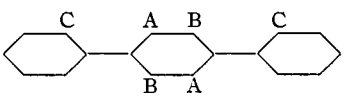
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

STEREOCHEMISTRY OF DIPHENYLBENZENES. THE CIS AND TRANS FORMS OF 2,5-DI-(3-BROMO-2,4,6-TRIMETHYLPHENYL)-1,3,4,6-TETRAHYDROXYBENZENES AND THE CORRESPONDING ACYLATES. XV[1]

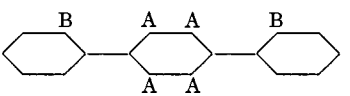
BY P. R. SHILDNECK[2] AND ROGER ADAMS

RECEIVED JANUARY 22, 1931 PUBLISHED JUNE 8, 1931

In previous papers the various possibilities for stereoisomerism in the diphenylbenzenes[1a,d] have been discussed and compounds have been synthesized which indicate the validity of the theoretical speculation. The compounds thus far studied have been of the general type (I) and have been found in meso and racemic modifications. Another very interesting type (II) is that in which all four groups on the central ring are the same and each of the two end rings is asymmetrically substituted. Assuming

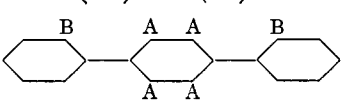


I

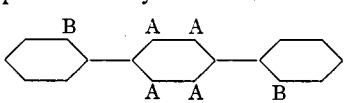


II

the same restricted rotation between the rings as in the diphenyl series, and therefore that the two end rings are not co-planar with the central ring, it would be impossible to obtain any compound the mirror image of which would not be identical with the object, so that optical isomerism is excluded. On the other hand there are two forms possible, represented by Formulas (III) and (IV). These correspond directly to *cis–trans* isomers



III



IV

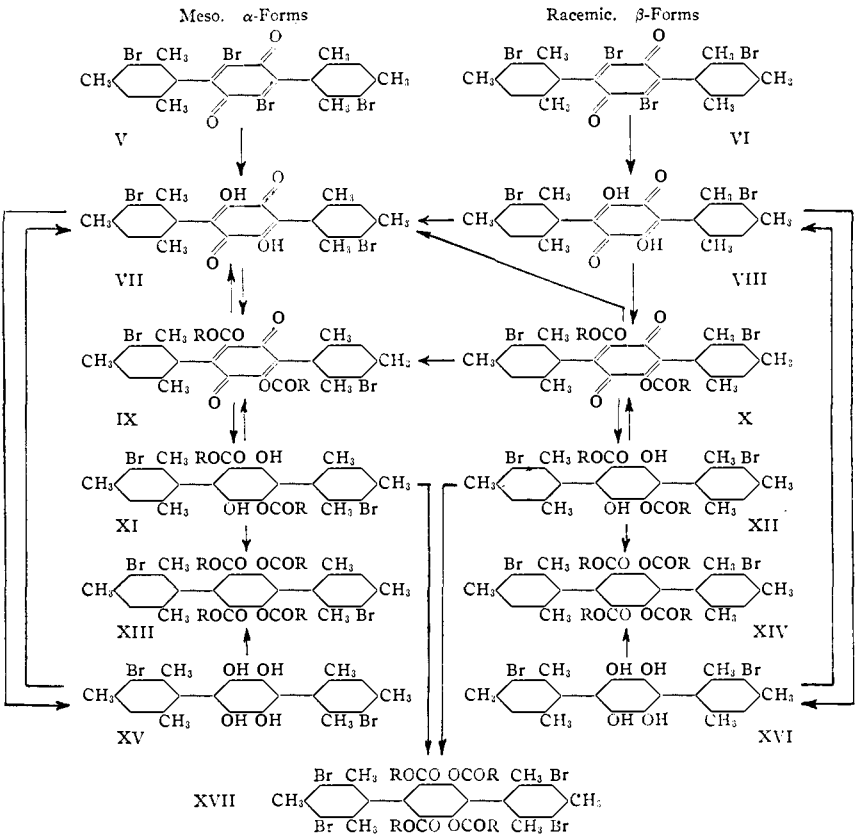
of the usual type, and neither is resolvable. If each of the two end rings in such molecules were symmetrically substituted, however, the two isomers indicated would become identical.

In this communication are described the synthesis and properties of *cis* and *trans* modifications of compounds falling in this group. The 2,5-di-(3-bromo-2,4,6-trimethylphenyl)-3,5-dibromoquinones (V) and (VI) described in the last publication in this series are readily converted by means of dilute sodium hydroxide solution into the corresponding hydroxy-

[1] For the last papers in this series see: (*a*) Browning and Adams, THIS JOURNAL, **52**, 4098 (1930); (*b*) Steele and Adams, *ibid.*, **52**, 4528 (1930); (*c*) Stoughton and Adams, *ibid.*, **52**, 5263 (1930); (*d*) Shildneck and Adams, *ibid.*, **53**, 343 (1931); (*e*) Bock and Adams, *ibid.*, **53**, 374 (1931).

