Further elution of the column with methanol gave 65 mg. of yellow gum which was not investigated further.

In another experiment, in which the temperature was allowed to rise to 50°, a white solid was isolated in approximately 35% yield. This is probably 1-keto-*cis*-5,6,7,8,9,10-hexahydro[4.4]paracyclophane, arising from oxidation of the benzyl position. One crystallization from methanol gave needles, m.p. 73.5–74.5°; $\lambda_{min.}$ 225 mμ (ε, 2,100), $\lambda_{max.}$ 253 mμ (ε, 12,100), $\lambda_{shoulder}$ 305 mμ (ε, 300).[14]

Anal. Calcd. for $C_{20}H_{28}O$: C, 84.45; H, 9.92. Found: C, 84.25; H, 9.74.

16-Amino-*cis*-5,6,7,8,9,10-hexahydro[4.4]paracyclophane.—A solution of nitro compound VIII (0.304 g., 0.000965 mole) in 95% ethanol (20 ml.) was shaken in hydrogen in the presence of 50 mg. of platinum oxide until absorption of hydrogen ceased (73.7 ml. at 22° (748 mm.), 103%). The catalyst and solvent were removed, the residue was dissolved in ether, and the solution was washed with water and dried. Removal of the ether gave 274 mg. (99%) of the amine, b.p. 200° (bath temp.) (0.1 mm.).

Anal. Calcd. for $C_{20}H_{31}N$: C, 84.15; H, 10.95; N, 4.91. Found: C, 84.36; H, 10.97; N, 4.98.

16-Acetamido-*cis*-5,6,7,8,9,10[4.4]paracyclophane (X).—The above amine (175 mg.) was heated under reflux for 25 minutes with 1 ml. of acetic anhydride, and the mixture was diluted with water. The resulting soapy solid was taken up in ethanol water (3:1) and filtered to give 141 mg. (70%) of crude amide, m.p. 184–186°. One crystallization from ethanol gave 119 mg. (needles) of X, m.p. 186–187°; $\lambda_{shoulder}$ 234 mμ (ε 7,350), $\lambda_{shoulder}$ 273 mμ (ε 885).

Anal. Calcd. for $C_{22}H_{33}ON$: C, 80.68; H, 10.16. Found: C, 80.84; H, 10.02.

6-Acetamido[4.4]paracyclophane (VII).—Acetamido compound X (172 mg.) was dehydrogenated with 35 mg. of 10% palladium-on-charcoal by heating at 280–300° until the evolution of hydrogen ceased. During this operation, a large amount of solid sublimed into the neck of the flask, thus making it impossible to ensure complete dehydrogenation. The product was then taken up in ethyl acetate and filtered. Removal of the ethyl acetate gave a solid which was crystallized once from aqueous methanol and once from cyclohexane to yield 73 mg. (43%) of the aromatic amide VII, m.p. 172–174°. The compound sublimed at 138° (0.05 mm.) to yield prisms, m.p. 173–174.5°; $\lambda_{shoulder}$ 233 mμ (ε, 5,660), $\lambda_{inflection}$ 273 mμ (ε, 997), $\lambda_{max.}$ 274 mμ (ε, 1,050).

(14) Compare the spectrum of this compound with that of 1-keto-7,8,9,10,11,12-hexahydro[6.6]paracyclophane (ref. 2.)

Anal. Calcd. for $C_{22}H_{27}ON$: C, 82.20; H, 8.47; N, 4.36. Found: C, 82.09; H, 8.31; N, 4.50.

6-Carboxyamido[4.4]paracyclophane.—A mixture of 308 mg. (0.001 mole) of acid VI and 1.5 ml. of thionyl chloride was heated on the steam-bath for 30 minutes, the excess thionyl chloride then being removed under vacuum. The residue, on treatment with cold concentrated ammonia, gave a viscous oil which slowly solidified. One crystallization of the compound from aqueous ethanol and recrystallization from cyclohexane gave 177 mg. (57.5%) of the amide of acid VI, m.p. 180–182°.

Anal. Calcd. for $C_{21}H_{25}ON$: N, 4.56. Found: N, 4.34.

Rearrangement of the Preceding Amide to 6-Acetamido-[4.4]paracyclophane (VII).—To a solution prepared from 14 mg. (0.6 mmole) of sodium and 0.4 ml. of methanol was added 92 mg. (0.3 mmole) of the preceding amide, followed by 48 mg. (0.3 mmole) of bromine, the resulting mixture being heated on the steam-bath for 10 minutes. The solvent was then removed under reduced pressure, and the residue was taken up in ether. The solution was washed with water, dried and evaporated to give an oil which partially solidified. This material was heated under reflux for 6 hours with 0.12 g. of potassium hydroxide in aqueous methanol in order to hydrolyze any unreacted starting material. The basic solution was diluted with water and extracted with ether. Removal of the ether gave an oil which was heated under reflux for 1 hour with 0.3 ml. of acetic anhydride and 0.4 ml. of pyridine. This solution was diluted with water and extracted with ether. The ethereal extract was washed with dilute acid and dilute base, dried, and evaporated. The residual solid on sublimation (140° (0.06 mm.)) gave 35 mg. (36%) of amide VII, m.p. 172–174°, undepressed upon admixture with the authentic specimen described above.

Schmidt Reaction with 6-Acetyl[4.4]paracyclophane (III).—Ketone III (0.708 g., 2.31 mmoles) was added to 7 g. of trichloroacetic acid and 0.68 g. of concentrated sulfuric acid, the resulting mixture being maintained at approximately 60° while 0.265 g. (4.1 mmoles) of sodium azide was added over a period of 25 minutes. After 90 minutes, the mixture was cooled, diluted with water and extracted with ether. The ethereal solution was washed with water and dilute base and dried. Removal of the ether gave 618 mg. of solid which was crystallized from 12 ml. of cyclohexane–benzene (3:1) to yield 513 mg. (69%) of the amide VII, m.p. 170–171.5°, undepressed upon admixture with the authentic specimen described above.

LOS ANGELES, CALIFORNIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF BIRKBECK COLLEGE]

The Structure of the Caryophyllene-Maleic Anhydride "Adduct"

BY ALEX NICKON[1]

RECEIVED AUGUST 9, 1954

The compound formed on combination of caryophyllene and maleic anhydride is shown to have the structure XI. Formulas for derived rearrangement products are proposed.

