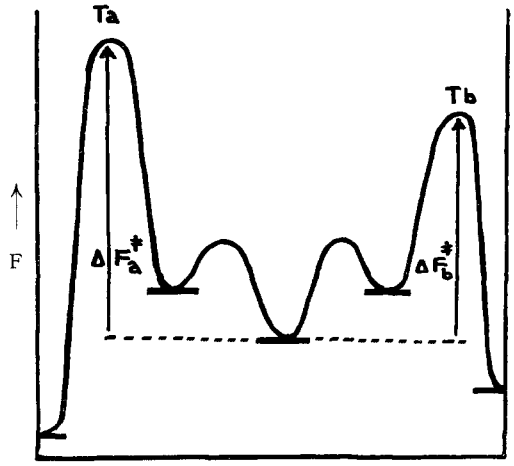


Fig. 1.

These transition states differ by a 180° rotation about the 2,3-carbon-to-carbon single bond. Since phenyl is a more bulky group than carbethoxyl, one might be tempted to predict that transition state Va, in which the carbethoxyl and phenyl groups are cisoid would be of lower energy than transition state Vb in which two phenyl groups are cisoid. However, it has been seen that Vb is of lower energy; hence van der Waals repulsive forces between the two phenyl groups cannot be the decisive factor. Rather, another driving force must be involved; this is "overlap control" which has been found[2a,b] to control the stereochemistry of a number of organic reactions.

In order to understand the operation of overlap control in the present instance, one should consider first the explanation advanced by Dewar some years ago for the facile bimolecular nucleophilic displacement of halogen alpha to a keto group. It was suggested by Dewar that the transition state was stabilized by overlap and conjugation of the C–O π-orbital with the orbitals of the bonds being formed and broken at α-carbon atom.[13]

Similarly, transitions states Va and Vb would be expected to be stabilized by delocalization of electrons from the relatively electron rich p-orbital on carbon-2 to the carbonyl π-orbital. It may be seen, however, that such delocalization imposes a conformational requirement on the single bond between carbon-2 and the carbethoxyl group, since the carbon-2 and the carbonyl group p-orbitals must be parallel for optimum overlap; thus the carbethoxyl group must lie in the plane defined by C-3, C-2 and the first carbon atom of the 2-phenyl group. This presents no difficulty for transition state Vb in which the carbethoxyl group is unhindered, being *trans* to the 3-phenyl group. However, in transition state Va, the carbethoxyl group is *cis* to the 3-phenyl group, and models indicate that the proper conformation is less easily attained.[14,15]

(13) M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford University Press, 1949, p. 73.

(14) The magnitude of the driving force lost by non-coplanarity of the carbethoxyl group may be estimated roughly by comparing (J. Hine, "Physical Organic Chemistry," McGraw–Hill Book Co., Inc., New York, N. Y., 1956, p. 158) the rate of SN2 displacement by iodide ion on phenacyl chloride with that on β-phenylethyl chloride. These are in the ratio of *ca.* 10^8 to 1. This corresponds to 7 kcal./mole. A high upper limit on *cis*-diphenyl van der Waals repulsive forces is 5.7 kcal./mole (ref. 2a).

(15) An exceptionally lucid demonstration of the requirement for coplanarity has been presented recently by P. D. Bartlett and E. N. Trachtenberg, THIS JOURNAL, **80**, 5808 (1958). It was felt by these authors that an additional factor of bonding of the nucleophile to the carbonyl carbon atom might be involved.

(16) H. H. Wasserman, N. E. Aubrey and H. E. Zimmerman, THIS JOURNAL, **75**, 96 (1953).

(17) H. H. Wasserman and N. E. Aubrey, *ibid.*, **77**, 590 (1955).

(18) S. Bodforss, *Ber.*, **51**, 192 (1918).

(19) N. Cromwell and R. Setterquist, THIS JOURNAL, **76**, 5752 (1954).

(20) H. Kwart and L. Kirk, *J. Org. Chem.*, **22**, 116 (1957).

(21) H. Dahn and L. Loewe, *Chimia*, **11**, 98 (1957).

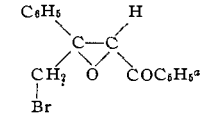
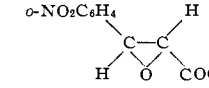
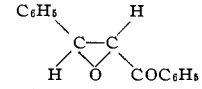
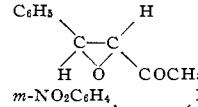
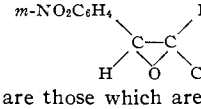
(22) H. O. House and R. S. Ro, THIS JOURNAL, **80**, 2428 (1958).

(23) In each case the product present initially in predominance is the one with an unhindered carbonyl group (*i.e.*, the *trans* isomer).

It having been demonstrated that the Darzens condensation of benzaldehyde with ethyl α-chlorophenylacetate proceeds by way of a reversible aldolization step followed by a rate and stereochemistry controlling cyclization in which the preferred transition state has an unhindered carbonyl group, it is of interest to consider the applicability of these findings to the literature of the Darzens reaction.

