[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] VII. Synthesis and Ammonolysis of Methyl 2,3-Anhydro-D-ribofuranoside

BY CHARLES D. ANDERSON, LEON GOODMAN AND B. R. BAKER

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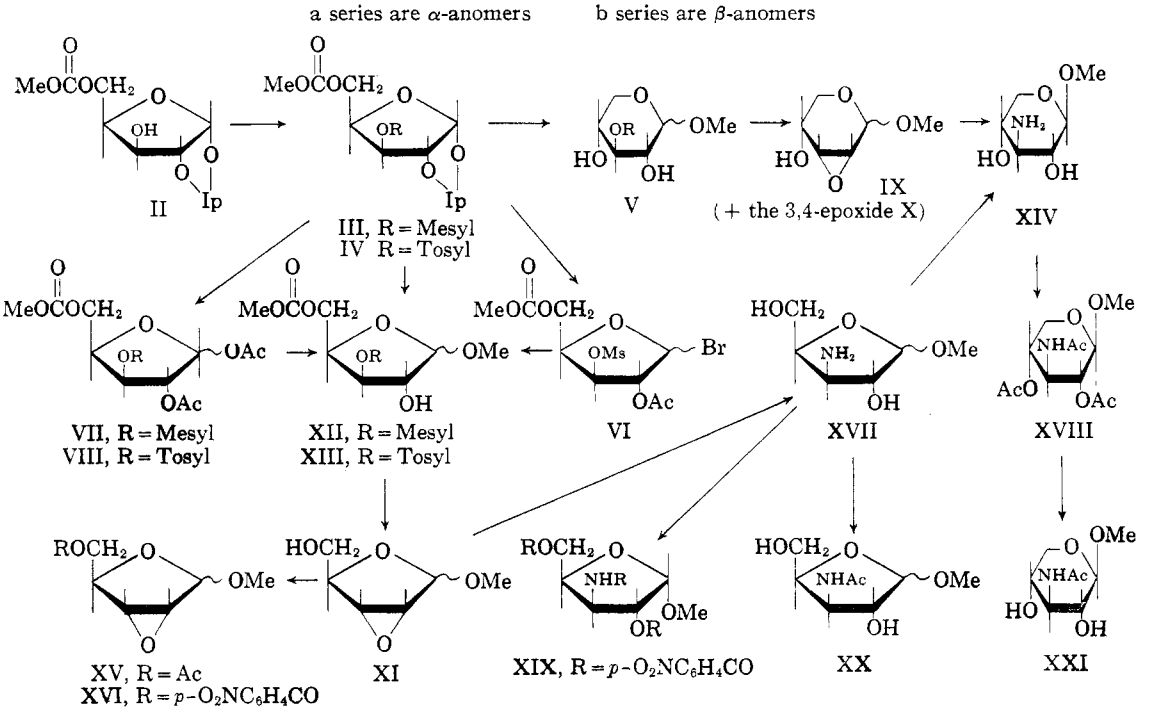
The anomeric methyl 2,3-anhydro-D-ribofuranosides were prepared *via* a five-step synthesis in 47% over-all yield from 1,2-*O*-isopropylidene-D-xylofuranose. Each anomer was subjected to ammonolysis, and the product in each case was shown to be the corresponding anomer of methyl 3-amino-3-deoxy-D-xylofuranoside, formed by nearly exclusive attack on the anhydrosugar at C.3.

The exploration of various new approaches[2] to the synthesis of sulfur-containing nucleosides and deoxynucleosides possessing potential anticancer activity required the synthesis of methyl 2,3-anhydro-D-ribofuranoside (XI). The separate anomers of XI have been prepared in good over-all yield, and the ammonolysis of these anhydrosugars has been studied.



The synthesis of XI has as its starting material the readily available 1,2-*O*-isopropylidene-D-xylofuranose[3] (I). This was converted to crystalline 1,2-*O*-isopropylidene-5-*O*-methoxycarbonyl-D-xylofuranose (II) by reaction with an excess of methyl chloroformate in pyridine, a procedure that takes advantage of the large difference in rate of acylation of the two hydroxyl groups in 1,2-*O*-isopropylidene-D-xylofuranose (I). The small amount of 3,5-di-*O*-methoxycarbonyl derivative formed readily was separated from the desired monosubstituted derivative II by crystallization.[4] Mesylation or tosylation of II in pyridine afforded crystalline 1,2-*O*-isopropylidene-3-*O*-mesyl (or tosyl)-5-*O*-methoxycarbonyl-D-xylofuranose (III and IV, respectively). The tosylate IV had been prepared by Haworth, Porter and Waine[4] to characterize II.