In 1935 Ruzicka and Zimmermann[2] reported that treatment of caryophyllene ($C_{15}H_{24}$) with maleic anhydride in hot benzene solution produced a crystalline (m.p. 98°), 1:1 addition product. Even though the constitution of caryophyllene itself was unknown at that time, their findings became of considerable interest when subsequent work revealed that the two double bonds in the original hydrocarbon were not conjugated.[3] Furthermore, the catalytic hydrogenation experiments of Ruzicka, Plattner and Balla[4] later revealed that the maleic anhydride addition product still retained two double bonds, and so indicated that this "adduct" was not one of the usual Diels–Alder type.

The nature of this unusual reaction became more understandable through an important fundamental discovery by Alder, Pascher and Schmitz in 1943.[5] These investigators found that many mono-unsaturated olefins combined with maleic anhydride at elevated temperatures (*ca.* 200°) to form products in which the anhydride residue was attached to the saturated carbon of an allylic system. The adjoin-

(1) National Research Council of Canada Postdoctorate Fellow; present address, National Research Council of Canada, Ottawa 2, Ontario.

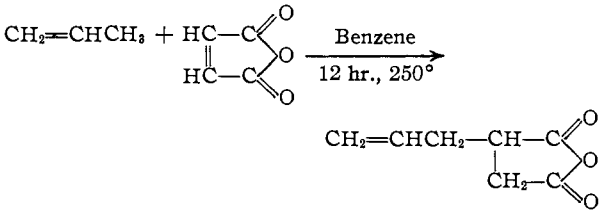
(2) L. Ruzicka and W. Zimmermann, *Helv. Chim. Acta*, **18**, 219 (1935).

(3) (a) N. F. Goodway and T. F. West, *J. Chem. Soc.*, 1853 (1939); (b) Y. R. Naves and E. Perrottet, *Helv. Chim. Acta*, **24**, 789 (1941).

(4) L. Ruzicka, P. A. Plattner and G. Balla, *ibid.*, **24**, 1219 (1941).

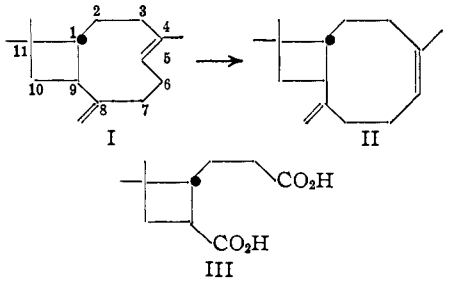
(5) K. Alder, F. Pascher and A. Schmitz, *Ber.*, **76B**, 27 (1943).

ing scheme illustrates the reaction for the case of propylene. That the caryophyllene–maleic anhy-



dride "adduct" is derived by some such allylic process has since been generally accepted,[6,7] although no structures have been proposed.[8]

The objective of this paper is to adduce evidence for the constitution of the "adduct" in the light of the recently established[9] structure for caryophyllene (I[10]). An important feature of the unique skeleton in the sesquiterpene is the presence of a *trans*-oriented, endocyclic double bond. That this ar-



rangement imparts steric strain to the system is clear from the observation that caryophyllene can be isomerized with nitrous acid to isocaryophyllene (II), which has the same endocyclic link in the more stable, *cis* configuration.[9] The relevance of these points is considered in the sequel.

Degradation of the "adduct" by oxidation has been attempted by Ruzicka, Plattner and Werner.[11] With the use of ozone followed by potassium permanganate at room temperature they obtained homocaryophyllenic acid, a substance now known to possess structure III.[12] Two conclusions concerning the "adduct" can be drawn from these results. Firstly, the four-membered ring remains intact; secondly, there is no unsaturation at the centers C-9, C-1, C-2 or C-3 (see I for numbering system).

Of the several transformations recorded by Ruzicka, Plattner and Balla[4] for the "adduct," the ready conversion to a saturated, tricyclic[13] lactonic acid (m.p. 208°) appears germane. This hydration–cyclization was originally conducted in aqueous acid or boiling water, but proceeds better in hot, dioxane–hydrochloric acid. Saponification of this substance gave the corresponding hydroxy–dibasic acid, from which the original lactonic acid was regenerated when melted.[4]

We believed that useful structural information could be obtained through additional investigation of such cyclization products, particularly in view of the wealth of knowledge on the rearrangements of caryophyllenic systems recently made available by the researches of Barton and his colleagues.[9,14]

The infrared absorption curve (CS_2) of the lactonic acid (m.p. 208°) exhibits bands at 1712 and 1734 cm.$^{-1}$. The former peak is attributed to the carboxyl group, and the latter one to the ester linkage of a δ-lactone system.[15] The spectrum of the derived methyl ester (CCl_4) shows only one carbonyl band in the infrared (1742 cm.$^{-1}$), of double the usual intensity.

A substance with probably the same tricyclic skeleton is obtained by the action of dry hydrogen chloride on a cold, chloroform solution of the "adduct." Under these conditions one molecule of hydrogen chloride is incorporated to yield a compound (see partial structure VI) that is saturated to tetranitromethane and that has the anhydride ring intact. This finding confirms the recent report that a monohydrochloride was formed on treatment of the "adduct" with ethereal, dry hydrogen chloride, but contradicts the suggestion that this hydrochloride has resulted from simple addition to one of the olefinic linkages.[16] The chloro compound on acid hydrolysis is transformed to the same δ-lactonic acid (VII) described above.

That the anhydride residue and the hydroxyl group involved in lactonization are attached to a pair of contiguous carbon atoms is clear from the following observations. Under the influence of N-bromosuccinimide in aqueous dioxane the "adduct" takes on the elements of HOBr and yields two isomeric products. One of these is a bromoalcohol with the anhydride ring intact (IV). The other substance is a bromo-γ-lactonic acid (V) as evidenced by the infrared absorption of the derived methyl ester (1740 cm.$^{-1}$ $COOCH_3$; 1775 cm.$^{-1}$ γ-lactone). Both products are saturated and therefore tricyclic. On very mild, acid-catalyzed hydration the bromoalcohol IV isomerizes to the bromo-γ-lactonic acid (V) in 50% yield,[17] whereas on stronger acid hydrolysis both substances IV and V generate an isomeric bromo-δ-lactonic acid (infrared spectra of methyl ester in CCl_4, 1744 cm.$^{-1}$ double normal intensity), represented by the part-structure VIII. Removal of the bromine from VIII with zinc dust or by catalytic hydrogenolysis proceeds smoothly and yields the original δ-lactonic acid (VII) obtained by Ruzicka, Plattner and Balla.

