in 6.3% yield, is evidently one of the possible stereoisomeric Diels-Alder adducts of III, from the following data: calcd. for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.30; H, 6.31. Infrared: 5.42, 5.63 μ (cyclic 5-ring anhydride) and 5.83 μ (6-ring saturated ketone). Ultraviolet: No high intensity maxima; λ_{max} 300 mμ, ϵ = 64. The adduct was slowly soluble in sodium hydroxide solution, decolorized permanganate rapidly, and was converted after the uptake of exactly two molar equivalents of hydrogen (Pt catalyst) to a tetrahydro derivative, m.p. 115.1–115.4° (calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.15; H, 7.74.) which was saturated to permanganate, and gave an infrared spectrum whose carbonyl region was substantially identical with that of the adduct.

The phenol (II) gave no trace of adduct under identical conditions, with an identical isolation procedure. The ether (I) gave no trace of adduct with maleic anhydride at 100° for three hours. However the pure ether, when heated alone at 200° for ten minutes, produced a mixture actually containing some dienone, since a small amount of the adduct could be isolated after treatment of the mixture with maleic anhydride at 100° for three hours. Finally, pyrolysis of the pure adduct in Nujol solution (200° for 3.75 hours) yielded phenol (II), isolated as the phenylurethan, m.p. 141.5–143°, identical with an authentic sample,[2] in 2% over-all yield. Evidently the dienone (III), when released from its adduct, can rearrange further to the final product (II).

The data require that I → III → (IV) → II is a reaction path actually used, if not the sole reaction path. In analogy to the *ortho* Claisen rearrangement, the dienone (III) is presumably formed from I through a six-membered transition state in which the bonds are made and broken simultaneously.[1,6] But unlike the enolizable dienone formed in the *ortho* rearrangement, III can return to an aromatic system only by an additional longitudinal flip of the allyl group, to give IV, which then enolizes to II. In a sense, the change III → IV is comparable to the thermal transformation of ethyl 1-cyclohexenylallylcyanoacetate to ethyl (2-allylcyclohexylidene)-cyanoacetate,[7] an all-carbon allylic rearrangement.

This mechanism for the *para*-Claisen rearrangement predicts no α-γ inversion of the allyl group in the over-all process, a result borne out by several previous experiments,[1,8] is consistent with the finding that an optically active allyl residue retains activity in *para* migration[4], and is in agreement with the fact[2] that both *ortho* and *para* rearrangements have comparable entropies of activation.

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(7) A. C. Cope, *et al.*, THIS JOURNAL, **62**, 441 (1940); **68**, 1843 (1941); **63**, 1852 (1941).

(8) NOTE ADDED APRIL 30, 1953.—Although some of the experiments of Mumm, *et al.* (ref. 1), seemed inconsistent with this view, these have very recently been repeated (S. J. Rhoads, R. Raulins and R. D. Reynolds, THIS JOURNAL, **75**, 2531 (1953)) and the difficulty resolved. *Cf.* also J. P. Ryan and P. R. O'Connor, *ibid.*, **74**, 5866 (1952), who demonstrated the point with *labelled* compounds.

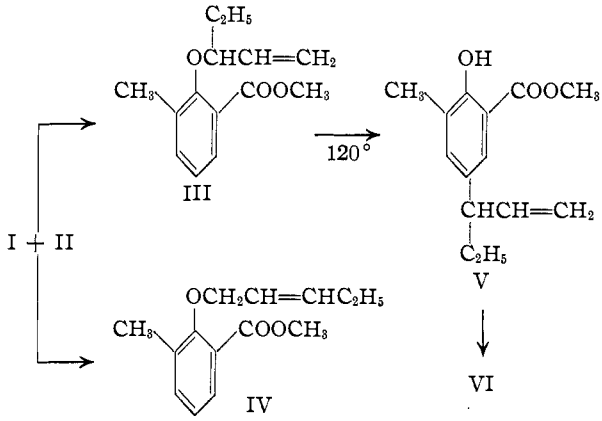
(9) Process Research, Merck & Co., Inc., Rahway, N. J.

