(92.0%) of crystalline $\Delta^{9,11}$ compound (**28**) showing a single spot on paper chromatography.

9α-Bromo-16α-fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (27).—A solution of 8.3 ml. of 70–72% perchloric acid in 53 ml. of water was added to 2.65 g. of **28** dissolved in 48 ml. of methylene chloride and 160 ml. of *t*-butyl alcohol. To this mixture was added 1.19 g. of N-bromoacetamide in 32 ml. of *t*-butyl alcohol. After stirring the reaction mixture for 15 min., an excess of dilute sodium sulfite solution was added. Most of the *t*-butyl alcohol was distilled under vacumn, and 200 ml. of water was added. The bromide (**27**) recovered by filtration weighed 2.98 g. (90.5%). Paper chromatography showed only one spot moving slower than the starting unsaturated compound.

16α-Fluoro-17α,21-dihydroxy-9β,11β-oxido-1,4-pregnadiene-3,-20-dione 21-Acetate (29).—A mixture of 2.98 g. of bromide (**27**) and 3.6 g. of potassium acetate in 160 ml. of acetone was heated under reflux for 17 hr. The solvent was distilled under vacuum and the residue triturated four times with methylene chloride. The methylene chloride solution was passed over 200 g. of Florisil. The fractions eluted with Skellysolve B–15% and 20% acetone were combined to yield 2.13 g. (84.0% yield) of oxide. A fraction of 367 mg. which contained both oxide and bromohydrin was recycled to yield 135 mg. (5.4% yield) of additional oxide.

9α,16α-Difluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (25).—A solution of 2.26 g. of oxide (**29**) dissolved in 88 ml. of methylene chloride was cooled to −20° and added to a similarly chilled solution of 18.1 g. of hydrogen fluoride dissolved in 31 ml. of freshly distilled tetrahydrofuran. After thorough mixing the solution was maintained at 4° for 15 hr. The reaction mixture was added to 2.3 l. of water containing 57 g. of potassium bicarbonate. The product was removed by extraction with methylene chloride. Chromatography over Florisil (eluted with Skellysolve B–20% acetone) afforded 2.02 g. (85.3% yield) of crystalline difluoride (**25**). Paper chromatography[19] showed only one spot. The analytical sample, prepared from ethyl acetate–Skellysolve B, melted at 265–268° dec.

Anal. Calcd. for $C_{23}H_{28}F_2O_6$: C, 63.00; H, 6.44; F, 8.67. Found: C, 62.61; H, 6.59; F, 8.60.

9α,16α-Difluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione (26).—A mixture of 1.31 g. of 9α,16α-difluoroprednisolone acetate (**25**), 1.3 g. of potassium bicarbonate, 13 ml. of water, and 130 ml. of methanol was stirred at 26° under nitrogen for 5 hr. The solution was neutralized with acetic acid and concentrated to dryness. The residue was triturated with water and filtered to yield 1.04 g. (89%) of crude product. Recrystallization from acetone afforded 700 mg. (59.4%) of **26**, m.p. 275–278° dec., and a second crop of 160 mg. (13.5%), m.p. 275–278° dec.

The analytical sample prepared from ethyl acetate–acetone melted at 278–280°.

Anal. Calcd. for $C_{21}H_{26}F_2O_5$: C, 63.62; H, 6.61. Found: C, 63.62; H, 6.60.

16α-Fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione (23).—Saponification of 880 mg. of **20** in the manner described for the preparation of **26** afforded 725 mg. (91.8%) of crude product. Recrystallization from acetone–ethyl acetate gave 450 mg. (57.0% yield) of **23**; m.p. 243–247° dec.; $[\alpha]_D$ +81° (acetone).

Anal. Calcd. for $C_{21}H_{27}FO_5$: C, 66.65; H, 7.19; F, 5.02. Found: C, 66.68; H, 7.55; F, 5.18.