The simplest explanation of these facts is that all the tricyclic compounds formulated partially in the accompanying reaction scheme possess an

(6) P. A. Plattner and L. Werner, *Helv. Chim. Acta*, **27**, 1010 (1944).

(7) J. L. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, The University Press, Cambridge, Eng., 1952, p. 69.

(8) For a discussion see, *Ann. Rep.*, **44**, 157 (1947).

(9) For pertinent data and leading references, see A. Aebi, D. H. R. Barton and A. S. Lindsey, *J. Chem. Soc.*, 3124 (1953). A review of the recent developments in caryophyllene chemistry is also available [A. Nickon, *Perfumery Essent. Oil Record*, **45**, 149 (1954)].

(10) A heavy dot represents the projection of a hydrogen atom above the plane of the molecule; an open circle denotes a center of unknown stereochemistry.

(11) L. Ruzicka, P. A. Plattner and L. Werner, *Helv. Chim. Acta*, **26**, 966 (1943).

(12) T. L. Dawson and G. R. Ramage, *J. Chem. Soc.*, 3382 (1951).

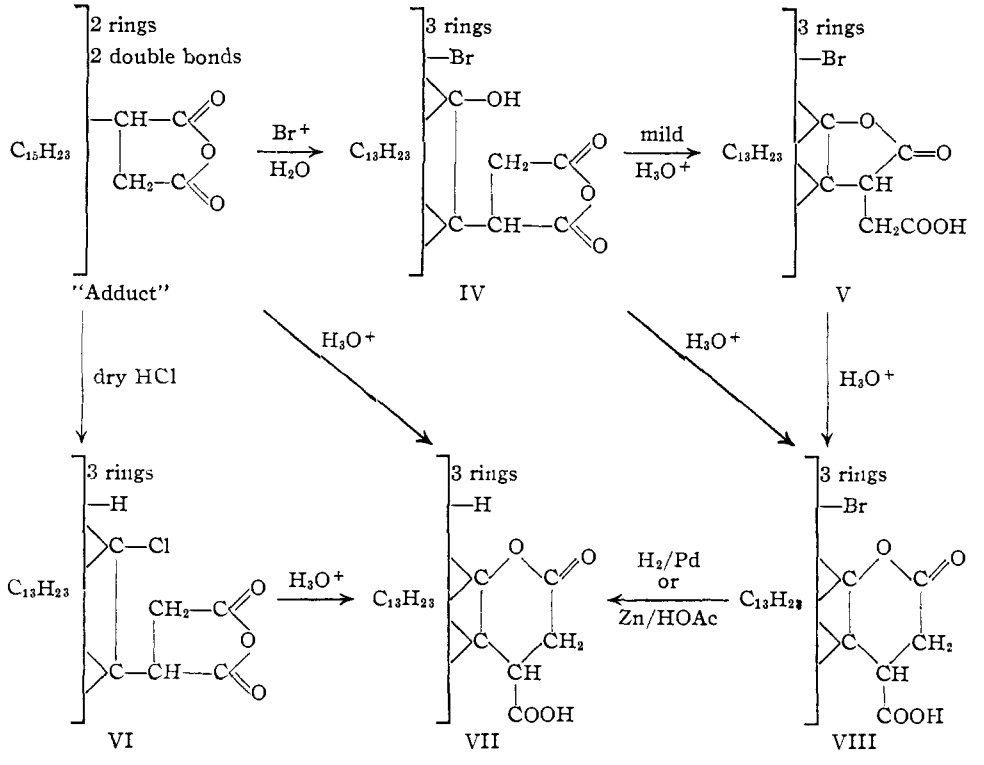
(13) This terminology refers to carbocyclic rings only and does not include lactone or anhydride systems.

(14) (a) D. H. R. Barton, T. Bruun and A. S. Lindsey, *J. Chem. Soc.*, 2210(1952); (b) A. Aebi, D. H. R. Barton, A. Burgstahler and A. S. Lindsey, *ibid.*, in press.

(15) Although the infrared evidence does not exclude lactonic rings of size greater than six atoms, their presence is substantially precluded by the ease of reclosure of the lactone system.

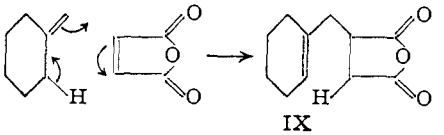
(16) G. S. Krishna Rao, S. Dev and P. C. Guha, *J. Indian Chem. Soc.*, **29**, 598 (1952); *C. A.*, **47**, 8697 (1953).

(17) The remainder is recovered starting material.



identical skeletal framework, and that the γ- and δ-lactone systems are derived from the two different carboxyl groups that comprise the anhydride ring. Furthermore, the migration of double bonds prior to cyclization is considered improbable under the essentially neutral conditions of the brominative cyclization, and so preliminary double bond shifts do not appear to play a part in the acid-induced rearrangements. Before attempting to formulate the tricyclic compounds in greater detail, we direct attention to experimental evidence that establishes the constitution of the "adduct"; and in this connection a closer consideration of the course of the maleic anhydride–olefin reaction is necessary.

The more recent researches by Alder and his associates have disclosed that an allylic shift of the double bond with consequent attachment of the maleic anhydride residue to the saturated end of the allylic system is a normal feature of this reaction.[18] In actual fact, combination of the two reactants without an attendant double bond migration is substantially without precedent.[19] This structural change is also apparent from the work of other groups[20] and has been emphasized by Arnold and Dowdell. To account for the invariable ethylenic shift, the last mentioned workers proposed that the two molecular species are oriented to form a quasi, six-membered ring, with subsequent electronic reallocations[21]; the later papers of Alder's school also carried a similar suggestion.[18b] The cyclic mechanism is illustrated for the case of methylenecyclohexane, which yielded IX on treatment with maleic anhydride.[21] The nature and timing of the electron movements are not yet established,



IX

however, certain published[18b,22] observations suggest that the formation of these 1:1 addition products does not proceed by a stepwise, free radical process.[23] A detailed mechanistic study of the reaction has been initiated.[24]

From the foregoing considerations we conclude that, irrespective of the precise mechanism invoked, an allylic shift of a double bond is to be expected when caryophyllene and maleic anhydride unite. The further important fact is now emphasized that the present "adduct" is formed in boiling benzene solution (80°), whereas the same reaction with all other olefins has required heat treatment (usually in sealed tubes) at temperatures in the range 180–250°. This marked reactivity difference indicates that the caryophyllenic double bond involved in "adduct" formation is the strained, endocyclic one (see I); the greater driving force in this case must surely be due to the release in steric tension when the ethylenic linkage shifts. Many analogies are available for the accelerated reactivity of strained olefinic bonds in rings of com-

(18) K. Alder, *et al.*, (a) *Ann.*, **565**, 57 (1949); (b) *ibid.*, **565**, 73 (1949); (c) *ibid.*, **565**, 99, 118, 126 (1949); (d) *Ber.*, **85**, 556 (1952); *Ann.*, **576**, 182 (1952).