It is indeed true that every example of the Darzens reaction whose stereochemistry is known leads at least predominantly to product with an unhindered carbonyl group (*cf.* Table I). Nevertheless,

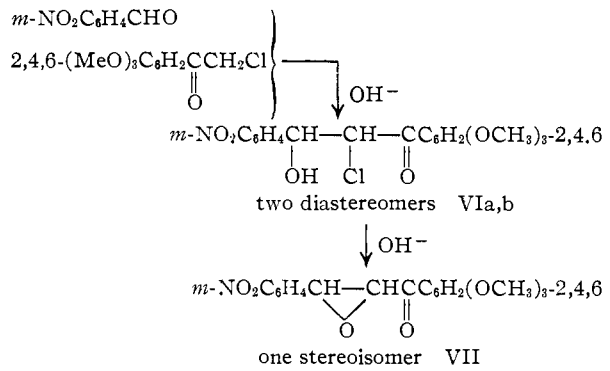
TABLE I

Example	Darzens reactants	Product	Ref.
1	$C_6H_5COCH_2Br$		16, 17
2	*o*-$NO_2C_6H_4CHO$ $ClCH_2COC_6H_5$		18, 19
3	C_6H_5CHO $C_6H_5COCH_2Cl$		17
4	C_6H_5CHO CH_3COCH_2Cl		20
	m-$NO_2C_6H_4CHO$ $ClCH_2COOEt$		21

[a] The products shown are those which are obtained initially; under more extended treatment the more insoluble *cis*-isomer separated as the major product.

because of the presence of an α-hydrogen atom in each of the products and in view of the known[22] base-catalyzed epimerization of such epoxycarbonyl compounds, three of the five examples of Table I do not unambiguously bear on the kinetic preference of the Darzens reaction. Fortunately, there is evidence that the kinetically preferred product of the self-condensation of phenacyl chloride as well as of the condensation of *o*-nitrobenzaldehyde with phenacyl chloride is the stereoisomer in which the carbonyl group is *trans* to the larger group as indicated in examples 1 and 2 of Table I.[23]

In attempting now to rationalize this kinetic preference, one must take into account two additional facts, these having been provided by Ballester.[6b,6c] Firstly, the aldolization step of the Darzens condensation of benzaldehyde with phenacyl chloride (example 3 of Table I) has been shown to be irreversible in contrast[24] to the situation described in the present paper for the benzaldehyde–ethyl α-chlorophenyl-acetate condensation. Secondly, Ballester has demonstrated that the hydroxide-catalyzed condensation of *m*-nitrobenzaldehyde with 2,4,6-trimethoxyphenacyl chloride affords under mild conditions both possible diastereomeric aldolization products (VIa and VIb) and that each of these under typical Darzens condensation conditions affords only the one epoxyketone stereoisomer VII which is the sole product of the Darzens condensation itself.



This evidence suggests that, despite the non-reversibility of aldolization in the benzaldehyde–phenacyl chloride condensation, the reaction stereochemistry is controlled again, as in the benzaldehyde–ethyl α-chlorophenylacetate case, in the cyclization rather than the aldolization step.[25] It is suggested that a second mode of interconversion of diastereomeric Darzens intermediates (*e.g.*, VIa and VIb) is by a rapid epimerization of an α-hydrogen atom; this would allow selective reaction of only that diastereomer which can cyclize with Walden inversion and with the carbonyl group unhindered as required by overlap control.

On longer or more drastic reaction, epimerization proceeded with crystallization of the more insoluble *cis* isomer. One may deduce from this that the *trans* isomer is kinetically preferred. The *cis* isomer may be said to be thermodynamically favored if one defines "thermodynamically" here as including the free energy of crystallization (The question of whether these *cis* isomers may be said to be thermodynamically favored has been discussed with differing viewpoints, by Kwart (ref. 20) and H. A. Berson, *Chemistry & Industry*, 814 (1951)). Cromwell, Schumacher and Edelfang have shown (THIS JOURNAL, in press) that by use of sufficient solvent to effect complete solution base catalyzed epimerization favors the *trans* isomer of *o*-nitrobenzalacetophenone oxide.

(24) The greater facility of dealdolization of β-hydroxycarbonyl compounds having an α-phenyl group derives both from the greater stability of the enolate anion thus formed and from the greater driving force available from relief of strain. This effect has been noted in the case of the bass catalyzed fission of β-hydroxyacids by D. Ivanov, *Bull. soc. chim. France*, **53**, 321 (1933); **7**, 569 (1940).

(25) It has been suggested, plausibly at the time, by several researchers (refs. 19, 20, 21) that the product stereochemistry was determined in the aldolization step with preferred formation of the more stable diastereomer, in which not only the large groups on the two asymmetric carbon atoms could be s-*trans* but in which the medium groups were s-*trans*. Also considered was the possibility that cyclization might control the reaction stereochemistry with a transition state having large groups avoiding one another being preferred.

One additional piece of evidence against this picture of control in the aldolization step is example 1 of Table I in which the diastereomer cyclizing to the kinetically controlled Darzens product is actually the one which cannot have large and medium groups simultaneously s-*trans*.

