period to 6 moles of aluminum chloride suspended in 30 moles benzene at 10°. After addition was completed, the mixture was stirred for an additional half-hour and then worked up in the normal manner. Distillation gave a main fraction of semi-solid hydrocarbons boiling at 115–135° (3 mm.), and amounting to 198 g. with 132 g. of residue. The solid hydrocarbon was separated in the usual manner, obtaining 36 g. of *meso*-2,3-diphenylbutane. The liquid portion (148.5 g.) was carefully refractionated obtaining 108 g. of pure α,α-dimethyldibenzyl.

Summary

1. The reaction of disubstituted ethylene oxides with aluminum chloride and benzene has been investigated.

2. The reaction with isobutylene oxide has been shown to yield neophyl alcohol together with two hydrocarbons, α,α-dimethyldibenzyl and *meso*-2,3-diphenylbutane, one the product of a rearrangement.

3. Both α,α-dimethyldibenzyl and dimethylbenzylcarbinol yield *meso*-2,3-diphenylbutane as the rearrangement product upon treatment with aluminum chloride and benzene.

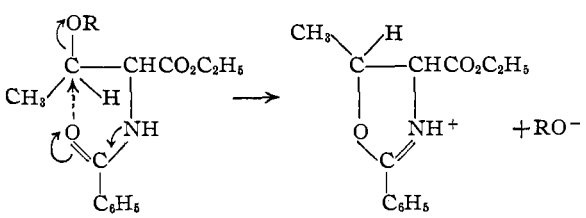
BROOKLYN, NEW YORK
ELIZABETH, NEW JERSEY RECEIVED NOVEMBER 28, 1949

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Ring Closure of the 2-Benzoylaminocyclohexanols. The Mechanism of Oxazoline Formation

BY WILLIAM S. JOHNSON AND ELLIOT N. SCHUBERT

In their recent studies on the interconversion of threonine and *allo*threonine *via* the oxazolines both Attenburrow, Elliott and Penny,[1] and Pfister, Robinson, Shabica and Tishler[2] have endorsed the mechanism suggested by Cornforth[3] which involves the postulation that the oxazoline ring is formed through a backside nucleophilic attack by the oxygen atom of the N-benzoyl group at the β-carbon atom with concomitant stereochemical inversion at this position and rupture of the β-C to O bond, *i. e.*



In our opinion this represents in essence a very reasonable *a priori* postulate particularly in view of the demonstration that the neighboring benzoylamino group can participate in nucleophilic displacements.[4] The cyclic intermediate postulated for such displacements is the oxazolinium ion, which in contrast with the oxygen analogs of Winstein, *et al.*,[4] would be expected to be quite stable. The isolation of the intermediary oxazoline III described in the present work, thus provides supporting evidence for the Winstein mechanism of participation of neighboring groups in such reactions. It occurred to us, moreover, that a convincing test of the inversion cyclization mechanism should evolve from a comparison of the behavior of the two stereoisomeric 2-aminocyclohexanols I and VI in these reactions, since the effect of the restricted rotation about the bond joining the two asymmetric carbon atoms, on the cyclization of the N-benzoyl derivatives should be to permit ring closure of the *trans*, but to inhibit cyclization of the *cis* form.

Both of the possible racemic 2-aminocyclohexanols are known; one melts at 68° and the other at 72°. The existing evidence, which is summarized and expanded by McCasland, Clark and Carter,[4] favors strongly the *trans* configuration (I) for the former and the *cis* (VI) for the latter. Of the two the *trans* isomer (I) is the more readily available, and for the present study was prepared by the ammonolysis of *trans*-2-chlorocyclohexanol.[5] When the crystalline N-benzoyl derivative (II) was treated with thionyl chloride and the resulting ether-insoluble hydrochloride (III) hydrolyzed with dilute hydrochloric acid according to the excellent procedure of Tishler, *et al.*,[2] the expected inversion product *cis*-2-aminocyclohexanol (VI) was isolated as the known hydrochloride, m. p. 187°, in about 19% over-all yield. When the thionyl chloride treatment was carried out at 52–54° instead of at room temperature, the yield of material of good quality was raised to 50%. This procedure thus constitutes the best method known to us for the preparation of the *cis* compound VI.[6] The intermediary oxazoline hydrochloride was not isolated in the pure form because on standing in air it was hydrolyzed to the *cis*-O-benzoyl derivative V.[7] However, if the oxazoline hydrochloride was immediately treated with dilute sodium hydroxide a crystalline base, m. p. 47°, was produced. Confirmation that

(1) Attenburrow, Elliott and Penny, *J. Chem. Soc.*, 310 (1948).