(19) This statement appears to be true for all those definitive cases of aliphatic olefins where adequate characterization of starting materials and products is considered to have been carried out.

(20) J. Ross, A. I. Gebhart and J. F. Gerecht, THIS JOURNAL, **68**, 1373 (1946).

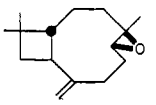
(21) R. T. Arnold and J. F. Dowdell, *ibid.*, **70**, 2590 (1948).

(22) R. T. Arnold, R. W. Amidon and R. M. Dodson, *ibid.*, **72**, 2871 (1950).

(23) Invariably, the normal addition product is accompanied by appreciable amounts of resinous or polymeric material, which may arise through radical propagation.

(24) C. S. Rondestvedt, Jr., and A. H. Filbey, *J. Org. Chem.*, **19**, 588 (1954).

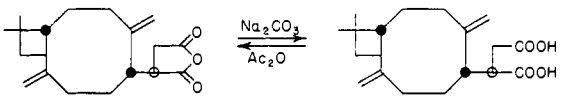
parable size.[9,25] This feature of the reaction also permits the conclusion that the endocyclic double bond does not isomerize or shift prior to its combination with maleic anhydride.[26]



X

The following experiments support these contentions and establish the exact locations of the two olefinic links. On Kuhn-Roth oxidation the "adduct" yields 0.16 mole of acetic acid, whereas caryophyllene under identical conditions gives 1.11 moles. Precautionary measures were taken to prevent bond migrations or cyclizations under the acid conditions of the Kuhn-Roth method.[27] The loss of the C-methyl in the "adduct" gives the first indication that the ring double bond has moved to the exocyclic position. That the one exocyclic methylene unit originally present in caryophyllene is retained in the "adduct" is proven by ozonolysis experiments. Thus, the "adduct" yields twice as much formaldehyde (64%, isolated as the dimedone derivative) as does the model compound caryophyllene oxide (X, 30% CH_2O), which is known to have the structure shown.[9] From these results and from the mechanistic considerations previously outlined, the structure of the "adduct" must be represented by XI; a cyclic mechanism for its genesis is readily envisaged.

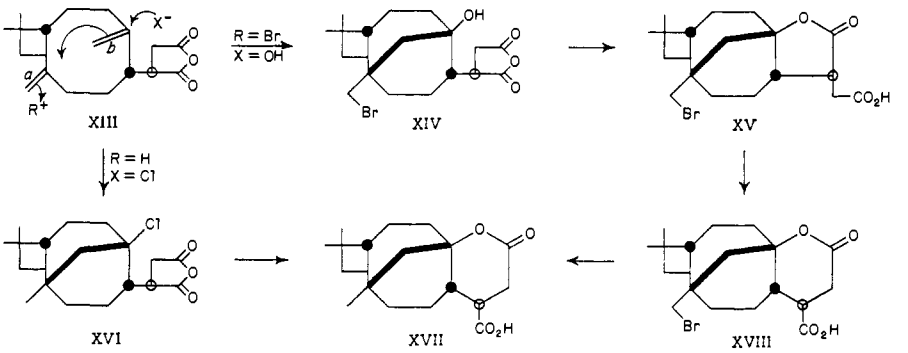
In agreement with this formula, the "adduct" exhibits strong infrared absorption at 886 cm.$^{-1}$ ($\rangle C{=}CH_2$), but a quantitative measure of the intensity is not possible owing to interfering bands. A compound well suited to this purpose proved to be the corresponding dicarboxylic acid XII, which is obtained by mild alkaline hydrolysis. When this dibasic acid is refluxed in acetic anhydride the "adduct" (XI) is regenerated; a reassurance that no other changes are produced during the alkaline saponification is thus provided. Quantitative inspection of the 886 cm.$^{-1}$ infrared band (in CS_2) conclusively showed that the "adduct" dicarboxylic acid (XII) contains two exocyclic methylene units. Here again caryophyllene oxide (X) was used as a comparison standard.



XI XII

Two new asymmetric centers are created on "adduct" formation and, although there is not sufficient evidence to permit rigorous stereochemical assignments, a reasonable prediction concerning the arrangement at C-5 can be made. On the assumption that the maleic anhydride molecule approaches the caryophyllene nucleus from the same side as do other reagents (*e.g.*, peracids, hydrogen peroxide),[9,14b] the new group at C-5 will project below the molecular plane as is depicted in XI.[28]

The formation of the tricyclic products described earlier in the text can now be readily conciliated with the structure established here for the "adduct." The isolation of the γ and δ-lactone systems demonstrates that the cyclization process is initiated by attack of the electrophilic agent (H^+ or Br^+) at linkage "a" (see XIII), and terminated by attachment of the nucleophilic species (*e.g.*, OH^- or Cl^-) at linkage "b". If we exclude non-Markownikoff attack at "a," the results are most simply interpreted on the basis of the cyclization shown in XIII. The compounds delineated earlier by partial formulas IV, V, VI, VII and VIII are now represented in their entirety by XIV, XV, XVI, XVII and XVIII, respectively.[29] It should be emphasized that the facts concerning these tricyclic compounds are not explicable on the basis of either of the two types of acid-catalyzed cyclizations that caryophyllene is known to undergo.[9] The present cases therefore appear to represent a novel cyclization in this series, although interestingly enough the carbon skeleton is very similar to that in caryolane-1-ol (XIX),[30] whose manner of genesis from caryophyllene[9] is illustrated.