Deacetonation of the sulfonate esters III and IV was achieved without concurrent loss of the 5-methoxycarbonyl group by acetolysis at room temperature with acetic acid–acetic anhydride containing sulfuric acid. Methanolysis of the resulting 1,2-diacetates VII and VIII with 1% methanolic hydrogen chloride at room temperature gave the corresponding, analytically pure C.3 sulfonate esters of methyl 5-*O*-methoxycarbonyl-α,β-D-xylofuranoside (XII and XIII, respectively). The tosylate XIII could be obtained crystalline (possibly as one anomer), but this involved considerable

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, and is in collaboration with the Sloan-Kettering Institute for Cancer Research. This paper was presented before the Division of Carbohydrate Chemistry of the American Chemical Society at the San Francisco Meeting, April, 1958. For the preceding paper in this series *cf.* C. W. Mosher, R. M. Silverstein, O. P. Crews, Jr., and B. R. Baker, *J. Org. Chem.*, **23**, in press (1958).

(2) A detailed discussion of these approaches and certain model experiments pertaining to them have been reported recently by L. Goodman, A. Benitez and B. R. Baker, THIS JOURNAL, **80**, 1680 (1958).

(3) B. R. Baker and R. E. Schaub, *ibid.*, **77**, 5900 (1955).

(4) W. N. Haworth, C. R. Porter and A. C. Waine, *Rec. trav. chim.*, **57**, 541 (1938). These authors prepared II by the use of methyl chloroformate in the presence of aqueous base, a procedure that gave a yield inferior to that obtained here.

loss in yield and was neither necessary nor advisable. An alternate deacetonation of the mesylate III was achieved by the use of hydrogen bromide in acetic acid at room temperature.[5,6] However, room temperature methanolysis of the 1-bromo-2-acetate VI thus obtained furnished XII which was inferior in quality to that obtained from the diacetate VII.

Finally, treatment of either of the sulfonate esters XII or XIII with sodium methoxide in methanol afforded the desired XI. The over-all yield of distilled XI through the five steps from I was about 47% in either the mesyl or tosyl series, indicating that the yield for each step averaged 86%. During distillation, the anhydrosugar XI separated readily into low and high boiling fractions which were respectively levo- and dextrorotatory. Their directions of optical rotation and conversion in high yield to different, crystalline *p*-nitrobenzoates (XVIb and a, respectively) indicated that they were the pure β- and α-anomers XIb and a, respectively. The β-anomer can have its C.5 hydroxyl group intramolecularly hydrogen-bonded with the glycosidic oxygen atom at C.1; such intramolecular bonding is not possible for the α-anomer, which therefore is the higher boiling. This hydrogen-bonding phenomenon, which allowed ready separation of the anomers, had been observed previously with methyl 3,5-*O*-isopropylidene-D-xylofuranoside.[7,8] The anomers of XI also were converted to their acetates XVa and b, which were required for some other studies.

The infrared spectra of both anhydrosugars XIa and b showed weak absorption at 3.26–3.27 μ. Henbest, *et al.*,[9] have concluded that absorption in this region (attributed to the C–H bonds on the three-membered ring) provides the most definitive infrared evidence for the presence of an epoxide ring. Another epoxide band found in the spectra of XIa and b occurs at about 11.6 μ. Certain other sugar epoxides[10] recently have been reported to absorb near 11.6 μ. This band is considerably more intense than the low wave length epoxide band, and thus the extent of ammonolysis of these epoxides could be determined by observing the decrease in absorption at 11.6 μ.