Experimental Section[26]

α-Chlorophenylacetyl Chloride.[27]—To 251 g. (1.2 moles) of phosphorus pentachloride in a 2-liter flask was added portionwise 100 g. (0.66 mole) of mandelic acid. The flask was then fitted with a condenser and drying tube. After 10 minutes the mixture began to froth and liquify; it was then heated to an internal temperature of 130° for 4 hours. At the end of this time the mixture was subjected to vacuum distillation. After a forerun of phosphorus oxychloride boiling at 24–35° at 15–20 mm., there was obtained 79.4 g. (63.5%) of product, b.p. 85–86° (2.0 mm).

Ethyl α-Chlorophenylacetate.—To 79.4 g. (0.42 mole) of α-chlorophenylacetyl chloride there was added in portions 32.6 g. (0.69 mole) of absolute ethanol; a vigorous reaction ensued at first; the action of the last 5-g. portion gave no visible reaction. The excess ethanol was distilled off under water-pump vacuum and the residue was subjected to vacuum distillation. There was obtained 83.0 g. (99%) of product distilling at 77–78° (2.0 mm), $n^{25}D$ 1.5123 (reported[28] $n^{20}D$ 1.5152).

Small Scale Darzens Condensation of Benzaldehyde with Ethyl α-Chlorophenylacetate.—A solution of potassium *t*-butoxide was prepared by adding 204 mg. (5.2 mmoles) of potassium to 4.50 ml. of dry *t*-butyl alcohol. This solution was then added to a mixture of 1.0 g. (5.04 mmoles) of ethyl α-chlorophenylacetate and 0.553 g. (5.2 mmoles) of benzaldehyde in 2.0 ml. of *t*-butyl alcohol and 1.0 ml. of dry benzene. The homogeneous solution was stirred under nitrogen at 15° during the mixing process and then was allowed to warm to room temperature. Following this, the mixture was stirred under nitrogen for an additional 3 hours. During this time the mixture became viscous. At the end of the reaction water was added and the whole extracted with ether. The organic phase was well washed with water, dried over sodium sulfate and concentrated *in vacuo;* finally, an oil-pump vacuum was applied. The oily residue crystallized. This product melted at 54.0–55.0° and weighed 0.90 g. (75%). Recrystallization from hexane brought the melting point to 57.0–58.0° (reported 59–60°,[4] 56–57°[5]), this representing pure ethyl 2,3-*cis*-diphenyl-2,3-epoxypropionate.

The aqueous phase was carefully acidified to a congo red end-point and quickly ether extracted. The extract was washed once with water, dried over sodium sulfate and concentrated *in vacuo;* this afforded 210 mg. of a viscous oil which crystallized when treated with chloroform–hexane. This solid melted at 107–110°, and its infrared spectrum indicated it to be essentially pure 2,3-*cis*-diphenyl-2,3-epoxypropionic acid.

Partial Darzens Condensation of Benzaldehyde with Ethyl α-Chlorophenylacetate; Synthesis of the Diastereomeric 2-Chloro-3-hydroxy-2,3-diphenylpropionate Esters.—An ethereal solution of ethylmagnesium bromide was prepared from 1.21 g. (0.05 mole) of magnesium turnings, 5.45 g. (0.05 mole) of ethyl bromide and 25 ml. of anhydrous ether. To this with stirring was added a solution of 5.05 g. (0.05 mole) of diisopropylamine in 15 ml. of dry ether. The addition required 15 min., and during this time a white suspension of diisopropylaminomagesium bromide resulted. The suspension was cooled to 0° with an ice–salt-bath, and a mixture of 2.87 g. (0.027 mole) of benzaldehyde and 5.05 g. (0.027 mole) of ethyl α-chlorophenylacetate in 50 ml. of dry ether was added with stirring over 30 min. The mixture was stirred for an additional hour at room temperature, resulting in formation of a white pasty material. This was cooled with an ice-bath and acidified with 6.0 g. of acetic acid dissolved in 30 ml. of water and stirred until the solid material had dissolved. The ethereal extracts of this solution were washed with dilute sodium bicarbonate solution, then with dilute hydrochloric acid and finally with water. The washed extract was then dried over sodium sulfate and

(26) All melting points were taken on a Hershberg apparatus checked with known compounds.

(27) Modification of literature preparation, C. A. Bischoff and P. Walden, *Ann.*, **279**, 122 (1894).

(28) P. Walden, *Z. physik. Chem.*, **17**, 715 (1895).

concentrated *in vacuo* to leave a brownish oil weighing 6.3 g., which would not crystallize.

Two grams of this oil was chromatographed on a silica gel column (Davidson 40–200 mesh; column size 18 × 450 mm.) slurry packed with 5% ether in hexane. The mixture was applied to the column with a small volume of the same solvent and eluted with this as well; 50-ml. fractions were collected. The first six fractions were empty. The eluting solvent was then changed to 10% ether in hexane. Fractions 7 through 9 were also void; 10 through 16 contained a mixture of benzaldehyde and ethyl α-chlorophenylacetate, identified by infrared and weighing 975 mg.; 17 contained no material. Fractions 18 through 24 afforded a viscous oil totaling 344 mg.; however, of these 20, 21 and 22 were seen to be pure from the constancy of the infrared spectra; these fractions weighed a total of 176 mg. and represented one diastereomer of ethyl 2-chloro-3-hydroxy-2,3-diphenylpropionate. Fractions 23 and 24 were mixtures of this diastereomer and the material to follow. Fractions 25 through 32 gave a total of 577 mg. of solid, m.p. 60–63°. Little additional material was obtained by further elution. Fraction 27 was recrystallized from hexane, bringing the melting point to 64.0–65.0°. This represented the second diastereomer of the chlorohydrin product. Its infrared spectrum, like that of its stereoisomer, possessed hydroxyl and carbonyl absorption bands. Both spectra were similar, especially below 10 μ. Past this wave length there were many distinct differences. For example, the following are strong bands characteristic of one of diastereomers and at a wave length where the other isomer is transparent: for the liquid stereoisomer, 9.51, 13.28 and 13.80 μ (CS_2); for the solid stereoisomer, 9.43, 13.52 and 15.07 μ (CS_2).

