solvent. Recrystallization from absolute ether gave pure material, m. p. 133.5–134.5°.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.66. Found: C, 75.59; H, 8.70.

Pregnene-4-diol-17,20-dione-3,11 Acetate-20 (XXII).—A solution of 860 mg. of pregnanediol-17,20-dione-3,11 acetate-20 in a mixture of 3 cc. of chloroform and 3 cc. of acetic acid was treated with 370 mg. of bromine in 3 cc. of acetic acid. After a few minutes the bromine was consumed. The mixture was then poured into chloroform and washed successively with water, dilute potassium carbonate and again with water. The chloroform was removed *in vacuo*, leaving crude bromo ketone as a gel. Trituration with a small volume of absolute alcohol gave 709 mg. of 4-bromopregnanediol-17,20-dione-3,11 acetate-20 (XXI) which melted at 150–155° (loss of alcohol of crystallization).

This bromoketone was refluxed for eight hours with 20 cc. of pyridine. The product was worked up as usual (see above), and finally crystallized from a small volume of ether. A first crop of 189 mg. of prisms was obtained which melted at 194–200°. Recrystallization from benzene gave fluffy solvated crystals which melted at 104° (loss of solvent) and remelted at 215–218°. A final recrystallization from chloroform–ether gave unsolvated material, m. p. 219–220°.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.09; H, 8.31. Found: C, 70.97; H, 8.12.

Pregnene-4-diol-17,20-dione-3,11 (XXIII).—A solution of 64 mg. of pregnene-4-diol-17,20-dione-3,11 acetate-20 in 5 cc. of methanol and 2 cc. of water containing 60 mg. of potassium bicarbonate and 100 mg. of potassium carbonate was permitted to stand at room temperature overnight. The solution was acidified with 3 drops of acetic acid, concentrated *in vacuo* and extracted with chloroform. The chloroform solution was washed with water and concentrated to dryness. The residue was triturated with a little water giving the crystalline hydrate. Two recrystallizations from water gave a product of m. p. 107–110° ($-H_2O$). For analysis the hydrate was dried in a weighing pig at 110° for two hours.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.78; H, 8.81. Found: C, 72.42; H, 8.61.

Adrenosterone from XXIII.—A solution of 90 mg. of crude pregnanediol-17,20-dione-3,11 (prepared by hydrolysis of 106 mg. of crude acetate of m. p. 201–211°) in 2 cc. of aqueous 80% methanol was treated with 100 mg. of periodic acid. After five hours the solution was diluted with water and extracted with chloroform. The washed chloroform extract was concentrated to dryness and the residue chromatographed. The fractions from absolute ether to 1:1 ether–chloroform were combined and recrystallized twice from alcohol. Adrenosterone was thus obtained in characteristic platelets, m. p. 219–221°. No depression was observed in admixture with an authentic sample.

Acknowledgment.—The author wishes to express his appreciation to Dr. Everett S. Wallis of Princeton University and to Dr. Karl Folkers and Dr. Randolph T. Major for their active association with this work.

Summary

Hydroxylation of a mixture of pregnene-17- and pregnene-20-dione-3,11 with osmium tetroxide gives both of the possible 20,21-glycols and one of the possible 17,20-glycols. From each of these compounds the corresponding $\Delta^{4,5}$-pregnene-diol-diones was prepared. Acetylation of the C-21 hydroxyl group in the 20,21-glycols followed by oxidation gave dehydrocorticosterone acetate.

RAHWAY, NEW JERSEY RECEIVED JULY 18, 1946

[CONTRIBUTION FROM THE LABORATORIES OF THE UNIVERSITY OF MARYLAND]

Studies in Pyrane Chemistry

BY G. FORREST WOODS AND HERMAN SANDERS

It has been found that 2,3-dihydropyrane is the precursor of a number of very reactive and versatile substances. R. Paul[1] observed that 2,3-dihydropyrane reacts readily with bromine to yield 2,3-dibromotetrahydropyrane and that this latter substance is relatively unstable. For instance, distillation thereof yields in part 1,5-epoxy-2-bromo-1-pentene with the elimination of hydrogen bromide, while hydrolysis of this substance leads to the hemi-acetal of 2-bromo-5-hydroxypentanal which does not appear to form any carbonyl derivatives. In his latest report which had just been obtained[2] is described the reaction of 2,3-dihydropyrane with chlorine. The product of this reaction is 2,3-dichlorotetrahydropyrane. He also observed that 2,3-dichlorotetrahydropyrane reacts with methyl alcohol in the presence of sodium methylate to form 2-methoxy-3-chlorotetrahydropyrane.