XIII XIV XV XVI XVII XVIII

(25) (a) V. Prelog, K. Schenker and W. Küng, *Helv. Chim. Acta*, **36**, 471 (1953); (b) V. Prelog, K. Schenker and H. H. Günthard, *ibid.*, **35**, 1602 (1952); (c) K. Ziegler and H. Wilms, *Ann.*, **567**, 1 (1950); (d) A. T. Blomquist, L. H. Liu and J. C. Bohrer, THIS JOURNAL, **74**, 3643 (1952).

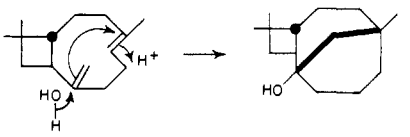
(26) Additional support of this conclusion is as follows. The heat treatment alone would not alter the double bond arrangement since caryophyllene is stable to distillation. Any isomerization by free radicals in the reaction mixture should produce isocaryophyllene (II[9]), which compound is known to afford only polymeric material and no crystalline adduct under identical maleic anhydride treatment (observation of D. H. R. Barton and A. Aebi; see also ref. 15).

(27) The precautionary technique consists in prior treatment of the unsaturated compound with ozone, and direct dichromate oxidation of the ozonide residue after the solvent is removed. In addition to the resulting immobilization of ethylenic bonds, the preliminary introduction of oxygen by ozone seems to render the compound more readily soluble in the dichromate mixture and to promote smoother oxidation. As in the present instance, the technique appears useful in those cases where acid-induced isomerizations or rearrangements would alter the number, or affect the environment, of the C-methyl groups present. Comparative C-methyl values on the adduct and on caryophyllene determined in the normal manner without these precautions are noted in the experimental section.

(28) Approach to the caryophyllene molecule is envisaged (in a diagrammatic sense) as occurring from above the plane of the molecule. The final projection of the new grouping (at C-5) below the plane is a consequence of the *trans* arrangement of the original double bond.

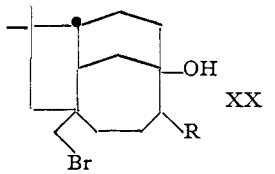
(29) An alternate formulation of these tricyclic compounds with the newly created methylene bridge projecting below the plane of the molecule is sterically less favorable, but is not excluded.

(30) This compound is known in the literature as β-carophyllene alcohol. For the newer nomenclature see ref. 14b.



XIX

Several other tricyclic systems (for *e.g.*, those derived by intervening expansion of the four-membered ring) are formally possible and, even though most of these may be reasonably precluded on geometric grounds or from mechanistic considerations, a separate consideration of each case would be necessary. In the absence of definitive experimental evidence however, an analysis of this type is unwarranted, and so systems such as that represented by XX (R = anhydride unit) are not emphatically rejected.



XX

Acknowledgment.—The author is deeply indebted to Professor D. H. R. Barton, F.R.S., for his many courtesies and helpful suggestions during the course of this work.

Experimental[31]

Caryophyllene (I).—Reigate brand caryophyllene was distilled at 14 mm., and those fractions boiling between 125 and 128.5° were employed in the present work; α_D −9 to −11° (*c* 3.0).

Caryophyllene–Maleic Anhydride "Adduct" (XI).—With some sacrifice in yield, the "adduct" was expediently prepared as follows. Caryophyllene (100 g.), maleic anhydride (200 g., freshly distilled) and dry benzene (230 cc.) were combined, and the solution gently refluxed for 22 hr. The benzene was removed in vacuum on the steam-bath, and 2 liters of carbon tetrachloride was added to precipitate a large portion of the unchanged maleic anhydride. The filtered solution was evaporated *in vacuo*, and the residual oil taken up in benzene. Four extractions with warm (60°) water (total volume 1 l.), followed by vacuum removal of the benzene, left a viscous oil. Petroleum ether (10 cc., b.p. 40–60°) was added to the cooled oil, which was then seeded and allowed to stand at 0° overnight. The solid mass that formed was fluidized with 10 cc. more of cold petroleum ether and collected with suction. The solid was washed sparingly with more cold solvent and then crystallized once from 200 cc. of petroleum ether (b.p. 60–80°); 28 g. of soft needles, m.p. 93–94°, ν^{CS_2} 1890, 1790 (anhydride), 886 ($\diagdown$C=CH$_2$) cm.$^{-1}$. The compound is unsaturated to tetranitromethane.

The reported[2] constants for the pure "adduct" are: m.p. 98°, α_D +28° (alc.), +49° (chf). According to a published observation, the slow decomposition of the "adduct" that occurs on long storage can be prevented by preservation in an evacuated tube that has previously been thoroughly cleaned with chromic acid.[16]

Conversion to the Tricyclic δ-Lactonic Acid,[4] XVII.—The "adduct" (XI) was refluxed 30 min. in a mixture of equal volumes of dioxane and 2 *N* hydrochloric acid. Dilution with water and extraction with ether was followed by extraction of the ether layer with 5% sodium carbonate solution. The aqueous alkaline layer was acidified with hydrochloric acid, and the precipitate taken up in ether. This solution was washed with water, dried with sodium sulfate and evaporated. The residue, after crystallization from chloroform–petroleum ether (b.p. 60–80°), had m.p. 204–206° (yield 80%) and was saturated to tetranitromethane; α_D −27° (*c* 1.12), ν^{CS_2} 1712 (COOH), 1734 (δ-lactone) cm.$^{-1}$.

The derived methyl ester,[4] prepared by treatment of XVII with ethereal diazomethane, was obtained as long, slender needles from aqueous ethanol, m.p. 157–158°; α_D −33° (*c* 1.12), ν^{CCl_4} 1742 (ester, double intensity) cm.$^{-1}$.

Conversion to the Tricyclic Hydrochloride XVI.[16,32]—The "adduct" (5.0 g.) in 150 cc. of ethanol-free, dry chloroform was cooled to −10°, and dry hydrogen chloride was bubbled through the solution for 30 min. The flask was stoppered and let stand at 0° overnight. Vacuum evaporation left the crystalline hydrochloride XVI, which was obtained from petroleum ether (b.p. 80–100°) in mica-like plates, m.p. 148–149.5° dec.; 4.6 g. This compound is saturated to tetranitromethane and has α_D −20° (*c* 1.05); ν^{CCl_4} 1870, 1790 (anhydride) cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{27}O_3Cl$ (338.87): C, 67.34; H, 8.03; Cl, 10.46. Found: C, 67.20; H, 8.08; Cl, 10.85.