Early in the development of the above synthesis of XI, direct deacetonation of the isopropylidene sulfonates III and IV in refluxing 1% methanolic hydrogen chloride was studied. These more severe conditions required for removal of the isopropylidene group caused significant, concurrent loss of the 5-*O*-methoxycarbonyl group. Loss of this blocking group permitted subsequent isomerization of the initially formed furanoside to methyl 3-*O*-mesyl (or tosyl)-D-xylopyranoside (V, R = Ms or Ts) during the deacetonation. Proof of this was obtained by reaction of a crude deacetonation product from III with sodium methoxide and ammonolysis of the product, which apparently was a mixture of the desired anhydrofuranoside XI and methyl 2,3(and/or 3,4)-anhydro-D-ribopyranoside[11] (IX and X, respectively). A 22% yield of crystalline methyl 3-amino-3-deoxy-β-D-xylopyranoside (XIV) was obtained, which was identified by comparison of its physical properties as well as those of its triacetyl (XVIII) and its N-acetyl (XXI) derivatives with the properties of the known L-enantiomers.[14] The pyranose nature of XIV was indicated also by a study of its periodate oxidation. Like its enantiomer,[14] it showed rapid consumption of two equivalents of oxidant and no consumption thereafter.

Opening of the epoxide ring of 2,3-anhydropentofuranosides by nucleophilic reagents has resulted in nearly exclusive attack at C.3 in all cases previously studied.[3,7,8,15] Consequently it was expected that ammonolysis of anhydrosugars XIa and XIb would result in the formation of 3-aminoxylosides essentially free of 2-aminoarabinosides.

Ammonolysis of XIa in concentrated ammonium hydroxide at 100°, the method of Myers and Robertson,[16] afforded a crude product which, when heated in an evaporative still at 0.10 mm. and 100° (bath temperature), distilled rapidly leaving essentially no residue. The distillate analyzed correctly for carbon and hydrogen but had a low nitrogen content. The non-nitrogenous impurity, probably methyl α-D-xylofuranoside (formed by competitive attack of water on XIa during ammonolysis), was separated readily by passage through a column of Amberlite IRC-50 (H).[17,18] This resin retained the expected methyl 3-amino-3-deoxy-α-D-xylofuranoside (XVIIa), which could then be eluted with 2 *N* aqueous methanolic ammonia in 88% yield (based on XIa). A distilled sample of this purified XVIIa analyzed satisfactorily and had $[\alpha]^{25}D$ +134°. This amino sugar was further characterized by conversion to its crystalline tri-*p*-nitrobenzoyl derivative XIX in moderate yield and to its N-acetyl derivative XXa. The latter was an analytically pure, apparently crystalline solid but had a broad and variable melting point range which was not improved by repeated recrystallization.

Ammonolysis of XIb correspondingly furnished methyl 3-amino-3-deoxy-β-D-xylofuranoside (XVIIb) in high yield. After ion-exchange purification, it analyzed correctly and had $[\alpha]^{24}D$ −66.1°. This anomer was comparatively non-volatile at 0.10 mm. and 100°. It was characterized by the preparation of its crystalline N-acetyl derivative XXb in good yield.

Periodate oxidation studies on the aminofurano-

(5) H. Ohle and H. Wilcke, *Ber.*, **71A**, 2316 (1938).

(6) B. Helferich and H. Jochinke, *ibid.*, **74B**, 719 (1941).

(7) B. R. Baker, R. E. Schaub and J. H. Williams, THIS JOURNAL, **77**, 7 (1955).

(8) J. M. Anderson and E. Percival, *J. Chem. Soc.*, 819 (1956).

(9) H. B. Henbest, G. D. Meakins, B. Nicholls and K. J. Taylor, *ibid.*, 1459 (1957).

(10) M. L. Wolfrom, J. B. Miller, D. I. Weisblat and A. R. Hanze, THIS JOURNAL, **79**, 6299 (1957).

(11) The β-anomer of IX is a low melting crystalline compound,[12,13] but no crystalline material separated from this distilled anhydrosugar mixture.

(12) P. W. Kent, M. Stacey and L. F. Wiggins, *J. Chem. Soc.*, 1232 (1949).

(13) R. Allerton and W. G. Overend, *ibid.*, 1480 (1951).

(14) B. R. Baker and R. E. Schaub, *J. Org. Chem.*, **19**, 646 (1954).

(15) J. Davoll, B. Lythgoe and S. Trippett, *J. Chem. Soc.*, 2230 (1951).

(16) W. H. Myers and G. J. Robertson, THIS JOURNAL, **65**, 8 (1943).

(17) B. R. Baker, J. P. Joseph and R. E. Schaub, *ibid.*, **77**, 5905 (1955).