Anal. Calcd. for $C_{17}H_{17}O_3Cl$: C, 67.00; H, 5.63. Found for 65° isomer: C, 67.38; H, 5.57. Found for liquid isomer: C, 66.89; H, 5.60.

Behavior of Ethyl 2-Chloro-3-hydroxy-2,3-diphenylpropionate under Darzens Reaction Conditions; the 65° Diastereomer.—A solution of potassium *t*-butoxide in *t*-butyl alcohol was prepared from 867 mg. (22 mmoles) of potassium and 22 ml. of *t*-butyl alcohol. This was added with stirring under nitrogen to a solution of 4.42 g. (14.5 mmoles) of ethyl 2-chloro-3-hydroxy-2,3-diphenylpropionate, m.p. 65°, dissolved in 6.0 ml. of dry benzene and 12.0 ml. of dry *t*-butyl alcohol cooled to 15°; the addition was made over 10 min. There was an immediate and exothermic reaction, and the solution became cloudy with formation of a reddish-brown color. With further stirring the color lightened and the solution became viscous. At the end of 4.5 hr. the mixture was diluted with water and immediately ether extracted. The ether extract was washed with water, dried over sodium sulfate and concentrated under vacuum to afford 2.222 g. of a neutral orange oil.

A 2.12-g. portion of this material was chromatographed on silica gel (35 × 650 mm.) slurry packed with 5% ether in hexane and eluted with 10% ether in hexane. The first three 50-ml. fractions were void. Fractions 4 through 8 contained a mixture of benzaldehyde and ethyl α-chlorophenylacetate weighing 125 mg. Fraction 9 was empty. Fraction 10 weighed 25 mg. and was oily; 11 through 18 weighed 952 mg. and consisted of solid melting at 64–65°; 19 through 21 weighed 32 mg. and contained oily crystalline material; 22 through 29 weighed 555 mg. and was crystalline, melting at 51–53°; 30 and 31 contained 34 mg. of oil. Further elution afforded no more material.

Recrystallization of the 65° material from hexane brought the m.p. to 67.5–68.0°. This was found to be *t*-butyl 2,3-*cis*-diphenyl-2,3-epoxypropionate, resulting from transesterification of the usual ethyl ester.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.81; H, 6.89.

A 182-mg. (0.615 mmole) portion of the *t*-butyl ester was saponified with 14.2 mg. (0.615 mmole) of sodium ethoxide in 8.0 ml. of abs. ethanol to which 12.0 mg. of water had been added; the reaction was run at room temperature for 1 hr. At the end of this time water was added with resulting turbidity; the mixture was then ether extracted and the aqueous phase was carefully acidified with cold dilute sulfuric acid. This was then immediately ether extracted, and the extracts were washed with water, dried over sodium sulfate and concentrated *in vacuo*. There remained 115 mg. of crystalline material, m.p. 120–122°, which did not depress when admixed with 2,3-*cis*-diphenyl-2,3-epoxypropionic acid, m.p. 122°.

The 53° material from fractions 22 through 29 was essentially pure ethyl 2,3-*cis*-diphenyl-2,3-epoxypropionate; recrystallization from hexane brought the m.p. to 58°.

The original basic washes where acidified, ether extracted and the extracts washed and dried. Concentration under vacuum afforded 1.204 g. of solid, m.p. 95–100°. The infrared spectrum of this material was essentially that of the 122° glycidic acid except for a band at 7.3 μ. A small sample was recrystallized from chloroform–hexane to give crystals, m.p. 110–112°. This did not depress the m.p. of 122° glycidic acid; also, it had an identical infrared spectrum as that of the pure 2,3-*cis*-diphenyl-2,3-epoxypropionic acid. However, further attempts at purification, both by crystallization or by chromatography on silica gel resulted in partial decomposition.

Action of Potassium *t*-Butoxide on Ethyl 2-Chloro-3-hydroxy-2,3-diphenylpropionate of M.p. 65° under Milder Reaction Conditions.—A potassium *t*-butoxide solution was prepared from 60.3 mg. (1.54 mmoles) of potassium and 15 ml. of dry *t*-butyl alcohol under nitrogen. This was added with stirring under nitrogen at 15° and during 15 min. to a solution of 450 mg. (1.48 mmoles) of the 65° isomer of ethyl 2-chloro-3-hydroxy-2,3-diphenylpropionate in 15 ml. of dry *t*-butyl alcohol. The solution immediately became cloudy due to crystallization of *t*-butyl alcohol; 5.0 ml. of dry benzene was then added to inhibit this. The solution was then stirred for an additional 2.5 hr. at room temperature. At the end of this time the mixture was diluted with water, ether extracted and the extracts washed and dried over sodium sulfate. Concentration under vacuum yielded 51 mg. of an oil which crystallized and then melted at 48–50°. The infrared spectrum indicated this to be essentially pure ethyl 2,3-*cis*-diphenyl-2,3-epoxypropionate and recrystallization from hexane brought the m.p. to 58°.