Conversion of the Hydrochloride XVI to the δ-Lactonic Acid (XVII).—A batch of XVI (m.p. 146–147°, 0.10 g.) in 3 cc. of dioxane and 1.5 cc. of 12% hydrochloric acid was digested on the steam-bath for 1 hr. The cooled solution was poured into excess water, extracted with ether, and the ether layer in turn extracted with 5% sodium carbonate solution. Acidification of the alkaline layer with hydrochloric acid, followed by extraction with ether and the usual washing techniques, provided crude XVII (0.094 g.), which had, after crystallization from chloroform–petroleum ether, m.p. 205–206° (0.066 g.); α_D −29° (*c* 1.11). A mixed m.p. with authentic XVII (m.p. 206–208°) was undepressed.

Action of N-Bromosuccinimide on the "Adduct" (XI).—The "adduct" (0.500 g., m.p. 94–98°) in 4 cc. of pure dioxane containing 1 cc. of water was treated with N-bromosuccinimide (0.300 g.) at room temperature. When the solution gave a negative potassium iodide–starch test (usually in about 1 hr.) it was poured into water, and the mixture extracted with ether. The acidic and neutral fractions were separated by rapid extraction with 5% sodium carbonate solution. The ethereal neutral fraction was washed with water and brine, then dried with sodium sulfate and evaporated *in vacuo*. The solid bromo-alcohol (XIV) was crystallized from chloroform–petroleum ether (b.p. 60–80°) as slender needles, m.p. 199–201° dec.; 0.118 g. Further purification from the same solvent pair provided the analytical sample; m.p. 209–210° (slightly dependent on rate of heating), α_D +17° (*c* 1.02), ν^{CS_2} 1870, 1784, ν^{Chf} 1863, 1778 (anhydride), 3620 (OH) cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{27}O_4Br$ (399.33): C, 57.14; H, 6.82; Br, 20.01. Found: C, 56.77; H, 6.72; Br, 20.47.

The alkaline aqueous layer (from above) on acidification with hydrochloric acid and extraction with ether yielded, after similar rectification of the ether layer, 0.368 g. of the γ-lactonic acid (XV), m.p. 176–182° dec. After one crystallization from aqueous ethanol, the compound melted with decomposition at 193–194° (0.27 g.) and appeared to be a mixture of two crystalline forms, which could be obtained individually if desired. Thus, when a chloroform solution of the compound was evaporated to dryness, a crystalline modification (m.p. 214–215°, dec) was left, whereas sometimes by slow crystallization from aqueous ethanol the compound appeared as slender needles, m.p. 187–188° dec. Compounded mixtures of the two forms melted in the region 193–205°, and either modification was convertible to the other by the addition of appropriate seeds to an aqueous ethanol solution. For analysis, normal crystallization from ethanol–water provided XV as needles, m.p. 193–194° dec.; α_D +25° (*c* 0.90), ν^{nujol} 1758 (γ-lactone), 1705 (COOH) cm.$^{-1}$, saturated to tetranitromethane.

Anal. Calcd. for $C_{19}H_{27}O_4Br$ (399.33): C, 57.14; H, 6.82; Br, 20.01. Found: C, 56.83; H, 6.86; Br, 19.94.

The methyl ester was prepared by treatment of an ethereal solution of XV with diazomethane at room temperature. Evaporation of the solvent left an oil, which was dis-

(31) All temperatures are uncorrected. Optical rotations were determined in chloroform solution with a sodium lamp, light source. Tetranitromethane tests were taken in chloroform solution. Infrared spectra were kindly determined by Dr. J. E. Page and his staff (of Messrs. Glaxo Laboratories Ltd.), with a Perkin–Elmer double beam spectrophotometer. Elemental analyses were performed by Messrs. Weiler and Strauss (Oxford).

(32) The collaboration of A. S. Lindsey in this experiment is gratefully acknowledged.

solved in 6:4 petroleum ether (b.p. 40–60°)–benzene and chromatographed on 12 g. of neutral alumina. Elution with solvents ranging from petroleum ether–benzene (1:1) to benzene–ether (9:1) provided oily fractions, some of which partly crystallized after a few days. Seeding soon induced crystallization in the recalcitrant fractions, and a little aqueous methanol was used to wash away some oily material that still adhered to the solids. Combination of the solid fractions and rechromatography on neutral alumina yielded fractions (m.p. 110–115°) on elution with petroleum ether–benzene. Crystallization from aqueous methanol (seeding) gave transparent rhombs, m.p., 121.5–122.5°; α_D +27° (*c* 0.88), ν^{CS_2} 1775 (γ-lactone), 1740 (COOMe) cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{29}O_4Br$ (413.35): C, 58.11; H, 7.07; Br, 19.33. Found: C, 58.27; H, 6.90; Br, 19.52.

Isomerization of XIV to the Bromo-δ-lactonic Acid (XVIII).—A 500-mg. batch of crude bromo-alcohol (XIV, m.p. 197–198°) in 7 cc. of dioxane containing 5 cc. of 12% hydrochloric acid was digested on the steam-bath for 15 min., then poured into water when cool. The mixture was extracted with ether, and the acidic fraction was shaken out with 5% sodium carbonate solution. Acidification of the alkaline layer with hydrochloric acid, and extraction of the resulting milky mixture with ether afforded a crude, white solid on normal work-up. One crystallization from chloroform–petroleum ether (b.p. 60–80°) gave XVIII as needles, m.p. 180–183° (0.30 g.). Further crystallization yielded clusters of fluffy needles (saturated to tetranitromethane), m.p. 188.5–189°; α_D −18° (*c* 1.16), ν^{CHf} 1720 (carbonyl, double intensity) cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{27}O_4Br$ (399.33): C, 57.14; H, 6.82; Br, 20.01. Found: C, 57.29; H, 6.58; Br, 20.07.

The methyl ester of XVIII was conveniently prepared with ethereal diazomethane. Purification from petroleum ether (b.p. 80–100°) gave fluffy needles, m.p. 164–165°; α_D −18° (*c* 1.10), ν^{CCl_4} 1744 (ester, double intensity) cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{29}O_4Br$ (413.35): C, 58.11; H, 7.07; Br, 19.33. Found: C, 58.45; H, 7.45; Br, 19.32.

Hydrogenolysis of XVIII to the δ-Lactonic Acid (XVII).