16α-Fluoro-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione (24).—16α-Fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione (**23**) (640 mg., made up in part of mother liquors) was dissolved in 6 ml. of pyridine, cooled to 0°, and 0.8 ml. of mesyl chloride added. After 15 hr. at 4° the dark solution was poured into 150 ml. of dilute hydrochloric acid. The yield of crude mesylate was 530 mg. This solid was dissolved in 30 ml. of acetone, 500 mg. of sodium iodide added, and the mixture heated under reflux for 15 min. The solvent was distilled under reduced pressure and the residue was taken up in 8 ml. of acetic acid. After 50 min. at 26° a solution of 0.6 g. of sodium thiosulfate in 8 ml. of water was added followed by 70 ml. of water. The steroid was recovered by extraction with methylene chloride. The extract was passed over 40 g. of Florisil. The fractions eluted with Skellysolve B–20% and 30% acetone were combined and recrystallized from acetone–ethyl acetate yielding 210 mg. of **24**, m.p. 256–260° dec. One recrystallization from acetone raised the melting point to 266–270° dec. (140 mg.).

Anal. Calcd. for $C_{21}H_{27}FO_4$: C, 69.59; H, 7.51. Found: C, 69.38; H, 7.54.

Acknowledgment.—The authors gratefully acknowledge the services of the Department of Physical and Analytical Chemistry of The Upjohn Company for analytical data, rotations, and absorption spectra, and to Mr. G. E. VandenBerg for technical assistance.

Purine Nucleosides. V. Preparation and Reactions of Some 9β-D-Ribofuranosyl-3,5′-purine Cyclonucleosides[1,2]

RICHARD E. HOLMES AND ROLAND K. ROBINS

Department of Chemistry, Arizona State University, Tempe, Arizona

Received June 27, 1963

The 3,5′-cyclonucleosides of guanosine and xanthosine have been prepared. It has been established that cyclization occurred at position 3 since acid hydrolysis gave a 3-substituted purine as judged by ultraviolet absorption data. The synthesis of 2′,3′-*O*-isopropylidene-3,5′-inosine cyclonucleoside has been accomplished. Acid hydrolysis of 2′,3′-*O*-isopropylidene-3,5′-adenosine cyclonucleoside *p*-tolylsulfonate resulted in cleavage of the glycosidic linkage at position 9 to give 3,5′-(5′-deoxy-D-ribofuranosyl)adenine (XIII).

The first reported isolation and characterization of a purine cyclonucleoside was that of Clark, Todd, and Zussman[3] who prepared 2′,3′-*O*-isopropylidene-3,5′-adenosine cyclonucleoside *p*-tolylsulfonate (I) from 2′,3′-*O*-isopropylidene-5′-*O*-(*p*-tolylsulfonyl)adenosine. An X-ray analysis confirmed the structure of I and provided proof of the β configuration of adenosine. Baker and Joseph[4] have reported a similar cyclization at position 3 with the compound 6-dimethylamino-9-(3′-amino-3′-deoxy-5′-mesyl-β-D-ribofuranosyl)purine 2′,3′-carbonate. The ease of formation of a 3,5′-purine cyclonucleoside has been related to the basicity of the heterocyclic system.[3,5] Khorana and co-workers[6] have reported that 2′,3′-*O*-isopropylideneguanosine 5′-*O*-[di(*p*-nitrophenyl)phosphate] was converted to a cyclonucleoside in refluxing acetonitrile. Baker and co-workers[5] treated 2′,3′-*O*-isopropylidene-5′-*O*-(*p*-tolylsulfonyl)guanosine with sodium iodide in acetonylacetone to obtain a 2′,3′-*O*-isopropylideneguanosine cyclonucleoside as the iodide

(1) This research was supported by grant NSF-G13291 from the National Science Foundation.

(2) Presented in part at the 144th National Meeting of the American Chemical Society, Division of Carbohydrate Chemistry, Los Angeles, Calif., April, 1963.

(3) V. M. Clark, A. R. Todd, and J. Zussman, *J. Chem. Soc.*, 2952 (1951).

(4) B. R. Baker and J. P. Joseph, *J. Am. Chem. Soc.*, **77**, 15 (1955).