(2) Pfister, Robinson, Shabica and Tishler, THIS JOURNAL, **71**, 1101 (1949).

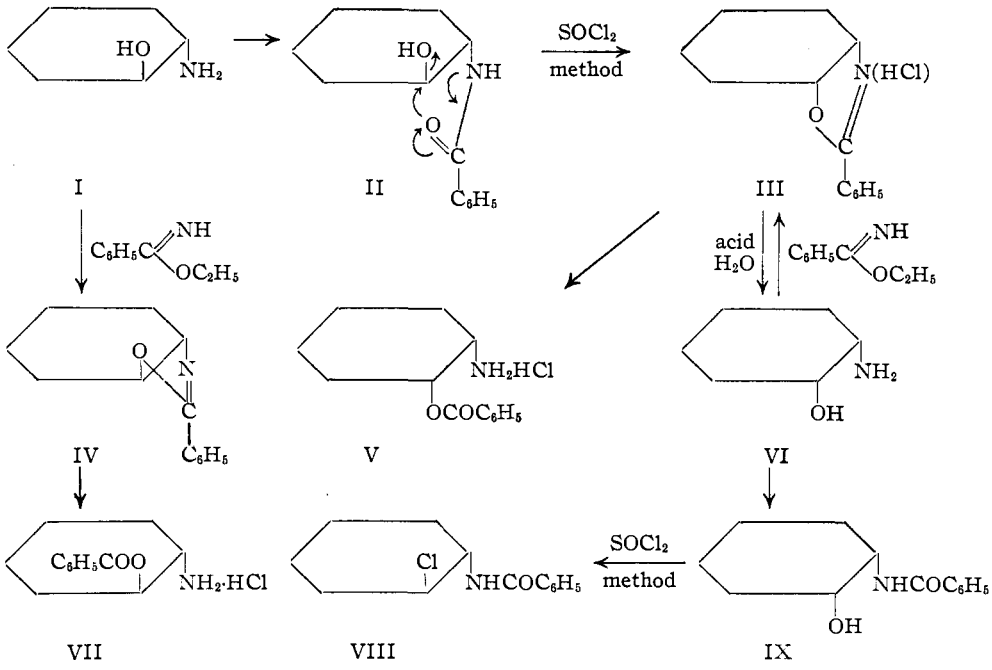
(3) See footnote 1, p. 314, ref. 1.

(4) McCasland, Clark and Carter, THIS JOURNAL, **71**, 637 (1949); *cf.* Winstein and co-workers, *ibid.*, **70**, 812–846 (1948).

(5) Wilson and Read, *J. Chem. Soc.*, 1272 (1935).

(6) The method of McCasland, Clark and Carter ref. 4 gave the inverted N-benzoyl derivative in about 10% over-all yield, and the method described in Swiss Patent 194,642-5 [*Chem. Zentr.*, **108**, I, 2260 (1937)] involving the hydrogenation of 2-acetaminophenol gave *cis*-2-acetylaminocyclohexanol in 11% yield, ref. 4.

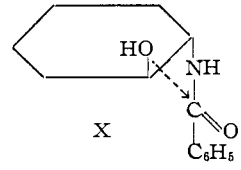
(7) *Cf.* the analogous behavior in the threonine series, ref. 1.



this was indeed the *cis*-oxazoline III was afforded by the preparation of the same substance from *cis*-2-aminocyclohexanol hydrochloride and ethyl iminobenzoate, a method which evidently gives oxazolines with retention of configuration.[2,8]