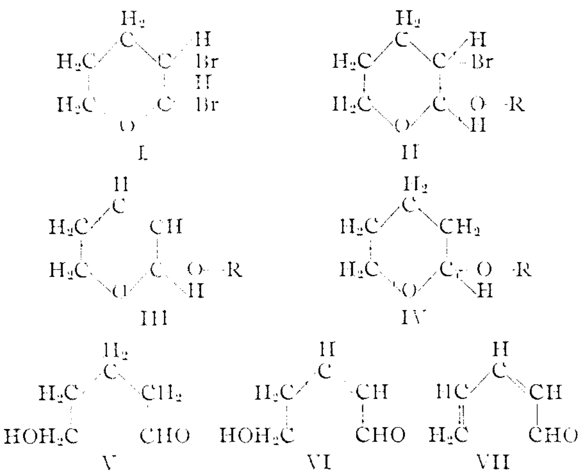
This study concerns the reaction of 2,3-dibromotetrahydropyrane (I) with alcohol, and the products derivable therefrom. The difference in the reactivity of the two bromine atoms of this substance was most noticeable. Alcoholysis of the bromine atom on the carbon adjacent to the oxygen linkage was readily accomplished in cold alcohol–sodium alcoholate or alcohol saturated with dry ammonia. The product of this reaction was 2-alkoxy-3-bromotetrahydropyrane (II). Under these conditions the second bromine atom was completely inert.

The more drastic treatment of refluxing 2-alkoxy-3-bromotetrahydropyrane with alcoholic potassium hydroxide led to the elimination of a molecule of hydrogen bromide with the formation of the corresponding 2-alkoxy-Δ^3-dihydropyrane (III). Reduction of 2-ethoxy-Δ^3-dihydropyrane with Adams catalyst afforded 2-ethoxytetrahydropyrane (IV) which, since it is an acetal was readily cleaved by mild acid hydrolysis. That these structures were correct was shown by the identity of the 2,4-dinitrophenylhydrazone of the acid hydrolysis product of 2-ethoxytetrahydropyrane with the 2,4-dinitrophenylhydrazone

(1) R. Paul, *Bull. soc. chim.*, [5] **1**, 1337 (1934).

(2) R. Paul, *Comp. rend.*, **218**, 122 (1944); *C. A.*, **40**, 2447 (1946).

of 5-hydroxypentanal (V). Attempts to isolate 5-hydroxy-Δ^2-pentenal (VI) by mild acid hydrolysis of 2-ethoxy-Δ^3-dihydropyrane were without success. The properties of the material obtained were those of a polymeric substance. However, if the hydrolysis was carried out in the presence of 2,4-dinitrophenylhydrazine, a 2,4-dinitrophenylhydrazone of 5-hydroxy-Δ^2-pentenal (VI) was obtained.



In our attempts to prepare 5-hydroxy-Δ^2-pentenal we encountered another reaction of 2-ethoxy-Δ^3-dihydropyrane. Steam distillation of the reaction mixture from acid hydrolysis of 2-ethoxy-Δ^3-dihydropyrane yielded an aldehyde of marked acrolein-like properties. This aldehyde was isolated from the steam distillate by salting out and extraction. Distillation of this aldehyde at reduced pressure after removal of the solvent yielded a fairly pure product, while distillation thereof at atmospheric pressure inevitably led to uncontrollable polymerization. This aldehyde formed a red 2,4-dinitrophenylhydrazone and a semicarbazone. On the basis of analyses of the aldehyde and its derivatives we have tentatively assigned the structure of the conjugated pentadienal (VII) to this substance. The reactions of this compound are being investigated further.

Experimental

2,3-Dibromotetrahydropyrane (I).—The procedure used for the bromination of 2,3-dihydropyrane[3] was essentially that of Paul.[1] To a solution of 2,3-dihydropyrane (252 g.) in carbon tetrachloride (150 ml.) cooled to −35–45° by means of a Dry Ice-bath was added dropwise a solution of bromine (480 g.) in carbon tetrachloride (200 ml.). The bromine solution was added until decolorization was no longer evident. The solvent was removed on a steam-bath under reduced pressure: yield, 628 g. of crude undistilled product.

Purification of a sample of the crude product yielded a straw colored oil, b. p. 80–82° (0.4 mm.). 2,3-Dibromotetrahydropyrane is not stable but darkens readily upon standing with noticeable evolution of hydrogen bromide.

2-Ethoxy-3-bromotetrahydropyrane (II).—To 450 ml. of well-cooled anhydrous alcohol saturated with ammonia was cautiously added with stirring 277 g. of 2,3-dibromotetrahydropyrane. In a few minutes precipitation of ammonium bromide occurred. After one hour at room temperature the reaction mixture was filtered and the ammonium bromide was well washed with ether. A nearly quantitative yield of ammonium bromide was obtained. The combined filtrate and ether washings were twice washed with water. After drying over sodium sulfate, the solvent was removed and the residue distilled: yield, 205 g. (86%); b. p. 94–96° (18 mm.); n^{25}D 1.4752.