[2] This communication is a portion of a thesis submitted by P. R. Shildneck in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry at the University of Illinois.

quinones, (VII) and (VIII). These, in turn, may be acylated to the diacyloxyquinones (IX) and (X) or reduced to the tetrahydroxybenzenes (XV) and (XVI). Moreover, the diacyloxyquinones may be hydrolyzed to the corresponding hydroxyquinones or reduced to the diacyloxyhydroquinones (XI) and (XII), which may be hydrolyzed to the corresponding tetrahydroxy compounds or acylated to the tetraacyloxy derivatives (XIII and (XIV).



Each of the original dibromoquinones gives its own characteristic derivatives in the series of reactions just described. The tetrahydroxy compounds and the tetraacyloxy compounds, therefore, represent the *cis* and *trans* modifications (III) and (IV); the hydroxyquinones, the acyloxyquinones and the acyloxyhydroquinones represent stereoisomers corresponding to type (I).

To show that such isomerism will disappear upon making the two ends symmetrical, the two tetraacetoxy compounds (XIII) and (XIV), were brominated with liquid bromine and there was thus obtained a single 2,5-di-(3,5-dibromo-2,4,6-trimethylphenyl)-1,3,4,6-tetraacetoxybenzene (XVII).

The derivatives from the less soluble dibromoquinone have been denoted as the α- and from the more soluble as the β-forms. Throughout the series with one exception a decided difference in solubility in the two forms is to be found.

Most of the compounds melt very high, generally in between 250 and 400°. The difference in the melting points of the α- and the β-forms of any of the substances varies usually from 10–25°. In the case of the diacetoxyquinones, however, the melting points are essentially identical and it was necessary to convert each of the compounds to the corresponding tetraacetoxy analog in order to show definitely that one was different from the other. The stereoisomeric dibutyroxyquinones, however, have a difference of 20° in the melting points. The use of mixed melting points in this work was more or less excluded since it was shown that in many instances it was impossible to get a lowering of the melting point from the mixture of a pair of isomers. In the case of the tetrabutyroxy compounds, however, which were comparatively low melting, five parts of the higher melting and 95 parts of the lower melting melted about 5° below the lower melting form. The identification of any individual compound was always made by conversion to the corresponding tetraacetoxy derivative, which was markedly different in melting point and solubility from its isomer. Owing to the high melting point of some of these compounds the Bloc Maquenne was employed for melting points above 350°.

In the examples of *cis–trans* isomerism known in other fields of organic chemistry the *trans* form is usually the higher melting of the two. As a consequence, the higher melting tetrahydroxy and tetraacyloxy compounds were assumed to be the *trans* modifications and the stereoisomeric forms the *cis* modifications. All of the α derivatives would, therefore, be *trans* modifications and all of the β derivatives *cis* modifications. Since, from the standpoint of optical isomerism, the *trans* modifications are meso forms, all of the compounds of the α series should be non-resolvable. The *cis* modifications or β forms on the other hand would be racemic derivatives and these should be capable of resolution. The decision as to whether the assumptions just made are correct or not will depend upon the results of resolution studies.

In most cases of *cis–trans* isomerism where one form is less stable than the other under action of heat or catalysts of the ordinary type, the *cis* is usually the unstable modification and is convertible into the *trans* form. It might be anticipated, therefore, that in these compounds certain of the *cis* derivatives might be converted into the *trans* modifications or from the standpoint of optical isomerism the racemic forms might be convertible into the meso forms, providing conditions could be found which would allow free rotation between the rings.

An attempt was made to convert each of the β derivatives into the corre-

sponding α derivatives. This was done by heating the β form, usually in mesitylene, sometimes in glacial acetic acid or in sodium hydroxide solution, for many hours at the boiling temperature. By this procedure it was found that the β-diacetoxyhydroquinone (XII), the β-tetrahydroxy (XVI), the β-tetraacetoxy (XIV) and the β-dibromoquinone (VI) derivatives were apparently, perfectly stable under the conditions used and no conversion took place. On the other hand, the β-dihydroxyquinone (VIII), the β-diacetoxyquinone (X) and the β-dibutyroxyquinone (X), when treated in the manner described were readily converted into the corresponding α modifications. By holding the β-dibutyroxy compound 20° above its melting point for three hours, a product resulted which after two crystallizations gave pure α form. Moreover, upon hydrolyzing the β-diacetoxyquinone (X) in glacial acetic acid and hydrochloric acid, the α-dihydroxyquinone (VII) was obtained.

It is interesting to consider these experiments from the standpoint of x-ray data which have been discussed from time to time in the previous communications. In the case of the β-diphenylbenzene compounds which were not convertible to α forms and which, therefore, resisted tendency to any free rotation between the rings, there are, with the exception of the β-dibromoquinone, between each of the two end rings and the center ring either two methyl groups and two hydroxyl groups or two methyl groups and one hydroxyl and one acylated hydroxyl group. On the assumption that the acylated hydroxyl group does not have an appreciably greater interference value than the unacylated group, the tetrahydroxy (XVI) compound may be considered to be characteristic of the three stable β compounds. The x-ray data show that there is appreciable interference on either side of each pair of rings in the molecule as follows: C—CH_3, 1.73 Å. + C—OH, 1.54 Å. = 3.19 Å. Subtracting from this value 2.90 Å. (the distance between the 2,2′-carbon atoms in the two rings) there is obtained a difference of 0.37 Å. on each side. This is, apparently, sufficient to prevent any rotation under the conditions used. On the other hand, in the case of the corresponding quinones the following interferences would be in force. On one side of each pair of rings in the molecule where the methyl and the hydroxyl meet, there would be an interference of 0.37 Å. On the other side, however, there would be C—CH_3, 1.73 Å. + C=O, 1.15 Å. = 2.88 Å., which is −0.02 Å. when the distance between the 2,2′-carbon atoms is subtracted from the total value. It follows, therefore, that if the rings are held in a more or less fixed relative position to one another, free rotation could not take place because one or the other of the methyl groups would interfere with the hydroxyl group and convertibility of the β-form to the α-form would be prevented. On the other hand, if the molecule is heated so that the rings may be bent toward each other in one or another direction, it is possible to reach a position where there is only