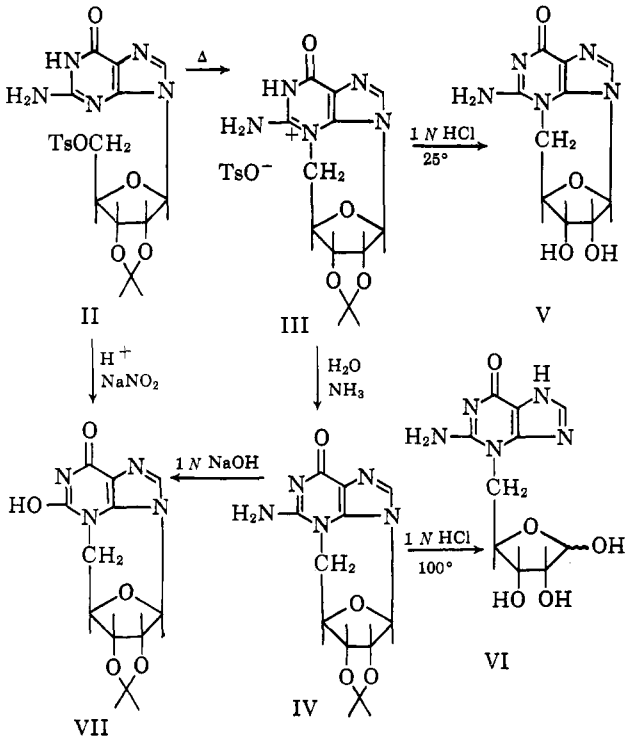
(5) E. J. Reist, P. A. Hart, L. Goodman, and B. R. Baker, *J. Org. Chem.*; **26**, 1557 (1961).

(6) R. W. Chambers, J. G. Moffatt, and H. G. Khorana, *J. Am. Chem. Soc.*, **79**, 3747 (1957).

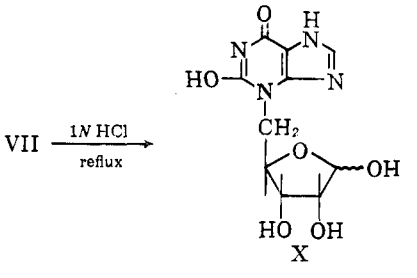
salt. Although in the instances of guanosine cyclonucleoside formation, quaternization was assigned tentatively to position 3, possible cyclization involving the 2-amino group was not excluded by these workers.[5,6] It has now been discovered that heating 2′,3′-*O*-isopropylidene-5′-*O*-(*p*-tolylsulfonyl)guanosine (II)[5] in acetonylacetone (in the absence of sodium iodide) is sufficient to cause cyclonucleoside formation.

The preparation of 2′,3′-*O*-isopropylidene-3,5′-guanosine cyclonucleoside *p*-tolylsulfonate (III) can be readily followed in this reaction by loss of the covalent sulfonate band at 8.5 μ in the infrared[5] and the appearance of a new band (ionic sulfonate) at 9.8 μ. When III was treated with ammonium hydroxide, 2′,3′-*O*-isopropylidene-3,5′-guanosine cyclonucleoside (IV), free of *p*-tolylsulfonate, was readily isolated. Treatment of III or IV with dilute hydrochloric acid cleaved the isopropylidene linkage to give 3,5′-guanosine cyclonucleoside (V). A refluxing solution of IV in 1 *N* hydrochloric acid resulted in the cleavage of the glycosidic linkage at position 9 and provided 3,5′-(5′-deoxy-D-ribofuranosyl)guanine (VI) in good yield. The ultraviolet absorption spectrum of VI proved to be similar to that of 3-methylguanine.[7] The ultraviolet absorption spectrum of a 3-alkylguanine is very characteristic,[7] and, therefore, the site of cyclonucleoside formation is established at position 3 in the guanosine molecule. Further evidence which excludes the 2-amino group as a site of cyclization was found in the reaction of 2′,3′-*O*-isopropylidene-3,5′-guanosine cyclonucleoside (IV) with hot 1 *N* sodium hydroxide. Under these conditions 2′,3′-*O*-isopropylidene-3,5′-xanthosine cyclonucleoside (VII) was obtained. This compound exhibited ultraviolet absorption maxima characteristic of 3,9-dimethylxanthine.[8] The preparation of VII directly *via* 2′,3′-*O*-isopropylidene-5′-*O*-(*p*-tolylsulfonyl)xanthosine (VIII) was not possible since VIII could not be obtained from 2′,3′-*O*-isopropylidenexanthosine and *p*-toluenesulfonyl chloride in pyridine. The 2′,3′-*O*-isopropylidenexanthosine required for this study was prepared by treatment of 2′,3′-*O*-isopropylideneguanosine[6] with sodium nitrite and acetic acid.