Anal.[4] Calcd. for $C_7H_{13}O_2Br$: C, 40.21; H, 6.27. Found: C, 40.28, 40.40; H, 6.20, 6.32.

No 2,4-dinitrophenylhydrazone of this substance could be obtained by operating in the usual manner.

2-Methoxy-3-bromotetrahydropyrane (II).—The procedure for the preparation of 2-ethoxy-3-bromotetrahydropyrane was followed using methyl alcohol in place of ethyl alcohol. From 228 g. of 2,3-dibromotetrahydropyrane was obtained 91 g. (50%) of 2-methoxy-3-bromotetrahydropyrane, b. p. 88–89° (18 mm.), n^{25}D 1.4838.

Anal. Calcd. for $C_6H_{11}O_2Br$: C, 36.94; H, 5.69. Found: C, 36.88; H, 5.99.

2-Ethoxy-Δ^3-dihydropyrane (III).—To a solution of sodium ethylate prepared from 40 g. of sodium in 600 ml. of absolute ethanol was added 170 g. of 2-ethoxy-3-bromotetrahydropyrane. The reaction mixture was refluxed for four hours, whereupon the mixture was cooled and filtered. The sodium bromide precipitate, of which a nearly quantitative yield was obtained, was well washed with ether. The combined filtrate and ether washings were washed with water and dried over sodium sulfate. After removal of the solvent the residue was distilled: yield of 2-ethoxy-Δ^3-dihydropyrane, 64 g. (62%), b. p. 153–155°, n^{25}D 1.4475.

If it was not desired to isolate the intermediate compound, 2-ethoxy-3-bromotetrahydropyrane, the preparation of 2-ethoxy-Δ^3-dihydropyrane was considerably simplified and the yield improved if the original ammoniacal alcoholic solution of 2-ethoxy-3-bromotetrahydropyrane obtained after filtration of the ammonium bromide was directly refluxed for several hours with alcoholic potassium hydroxide. A 100% excess of potassium hydroxide was used. The product was isolated as above, b. p. 153–155°, n^{25}D 1.4475. Treatment of either product by refluxing with sodium alcoholate or sodium did not alter the boiling point or the refractive index.

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.71; H, 9.60.

2-Methoxy-Δ^3-dihydropyrane (III).—To a solution of 37.5 g. of commercial sodium methylate in 250 ml. of methanol was added 68 g. of 2-methoxy-3-bromotetrahydropyrane. The reaction mixture was refluxed for four hours, then cooled and filtered. The nearly quantitative precipitate of sodium bromide was well washed with ether. The combined filtrate and ether washings were then washed with water. After drying over sodium sulfate the solvent was removed and the residue distilled: yield 20 g. (51%) of 2-methoxy-Δ^3-dihydropyrane, b. p. 136–138°; n^{25}D 1.4425.

Anal. Calcd. for $C_6H_{10}O_2$: C, 63.13; H, 8.83. Found: C, 63.00; H, 9.15.

5-Hydroxy-Δ^2-pentenal-2,4-dinitrophenylhydrazone (VI).—The 2,4-dinitrophenylhydrazones prepared in the usual manner from the solutions obtained by acid hydrolysis of both 2-ethoxy- and 2-methoxy-Δ^3-dihydropyrane were identical, m. p. 159–160°.

Anal. Calcd. for $C_{11}H_{12}O_5N_4$: C, 47.14; H, 4.32. Found: C, 47.36; H, 4.41.

2-Ethoxytetrahydropyrane (IV).—Reduction of 25.6 g. of 2-ethoxy-Δ^3-dihydropyrane with Adams catalyst and hydrogen (3 atm.) at room temperature required approximately two hours for calculated hydrogen uptake. After removal of the catalyst the product was distilled and a nearly quantitative yield of 2-ethoxytetrahydropyrane was obtained, b. p. 145–146°, n^{25}D 1.4250.

(3) "Organic Syntheses," **23**, 25 (1943).

(4) Microanalyses by Miss Eleanor Werble.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.28; H, 10.93.

The 2,4-dinitrophenylhydrazone prepared in the usual manner from the product obtained by acid hydrolysis of 2-ethoxytetrahydropyrane melted at 109° and gave no depression in a mixed melting point determination with the 2,4-dinitrophenylhydrazone prepared from 5-hydroxypentanal.[5]

2,4-Pentadienal (VII).—To a solution of 40 ml. of 85% phosphoric acid in 200 ml. of water was added with stirring 40 g. of 2-ethoxy-Δ^3-dihydropyrane. Within a few minutes the solution became homogeneous. This solution was added dropwise to a solution of 50 ml. of 85% phosphoric acid in 200 ml. of water which was already undergoing steam distillation. Steam distillation was continued until the distillate no longer had the characteristic odor of pentadienal. The steam distillate was itself steam distilled to concentrate the aldehyde. After the addition of potassium chloride, the pentadienal was extracted with ether and dried over sodium sulfate. After removal of the ether under reduced pressure, the aldehyde was distilled; yield 14 g. (55%), b. p. 36–37° (20 mm.), $n^{25}D$ 1.5163.