0.175 Å. interference simultaneously on each of the two sides [(0.37 Å. − 0.02 Å.)/2 = 0.175 Å.]. It may, therefore, be either that an interference of 0.175 Å. can be overcome by a high temperature so as to allow free rotation, or that free rotation is possible on account of the quinone ring, about which comparatively little is known as far as its exact structure is concerned. It may be expected that a quinone nucleus is more mobile within itself than a benzene ring and, therefore, might readily be distorted somewhat by a decided temperature change. On the other hand, the stability of the β-dibromoquinone to rearrangement indicates that the size of the groups even in the quinones is an important factor. The interference in this compound (C–CH_3, C–Br and C–CH_3, C=O) when the rings are in a relative position most advantageous for free rotation is 0.39 Å., [(0.80 Å. − 0.02 Å.)/2 = 0.39 Å.], a value which has been shown in previous diphenyl compounds to be sufficient to prevent free rotation under ordinary methods of treatment. The 0.80 Å. represents the interference between the methyl and bromine groups (C–CH_3, 1.73 Å. + C–Br, 1.97 Å. = 3.70 Å. − 2.90 Å. = 0.80 Å.) and the −0.02 Å. that between the methyl and carbonyl group as indicated above.

Experimental

2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-3,6-dihydroxyquinone (α-Form), (VII).—In a 5-liter, two-necked flask equipped with a mechanical stirrer and reflux condenser, were placed 35 g. of α-2,5-di-(3-bromo-2,4,6-trimethylphenyl)-3,6-dibromoquinone, V, m. p. 295–296° (corr.); 2 liters of 95% ethyl alcohol and a solution of 300 g. of sodium hydroxide in 1200 cc. of water. The mixture was stirred and refluxed for eight hours. During this time the dibromoquinone dissolved, forming a deep red solution, and a portion of the dihydroxyquinone precipitated in small flakes as the scarlet sodium salt.

After filtration and drying, the sodium salt amounted to 20 g. The clear red filtrate was diluted with 2 liters of water, and acidified with concentrated hydrochloric acid. Upon heating nearly to boiling a flocculent, orange precipitate coagulated. The product was filtered on a Büchner funnel, washed free of chloride with hot water and sucked to a completely dry powder on the filter paper. The sodium salt obtained from the original reaction mixture was dissolved in hot water and acidified with 6 *N* hydrochloric acid and the hydroxy compound washed and dried as described. The yield amounted to 25.4 g. (7 g. from the filtrate and 18.4 g. from the filtered sodium salt) of the α-dihydroxyquinone or 90% of the theoretical. The dihydroxyquinone as obtained was essentially pure and was used directly for conversion into derivatives.

The α-dihydroxyquinone is practically insoluble in all the common organic solvents except nitrobenzene, from which it crystallizes in very minute yellow needles. It is sparingly soluble in ether, glacial acetic acid and mesitylene. One hundred cc. of boiling mesitylene dissolves about 0.05 g. The needles from mesitylene are larger than those obtained from nitrobenzene and are orange in color. Samples recrystallized to purification from either solvent decomposed on the Bloc Maquenne at 397–400° (obs.).

Anal. (Parr Bomb) Calcd. for $C_{24}H_{22}O_4Br_2$: Br, 29.93; C, 53.93; H, 4.16. Found: Br, 29.85; C, 53.42; H, 4.18.

Sodium Salt of the α-Dihydroxyquinone, (VII).—The sodium salt obtained from the hydrolysis of the α-dibromoquinone was purified by recrystallization from an alkaline water–alcohol mixture (2 g. of salt in 600 cc. of 50% alcohol and 5 g. of sodium hy-

droxide). The red flakes were washed with acetone and air dried. For analysis 0.5 g. was finely pulverized and dried under reduced pressure at 110°.

Anal. (Parr Bomb). Calcd. for $C_{24}H_{20}O_4Br_2Na_2$; Br, 27.65. Found: Br, 27.28.

2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-3,6-diacetoxyquinone (α-Form), (IX).—A mixture of 4 g. of the α-dihydroxyquinone VII was placed in a 300-cc. Erlenmeyer flask with 80 cc. of acetic anhydride and brought to a boil under a reflux condenser. Through the condenser was added 80 cc. of pyridine, the solution again brought to a boil and held for one minute. The orange solution was then poured rapidly with stirring into 1 liter of 4 *N* hydrochloric acid. The yellow, crystalline product was filtered from the hot mixture and washed with 4 *N* hydrochloric acid, followed by cold water. The yield was quantitative, the weight of air-dried product amounting to 4.7 g. Two recrystallizations from 200 cc. and 150 cc., respectively, of *n*-butyl alcohol yielded a product consisting of yellow plates melting constantly at 272–273° (corr.). It is very soluble in mesitylene, somewhat less soluble in toluene, moderately soluble in glacial acetic acid and acetone and sparingly soluble in 95% ethyl alcohol.