When *cis*-2-aminocyclohexanol was converted to the N-benzoyl derivative IX and this in turn treated with thionyl chloride exactly as described above for the formation of the *cis* oxazoline III, there was *no evidence of ring closure*. Instead of an oxazoline, there was obtained in 61% yield, a neutral chloro compound, m. p. 163.5–164.5° (pure), analysis of which suggested that it was a 2-benzoylaminochlorocyclohexane. A compound of this structure, already described as melting at 154–155°, has been assigned the *cis* configuration because of the striking lack of reactivity of the chlorine atom even toward silver acetate.[4] This implication that our 164° compound is the *trans* isomer VIII—the replacement of the hydroxyl group in IX having involved inversion—was confirmed by testing its reactivity toward silver acetate in wet acetic acid (conditions favoring inversion[9]). The chlorine atom was indeed labilized by the neighboring *trans*-benzoylamino group and readily underwent replacement with inversion giving *cis*-2-benzoylaminocyclohexanol (IX) in good yield. The presumed intermediary oxazoline is apparently cleaved under these conditions so as to give the N- rather than the O-benzoyl derivative (see above).[10]

The foregoing demonstration that only the *trans*-benzoylaminocyclohexanol gives the oxazoline thus provides strong evidence favoring the inversion cyclization mechanism. That the *trans*-oxazoline IV is capable of stable existence was shown by its preparation from *trans*-2-aminocyclohexanol hydrochloride and ethyl iminobenzoate. This oxazoline melted at 66–67° and like the *cis* isomer, was readily hydrolyzed with hydrochloric acid giving in this case the *trans*-O-benzoyl derivative VII. In view of the greater stability of 5/6 ring systems fused in the *cis* rather than the *trans* configuration, it was expected that the rate of the reaction I → IV would be measurably lower than that of the corresponding transformation (VI → III) in the *cis* series.[11] Unfortunately the reaction systems were heterogeneous, and since the *cis*-2-aminocyclohexanol hydrochloride was less soluble in the reaction medium (ethylene dichloride) than the *trans* isomer, the former reacted more slowly.



X

Fodor and Kiss[12] have recently reported that hydrogen chloride effects isomerization of *trans*-N-benzoylaminocyclohexanol (II) into the O-benzoyl compound with retention of configuration. We also have been able to effect this transformation in about 39% yield by treatment of II with hydrogen chloride in dioxane. The

(8) Elliott, *J. Chem. Soc.*, 589 (1949).
(9) Winstein, *et al.*, THIS JOURNAL, **64**, 2787 (1942).
(10) *Cf.* ref. 4.
(11) *Cf.* the greater ease for closing a five-membered ring fused to a six- in the *cis* than in the *trans* configuration: Bachmann and Ramirez, THIS JOURNAL, **71**, 2274 (1949).
(12) Fodor and Kiss, *Nature*, **164**, 917 (1949); *cf.* Welsh, THIS JOURNAL, **71**, 3500 (1949).

mechanism of this transformation probably involves a nucleophilic attack by the oxygen of the hydroxyl group on the carbon of the carbonyl group (see formula X), a scheme which is analogous to that proposed by Welsh in the ephedrine series.[12]

Acknowledgment.—We are indebted to the late Professor Homer Adkins who, during a study with one of us (E. N. S.) of the hydrogenation of 2-oximinocyclohexanone over W-6 Raney nickel, obtained *cis*-2-aminocyclohexanol, isolated as the hydrochloride in about 5% yield. The present study was suggested as the result of an investigation of methods of preparing an authentic specimen of the amino alcohol for comparison.

We wish to thank Dr. B. K. Bhattacharyya for checking some of the critical experiments recorded herein.

Experimental Part[13,14]

d,l-cis-2-**Aminocyclohexanol** (VI).—*d,l-trans*-2-Chlorocyclohexanol[15] was ammonolyzed according to the method of Wilson and Read,[5] and the resulting *d,l-trans*-2-aminocyclohexanol (I), m. p. 64–66°, was converted to the N-benzoyl derivative II, m. p. 171–172°, by the general procedure of Leffler and Adams.[16,10]