The aqueous washes were acidified with acetic acid, ether extracted and concentrated *in vacuo* to afford 119 mg. of a solid, m.p. 110–112°; this material was recrystallized from hexane, bringing the m.p. to 116–117°. The mixed m.p. with mandelic acid was not depressed and the infrared spectrum was identical with that of mandelic acid.

Behavior of the Oily Diastereomer of Ethyl 2-Chloro-3-hydroxy-2,3-diphenylpropionate under Darzens Reaction Conditions.—A solution of potassium *t*-butoxide was prepared from 248 mg. (6.34 mmoles) of potassium and 6.5 ml. of *t*-butyl alcohol. This was added with stirring and cooling to 15° under nitrogen to a solution of 1.682 g. (5.5 mmoles) of the liquid diastereomer of ethyl 2-chloro-3-hydroxy-2,3-diphenylpropionate in 2.0 ml. of dry benzene and 4.0 ml. of dry *t*-butyl alcohol. As with the diastereomeric starting material there was an immediate exothermic reaction and a reddening and thickening of the reaction mixture. At the end of 4.5 hr. at room temperature the reaction mixture was worked up as in the case of the diastereomeric run. There was obtained from the original ether extracts 960 mg. of neutral crystalline material which possessed an odor of benzaldehyde. When washed with cold hexane the residual solid melted at 54–55°. One crystallization from hexane afforded 775 mg. of ethyl 2,3-*cis*-diphenyl-2,3-epoxypropionate, m.p. 56.0–57.0°.

The basic washes when acidified yielded 297 mg. of solid of m.p. 115–117°; The infrared spectrum of this material was identical with that of 2,3-*cis*-diphenyl-2,3-epoxypropionic acid. Attempts at further crystallization led to decomposition.

Action of Potassium *t*-Butoxide on the Liquid Diastereomer of Ethyl 2-Chloro-3-hydroxy-2,3-diphenylpropionate under Mild Reaction Conditions.—A solution of potassium *t*-butoxide prepared from 150 mg. (3.8 mmoles) of potassium and 3.5 ml. of dry *t*-butyl alcohol was added with stirring and under nitrogen at 15° to a solution of 1.07 g. (3.5 mmoles) of the liquid diastereomer of ethyl 2-chloro-3-hydroxy-2,3-diphenylpropionate in 2.0 ml. of *t*-butyl alcohol and 1.0 ml. of benzene; the addition was made over 15 min. There was an immediate cloudiness, and after stirring for 30 min. at this temperature the mixture had become quite viscous. The mixture was then stirred at room temperature for an additional 2 hours. Water was added and the mixture was immediately ether extracted. The organic phase was washed with water, dried over sodium sulfate and concentrated under vacuum to yield 485 mg. of an oil which smelled of benzaldehyde. This material was chromato-

graphed on a silica gel column (18×450 mm.) slurry packed with 5% ether in hexane and eluted with 10% ether in hexane. The first four 50-ml. fractions were empty. Fractions 5 and 6 contained 105 mg. of ethyl α-chlorophenylacetate identified by infrared spectrum. Fraction 7 contained 55 mg. of benzaldehyde. Fractions 8 and 9 yielded 68 mg. of a mixture of benzaldehyde and glycidic ester. Fractions 10 through 12 afforded 175 mg. of ethyl 2,3-*cis*-diphenyl-2,3-epoxypropionate, melting at 53–54°: crystallization from hexane brought the m.p. to 58°. Fractions 13 and 14 contained a total of 15 mg. of colored oil. Further elution gave no more material.

Fractions 5 and 6 were treated with refluxing alcoholic potassium hydroxide for 1 hour, cooled, acidified and ether extracted. The extracts were dried over sodium sulfate and concentrated. The residue was crystallized from hexane to yield 55 mg. of mandelic acid, m.p. 116.5–117°; this was characterized by infrared and mixed melting point. Fraction 7 was treated with 2,4-dinitrophenylhydrazine reagent to give an orange 2,4-dinitrophenylhydrazone, m.p. 234.0–235.0° (benzaldehyde 2,4-DNP melts at 237°).

The basic washes on careful acidification, ether extraction and washing with water, drying over sodium sulfate and concentration afforded 332 mg. of an oil solidifying on standing; this melted at 98–102°. The infrared spectrum of this material showed that it was mainly 2,3-*cis*-diphenyl-2,3-epoxypropionic acid, possibly containing some mandelic acid. Purification by crystallization led to decomposition.