Anal. (Parr Bomb). Calcd. for $C_{28}H_{26}O_6Br_2$: Br, 25.86. Found: Br, 25.71.

Hydrolysis of α-Diacetoxy Compound, (IX).—The diacetoxy compound is hydrolyzed rapidly upon heating for twenty to thirty minutes in a mixture consisting of 80% of glacial acetic acid and 20% of 6 *N* hydrochloric acid (50 cc. of glacial acetic acid, 10 cc. of 6 *N* hydrochloric acid, 0.25 g. of diacetoxy quinone) to the insoluble α-dihydroxyquinone (VII) melting at 397–400° on the Bloc Maquenne. A portion of the dihydroxyquinone so obtained (0.21 g.) was reacetylated to an acetyl derivative identical with the above in melting point, solubility and crystalline appearance.

2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-1,3,4,6-tetrahydroxybenzene (α-Form), (XV).—A mixture of 5 g. of the α-dihydroxyquinone (VII), 500 cc. of 95% ethyl alcohol and 10 g. of stannous chloride was refluxed for fifteen minutes. A greenish-yellow precipitate formed. Addition of 10 cc. of 6 *N* hydrochloric acid dissolved the precipitate. About 40 cc. more of the acid was then added. This was followed by ten minutes of refluxing, after which a clear, colorless solution had formed. Hot water was gradually added to the boiling solution until a faint turbidity appeared. The condenser was removed and alcohol removed by distillation until a considerable crop of white crystals appeared in the boiling mixture. The mixture was cooled and filtered. The minute, crystalline flakes were washed several times with 6 *N* hydrochloric acid and finally with cold water. The white product so obtained was air dried in the dark, since light discolored it; yield, 4.8 g. Two recrystallizations from dilute alcohol containing hydrochloric acid and a trace of stannous chloride yielded small, white, shining flakes melting with decomposition at 360–362° (obs.) on the Bloc Maquenne.

It is readily soluble in alcohol, acetone and pyridine. The pyridine solution rapidly turns dark red in air.

Anal. (Parr Bomb). Calcd. for $C_{24}H_{24}O_4Br_2$: Br, 29.82. Found: Br, 30.14.

Oxidation of the α-Form of the Tetrahydroxy Compound, (XV).—Addition of *p*-benzoquinone to an alcoholic solution of the α-tetrahydroxy compound caused an immediate precipitate of the orange, insoluble α-dihydroxyquinone melting with decomposition at 397–400° on the Bloc Maquenne.

2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-1,3,4,6-tetraacetoxybenzene (α-Form), (XIII).—A mixture of 4 g. of the α-tetrahydroxy compound (XV) and 50 cc. of acetic anhydride was placed in a 300-cc. Erlenmeyer flask and brought to a boil under a reflux condenser. Then 50 cc. of pyridine was added through the condenser and the solution was refluxed for one minute. The solution was then added with stirring to 750 cc. of 4 *N* hydrochloric acid. The white, crystalline product was filtered from the hot solution,

washed twice with 4 *N* hydrochloric acid and then free of the acid with water. A quantitative yield, 5.2 g., of the air-dried tetraacetate was obtained. The crude product was recrystallized first from a mixture of 50 cc. of acetic anhydride and 50 cc. of pyridine and then from 50 cc. of acetic anhydride. Finally one crystallization from *n*-butyl alcohol gave a pure product consisting of long, white needles, melting constantly at 294–295° (corr.).

Anal. (Parr Bomb). Calcd. for $C_{32}H_{32}O_8Br_2$: Br, 22.76. Found: Br, 22.93.

2,5-Di-(3,5-dibromo-2,4,6-trimethylphenyl)-1,3,4,6-tetraacetoxybenzene, (XVII). In a 20-cm. test-tube was placed 1.5 g. of the crude α-tetraacetoxy compound (XIII) and 3 cc. of dry, liquid bromine was added with stirring in 1-cc. portion. The contents were thoroughly stirred and allowed to stand for thirty minutes at room temperature. Hydrogen bromide was freely evolved. The excess bromine was removed by suction and the light yellow solid material remaining was removed and triturated with a saturated solution of sodium bisulfite. It was then filtered, washed with hot water and air dried. The yield of crude product amounted to 1.8 g. It was recrystallized twice from a mixture of 45 cc. of acetic anhydride and 5 cc. of pyridine and a third time from 70 cc. of acetic anhydride alone. There was obtained 1 g. of short white needles melting constantly at 347–348° (corr.).

Anal. (Parr Bomb). Calcd. for $C_{32}H_{30}O_8Br_4$: Br, 37.09. Found: Br, 36.76.

2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-3,6-diacetoxyhydroquinone (α-Form), (XI).—A mixture of 3 g. of the α-diacetoxyquinone (IX), 200 cc. of 95% ethyl alcohol and 5 g. of stannous chloride was refluxed for fifteen minutes. Then 25 cc. of 6 *N* hydrochloric acid was added to discharge the pale yellow color and hot water immediately and gradually added to precipitate the product as white, short, slender needles. The mixture was quickly cooled under the tap and filtered. The mat of needles was washed with 4 *N* hydrochloric acid and then with hot water. The yield was 2.9 g. Two recrystallizations from 75 cc. and 60 cc. of carbon tetrachloride, respectively, gave a white product consisting of short, slender needles, melting constantly at 251–252° (corr.). The compound is readily soluble in acetone, ethyl alcohol and pyridine. The pyridine solution remains colorless in air, in contrast to the pyridine solution of the tetrahydroxy derivative, which quickly turns deep red when exposed to the air.