To 28.5 ml. of redistilled thionyl chloride was added in small portions with swirling and cooling, 10.30 g. of the *trans*-N-benzoyl compound II. Dissolution of each portion was awaited before another was added, the total addition thus requiring about one hour. The flask containing the pale yellow solution was then attached (ground glass joint) to a reflux condenser protected from atmospheric moisture by a calcium chloride tube, and immersed in an oil-bath at 52–54° for two and one-half hours. The light red reaction mixture was cooled and poured into 750 ml. of anhydrous ether whereupon a reddish oil separated. After standing in the cold for several hours the ether layer was decanted from the oil which was then dissolved in 125 ml. of 10% hydrochloric acid and heated under reflux for five hours. The solution was chilled, the benzoic acid (3.50 g.) which crystallized was removed by filtration, and the filtrate evaporated to dryness at 25–35 mm. The colorless residue was dissolved in ethanol, again evaporated to dryness, and then transferred with anhydrous ether to a suction filter where it was washed with ether. This product proved to be fairly pure *d,l-cis*-2-aminocyclohexanol hydrochloride, m. p. 184–187°; yield 3.60 g. (50.5%). A sample recrystallized from ethanol was obtained as colorless plates, m. p. 185.4–187.2° (reported, 189–190°,[4] and 185[17]).

Anal. Calcd. for $C_6H_{14}ONCl$: C, 47.52; H, 9.31. Found: C, 47.72; H, 9.20.

A sample of the hydrochloride described above was converted into the free base by treatment with the calculated amount of 0.3 *N* ethanolic sodium hydroxide at 0°.[10] After one hour at 0°, the mixture was filtered to remove sodium chloride, and evaporated to dryness. The colorless crystalline residue melted at 71–72° (reported m. p.,[4,17] 72–73°).

d,l-cis-2-**Phenyl-4,5-cyclohexanoöxazoline** (III). (a) **By the Cyclization of** *d,l-trans*-2-**Benzoylaminocyclohexanol.**—A 2.19-g. sample of the *trans*-benzoyl compound II was cyclized with 10 ml. of thionyl chloride essentially as described above, except that heating was carried out on the steam-bath for one hour and instead of pouring the reaction mixture into ether, the excess thionyl chloride was removed by distillation at 25–30 mm., and the residual reddish oil triturated with two 50-ml. portions of dry ether. A third portion of ether was added and the mixture allowed to stand in the refrigerator overnight; in this way the oil was induced to solidify. The gray oxazoline hydrochloride thus obtained was separated by filtration and washed with anhydrous ether. This product, m. p. 96.5–101°, amounted to 1.34 g. (56% yield), was quite hygroscopic and could not be recrystallized satisfactorily. A sample treated with an excess of 5% aqueous sodium hydroxide yielded the free base as an oil which was taken up in ether, dried over anhydrous sodium sulfate, and after removal of the ether, evaporatively distilled at 80–100° (0.25 mm.). The distillate crystallized on scratching giving colorless *cis*-oxazoline, m. p. 45–47°. On admixture with the specimen of *cis*-oxazoline prepared by the iminoester method (see below) there was no depression of the m. p.

(b) **By the Iminoester Method.**—Ethyl iminobenzoate was prepared from the hydrochloride[18] by the procedure of Ross,[19] which involves treatment of the hydrochloride with a saturated solution of potassium carbonate and isolation of the free base by ether extraction.

The following procedure was adapted from a method described by Ross.[19] A mixture of 3.03 g. of *d,l-cis*-2-aminocyclohexanol hydrochloride, 3.73 g. of ethyl iminobenzoate and 200 ml. of dry ethylene dichloride was heated under reflux for twenty-four hours. After cooling, the mixture was filtered to remove suspended salt (2.34 g.) and the filtrate was concentrated at 20 mm. Distillation of the residue gave 1.90 g., b. p. 105–108° (20 mm.) and 0.60 g., b. p. 163–166° (20 mm.). The latter fraction melted at 38–46° and apparently consisted of the *cis*-oxazoline contaminated with some benzamide which could be largely removed by treatment with cyclohexane. The mixture was filtered to remove the insoluble amide, the filtrate concentrated, and the residue evaporatively distilled at 60–70° (0.10 mm.). The distillate was recrystallized from ethanol and again evaporatively distilled, giving colorless oxazoline, m. p. 46–48°.

Anal. Calcd. for $C_{13}H_{15}ON$: C, 77.58; H, 7.51. Found: C, 77.43; H, 7.33.

d,l-cis-2-**Benzoyloxycyclohexylamine hydrochloride** (V) was produced readily from the crude *cis*-oxazoline hydrochloride described above (part a). When this salt was allowed to stand in air for about three days it gradually turned to a viscous oil, which was dissolved in chloroform. On the addition of dry ether, the O-benzoyl compound precipitated. Repetition of this precipitation process finally gave material m. p. 212–213° (dec.). Fodor and Kiss[12] report the m. p. of 228° for this substance, but no procedures or analyses are given.