The Reaction of the 65° Diastereomer of Ethyl 2-Chloro-3-hydroxy-2,3-diphenylpropionate with Potassium *t*-Butoxide in the Presence of *m*-Nitrobenzaldehyde.—A solution of potassium *t*-butoxide prepared from 190 mg. (4.87 mmoles) of potassium and 5.0 ml. of dry *t*-butyl alcohol was added to a solution of 1.91 g. (12.7 mmoles) *m*-nitrobenzaldehyde, 1.286 g. (4.22 mmoles) of the 65° chlorohydrin ester, 3.0 ml. of *t*-butyl alcohol and 2.0 ml. of dry benzene. The reaction was run under nitrogen at 15° with stirring; after completion of the addition the temperature was allowed to rise to that of the room. The usual red color and exothermic reaction was noted. At the end of 1 hour at room temperature the mixture had become colorless and quite viscous. The total reaction time was 3.5 hr. Water was then added and the mixture was ether extracted. The ether extracts were washed with water, dried over sodium sulfate and concentrated under vacuum to yield 2.45 g. of a viscous oil containing some solid and smelling strongly of benzaldehyde. This material was taken up in ether and washed four times with saturated sodium bisulfite solution followed by washing with water and drying over calcium chloride. Concentration *in vacuo* gave 955 mg. of a yellow oil which crystallized on standing and then melted at 75–80°. The infrared spectrum indicated the presence of a nitro group. Recrystallization brought the melting point to 83.0–83.5°. This represented pure ethyl 2-phenyl-3-*m*-nitrophenyl-2,3-epoxypropionate.

Anal. Calcd. for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.82; N, 4.47. Found: C, 64.85; H, 4.95; N, 4.68.

The usual workup of the basic aqueous washes afforded 93 mg. of a colorless viscous oil which resisted attempts at crystallization.

Competition Experiment; Reaction of Ethyl α-Chlorophenylacetate with a Mixture of Anisaldehyde and *p*-Nitrobenzaldehyde in the Presence of Potassium *t*-Butoxide.—A solution of potassium *t*-butoxide was prepared from 0.94 g. (0.024 mole) of potassium and 30 ml. of dry *t*-butyl alcohol. The solution was allowed to stand overnight, since traces of unreacted potassium caused side reactions. This solution was added over a period of 25 min. to a stirred mixture of 4.00 g. (0.0202 mole) of ethyl α-chlorophenylacetate, 3.14 g. (0.0208 mole) of *p*-nitrobenzaldehyde (m.p. 105–106°) and 2.84 g. (0.0208 mole) of anisaldehyde in 10.0 ml. of dry benzene and 5.0 ml. of *t*-butyl alcohol; the reaction mixture was kept at 5–10° during the addition and a nitrogen atmosphere was employed. The mixture turned reddish and turbid. Then the reaction mixture was stirred for an additional 2 hours at 10°. The mixture was worked up by adding 50 ml. of water and ether extracting. The extract was washed and then dried over sodium sulfate. Concentration yielded 3.79 of an oily solid whose infrared spectrum suggested the presence of anisaldehyde and a nitroglycidic ester. This material was chromatographed on silica gel (38 × 600 mm.) slurry packed with 5% ether in hexane and eluted with 10% ether in hexane; 75-ml. fractions were collected. The first twenty 75-ml. fractions were void. Fractions 21 through 26 afforded 1.02 g. of pure anisaldehyde, identified by infrared spectrum and 2,4-dinitrophenylhydrazone, m.p. 235°. Fractions 27 through 42 contained a mixture of anisaldehyde and nitroglycidic ester weighing 5.75 g. Fractions 43 through 49 gave 1.07 g. of essentially pure ethyl 2-phenyl-3-*p*-nitrophenyl-2,3-epoxypropionate, m.p. 104–106°. Fraction 50 contained 120 mg. of colored oil. Further elution failed to give more material.

Fractions 27 through 42 were dissolved in ether and extracted with saturated sodium bisulfite solution; the ether phase was then washed with water, dried over sodium sulfate and concentrated *in vacuo* to afford 4.38 g. of crystals, m.p. 103–105°. Recrystallization from hexane–chloroform gave colorless crystals of ethyl 2-phenyl-3-*p*-nitrophenyl-2,3-epoxypropionate, m.p. 108–109.0°. The total yield was 86.5%.

Anal. Calcd. for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.82; N, 4.47. Found: C, 64.85; H, 4.89; N, 4.73.

Acidification of the alkaline aqueous washes with dilute hydrochloric acid followed by ether extraction, washing and drying of the extracts, and finally concentration *in vacuo* afforded 0.39 g. of yellow solid, m.p. 115–140° dec. This material was chromatographed on a silica gel column (18 × 450 mm.) slurry packed with 50% ether in hexane and eluted with the same solvent. The first two 50-ml. fractions were empty. The following seven fractions contained a colorless solid, m.p. 154–155°. This was followed by an empty fraction and then by a fraction containing material, m.p. 123–126°. Recrystallization of the 154–155° material from hexane–chloroform did not raise the m.p. This material was 2-phenyl-3-*p*-nitrophenyl-2,3-epoxypropionic acid.

Anal. Calcd. for $C_{15}H_{11}O_5N$: C, 63.16; H, 3.89; N, 4.91. Found: C, 62.79; H, 3.88; N, 5.14.