Anal. (Parr Bomb). Calcd. for $C_{28}H_{28}O_6Br_2$: Br, 25.78. Found: Br, 25.61.

Hydrolysis of α-Diacetoxyhydroquinone, (XI).—A mixture of 0.1 g. of the α-diacetoxyhydroquinone (XI), 30 cc. of glacial acetic acid and 5 cc. of 6 *N* hydrochloric acid was refluxed for fifteen minutes. The product was precipitated by adding water. The crude product thus obtained showed no signs of melting or charring at 325° (obs.) in a paraffin-bath and yielded an acetyl derivative with acetic anhydride and pyridine which, when recrystallized from *n*-butyl alcohol, was identical with the α-tetraacetate (XIII) in melting point, solubility and crystalline appearance.

Acetylation of α-Diacetoxyhydroquinone, (XI).—The α-diacetoxyhydroquinone (XI) yielded an acetyl derivative with acetic anhydride and pyridine identical in melting point, solubility and crystalline appearance with the α-tetraacetoxy compound (XIII) obtained by acetylation of the α-tetrahydroxy compound (XV).

2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-3,6-dihydroxyquinone (β-Form), (VIII).—In a 5-liter, round-bottomed flask equipped with a mechanical stirrer were placed 30 g. of β-2,5-di-(3-bromo-2,4,6-trimethylphenyl)-3,6-dibromoquinone (VI), m. p. 284–285° (corr.), 2 liters of 95% ethyl alcohol and a cold solution of 300 g. of sodium hydroxide in 1500 cc. of water. The mixture was stirred at room temperature for forty-eight hours. As with the α-bromoquinone, the β-bromoquinone slowly dissolved, forming a deep red solution from which part of the β-dihydroxyquinone crystallized in flakes as the deep

red sodium salt. Only 7 g. of the sodium salt was thus obtained. The filtrate from this was diluted with 4 liters of water, allowed to stand for twenty-four hours, decanted and filtered from a small amount of insoluble material and acidified with concentrated hydrochloric acid. The orange, flocculent precipitate was sucked dry on a Büchner funnel. The sodium salt was converted to the dihydroxy compound as described under the alpha compound. The yield of free β-dihydroxyquinone amounted to 22 g. (91%). This material was used for preparing derivatives. It was purified by crystallization from benzene or toluene and formed minute yellow needles melting with decomposition at 387–390° on the Bloc Maquenne.

Anal. (Parr Bomb). Calcd. for $C_{24}H_{22}O_4Br_2$: Br, 29.93; C, 53.93; H, 4.16. Found: Br, 30.03; C, 53.48; H, 4.20.

The difference in solubility in acetone of the α- and β-forms of the dihydroxyquinone is quite marked: 0.05 g. of the β-form dissolved in 10 cc. of hot acetone to a clear, orange-colored solution; 0.05 g. of the α-form would not form a clear solution in 150 cc. of boiling acetone. Likewise the β-form was found to be more soluble in benzene and toluene, in both of which solvents the α-form is practically insoluble. The β-form is also slightly soluble in glacial acetic acid and mesitylene but when attempts were made to crystallize from those solvents a partial conversion of the β-form into the α-form was found to take place.

Sodium Salt of the β-Dihydroxyquinone, (VIII).—The sodium salt of the β-dihydroxyquinone (VIII) was recrystallized from 3% sodium hydroxide solution (4 g. of salt in 150 cc. of alkaline solution). For analysis 0.5 g. was finely pulverized and dried at 110° under reduced pressure.

Anal. (Parr Bomb). Calcd. for $C_{24}H_{20}O_4Br_2Na_2$: Br, 27.65. Found: Br, 27.32.

2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-3,6-diacetoxyquinone (β-Form), (X).—The β-dihydroxyquinone (VIII) was acetylated with acetic anhydride and pyridine under the same conditions as the α-form. Purification from 70% acetone gave light yellow prisms melting constantly at 272–273° (corr.).

Anal. (Parr Bomb). Calcd. for $C_{28}H_{26}O_6Br_2$: Br, 25.86. Found: Br, 25.70.

It is to be noticed that the β-diacetoxyquinone melts at the same point as the α-form. However, there can be no doubt about the existence of two forms, since the solubility of the β-form in acetone is four times as great as the α-form and in 95% ethyl alcohol three to four times greater. Moreover, conversion into various derivatives showed the β-form to be different.

Hydrolysis of β-Diacetoxyquinone, (X).—Upon refluxing 0.25 g. of the β-diacetoxyquinone X for one hour with a mixture of 50 cc. of glacial acetic acid and 10 cc. of 3 *N* hydrochloric acid, the α-dihydroxyquinone (VII) separated as an orange, crystalline precipitate in the boiling solution and separated completely on cooling (0.22 g.). The product was insoluble in acetone. To identify further the α-dihydroxyquinone prepared in this way, it was reduced and acetylated in the manner used previously for this compound and yielded, after purification from *n*-butyl alcohol, long white needles (0.22 g.) which melted at 294–295° (corr.) and proved to be identical with the α-tetraacetoxy compound (XIII).