Anal. Calcd. for C_5H_6O: C, 73.14; H, 7.37. Found: C, 72.99; H, 7.85.

Pentadienal Semicarbazone.—The semicarbazone of 2,4-pentadienal prepared in the usual manner was a white crystalline compound which was recrystallized from water. This substance decomposed progressively on heating to 260°.

Anal. Calcd. for $C_6H_9ON_3$: C, 51.77; H, 6.52. Found: C, 51.67, 51.65, 52.08; H, 6.21, 6.49, 6.67.

2,4-Pentadienal-2,4-dinitrophenylhydrazone.—2,4-Pentadienal was converted in the usual way almost quantitatively into a red 2,4-dinitrophenylhydrazone. The product was recrystallized from ethyl alcohol, m. p. 176–177°.

Anal. Calcd. for $C_{11}H_{10}O_4N_4$: C, 50.38; H, 3.84. Found: C, 50.11, 50.38; H, 3.81, 3.88.

(5) Woods and Sanders, THIS JOURNAL, **68**, 2111 (1946).

Summary

1. 2,3-Dibromotetrahydropyrane reacts with methyl and ethyl alcohol to form the corresponding 2-alkoxy-3-bromo-tetrahydropyrane.

2. 2-Alkoxy-Δ^3-dihydropyranes are formed by the reaction of 2-alkoxy-3-bromotetrahydropyrane with alcoholic potassium hydroxide or sodium alcoholate.

3. The preparation of 2,4-pentadienal is described. The semicarbazone and 2,4-dinitrophenylhydrazone of this compound are characterized.

COLLEGE PARK, MD. RECEIVED JUNE 11, 1946

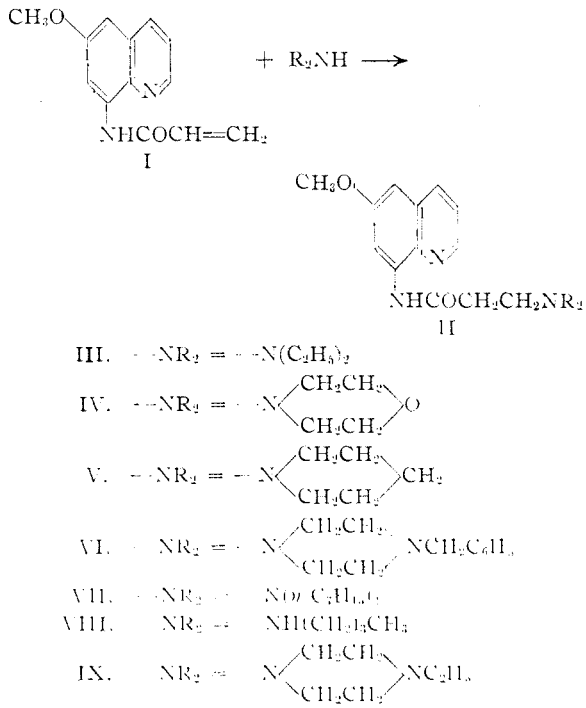
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of Some 6-Methoxy-8-(β-aminopropionylamino)-quinolines

BY H. R. SNYDER AND HERBERT E. FREIER[1]

In the search for an antimalarial drug which might possess the desirable properties of plasmochin but have a lower toxicity, a number of amides of the type represented by formula II have been prepared.[2] The principal difference between the compounds prepared and plasmochin lies in the fact that in the former the aromatic amino group is joined to an acyl group rather than to an alkyl group; there are differences also in the details of structure of the side chains and in the distance between the two acyclic nitrogen atoms.

The new compounds were prepared by the addition of the appropriate amines to 6-methoxy-8-acrylaminoquinoline (I). The acrylamide (I) was obtained in 57% yield by the reaction of the aminoquinoline with acrylyl chloride (prepared from sodium acrylate and phosphorus oxychloride according to the procedure of Kohler[3]). The reaction of I with diethylamine was carried out in an excess of the aliphatic amine; the reactions of I with other amines were carried out in benzene solutions. It is possible that the reagents



and products are sufficiently basic to act as catalysts in these reactions; no other catalyst was employed.

(1) Present address: Department of Chemistry, University of North Dakota, Grand Forks, North Dakota.

(2) The present work was substantially complete at the time of the announcement of other similar amides by Bruce and Bowman in a paper presented before the Division of Organic Chemistry at the Atlantic City meeting of the American Chemical Society on April 10, 1946.

(3) Kohler, *Am. Chem. J.*, **42**, 380 (1909).