ON THE *PARA*-CLAISEN REARRANGEMENT

Sir:

Renewed interest in the *para*-Claisen rearrangement[1,2] prompts us to report our findings on reinvestigation of the work of Mumm, Hornhardt and Diederichsen[3] on the preparation and rearrangement of the α- and γ-ethylallyl ethers of methyl cresotinate, III and IV. Contrary to the conclusions reached by the earlier workers, we have obtained evidence that the *para*-rearrangement proceeds *without inversion* of the migrating group in both III and IV.

The reaction of sodio-methyl cresotinate, I, with α-ethylallyl chloride, II, in methanol gives rise to a mixture of III and IV as well as a phenolic fraction containing both possible C-allylated phenols. The separation of the neutral and phenolic fractions *cannot* be accomplished with 2 *N* sodium hydroxide (*cf.* ref. 3) but requires the use of Claisen alkali.



Vacuum distillation of the ethereal fraction gives material with a negative ferric chloride test, b.p. 92–116° at 0.2 mm., $n^{25}D$ 1.5072–1.5119. Methanolic potassium hydroxide hydrolysis of the higher boiling end fraction of this material yields the acid corresponding to the γ-ether, IV, m.p. 63.5–64°, identical by mixed m.p. with an authentic sample. Hydrolysis of the lower boiling end fraction of the ethereal material proceeds *without rearrangement* (*cf.* ref. 3) furnishing an oil which crystallizes at −5° but remelts at room temperature. Ozonolysis of the ethereal fraction produces formaldehyde in amounts corresponding to 40 ± 5% of an ether with a terminal methylene group. Ozonolysis of the same ethereal material, followed by hydrogen peroxide-acetic acid oxidation permits the isolation of 2-carboxy-6-methylphenoxyacetic acid (20–30%), identical with that produced by the oxidation of pure IV. Comparision of the infrared spectra of the ethereal fraction, authentic γ-ether and a model compound, the allyl ether of methyl cresotinate, confirms the presence of IV in the α-ether preparation, but the characteristic 10.7–10.8μ peak of the terminal methylene group is also detectable.

Separation of III and IV by fractional distillation is precluded by the thermal sensitivity of the

(1) J. P. Ryan and P. R. O'Connor, THIS JOURNAL, **74**, 5866 (1952).

(2) H. Schmid and K. Schmid, *Helv. Chim. Acta*, **35**, 1879 (1952).

(3) O. Mumm, H. Hornhardt and J. Diederichsen, *Ber.*, **72**, 100 (1939); O. Mumm and J. Diederichsen, *ibid.*, **72**, 1523 (1939).

ethers. A preferential rearrangement of the α-ether III has proved feasible, however. When held at 120° for 18 hours III undergoes rearrangement with the appearance of a deep blue ferric chloride test; a sample of pure IV, under the same conditions, develops only a very faint ferric chloride test. Claisen alkali extraction of the preferentially rearranged α-ether preparation permits the isolation of relatively pure rearranged α-ether, V, b.p. 95–96° at 0.18 mm; $n^{20}D$ 1.5266. Hydrolysis of V yields an acid, VI, m.p. 102.5–103°, *not identical* with the corresponding acid from the rearranged γ-ether, m.p. 115–116°[3], mixed m.p. 72–94°. *Anal.* of VI, calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.33; Found, C, 70.68; H, 7.58. Ozonolysis of V produces formaldehyde in amounts corresponding to 84 ± 8% rearrangement product with a terminal methylene group. Infrared spectra likewise confirm the terminal methylene group of V.

The generally accepted idea concerning the course of the *para*-Claisen rearrangement, *i.e.*, that the rearrangement proceeds in a way that allows equilibration of the migrating allylic system,[4,5,6] appears, therefore, erroneous; instead the rearrangement proceeds without inversion and must involve partial bonding of a sort which maintains, or restores, the original structure of the migrating fragment. Our findings accord with the results of Ryan and O'Connor[1] and with observations made by Marvell on a comparable pair of ethers.[7]

This work received support from the Research Corporation and the American Academy of Arts and Sciences.

(4) D. S. Tarbell, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 3.

(5) G. W. Wheland, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 548.