2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-1,3,4,6-tetrahydroxybenzene (β-Form), (XVI).—The β-dihydroxyquinone (VIII) was reduced to the tetrahydroxy derivative in the same manner as the α-form. The β-tetrahydroxy compound crystallized from dilute alcohol in white, shining plates melting constantly at 355–357° (obs.) on the Bloc Maquenne.

Anal. (Parr Bomb). Calcd. for $C_{24}H_{24}O_4Br_2$: Br, 29.82. Found: Br, 29.62.

It is readily soluble in acetone, ethyl alcohol and pyridine. As with the α-form, the

pyridine solution of the β-form rapidly turns red in air. The β-form is more soluble in dilute alcohol, dilute acetone and glacial acetic acid than the α-form.

Oxidation of the β-Tetrahydroxy Compound, (XVI).—Addition of *p*-benzoquinone to an alcoholic solution of the β-tetrahydroxy compound (XVI) immediately caused a precipitate of the orange, insoluble β-dihydroxyquinone (VIII). That it was the β-dihydroxyquinone rather than the α-form was determined by the fact that the product had the proper melting point and solubility.

2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-1,3,4,6-tetraacetoxybenzene (β-Form), (XIV).—The β-tetrahydroxy compound (XVI) was acetylated with pyridine and acetic anhydride, following the procedure employed for the α-form. After two recrystallizations from *n*-butyl alcohol, a product consisting of long, white needles was obtained, melting constantly at 269–270° (corr.) without decomposition.

Anal. (Parr Bomb). Calcd. for $C_{32}H_{32}O_8Br_2$: Br, 22.76. Found: Br, 22.61.

Of all the derivatives of the two series the tetraacetates differ most widely with respect to melting point and solubility; 0.05 g. of the β-form dissolves in 2 cc. of boiling *n*-butyl alcohol, whereas 0.05 g. of the α-form requires 10–12 cc. of boiling *n*-butyl alcohol. There exists a similar difference in solubility in glacial acetic acid and acetic anhydride.

Bromination of the β-Tetraacetoxy Compound, (XIV).—The β-tetraacetoxy compound (XIV) was brominated in the same way as the α-form. The product was identical with that obtained from the α-form with respect to melting point, solubility, crystalline appearance and bromine content.

Anal. (Parr Bomb). Calcd. for $C_{32}H_{30}O_8Br_4$: Br, 37.09. Found: Br, 36.86.

2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-3,6-diacetoxyhydroquinone (β-Form), (XII).—The β-diacetoxyquinone (X) was reduced and the product purified according to the procedure used for the α-form. After two recrystallizations from carbon tetrachloride, a product consisting of short, fine, white needles was obtained melting constantly at 240–241° (corr.).

Anal. (Parr Bomb). Calcd. for $C_{28}H_{28}O_6Br_2$: Br, 25.78. Found: Br, 25.65.

The two forms have approximately the same solubility in carbon tetrachloride, ethyl alcohol and glacial acetic acid, but the β-form is more soluble in acetone. The pyridine solution of the diacetoxyhydroquinone remains colorless in air in contrast to the tetrahydroxy compound which turns red.

Hydrolysis of the β-Diacetoxyhydroquinone, (XII).—A mixture of 0.1 g. of the β-diacetoxyhydroquinone (XII) with 30 cc. of glacial acetic acid and 5 cc. of 6 *N* hydrochloric acid was refluxed for thirty minutes. The product was precipitated with water. In the crude state it showed no sign of melting at 325° in an oil-bath. It was acetylated with pyridine and acetic anhydride and the crude product recrystallized from *n*-butyl alcohol. It melted constantly at 269–270° (corr.), the pure β-tetraacetoxy compound.

Acetylation of β-Diacetoxyhydroquinone, (XII).—Acetylation of 2 g. of the β-diacetoxyhydroquinone (XII) with pyridine and acetic anhydride according to the procedure employed for acetylation of the α-tetrahydroxy compound (XV) yielded an acetyl derivative identical in melting point, solubility and crystalline appearance with the β-tetraacetate.

2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-3,6-dibutyroxyquinone (α-Form), (IX).—A solution of 1.5 g. of the α-dihydroxyquinone (VII) in 20 cc. of pyridine and 10 cc. of *n*-butyric anhydride was boiled for one minute and immediately thrown into 250 cc. of 6 *N* hydrochloric acid. The mixture was shaken until all of the butyric anhydride was decomposed and the light yellow product solidified. The crude yield amounted to 2.0 g.

It was recrystallized twice from 95% ethyl alcohol, using 80 cc. the first time and 65 cc. the second. One and one-half grams of yellow plates melting constantly at 167° (corr.) was obtained.

Anal. (Parr Bomb). Calcd. for $C_{32}H_{34}O_6Br_2$: Br, 23.72. Found: Br, 23.92.

2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-3,6-dibutyroxyquinone (β-Form), (X).—The β-dibutyroxy form was made in exactly the same way as the α-form. It was crystallized twice from 95% ethyl alcohol. From 1.4 g. of β-dihydroxyquinone (VIII) 1.1 g. of large yellow needles of the β-dibutyroxyquinone melting constantly at 147° (corr.) was obtained. The β-form is more soluble in ethyl alcohol, methyl alcohol and acetone than the α-form.