Anal. Calcd. for $C_{13}H_{18}O_2NCl$: C, 61.05; H, 7.09. Found: C, 60.87; H, 6.96.

Attempted Cyclization of *d,l-cis*-2-**Benzoylaminocyclohexanol** (IX).—The *cis*-aminocyclohexanol hydrochloride (1.10 g.) was benzoylated with 14 ml. of 10% sodium hydroxide and 1.52 g. of benzoyl chloride. The solid product amounted to 1.17 g. of material melting at 183–185°. After recrystallization from benzene, the m. p. was 184–185° (reported,[4] 189–190° and 192–193°).

Anal. Calcd. for $C_{13}H_{17}O_2N$: C, 71.20; H, 7.82. Found: C, 70.87; H, 7.78.

A 1.10-g. sample of the N-benzoyl derivative was treated with 5 ml. of thionyl chloride just as described above for the isolation of the *cis*-oxazoline hydrochloride (part a). When the oily residue was treated with anhydrous ether (200 ml. total) there was practically no insoluble material left indicating that no appreciable oxazoline hydrochloride had formed. The residue obtained on evaporation of the ether was triturated with a little cold benzene which left 0.72 g. (61% yield) of almost colorless *d,l-trans*-2-benzoyl-

(13) All melting points are corrected for stem exposure.

(14) We are indebted to Bennett G. Buell and Edward A. Shiner for the microanalyses reported herein.

(15) Coleman and Johnstone, *Org. Syn.*, Coll. Vol. I, 158 (1932).

(16) Leffler and Adams, THIS JOURNAL, **59**, 2256 (1937).

(17) Swiss Patent 194,642-5 [*Chem. Zentr.*, **108**, I, 2260 (1937)].

(18) Dox, *Org. Syn.*, Coll. Vol. I, 6 (1932).

(19) Robert M. Ross, Ph.D. Thesis, University of Wisconsin (1948).

aminocyclohexyl chloride (VIII), m. p. 159–161°. Recrystallization from benzene gave a colorless product, m. p. 163.5–164.5°.

Anal. Calcd. for $C_{13}H_{16}ONCl$: C, 65.68; H, 6.78; Cl, 14.92. Found: C, 66.03; H, 6.79; Cl, 14.78, 14.95.

Hydrolysis of *d,l-trans*-2-Benzoylaminocyclohexyl Chloride (VIII).—A mixture of 0.119 g. of the chloride VIII, 10 ml. of ordinary acetic acid (undried), and 0.105 g. of silver acetate was heated under reflux with stirring for five hours. The silver chloride was removed by filtration, and the light red filtrate was made basic with dilute (1:1) ammonium hydroxide solution. The cloudy mixture was then concentrated at 20 mm. until crystals began to form, then cooled, and the precipitate was separated by suction filtration and washed with cold water. The crude tan product amounted to 0.077 g. (70% yield), m. p. 170–175°. Recrystallization from benzene gave 0.034 g. of colorless crystals, m. p. 183–185°, undepressed on admixture with the sample of *d,l-cis*-2-benzoylaminocyclohexanol described above.

***d,l-trans*-2-Phenyl-4,5-cyclohexanoöxazoline (IV).**—*d,l-trans*-2-aminocyclohexanol hydrochloride (3.03 g.) was treated with ethyl iminobenzoate (3.73 g.) in ethylene dichloride (200 ml.) just as described above for the *cis* series. The insoluble salts amounted to 1.80 g., and the distillation gave 1.25 g., b. p. 103–104° (20 mm.) and 1.70 g., b. p. 170–175° (19 mm.). The latter fraction melted at 73–77° and represented crude *trans*-oxazoline. Further purification (see above) yielded after a final evaporative distillation at 70–80° (0.10 mm.), colorless material, m. p. 66.2–67.6°.

Anal. Calcd. for $C_{13}H_{15}ON$: C, 77.58; H, 7.51. Found: C, 77.60; H, 7.48.