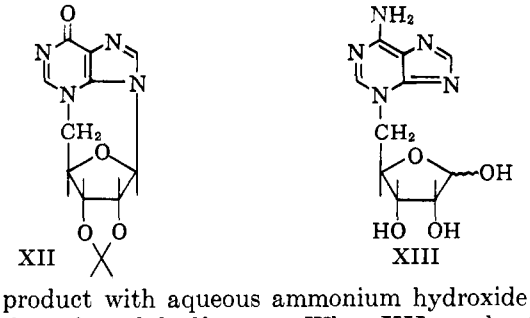
REACTION SCHEME I



An attempt was made to prepare 2′,3′-*O*-isopropylidene-5′-*O*-(*p*-tolylsulfonyl)xanthosine (VIII) from 2′,3′-*O*-isopropylidene-5′-*O*-(*p*-tolylsulfonyl)guanosine (II) with sodium nitrite and glacial acetic acid. This treatment however resulted in the isolation of 2′,3′-*O*-isopropylidene-3,5′-xanthosine cyclonucleoside (VII) in good yield. It was clear that replacement of the 2-amino group by hydroxyl preceded cyclonucleoside formation at position 3 since under identical conditions IV failed to diazotize. The failure of the diazotization of 3-methylguanine under similar conditions has previously been noted.[7] Treatment of VII with dilute hydrochloric acid cleaved the isopropylidene group to give 3,5′-xanthosine cyclonucleoside (IX). Refluxing aqueous mineral acid cleaved the glycosidic linkage and gave 3-5′(5′-deoxy-D-ribofuranosyl)xanthosine (X). The ultraviolet absorption spectra of X exhibited the same maxima as 3-methylxanthine.[8] This is additional confirmation of position 3 as the site of cyclization in these purine cyclonucleosides.



Although 2′,3′-*O*-isopropylidene-5′-*O*-(*p*-tolylsulfonyl)inosine (XI) has been noted[5] to be resistant to cyclonucleoside formation,[4,9,10] the synthesis of 2′,3′-*O*-isopropylidene-3,5′-inosine cyclonucleoside (XII) is here reported for the first time, prepared by heating XI in refluxing dioxane. The formation of XII is characterized by a shift of λ_{max}^{EtOH} from 250 to 256 mμ, as well as a change of the covalent *p*-tolylsulfonate band to ionic as noted in the infrared. Treatment of



the product with aqueous ammonium hydroxide gave XII free of *p*-tolylsulfonate. When XII was heated in 1 *N* hydrochloric acid for one hour on the steam bath, the formation of at least five different products was noted as judged by paper chromatography. The re-

(7) L. B. Townsend and R. K. Robins, *J. Am. Chem. Soc.*, **84**, 3008 (1962); G. B. Elion, *J. Org. Chem.*, **27**, 2478 (1962).

(8) W. Pfleiderer and G. Nübel, *Ann.*, **647**, 155 (1961).

(9) J. Baddiley, *J. Chem. Soc.*, 1348 (1951).

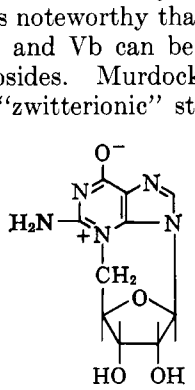
(10) K. Satoh and K. Makino, *Nature*, **167**, 238 (1951).

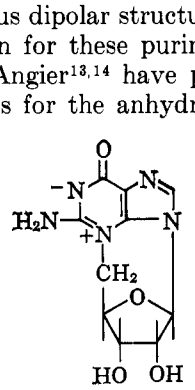
action mixture was, therefore, not investigated further.

Although Levene and Tipson[11] claim to have changed 2′,3′-*O*-isopropylidene-5′-*O*-(*p*-tolylsulfonyl)inosine to the corresponding covalent 5′-iodo derivative with sodium iodide and acetone in a sealed tube at 100°, the product was not adequately characterized. When this procedure was repeated in our laboratory, the presence of XII in the reaction products was indicated by paper chromatography and ultraviolet absorption data.