(a) Catalytic.—To 0.10 g. of the bromo-δ-lactonic acid (XVIII) (m.p. 180–182°) in 15 cc. of anhydrous ethanol containing 0.2 cc. of diethylamine was added 0.10 g. of 10% palladium–calcium carbonate catalyst, and the mixture was reduced overnight with hydrogen at one atmosphere. Normal work-up procedure gave 0.077 g. of crude XVII, m.p. 185–190° dec. Purification from chloroform–petroleum ether (b.p. 60–80°) raised the m.p. to 202–204°; α_D −23° (*c* 0.36).

(b) Zinc Dust.—The bromo-δ-lactonic acid (XVIII) (0.10 g., m.p. 179–181°) in 2 cc. of glacial acetic acid was refluxed with 0.70 g. of zinc dust for 1.5 hr. The mixture was filtered, and the zinc was washed with acetic acid, then methanol. Vacuum evaporation of the combined filtrates provided a residue, which was taken up in ether and water. The ether layer was washed with brine, dried with sodium sulfate and evaporated. Crystallization of the residual solid from chloroform–petroleum ether (b.p. 60–80°) gave XVII (0.046 g.) with m.p. 200–203°, raised to 203–206° by one more crystallization; α_D −27° (*c* 1.34).

The melting point of the material from (a) or (b) was undepressed when admixed with an authentic specimen of XVII; m.p. 204–206°, α_D −27° (*c* 1.12).

Isomerization of the Bromo-alcohol XIV to the Bromo-γ-lactonic Acid (XV).—To the bromo-alcohol XIV (m.p. 199–201° dec., 30 mg.) in 1 cc. of dioxane and 0.25 cc. of water was introduced 0.1 cc. of an acid solution, prepared by addition of 0.1 cc. of concentrated hydrochloric acid to 5 cc. of dioxane. The reaction solution was kept at 35° for 1.5 hr. Dilution with water was followed by ether extraction and separation into neutral and acidic components by moderately rapid extraction with 5% sodium carbonate solution. The usual work-up of the ethereal neutral layer provided 14 mg. of starting material; m.p. 205–207° dec., undepressed on admixture with a pure specimen of XIV (m.p. 208°).

Acidification of the alkaline layer precipitated material, which was extracted with ether and rectified in the normal manner to leave 15 mg. of crude XV; m.p. 200–201° dec. after crystallization from aqueous ethanol. The m.p. was not lowered on admixture with a genuine sample of bromo-γ-lactonic acid having m.p. 200–201° dec.

Moderate variations in this mild isomerization procedure in all cases afforded comparable mixtures of starting material and bromo-γ-lactonic acid. More vigorous acid treatment gave the bromo-δ-lactonic acid XVIII (see below).

Isomerization of the Bromo-γ-lactonic Acid (XV) to the Bromo-δ-lactonic Acid (XVIII).—A solution of XV (90 mg., m.p. 185–187°) in 2.5 cc. of pure dioxane and 1 cc. of 12% hydrochloric acid was warmed on the steam-bath for 20 min., then was poured into water, and the mixture was extracted with ether. Washings with water and brine, followed by sodium sulfate drying, and evaporation, left a solid residue (0.087 g.), m.p. 167–169°. Two crystallizations from chloroform–petroleum ether (b.p. 60–80°) gave fluffy needles (m.p. 185.5–186.5°, α_D −14° (*c* 0.60)), which did not depress the m.p. of genuine bromo-δ-lactonic acid (XVII).

Saponification of the "Adduct" to the Dicarboxylic Acid XII.—The dicarboxylic acid XII has been reported by Ruzicka, Plattner and Balla,[4] who did not succeed in obtaining it crystalline. We had no difficulty in this regard with the use of the following procedure. A suspension of the "adduct" (2.0 g.) in 40 cc. of 2 *N* sodium carbonate solution was warmed on the steam-bath for 15 min., cooled in ice, and then diluted with 50 cc. of ice-cold water. To the cold solution, glacial acetic acid (5.0 cc.) was added dropwise with swirling. The white solid that separated was extracted with ether, the organic layer washed twice with water and once with brine, dried with sodium sulfate and evaporated *in vacuo* to a volume of 2–3 cc. Addition of 3–4 cc. of petroleum ether (b.p. 40–60°) gave a solution from which a mass of solid soon crystallized. The material was collected and washed with a small amount of petroleum ether; m.p. 155–160° (1.86 g.). Recrystallization from aqueous methanol afforded the dicarboxylic acid XII as transparent, irregular crystals, m.p. 164–165.5°; α_D, +63° (*c* 1.11), ν^{CS_2} 3200–3000 (bonded OH), 1714 (COOH), 886 ($>C=CH_2$) cm.$^{-1}$. The intensity of the 886 cm.$^{-1}$ band, calculated on a molecular basis, was twice that observed for caryophyllene oxide (X), which was prepared by hydrogen peroxide treatment of caryophyllene as reported.[33] An independent preparation[32] of the dicarboxylic acid XII gave the following constants: m.p. 161–162°, α_D +66 (*c* 2.22).

Anal. Calcd. for $C_{19}H_{28}O_4$ (320.42): C, 71.22; H, 8.81; equiv. wt., 160. Found: C, 71.60; H, 8.70; equiv. wt., 162.

The "adduct" (XI) was regenerated by reflux treatment of the dicarboxylic acid XII in acetic anhydride.

Isomerization of the Dicarboxylic Acid XII to the δ-Lactonic Acid (XVII).—When refluxed for 1.5 hr. in 3 cc. of acetic acid containing 1 g. of zinc dust and 0.030 g. of fused zinc chloride, the dicarboxylic acid XII (0.134 g., m.p. 159–161°) afforded, on normal work-up, 0.118 g. of gummy material, from which 0.040 g. of δ-lactonic acid was isolated by crystallization, first from aqueous methanol, then from chloroform–petroleum ether (b.p. 60–80°); m.p. 203–205°, α_D −28° (*c* 1.06). The appropriate mixed m.p. was not depressed.

Formaldehyde Determinations.—The method used is modelled on that of Clemo and Macdonald[34] with some modifications. A solution of the "adduct" XI (0.340 g.) in 20 cc. of dry methylene chloride was ozonized at −10° for 2 hr. The solvent was removed *in vacuo* at room temperature, and to the residue was added 25 cc. of water, 3 cc. of glacial acetic acid, and 2–3 g. of zinc dust. The mixture was immediately connected to a distillation apparatus and slowly distilled into 5 cc. of cold water until a residual volume of 5 cc. remained in the distillation flask. Dimedone (0.600 g.) dissolved in a small amount of warm ethanol was added to the distillate, and the solution heated on the steam-bath for 15 min. The mixture was cooled, and the precipitated derivative collected and dried; 0.212 g. (64%), m.p. 185–187°. The procedure was identically repeated with caryophyllene oxide (X, 0.494 g.), which gave 0.200 g. (30.4%) of the formaldehyde derivative, m.p. 184–189°.