Anal. (Parr Bomb). Calcd. for $C_{32}H_{34}O_6Br_2$: Br, 23.72. Found: Br, 23.80.

2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-1,3,4,6-tetrabutyroxybenzene (α-Form), (XIII).—A mixture of 1.5 g. of the α-dihydroxyquinone (VII), 150 cc. of 95% ethyl alcohol, and 3.0 g. of stannous chloride was refluxed for fifteen minutes. Fifteen cc. of 6 *N* hydrochloric acid was added and refluxing continued until a colorless solution had formed. The α-tetrahydroxy compound was precipitated by adding hot water. It was filtered and treated with a mixture of 10 cc. of *n*-butyric anhydride and 20 cc. of pyridine. The 2.0 g. of crude product was isolated in the same way as the dibutyroxyquinones and crystallized three times from methyl alcohol, using 15 cc., 12 cc. and 9 cc., respectively. One gram of white prisms melting constantly at 124° (corr.) was obtained.

Anal. (Parr Bomb). Calcd. for $C_{40}H_{48}O_8Br_2$: Br, 19.58. Found: Br, 19.57.

2,5-Di-(3-bromo-2,4,6-trimethylphenyl)-1,3,4,6-tetrabutyroxybenzene (β-Form), (XIV).—Two and one-half grams of the β-dihydroxyquinone (VIII) was reduced and converted to the tetrabutyrate following the method used for the α-form. The crude product was colored dark blue, but three crystallizations from methyl alcohol, using 15 cc., 10 cc. and 5 cc. respectively, yielded 1.3 g. of pure white prisms melting constantly at 103° (corr.). The β-form is more soluble in methyl alcohol than the α-form. A mixture of 95 parts of this β-form and 5 parts of the corresponding α-form melted 98–99.5°.

Anal. (Parr Bomb). Calcd. for $C_{40}H_{48}O_8Br_2$: Br, 19.58. Found: Br, 19.64.

Conversion of the β-Dihydroxyquinone (VIII) to the α-Form in Boiling Mesitylene or in Boiling Glacial Acetic Acid.—A solution of 0.25 g. of the β-dihydroxyquinone (VIII) in 150 cc. of mesitylene was refluxed for ten hours. Then 125 cc. of mesitylene was distilled off. The distilling flask was cooled and the product filtered; 0.24 g. of fine orange needles was recovered. It was reduced with 95% ethyl alcohol, 6 *N* hydrochloric acid and stannous chloride. The white product thus obtained was acetylated with 5 cc. of acetic anhydride and 5 cc. of pyridine. The crude tetraacetate weighed 0.27 g. It was crystallized from 60 cc. of *n*-butyl alcohol, from which was obtained 0.23 g. of white needles melting constantly at 294–295° (corr.). This product had all the properties of the α-tetraacetate (XIII).

A solution of 0.25 g. of the β-dihydroxyquinone (VIII) in 250 cc. of glacial acetic acid was refluxed for ten hours. Initially all of the material was in solution. At the end of five hours a precipitate of short, fine, yellow needles appeared. By distillation 225 cc. of solvent was removed and the remaining mixture cooled and filtered; 0.24 g. of material was recovered. It was reduced and acetylated as usual. The 0.25 g. of crude tetraacetate was crystallized from 60 cc. of *n*-butyl alcohol. There was obtained 0.21 g. of white needles of the α-tetraacetate melting at 294–295° (corr.) (XIII).

Conversion of the β-Diacetoxyquinone (X) to the α-Form in Boiling Mesitylene.—A solution of 0.25 g. of the β-diacetoxyquinone (X) in 50 cc. of mesitylene was refluxed for ten hours. Then 40 cc. of mesitylene was removed by distillation; the remainder was

steam-distilled out. The solid, yellow residue was reduced with ethyl alcohol, hydrochloric acid and stannous chloride. The white diacetoxyhydroquinone was precipitated by adding water. The product was acetylated with pyridine and acetic anhydride and the tetraacetate isolated as usual by pouring into excess 4 *N* hydrochloric acid. The yield of crude product amounted to 0.22 g. This, when crystallized from 50 cc. of *n*-butyl alcohol, gave 0.18 g. of material melting at 292–294° (corr.). Another crystallization gave the correct melting point of 294–295° for the α-tetraacetate (XIII).

Conversion of the β-Dibutyroxyquinone (X) to the α-Form in Boiling Mesitylene or by Heating.—A solution of 0.2 g. of the β-dibutyroxyquinone (X) in 50 cc. of mesitylene was refluxed for ten hours. By distillation 40 cc. of mesitylene was removed and the remainder was steam-distilled out. There was thus obtained 0.17 g. of product which was crystallized from 8 cc. of methyl alcohol; 0.13 g. of yellow plates melting at 165–167° was obtained which was obviously the α-dibutyroxy form (IX).

One-tenth gram of the β-dibutyroxyquinone (X) was placed in a 2-inch test-tube and heated at 175–180° (corr.) for three hours. The tube was carefully broken and the contents crystallized twice from 95% ethyl alcohol. There was obtained 0.04 g. of small yellow plates melting at 166–167° (corr.), the α-form (IX).