Acid hydrolysis of 2′,3′-*O*-isopropylidene-3,5′-adenosine cyclonucleoside[3] resulted in cleavage of the glycosidic linkage at position 9 to give 3-5′(5′-deoxy-D-ribofuranosyl)adenine (XIII). The ultraviolet absorption spectra of XIII were found to be similar to those recorded for 3-methyladenine.[12]

It is noteworthy that various dipolar structures such as Va and Vb can be written for these purine cyclonucleosides. Murdock and Angier[13,14] have proposed such "zwitterionic" structures for the anhydronucleo-


Va


Vb

sides of thymine and uracil. Our study of the purine cyclonucleosides reveals that these compounds, in general, exhibit unusually high solubility in water and run much slower than the corresponding naturally occurring purine nucleosides in the usual chromatographic solvent systems such as butanol saturated with water or butanone–water (9:1).[14] Such behavior has previously been correlated with the ionic structures of certain nucleosides.[14,15] From these observations it would appear that dipolar forms certainly make a considerable contribution to the structures of such compounds as V, VII, and XII.

Experimental

2′,3′-*O*-Isopropylidene-3,5′-guanosine Cyclonucleoside *p*-Tolylsulfonate (III).—2′,3′-*O*-Isopropylidene-5′-*O*-(*p*-tolylsulfonyl)guanosine[5] (30 g.) was added to 500 ml. of acetonylacetone. The mixture was heated, with stirring, at 100–110° for 4 hr. and then cooled overnight in the refrigerator. The mixture was filtered and the filter cake washed with a little acetone and dried to yield 28 g. of product approximately 90% pure. Recrystallization from water gave a pure product melting at >300°. The infrared spectrum exhibited an ionic sulfonate band at 9.8 μ and no covalent sulfonate band at 8.5 μ. This compound exhibited ultraviolet absorption spectra similar to that recorded for 2′,3′-*O*-isopropylidene-3,5′-guanosine cyclonucleoside iodide[5] and 2′,3′-*O*-isopropylidene-3,5′-guanosine cyclonucleoside di(*p*-nitrophenyl)phosphate.[6]

Anal. Calcd. for $C_{20}H_{23}N_5O_7S$: C, 50.2; H, 4.8; N, 14.6. Found: C, 49.9; H, 4.6; N, 14.3.

2′,3′-*O*-Isopropylidene-3,5′-guanosine Cyclonucleoside (IV).—2′,3′-*O*-Isopropylidene-3,5′-guanosine cyclonucleoside *p*-tolylsulfonate (III, 28 g., finely ground) was added to a stirring solution of 200 ml. of water. The pH of the solution was adjusted to 7 by the addition of 4 ml. of concentrated ammonium hydroxide. The mixture was cooled in the refrigerator overnight, and the product was filtered and recrystallized from water to yield 14.3 g. of long white needles, m.p. 250° dec.; ultraviolet data, $\lambda_{max}^{pH\ 1}$ 247 mμ (ε 19,700), $\lambda_{max}^{pH\ 11}$ 266 mμ (ε 18,100). No ionic *p*-tolylsulfonate band at 9.8 μ could be found in the infrared spectrum.

Anal. Calcd. for $C_{13}H_{15}N_5O_4$: C, 51.2; H, 4.9; N, 22.9. Found: C, 51.3; H, 5.4; N, 22.5.

3,5′-Guanosine Cyclonucleoside (V).—2′,3′-*O*-Isopropylidene-3,5′-guanosine cyclonucleoside (IV, 3 g.) was added to 20 ml. of 1 *N* hydrochloric acid. The solution was stirred overnight at room temperature, then neutralized to pH 7 with ammonium hydroxide, and evaporated to dryness *in vacuo* at room temperature. The resulting solid was dissolved in a minimum amount of hot water, and the solution was cooled overnight in the refrigerator. The precipitate that formed was filtered and washed with a little water and then recrystallized again from water to yield 1.6 g. of product, m.p. >255° dec.; ultraviolet data, $\lambda_{max}^{pH\ 1}$ 247 mμ (ε 11,800), $\lambda_{max}^{pH\ 11}$ 265 mμ (ε 11,500).

Anal. Calcd. for $C_{10}H_{11}N_5O_4$: C, 45.3; H, 4.2; N, 26.4. Found: C, 45.0; H, 4.5; N, 25.9.