(18) A weak-acid cation exchange resin manufactured by the Rohm and Haas Company, Philadelphia, Pa.

sides XVIIa and b gave varying results, showing slow consumption of up to two and three moles of oxidant per mole of substrate. There was no indication of even a temporary slackening of oxidation after the consumption of the first mole of periodate. Similar results obtained during periodate oxidation of certain 3-aminofuranosyl nucleosides have been reported recently by Kissman and Weiss.[19]

The essential homogeneity of the three aminopentosides XIV, XVIIa and XVIIb was shown by paper chromatography of both the free amines and their N-acetyl derivatives. The crystalline pyranoside XIV traveled as a single spot in solvents A, B, C and D (see Table I). The non-crystalline

TABLE I

PAPER CHROMATOGRAPHY OF AMINOPENTOSIDES

Compound	R_f in solvent[a] A	B	C	D
XIV	0.48[b]	0.68	0.42	0.40
XVIIa	.49	.66[c]	.39	.37
XVIIb	.49	.72[c]	.49	.45

[a] For solvent composition, see Experimental. [b] The spots were detected by ninhydrin; XIV gave a purple spot, XVIIa a tan spot and XVIIb a brown spot. [c] The aminofuranosides XVIIa and XVIIb showed a very faint, second spot at R_f 0.42 in solvent B, 0.16 in C and 0.08 in D. These (pink) spots did not appear until several hours after spraying, whereas the major spots appeared immediately.

furanosides XVIIa and b traveled as a single spot in solvent A, but in the other three solvents a trace contaminant resulted in a very faint, second spot. The striking aspect of these chromatograms was that in solvents B, C and D the anomers XVIIa and b were distinctly and reproducibly resolved. This parallels the marked difference in volatility of these anomers. None of the solvents adequately differentiated the pyranoside XIV and the α-furanoside XVIIa, but this was accomplished by paper chromatography of their N-acetyl derivatives (see Table II). The N-acetyl derivatives

TABLE II

PAPER CHROMATOGRAPHY OF ACETAMIDOPENTOSIDES

Compound	R_f in solvent[a] D	E	F
XXI	0.37 ± 0.01[b]	0.76	0.89
XXa	.51 ± .02	0.78 ± 0.01	0.93 ± 0.02
XXb	.49 ± .04	.80 ± .02	.92 ± .02

[a] For solvent composition, see Experimental. [b] The uncertainties listed are the average deviations from the average observed R_f. The spots were detected by the use of chlorine and starch-potassium iodide.[20]

XXI, XXa and XXb traveled as single spots in solvents D, E and F. In solvents E and F all three derivatives had the same R_f. In solvent D only the two furanosides XXa and b had a common R_f, the pyranoside XXI having an appreciably lower R_f. Paper chromatograms of the mother liquor residues from the purification of XXa and b run in solvent D showed no trace of a spot due to XXI. Establishment of the limits of detection of XXI made it possible to conclude that the aminofuranosides XVIIa and b could contain at most about 2% of the pyranoside isomer XIV.

(19) H. M. Kissman and M. J. Weiss, THIS JOURNAL, **80**, 2575 (1958), footnote 14.

(20) H. N. Rydon and P. W. G. Smith, *Nature*, **169**, 922 (1952).

With this demonstration of the essential homogeneity of the aminosugars XVIIa and b, it remained to prove only that these sugars were indeed 3-aminoxylosides and not 2-aminoarabinosides. This was accomplished by isomerization in refluxing 1% methanolic hydrogen chloride to the pyranoside XIV, a compound unequivocally known to be a 3-aminoxyloside. Compound XVIIa afforded pure, crystalline XIV in 5.4% yield, and XVIIb afforded pure XIV in 13% yield. These yields are undoubtedly minimum figures reflecting the difficulties inherent in the isolation of XIV from these isomerization mixtures. These isomerizations, in combination with the previous proof that aminofuranosides XVIIa and b are homogeneous materials free of the pyranoside XIV, indicate that ammonolysis of the anhydrosugars XIa and b yields nearly exclusively the corresponding anomer of the expected methyl 3-amino-3-deoxy-D-xylofuranoside (XVII).