Attempted Conversion of β-Forms to α-Forms.—The β-diacetoxyhydroquinone (XII), the β-tetrahydroxy (XVI) compound and the β-tetraacetoxy (XIV) compound could not be converted to the α-forms after ten hours in boiling mesitylene. Neither could the β-dihydroxyquinone in boiling 3 *N* sodium hydroxide solution be converted to the α-form. The procedures followed were those employed in the above conversions.

The conversion of the β-dibromoquinone (VI) was attempted in two ways. A solution of 0.50 g. of the β-dibromoquinone in 100 cc. of boiling glacial acetic acid was refluxed for ten hours. Upon cooling 0.25 g. of orange prisms separated. The remainder in solution was precipitated by adding water to the mother liquor; total material recovered, 0.49 g. This was reduced with pyridine and stannous chloride. The white reduction product was crystallized from a mixture of 10 cc. of acetone and 2 cc. of water containing ten drops of 6 *N* hydrochloric acid and a trace (10 mg.) of stannous chloride. Upon standing, long, slender, white needles formed. The first crop amounted to 0.15 g. and melted at 294–295° (corr.), the pure β-dibromohydroquinone.

A solution of 1.5 g. of the β-dibromoquinone in 150 cc. of mesitylene was refluxed for ten hours. The orange tint of the solution deepened somewhat. The mesitylene was steam distilled out and the orange solid remaining, which could not be crystallized satisfactorily from toluene, was dissolved in 750 cc. of boiling 95% ethyl alcohol to which 0.5 g. of benzoquinone was added. The orange-colored solution was filtered and concentrated to 200 cc., during which time an orange, crystalline precipitate appeared. After cooling, this was filtered and washed with cold methyl alcohol (0.50 g.). In the same bath with the pure β-dibromoquinone the orange material isolated above melted with decomposition at 282–283° (corr.); the pure β-form at 284–285° (corr.). The product was reduced with pyridine and stannous chloride. The white hydroquinone was crystallized from a mixture of 10 cc. of acetone and 2 cc. of water containing ten drops of 6 *N* hydrochloric acid and 5 mg. of stannous chloride. The first crop of long, slender, white needles amounted to 0.13 g. and melted at 294–295° (corr.), the pure β-dibromohydroquinone.

Summary

1. By treatment of the two diastereoisomeric 2,5-di-(3-bromo-2,4,6-trimethylphenyl)-3,6-dibromohydroquinones (V + VI) with aqueous sodium hydroxide there were obtained two stereoisomeric 2,5-di-(3-bromo-2,4,6-trimethylphenyl)-3,6-dihydroxyquinones (VII + VIII).

2. Each of these two latter compounds formed an individual series of derivatives—namely, the diacetoxyquinone, the dibutyroxyquinone, the diacetoxyhydroquinone, the tetrahydroxy compound, the tetraacetoxy and tetrabutyroxy compounds.

3. The two series were designated as α and β. The α denotation was given to the series of higher melting and less soluble compounds, the β was given to the series of lower melting and more soluble compounds. On the assumption that the higher melting tetrahydroxy and tetraacylated derivatives are the *trans* modifications, it follows that throughout the two series, the *trans* or α forms are meso, the *cis* or β forms are racemic.

4. The α and β tetrahydroxy, tetraacetoxy and tetrabutyroxy derivatives represent pairs of *cis* and *trans* isomers. No individual in any pair is capable of resolution. On the other hand, the α and β hydroxyquinones, acetoxyquinones, butyroxyquinones and the acylated hydroquinones represent pairs of *cis* and *trans* forms, in each pair of which one is a meso and the other a racemic modification.

5. The β-dihydroxyquinone, the β-diacetoxyquinone and the β-dibutyroxyquinone can be converted to the corresponding α forms by heating in a high boiling solvent. The β-diacetoxyquinone on hydrolysis gives the α-dihydroxyquinone.

6. The α and β tetraacetoxy compounds, on bromination, give the same compound, 2,5-di-(3,5-dibromo-2,4,6-trimethylphenyl)-1,3,4,6-tetraacetoxybenzene.

URBANA, ILLINOIS

[CONTRIBUTION NO. 73 FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

DESOXYCODEINE STUDIES. I. THE DESOXYCODEINES[1]

BY LYNDON F. SMALL AND FRANK L. COHEN

RECEIVED FEBRUARY 9, 1931 PUBLISHED JUNE 8, 1931

The name desoxycodeine has been used to designate the compound $C_{18}H_{21}O_2N$, containing one less oxygen atom than codeine. It was first described and investigated by Knorr and Waentig,[2,3] who prepared it by refluxing α-chlorocodide (II), bromocodide, β-chlorocodide[4] or pseudo-

[1] This investigation was supported by a grant from the Committee on Drug Addiction of the National Research Council from funds provided by the Bureau of Social Hygiene, Inc.

[2] Knorr and Waentig, *Ber.*, **40**, 3860 (1907).

[3] A base having the same formula was mentioned by Wright [*Proc. Roy. Soc.* (London), **19**, 371 (1870); *J. Chem. Soc.*, **24**, 404 (1871)] as being formed when codeine is heated with hydrobromic acid; Wright's desoxycodeine has never been further investigated.

[4] Knorr and Hörlein, *Ber.*, **40**, 4883 (1907).