3-5′(5′-Deoxy-D-ribofuranosyl)guanine (VI).—2′,3′-*O*-Isopropylidene-3,5′-guanosine cyclonucleoside (IV, 3 g.) was added to 20 ml. of 1 *N* hydrochloric acid. The solution was heated for 50 min. on the steam bath, then treated with charcoal, filtered, neutralized to pH 7 with ammonium hydroxide, and set in the refrigerator overnight. The precipitate was filtered and recrystallized from water to yield 1.7 g. of product, m.p. >200°; gradually dec.; ultraviolet data, $\lambda_{max}^{pH\ 1}$ 263 mμ (ε 11,900), $\lambda_{max}^{pH\ 11}$ 273 mμ (ε 14,200).

Anal. Calcd. for $C_{10}H_{13}N_5O_5$: C, 42.4; H, 4.6; N, 24.8. Found: C, 42.3; H, 4.8; N, 25.1.

2′,3′-*O*-Isopropylidenexanthosine.—To a stirred solution of 500 ml. of glacial acetic acid and 500 ml. of water was added a solution of 50 g. of 2′,3′-*O*-isopropylideneguanosine and 50 g. of sodium nitrite dissolved in 1% sodium hydroxide solution (750 ml.). The temperature was kept between 20–25° during the addition (approximately 5 min.). After 45 min. a precipitate began to form, and the reaction was allowed to continue for 3 hr. The solution was then allowed to stand overnight at 5°, and the precipitate was filtered and washed with water. After recrystallization from water, 24.8 g. of product was obtained; m.p. >300° dec.; ultraviolet data, $\lambda_{max}^{pH\ 1}$ 263 and 235 mμ (ε 9100 and 7900), $\lambda_{max}^{pH\ 11}$ 277 and 248 mμ (ε 8600 and 10,100).

Anal. Calcd. for $C_{13}H_{16}N_4O_6$: C, 48.1; H, 4.9; N, 17.3. Found: C, 47.9; H, 5.1; N, 17.3.

2′,3′-*O*-Isopropylidene-3,5′-xanthosine Cyclonucleoside (VII). Method A.—2′,3′-*O*-Isopropylidene-3,5′-guanosine cyclonucleoside (IV, 10 g.) was added to 60 ml. of 1 *N* sodium hydroxide. The solution was heated on the steam bath for 1 hr., cooled, and neutralized to pH 7 with 50% acetic acid. After cooling the solution overnight in the refrigerator, a product separated. The precipitate was filtered and recrystallized from water to yield 4.8 g. of colorless platelets, m.p. 210–212°; ultraviolet data, $\lambda_{max}^{pH\ 1}$ 265 and 240 mμ (ε 8800 and 7200), $\lambda_{max}^{pH\ 11}$ 267 mμ (ε 9700).

Anal. Calcd. for $C_{13}H_{14}N_4O_5 \cdot H_2O$: C, 48.1; H, 4.9; N, 17.3; H_2O, 5.6. Found: C, 48.4; H, 5.4; N, 17.3; H_2O, 6.2.

Method B.—To a mixture of 5 g. of 2′,3′-*O*-isopropylidene-5′-*O*-(*p*-tolylsulfonyl)guanosine,[5] in 50 ml. of glacial acetic acid, was slowly added with stirring 5 g. of sodium nitrite. The reaction was allowed to continue for 3 hr., and then the excess glacial acetic acid was removed *in vacuo* at room temperature. The resulting solid was dissolved in a small amount of boiling water, and the solution was allowed to cool in the refrigerator. The crystallized product was filtered and recrystallized from water to give 1.9 g. of colorless platelets, m.p. 210–212°. The infrared and ultraviolet absorption spectra were identical to those of the product prepared by method A.

Method C.—2′,3′-*O*-Isopropylidene-5′-*O*-(*p*-tolylsulfonyl)-guanosine[5] (5 g.) was added to 50 ml. of 1 *N* sodium hydroxide, and the mixture was heated on the steam bath for 1 hr. The hot solution was treated with charcoal, filtered, and then neutralized to pH 7 with glacial acetic acid. The mixture was cooled overnight in the refrigerator, and the precipitate that formed was filtered and recrystallized from water to yield 1.5 g. of product, m.p. 210–212°. The infrared and ultraviolet absorption spectra

(11) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **111**, 313 (1935).
(12) J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.*, **84**, 1914 (1962).
(13) K. C. Murdock and R. B. Angier, *Tetrahedron Letters*, 415 (1962).
(14) K. C. Murdock and R. B. Angier, *J. Am. Chem. Soc.*, **84**, 3748 (1962).
(15) J. W. Jones and R. K. Robins, *ibid.*, **85**, 193 (1963).

of the product prepared by methods A, B, and C were identical. Mixture melting points also established the identity of the products.