Experimental[21]

1,2-*O*-Isopropylidene-5-*O*-methoxycarbonyl-D-xylofuranose (II).—To a stirred solution of 71.5 g. (0.376 mole) of 1,2-*O*-isopropylidene-D-xylofuranose[3] (I) in 360 g. of reagent pyridine and 205 g. of reagent chloroform, protected from moisture and cooled in an ice-salt bath, was added dropwise 58.6 g. (0.620 mole) of methyl chloroformate at such a rate that the temperature was maintained at −5 to 0° (1 hour). After being stirred for an additional 2.5 hr. in the cooling bath, the mixture was stored at 0° for 64 hr., then poured into 1500 ml. of water. The product was extracted with chloroform (3 × 215 ml.). The combined extracts, washed with water (2 × 360 ml.) and dried with magnesium sulfate, were evaporated to dryness *in vacuo*. Recrystallization from 600 ml. of 1:1 benzene–hexane gave 68.6 g. (74%) of product, m.p. 134–137.5°, that was suitable for the next step. Further recrystallization from benzene–hexane gave white crystals of m.p. 135.5–136.5° cor. and $[\alpha]^{24}_{589}$ −13.1° and $[\alpha]^{24}_{546}$ −15.8° (1.09% in MeOH) (lit.[4] m.p. 135–136°, $[\alpha]_D$ −13° (2.0% in MeOH)); λ^{KBr}_{max} 2.98 μ (OH), 5.76 μ (carbonate C=O), 7.22, 7.30, 8.60 μ (isopropylidene), 7.75–7.90 μ (carbonate C–O–C).

Evaporation of the mother liquor gave a viscous oil, whose infrared spectrum indicated it to be largely 1,2-*O*-isopropylidene-3,5-di-*O*-methoxycarbonyl-D-xylofuranose.

1,2-*O*-Isopropylidene-3-*O*-mesyl-5-*O*-methoxycarbonyl-D-xylofuranose (III).—To a solution of 1.84 g. (7.42 mmoles) of II in 6 ml. of reagent pyridine cooled in an ice-bath was added 1.70 g. (14.8 mmoles) of methanesulfonyl chloride. After 29 hr. at room temperature in a stoppered flask, the mixture was diluted with 20 ml. of water and extracted with chloroform (4 × 5 ml.). The combined extracts, washed with 6% aqueous sodium bicarbonate (4 × 10 ml.) and water (3 × 10 ml.), were dried with magnesium sulfate, then evaporated to dryness *in vacuo;* yield 2.20 g. (91%) of crystalline residue, m.p. 60–64°, that was suitable for the next step. Several recrystallizations from benzene–hexane gave white crystals, m.p. 62–63°; $[\alpha]^{25}_{589}$ −28.2° and $[\alpha]^{25}_{546}$ −33.9° (1.02% in $CHCl_3$); λ^{KBr}_{max} 5.70 μ (carbonate C=O), 7.35 and 8.51 μ (sulfonate), 7.84 μ (carbonate C–O–C).

Anal. Calcd. for $C_{11}H_{18}O_9S$: C, 40.5; H, 5.55; S, 9.84. Found: C, 40.3; H, 5 29; S, 9.88.

1,2-*O*-Isopropylidene-5-*O*-methoxycarbonyl-3-*O*-tosyl-D-xylofuranose (IV).—A solution of 17.8 g. (0.072 mole) of II and 18.0 g. (0.094 mole) of *p*-toluenesulfonyl chloride in 120 ml. of reagent pyridine was heated at 60–70° for 6 hr., protected from moisture. The cooled mixture was poured onto 640 g. of ice and water. The tan crystals which formed were collected on a filter, washed thoroughly with

(21) Melting points were taken on a Fisher–Johns apparatus and are uncorrected unless otherwise specified. Optical rotations were measured with a Standard Polarimeter Model D attachment to the Beckman DU spectrophotometer calibrated with standard sucrose solution [*cf.* A. S. Keston, Abstracts of 127th Meeting, American Chemical Society, 18C, 1955].

ice-water, then dried *in vacuo;* yield 25.1 g. (87%), m.p. 101–103°, suitable for the next step. Recrystallization from 70% aqueous ethanol afforded 20.8 g. (72%) of white crystals, m.p. 105–106° cor., $[\alpha]^{24}_{589}$ −14.6° and $[\alpha]^{24}_{546}$ −17.0° (1.22% in MeOH); λ^{KBr}_{max} 5.66 μ (carbonate C=O), 7.25, 8.40 μ (sulfonate), 7.90 μ (carbonate C–O–C).

Haworth, Porter and Waine[4] have recorded a m.p. 106° and $[\alpha]^{22}D$ −14° (2.5% in MeOH) for this product, prepared with one equivalent of tosyl chloride in unspecified yield.