Ethyl 2,3-*trans*-Diphenyl-2,3-epoxypropionimidate.—A solution of 6.50 g. (29.4 mmoles) of 2,3-*trans*-diphenyl-2,3-epoxypropionitrile,[2a] m.p. 69–70°, in 90 ml. of absolute ethanol was added to a solution of sodium ethoxide prepared from 770 mg. (33.5 mmoles) of sodium and 90 ml. of absolute ethanol. The mixture was allowed to stand for 20 hr., protected with a potassium hydroxide-filled drying tube. The mixture was then concentrated *in vacuo*, the residue taken up in ether, washed with water, dried and evaporated to leave 6.32 g. of a viscous oil. Chromatography on a 35 × 650 mm. silica gel column slurry packed with 5% ether in hexane and eluted with the same solvent gave sixty 50-ml. fractions. The first ten fractions were void. Fractions 11 through 45 were void and the solvent was changed to 30% ether in hexane. Fractions 46 through 53 contained 850 mg. melting at 73–74°. Fraction 54 melted at 145–180° and fractions 55 through 60 weighed 1.15 g. and melted at 197–199°. The material melting at 68–70° was recovered starting material. The 73–74° material was recrystallized from hexane to give needles, m.p. 76–77°, and weighing 640 mg. This was the desired product. Fractions 55 through 60 were recrystallized from chloroform–hexane to yield the corresponding amide, m.p. 203–204°.

Anal. Calcd. for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41: N, 5.24. Found: C, 75.91; H, 6.31; N, 5.45.

Ethyl 2,3-*trans*-Diphenyl-2,3-epoxypropionate.—A solution of 1.10 g. (4.13 mmoles) of the ethyl 2,3-*trans*-diphenyl-2,3-epoxypropionimidate prepared above, 310 mg. of 96% sulfuric acid (6.07 meq.), 1.15 g. (64 mmoles) of water and 70 ml. of absolute alcohol was refluxed for 1.5 hr. The mixture was then cooled, 1.0 g. of sodium acetate was added and the resulting mixture concentrated *in vacuo*. The residue was taken up in ether, which was then washed with sodium carbonate solution, dried over sodium sulfate and concentrated *in vacuo*, leaving 960 mg. of an oily solid. The solid was crystallized from hexane–chloroform to yield somewhat impure epoxyamide melting at 190–193°. The filtrate was concentrated to afford 780 mg. of a viscous oil.

This material was chromatographed on a 18 × 450 mm. silica gel column slurry packed with 5% ether in hexane and eluted with this solvent. The first five 50-ml. fractions were empty. Then followed six fractions of a colorless oil totaling 675 mg. The infrared spectrum of this material in CS_2 exhibited a doublet carbonyl absorption band (5.70 and 5.75 μ) in contrast to the *cis*-diphenyl stereoisomer; in chloroform only a singlet was noted. In addition the

oily product, which represented ethyl 2,3-*trans*-diphenyl-2,3-epoxypropionate, possessed bands in the infrared at 10.70 and 15.60 μ where the *cis*-diphenyl stereoisomer was transparent. Also, the *cis*-diphenyl stereoisomer, m.p. 58°, possessed a band at 7.96 μ where the oily stereoisomer was transparent.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.97; H, 5.65.

2,3-*trans*-Diphenyl-2,3-epoxypropionic Acid.—A solution of 75 mg. of the oily glycidic ester obtained above (0.28 mmole) in 5.0 ml. of absolute ethanol was added to a sodium ethoxide solution prepared from 25 mg. (1.10 mmoles) of sodium, 5.0 ml. of absolute ethanol and 350 mg. of water. The mixture was allowed to stand at room temperature for 11 hours. It was then concentrated *in vacuo*, diluted with water and ether extracted. The aqueous phase was cooled in ice and carefully acidified with dilute hydrochloric acid and immediately ether extracted. The ether extract was washed free of acid and dried over Drierite and concentrated to afford 55 mg. of a solid melting at 90–92°. One crystallization from hexane–ether gave 32 mg. of acid, m.p. 96–98°. One further crystallization yielded material melting at 97.0–98.0° (reported[3] 100°).

Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.26, 75.62; H, 5.40, 4.89.

Acknowledgment.—Support of this research by the Office of Ordnance Research, U. S. Army, is gratefully acknowledged.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF KANSAS, LAWRENCE, KANS.]

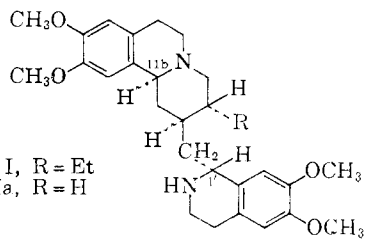
Synthetic Applications of Hexahydrogallic Acid. I. A New Route to Emetine[1]

BY ALBERT W. BURGSTAHLER AND ZOE J. BITHOS

RECEIVED MARCH 10, 1960

A synthetic route to the Ipecac alkaloid emetine (I) from hexahydrogallic acid and homoveratrylamine is described.