3,5′-Xanthosine Cyclonucleoside (IX).—2′,3′-*O*-Isopropylidene-3,5′-xanthosine cyclonucleoside (VII, 4 g.) was stirred overnight in 30 ml. of 1 *N* hydrochloric acid. The solution was neutralized to pH 7 with ammonium hydroxide and then evaporated to dryness *in vacuo*. The solid residue was dissolved in a minimum amount of hot water, and the solution was allowed to cool overnight in the refrigerator. The solid that precipitated was filtered to yield 1.8 g. A small sample was recrystallized from a little water to give a product, m.p. 222–224°; ultraviolet data, $\lambda_{max}^{pH\ 1}$ 265 and 240 mμ (ε 8000 and 6500), $\lambda_{max}^{pH\ 11}$ 267 mμ (ε 9100).

Anal. Calcd. for $C_{10}H_{10}N_4O_5$: C, 45.1; H, 3.8; N, 21.1. Found: C, 44.7; H, 3.4; N, 21.4.

3-5′(5′-Deoxy-D-ribofuranosyl)xanthosine (X).—2′,3′-*O*-Isopropylidene-3,5′-xanthosine cyclonucleoside (VII, 2 g.) was dissolved in 50 ml. of 1 *N* hydrochloric acid. The solution was heated for 1 hr. on the steam bath, cooled, treated with charcoal, filtered, and neutralized to pH 7 with ammonium hydroxide. The resulting solution was evaporated to dryness *in vacuo*, and the residue was dissolved in a minimum amount of hot water and allowed to cool overnight in the refrigerator. The precipitate was filtered and recrystallized from water to give a product (0.6 g.), m.p. 179–182° dec.; ultraviolet data, $\lambda_{max}^{pH\ 1}$ 269 mμ (ε 10,200), $\lambda_{max}^{pH\ 11}$ 274 mμ (ε 11,700).

Anal. Calcd. for $C_{10}H_{12}N_4O_6$: C, 42.3; H, 4.2; N, 19.7. Found: C, 41.9; H, 4.5; N, 19.4.

3-5′(5′-Deoxy-D-ribofuranosyl)adenine (XIII).—2′,3′-*O*-Isopropylidene-3,5′-adenosine cyclonucleoside *p*-tolylsulfonate[3] (3 g.) was added to 30 ml. of 1 *N* hydrochloric acid. The solution was heated on the steam bath for 40 min., cooled, treated with charcoal, filtered, neutralized to pH 7 with ammonium hydroxide, and evaporated to dryness *in vacuo*. The residue was dissolved in a small amount of hot water, and the solution was cooled overnight in the refrigerator. The resulting precipitate was filtered and recrystallized from water to yield 0.9 g. of product, m.p. >180° dec.; ultraviolet data, $\lambda_{max}^{pH\ 1}$ 274 mμ (ε 18,000), $\lambda_{max}^{pH\ 11}$ 274 mμ (ε 12,600).

Anal. Calcd. for $C_{10}H_{13}N_5O_4 \cdot H_2O$: C, 42.1; H, 5.3; N, 24.6; H_2O, 6.3. Found: C, 41.8; H, 5.5; N, 24.4; H_2O, 6.9.

2′,3′-*O*-Isopropylidene-3,5′-inosine Cyclonucleoside *p*-Tolylsulfonate.—2′,3′-*O*-Isopropylidene-5′-*O*-(*p*-tolylsulfonyl)inosine[11] (5 g.) was heated, with continuous stirring, in 60 ml. of refluxing dioxane. Solution was complete after 10–15 min., and after 2 hr., a white precipitate began to form. Heating was continued for another 2 hr., and then the solution was cooled overnight in the refrigerator. The precipitate was filtered, washed with a little ethanol, and recrystallized from ethanol to yield 4.1 g. of product, m.p. 188–191° dec. The infrared spectrum exhibited no covalent *p*-tolylsulfonate band at 8.5 μ but showed an ionic *p*-tolylsulfonate band at 9.8 μ; ultraviolet data, $\lambda_{max}^{pH\ 1}$ 255 mμ (ε 10,600), $\lambda_{max}^{pH\ 11}$ 257 mμ (ε 9700).