(6) P. D. Bartlett, "Organic Chemistry, an Advanced Treatise," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 72.

(7) Dr. E. N. Marvell, private communication.

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RECEIVED APRIL 18, 1953

ISOLATION AND CHARACTERIZATION OF GLYCOPROTEINS FROM HUMAN PLASMA

Sir:

Human plasma contains several glycoproteins which are distinguished by their acid isoelectric points and their low molecular weights. Recently, the major component of these glycoproteins (the "acid glycoprotein," an α_1-globulin) has been described.[1,2]

The purpose of this note is to report the isolation from human plasma of a further group of such glycoproteins and to describe some of their properties.

The starting material for these studies was the supernatant solution of Fraction V obtained after precipitation of over 98% of the proteins from pooled normal human plasma, according to the low temperature–low salt–ethanol fractionation method.[3] The proteins (Fraction VI) in this supernatant solution were concentrated with the aid of zinc hydroxide and fractionated by a method described earlier.[2] Following removal of the proteins identical with those of Fraction V and of the acid glycoprotein from Fraction VI, the remaining protein fraction appeared essentially homogeneous in the ultracentrifuge ($S_{20,w}$ approximately 3) and by electrophoresis at *p*H 8.6. The electrophoretic mobility, $u = -4.2 \times 10^{-5}$ cm.^{2}/volt × sec., corresponded to an α_2-globulin.

In acetate buffer solutions of ionic strength 0.1, this α_2-protein fraction separated into three components. Taking advantage of the specific interaction with cations, these α_2-glycoproteins were fractionated from each other. Two proteins were rendered insoluble, at low ionic strength, *p*H 5.7 and at −5°, in a solution containing 19% ethanol by addition of barium acetate to give a final concentration of 0.02 *M*. Further addition of an equal amount of zinc acetate to the supernatant solution precipitated the third glycoprotein[4] which was isoelectric between *p*H 4.1 and 4.3. The optical density in a 1-cm. cuvette of a 1% solution ($E^{1\%}_{1\,cm.}$) of the latter protein was approximately 15 at 278 mμ. The "barium-insoluble" proteins were separated from each other under similar conditions. After exchange of the protein-bound barium ions for zinc ions, one of these plasma constituents was removed as insoluble zinc-lead-complex upon the addition of lead acetate. This "lead-insoluble" glycoprotein, showing an extinction coefficient of approximately 5 at 278 mμ, was denatured in acid phosphate buffer solutions as judged by the insolubility in 0.15 *M* NaCl solution. Its isoelectric point was found to be between *p*H 3.5 and 3.8. The protein which remained in solution and represented the major component of these α_2-glycoproteins, absorbed at 278 mμ with a coefficient ($E^{1\%}_{1\,cm.}$) of about 5. Its isoelectric point was near *p*H 4.

Further details of these investigations will be reported later.

The author wishes to thank Dr. J. A. McComb, director of the Division of Biologic Laboratories, Massachusetts Department of Health, for providing the starting material.

(1) H. E. Weimer, J. W. Mehl and R. J. Winzler, *J. Biol. Chem.*, **185**, 561 (1950).

(2) K. Schmid, THIS JOURNAL, **75**, 60 (1953).

(3) E. J. Cohn, L. E. Strong, W. L. Hughes, Jr., D. J. Mulford, J. N. Ashworth, M. Melin and H. L. Taylor, *ibid.*, **68**, 459 (1946).

(4) This was the only glycoprotein which was colored.

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THE REARRANGEMENT OF THE NEOPHYL RADICAL

Sir:

Although several examples of the migration of a phenyl group to an adjacent radical center have been published,[1] no evidence concerning the process by which this rearrangement takes place has been reported. It has now been found that, in contrast to similar ionic migrations which pro-

(1) (a) W. H. Urry and M. S. Kharasch, THIS JOURNAL, **66**, 1438 (1944); (b) S. Winstein and F. H. Seubold, Jr., *ibid.*, **69**, 2916 (1947); (c) W. H. Urry and N. Nicolaides, *ibid.*, **74**, 5163 (1952); (d) D. Y. Curtin and M. J. Hurwitz, *ibid.*, **74**, 5381 (1952).