The above oxazoline was easily selectively hydrolyzed to what is undoubtedly *d,l-trans*-2-benzoyloxycyclohexylamine hydrochloride (VII), by allowing the hydrochloride (prepared in anhydrous ether) to stand overnight in air (see above). After sublimation at 135–140° (<0.015 mm.) the product melted at 261–263° (dec.) with darkening at 257° when introduced at 250°. This material showed no m. p. depression on admixture with the specimen of VII described below.

Exhaustive hydrolysis with dilute hydrochloric acid gave a crude hydrochloride, m. p. 163–166°, which after three recrystallizations from ethanol melted at 166.5–169°. On admixture with pure *d,l-trans*-2-aminocyclohexanol hydrochloride (m. p. 175.5–177°), the m. p. was 166–172°, while on admixture with the pure *cis*-isomer, the m. p. was depressed to 142–155°.

Isomerization of *d,l-trans*-2-Benzoylaminocyclohexanol to the O-Benzoyl Derivative.—A solution of 0.85 g. of the N-benzoyl compound in 80 ml. of dry dioxane was saturated with hydrogen chloride and then heated under reflux for three hours. Toward the end of the second hour crystals began to form. After cooling these amounted to 0.39 g. (39% yield), m. p. 246–248° (dec.). Sublimation at 135–140° (<0.015 mm.) gave colorless crystals, m. p. 264–265° (dec.) with darkening at 257° when introduced in bath at 250°. Recrystallization from ethanol–ether did not change the m. p. behavior. Fodor and Kiss[12] report the m. p. of 284° for this substance, but no procedures or analyses are given.

Anal. Calcd. for $C_{13}H_{18}O_2NCl$: C, 61.05; H, 7.09. Found: C, 60.99; H, 6.93.

Summary

An examination of the behavior of *cis*- and *trans*-2-benzoylaminocyclohexanol toward thionyl chloride has provided evidence supporting the inversion-cyclization mechanism of oxazoline formation. The *trans* compound cyclized readily giving the *cis*-oxazoline which on acid hydrolysis yielded *cis*-2-aminocyclohexanol. With the *cis*-N-benzoyl compound, in contrast, there was no evidence of oxazoline formation, but instead the hydroxyl group was replaced by chlorine with inversion to the *trans* series.

Both the *cis* and *trans*-2-phenyl-4,5-cyclohexanoöxazoline were prepared by the interaction of the salts of the corresponding 2-aminocyclohexanols with ethyl iminobenzoate.

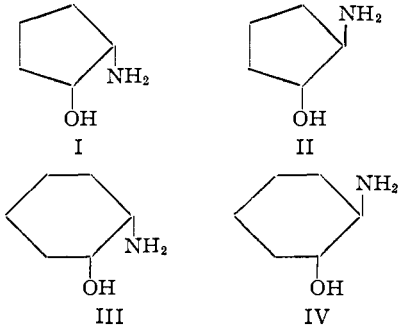
MADISON, WISCONSIN RECEIVED JANUARY 16, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TORONTO]

Stereochemistry of Aminocyclanols. Synthesis of *cis* Epimers *via* Oxazolines. The 2-Aminocyclopentanols*

BY G. E. McCASLAND AND DONALD ARTHUR SMITH[1]

In order to extend to the cyclopentane series our studies[2] of the effect of *cis-trans* configuration on stereochemical behavior we needed to prepare *d,l-cis*-2-aminocyclopentanol (I). The *trans* epimer (II) of this compound, or of 2-aminocyclohexanol, is readily obtained by amination of the corresponding epoxide. The *cis* epimer (III) of 2-aminocyclohexanol (N-acetyl) is obtained, in about 10% yield, by hydrogenation of the corresponding aromatic compound. This method is obviously not applicable to the cyclopentane derivative.



A previous publication[2a] described the preparation of *cis*-2-aminocyclohexanol by the detosylation of *trans*-2-benzoylaminocyclohexyl-*p*-toluenesulfonate in a wet acetic acid (or dry alcohol) solution of sodium acetate. For this and other

(*) Presented before the Organic Division at the Philadelphia meeting of the American Chemical Society, April 1950.

(1) Fellow of the Canadian Industries Limited, 1949–1950.

(2) For related publications see: (a) McCasland, Clark and Carter, THIS JOURNAL, **71**, 637 (1949); (b) Carter, Clark, Lytle and McCasland, *J. Biol. Chem.*, **175**, 683 (1948); also *J. Biol. Chem.*, **174**, 415 (1948).