Anal. Calcd. for $C_{20}H_{22}N_4O_7S$: C, 51.9; H, 4.8; N, 12.1. Found: C, 52.0; H, 4.9; N, 11.9.

2′,3′-*O*-Isopropylidene-3,5′-inosine Cyclonucleoside (XII).—2′,3′-*O*-Isopropylidene-3,5′-inosine cyclonucleoside *p*-tolylsulfonate (5 g.) was dissolved in 30 ml. of water, and the pH of the solution was adjusted to 7 with 14% aqueous ammonia. The solution was stirred for 6 hr., during which time a precipitate gradually formed. The mixture was then cooled and filtered and the product recrystallized from ethanol to yield 1.9 g., m.p. 266–269° dec. The infrared spectrum showed no ionic *p*-tolylsulfonate band at 9.8 μ; ultraviolet data, $\lambda_{max}^{pH\ 11}$ 256 mμ (ε 8600).

Anal. Calcd. for $C_{13}H_{14}N_4O_4 \cdot H_2O$: C, 50.6; H, 5.2; N, 18.2. Found: C, 50.6; H, 5.2; N, 18.2.

New Reaction of a Quinone Methide

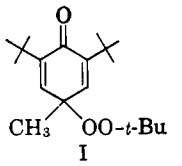
NORMAN P. NEUREITER

Humble Oil and Refining Company, Research and Development, Baytown, Texas

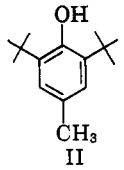
Received July 19, 1963

From the reaction of the quinone methide III with 2,6-di-*t*-butylphenol a 17% yield of compound VI has been isolated. A possible mechanism for its formation is discussed, as well as the implications of such a mechanism for inhibition of oxidation by 2,6-di-*t*-butyl-4-methylphenol.

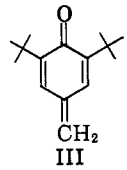
Considerable effort has been devoted in our studies of the mechanism of antioxidant action[1] to the chemistry of the 4-peroxydienone intermediate I which is



I



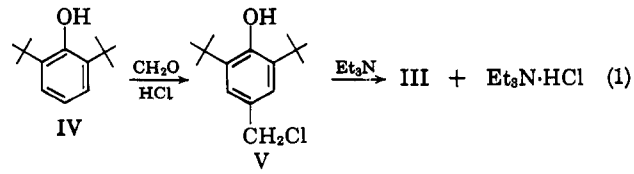
II



III

formed from the reaction of 2,6-di-*t*-butyl-4-methylphenol (II) with *t*-butylperoxy radicals.[2] The formation of certain products during reduction or thermal decomposition of I suggested the intermediacy of the quinone methide III.[3] Accordingly, a study of the reactions of III was undertaken. While little evidence was acquired for the postulated appearance of III during reactions of I, the work was redeemed by an intriguing peripheral dividend. This paper describes a previously unreported reaction of the quinone methide III.

For the preparation of III, 2,6-di-*t*-butylphenol (IV) was chloromethylated and the reaction product in petroleum ether (b.p. 30–60°) was treated with triethylamine[4] (eq. 1). When the clear yellow filtrate after removal of the solid amine hydrochloride was let



stand, the color steadily deepened. After several days the dark red solution had deposited a small quantity of large colorless crystals, which after recrystallization from chloroform and methanol melted at 264–265° with some decomposition. Exposure to light and air resulted in a gradual yellowing of the solid.

Elemental analysis, molecular weight determination,

(1) N. P. Neureiter and D. E. Bown, *Ind. Eng. Chem. Prod. Res. Develop. Quart.*, **1**, 236 (1962).

(2) Many peroxides of this type are known. See T. W. Campbell and G. M. Coppinger, *J. Am. Chem. Soc.*, **74**, 1469 (1952); C. D. Cook, R. C. Woodworth, and P. Fianu, *ibid.*, **78**, 4159 (1956); A. F. Bickel and E. C. Kooyman, *J. Chem. Soc.*, 638 (1953); C. E. Boozer, G. S. Hammond, C. E. Hamilton, and J. N. Sen, *J. Am. Chem. Soc.*, **77**, 3233 (1955).

(3) Unpublished work by N. P. N.

(4) This procedure was used by L. J. Filar and S. Winstein, *Tetrahedron Letters*, No. **25**, 9 (1960).