(33) W. Treibs, *Ber.*, **80**, 56 (1947).

(34) G. R. Clemo and J. M. Macdonald, *J. Chem. Soc.*, 1294 (1935).

C-Methyl Determinations.—A weighed quantity of pure "adduct" contained in the oxidation flask was dissolved in dry methylene chloride and ozonized at room temperature for 1.5 hr. After removal of the solvent *in vacuo*, the oxidation mixture was introduced, and the determination performed according to Pregl.[35] The "adduct" yielded 0.16 mole of acetic acid. Identical treatment of caryophyllene gave 1.11 moles of acetic acid. Two independent[36] C-methyl determinations, performed on the "adduct" without the precautionary ozonolysis, afforded 0.29 (and 0.29) mole of acetic acid, and consumed 7.87 (and 8.23) moles of the dichromate reagent.

In the normal C-methyl determination, caryophyllene is known to give 0.77 mole of acetic acid (5.94 moles of dichromate consumed), and caryophyllene oxide (X) gives 0.63 mole of acid (5.52 moles of dichromate reagent consumed).[37]

(35) F. Pregl, "Quantitative Organic Microanalysis," 3rd ed., J. & A. Churchill Ltd., London, 1937, p. 201.

(36) We are indebted to E. J. Eisenbraun at the University of Wisconsin, Madison, for these determinations.

(37) E. J. Eisenbraun, S. M. McElvain and B. F. Aycock, THIS JOURNAL, **76**, 607 (1954).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WELLESLEY COLLEGE]

Flower Pigments. I. Further Studies on the Structure of Stillopsin

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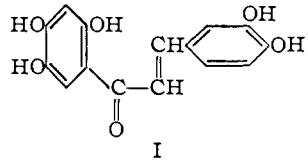
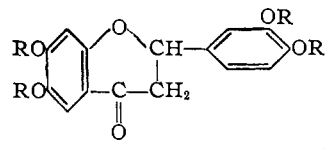
By synthesis of 3',4',6,7-tetraacetoxyflavanone and its isolation as a degradation product of stillopsin octaacetate and by paper chromatography of the sugar obtained on hydrolysis of the glycosidic pigment, the structure of the yellow pigment stillopsin, from *Coreopsis stillmanii*, has been verified as a glucoside of 3,4,2',4',5'-pentahydroxychalcone. An anion exchange resin has been used to deacidify hydrolysis filtrates preceding analysis by paper chromatography.

Previous work[3] had shown that stillopsin, the yellow pigment of *Coreopsis stillmanii*, was a glycoside of 3,4,2,',4',5'-pentahydroxychalcone (I); the proof of the position of the hydroxyl groups was based on the identity of the sample of tetra-



I

methoxyflavanone derived from the pigment with a synthetic sample of 3',4',6,7-tetramethoxyflavanone (II). This structure has now been substanti-



II, R = CH_3; III, R = CH_3CO; VI, R = H

ated by means of a similar comparison of 3',4',6,7-tetraacetoxyflavanone (III) derived from synthetic and natural sources. In addition the glycosidic group has been shown to be glucose by means of paper chromatography.

III was obtained from stillopsin by acetylating the crude hydrolysis product of pure stillopsin octaacetate (IV), the form in which the pigment was isolated from the flower. It was synthesized by the following method: quinone was converted to hydroxyhydroquinone triacetate by treatment with acetic anhydride and sulfuric acid[4]; the ring acetyl group was introduced by means of acetic acid and zinc chloride,[5] the phenolic acetyl groups being removed in the process; the resultant 2,4,5-trihydroxyacetophenone (V) was condensed in cold basic solution under nitrogen with protocatechualdehyde to give chalcone I; this was isomerized by acid to 3',4',6,7-tetrahydroxyflavanone (VI) which was acetylated to the tetraacetyl derivative III. The two samples of III were shown to be identical by analysis, mixed melting point, the distinctive ink-blue color test with ethanol, magnesium and hydrochloric acid[3] and by absorption spectra (Table I).

Since this work was completed, King, King and Neill[6] have reported the isolation of both the free chalcone I, called neoplathymenin, and the corresponding flavanone VI, called plathymenin, from the heartwood of *Plathymenia reticulata*, and they have also prepared the acetyl derivatives. They proved the structure of their compounds by preparing the tetramethyl ether of plathymenin, identical with the known compound II and by oxidative degradation of this ether to 2-hydroxy-4,5-dimethoxybenzoic acid and veratric acid. The present complete synthesis of 3,4,2',4',5'-pentaacetoxychalcone (VII) and 3',4',6,7-tetraacetoxyflavanone (III) substantiates their identification.[7]

The sugar solution obtained after hydrolyzing IV with hydrochloric acid and separating VI was deacidified by the anion exchange resin Amberlite IR-4-BA.G.[8] After evaporation, it was chromatographed on paper with butanol–acetic acid–water[9] as the developing solvent. Spraying with *m*-phenyl-

(1) Submitted, June, 1952, in partial fulfillment of the requirements for the B.A. degree with honors.

(2) Chromatographic analysis from Miss Thompson's M.A. thesis, June, 1953.

(3) M. K. Seikel and T. A. Geissman, THIS JOURNAL, **72**, 5720 (1950).

(4) E. B. Vliet, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 317.

(5) M. Healey and R. Robinson, *J. Chem. Soc.*, 1628 (1934); T. C. Chadha and K. Venkataraman, *ibid.*, 1074 (1933).

(6) F. E. King, T. J. King and K. G. Neill, *ibid.*, 1055 (1953).

(7) A comparison of the acetyl derivatives reported by King, *et al.*, with those synthesized in the present work offers more convincing proof of the identity of the two series than a comparison of the free hydroxy compounds since the latter show a considerable divergency in melting points. This probably resulted because the hydroxy compounds melt with decomposition.

(8) Rohm and Haas, Philadelphia, Penna.

(9) S. M. Partridge, *Biochem. J.*, **42**, 238 (1948).