Primarily because of its powerful amoebicidal but undesirable toxic properties, emetine (I), the principal member of the Ipecac group of isoquinoline alkaloids, has long been a popular subject of extensive degradative, structural and synthetic studies.[2] Intensified considerably in recent years, these investigations have grown in importance and have now resulted in a number of independent total syntheses of emetine,[3] a significant partial synthesis,[4] and the complete elucidation of the stereochemistry and absolute configuration of the alkaloid.[5]



I, R = Et
Ia, R = H

In the present report, as part of a program concerned with synthetic applications of the hexahydrogallic acid obtained by catalytic hydrogenation of gallic acid,[6] a fundamentally new route to emetine is described.[1] This synthesis involves, as its key step, formation of the tricyclic lactam aldehyde IV by cyclodehydration of the β-substituted glutaraldehyde III, the latter, in turn, being obtained by periodate oxidation[7] of the homologated hexahydrogallic acid derivative II.[8]

A two-step hydrogenation of gallic acid, first with Raney nickel in aqueous base and then with platinum oxide in methanol, has been reported[6a] to furnish a homogeneous hexahydrogallic acid (VI) of m.p. 198° (uncor.) (203° cor.)[6b] in an over-all yield of 13 to 19%. In the present work, reduction of gallic acid under high pressure with 5% rhodium-on-alumina in ethanol has been found to afford this same product directly in yields of 45 to 50%. Like γ-pyrogallitol (*cis-cis*-1,2,3-cyclohexanetriol, V), which is the major product formed in the closely related hydrogenation of pyrogallol over the same catalyst (or over palladium or nickel),[9] this particu-

(1) Taken in part from the M.S. Thesis of Z.J.B., Univ. of Kansas, 1958. First reported in a Communication to the Editor, THIS JOURNAL, **81**, 503 (1959). A portion of this work was also presented before the Division of Organic Chemistry at the 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April 13–18, 1958.

(2) For an excellent guide to much of the pertinent literature, *cf.* A. Brossi, H. Lindlar, M. Walter and O. Schnider, *Helv. Chim. Acta*, **41**, 119 (1958); see also papers cited in ref. 3 and 5.

(3) (a) R. P. Evstigneeva, R. S. Livshitz, L. I. Zakharkin, M. S. Bainova and N. A. Preobrazhensky, *Doklady Akad. Nauk, S.S.S.R.*, **75**, No. 4, 539 (1950), and later papers; (b) M. Barash and J. M. Osbond, *Chemistry & Industry*, 490 (1958); (c) A. R. Battersby and J. C. Turner, *ibid.*, 1324 (1958); (d) R. P. Evstigneeva and N. A. Preobrazhensky, *Tetrahedron*, **4**, 223 (1958); (e) A. Brossi, M. Baumann and O. Schnider, *Helv. Chim. Acta*, **42**, 1515 (1959); (f) A. Grüssner, E. Jaeger, J. Hellerbach and O. Schnider, *ibid.*, **42**, 2431 (1959); (g) M. Barash, J. M. Osbond and J. C. Wickens, *J. Chem. Soc.*, 3530 (1959); (h) A. R. Battersby and J. C. Turner, *ibid.*, 717 (1960).

(4) A. R. Battersby and B. J. T. Harper, *ibid.*, 1748 (1959).

(5) (a) E. E. van Tamelen, P. E. Aldrich and J. B. Hester, THIS JOURNAL, **81**, 6214 (1959), (b) A. R. Battersby and S. Garratt, *J. Chem. Soc.*, 3512 (1959); (c) A. Brossi, A. Cohen, J. M. Osbond, P. Plattner, O. Schnider and J. C. Wickens, *ibid.*, 3630 (1959); (d) Y. Ban, M. Terashima and O. Yonemitsu, *Chemistry & Industry*, 568, 569 (1959).

(6) (a) W. Mayer, R. Bachmann and F. Kraus, *Ber.*, **88**, 316 (1955); (b) W. Mayer and L. Keller, *ibid.*, **92**, 213 (1959).

(7) The potential synthetic use of the hexahydrogallic acid structure as a source of a β-substituted glutaraldehyde intermediate was apparently first recognized by H. O. L. Fischer and G. Dangschat [*Helv. Chim. Acta*, **17**, 1200 (1934)] in connection with dihydroshikimic acid. A possible role of shikimic acid in the biosynthesis of emetine and related alkaloids has been amplified recently by E. Wenkert and N. V. Bringi, THIS JOURNAL, **81**, 1474 (1959). It also should be noted that use of a β-substituted glutaraldehyde in the synthesis of strychnine has been proposed by R. Robinson and J. E. Saxton, *J. Chem. Soc.*, 2596 (1953); *cf.* A. R. Katritzky, *ibid.*, 2581, 2586 (1955).

(8) A similar reaction sequence has also been applied in the total synthesis of yohimbine [E. E. van Tamelen, M. Shamma, A. W. Burgstahler, J. Wolinsky, R. Tamm and P. E. Aldrich, THIS JOURNAL, **80**, 5006 (1958)]. For a closely related cyclodehydration to form the erythrinane and erysotrine skeletons, *cf.* B. Belleau, *ibid.*, **75**, 5765 (1953); *Can. J. Chem.*, **35**, 651, 663 (1957); A. Mondon, *Angew. Chem.*, **68**, 578 (1956); *ibid.*, **70**, 406 (1958); also V. Boekelheide, *et al.*, THIS JOURNAL, **81**, 3955, 3959 (1959).

(9) W. R. Christian, C. J. Gogek and C. B. Purves, *Can. J. Chem.*, **29**, 911 (1951); *cf.* S. J. Angyal and D. J. McHugh, *J. Chem Soc.*, 3682 (1957).