1,2-Di-*O*-acetyl-3-*O*-mesyl-5-*O*-methoxycarbonyl-D-xylofuranose (VII).—To a stirred solution of 38.3 g. (0.117 mole) of III in 530 ml. of acetic acid and 59 ml. of acetic anhydride was added dropwise 32 ml. of 96% sulfuric acid with ice-cooling at such a rate that the temperature was maintained at 15–20°. After standing at room temperature for 19 hr. in a closed flask, the solution was poured onto 2600 g. of ice and water, then extracted with chloroform (2 × 460 ml.). The combined extracts, washed with 1 *N* sodium bicarbonate (3 × 310 ml.) and dried with magnesium sulfate, were evaporated to dryness *in vacuo;* yield 47.6 g. (110%) of an amber gum that contained some acetic anhydride, but was suitable for the next step. The compound had λ^{film}_{max} 5.46 μ (anhydride C=O), 5.69 μ (broad C=O of carbonate, acetate and anhydride), 7.29, 8.47 μ (sulfonate), 7.82 μ (carbonate C–O–C), 8.08, 8.21 μ (C–O–C).

1,2-Di-*O*-acetyl-5-*O*-methoxycarbonyl-3-*O*-tosyl-D-xylofuranose (VIII).—Acetolysis of 45.7 g. of IV as described for the preparation of VII gave an 88% yield of product as an amber gum suitable for the next step. A sample was dissolved in benzene, and the solution was clarified with Norit A and evaporated *in vacuo.* The colorless oil, dried at 56° and 0.1 mm., had λ^{film}_{max} 5.69 μ (C=O of acetate and carbonate), 7.26, 8.39, 8.48 μ (sulfonate), 7.82 μ (carbonate C–O–C), 8.08, 8.24 μ (acetate C–O–C) and was nearly pure.

Anal. Calcd. for $C_{18}H_{22}O_{11}S$: C, 48.4; H, 4.97; S, 7.18. Found: C, 49.2; H, 5.11; S, 6.93.

Methyl 3-*O*-Mesyl-5-*O*-methoxycarbonyl-D-xylofuranoside (XII).—A solution of 47.6 g. (0.129 mole) of VII in 1.00 l. of 1% methanolic hydrogen chloride was allowed to stand in a stoppered flask for 19 hr., then neutralized by the portionwise addition of 32 g. of sodium bicarbonate. The filtered solution was evaporated *in vacuo.* The residue was extracted with two 210-ml. portions and one 100-ml. portion of boiling dichloromethane, Celite being added to aid filtration. Evaporation of the combined extracts to dryness *in vacuo* gave 31.7 g. (90% based on III) of brown, viscous residue; λ^{film}_{max} 2.85 μ (OH), 5.70 μ (carbonate C=O), 7.82 μ (carbonate C–O–C), 8.50 μ (sulfonate).

Anal. Calcd. for $C_9H_{16}O_9S$: C, 36.0; H, 5.37; S, 10.7. Found: C, 35.8; H, 5.67; S, 10.9.

Methyl 5-*O*-Methoxycarbonyl-3-*O*-tosyl-D-xylofuranoside (XIII).—Methanolysis of 42.5 g. of VIII, as described for the preparation of XII, gave 30.9 g. (76% based on IV) of product as a brown gum that slowly crystallized; it was suitable for the next step. After several recrystallizations from benzene–hexane, one anomer was obtained as tan crystals, m.p. 81–82.5°; $[\alpha]^{26}_{589}$ +37.3° and $[\alpha]^{26}_{546}$ +43.3° (2.01% in $CHCl_3$); λ^{KBr}_{max} 2.85 μ (OH), 5.70 μ (carbonate C=O), 7.30, 8.40, 8.50 μ (sulfonate), 7.82 μ (carbonate C–O–C), and no acetate C–O–C near 8 μ.

Anal. Calcd. for $C_{15}H_{20}O_9S$: C, 47.9; H, 5.36; S, 8.52. Found: C, 48.1; H, 5.52; S, 8.50.

Methyl 2,3-Anhydro-α(and β)-D-ribofuranoside (XI). (A).—To an ice-cold solution of 31.2 g. (0.104 mole) of XII in 67 ml. of reagent methanol was added an ice-cold solution of 6.41 g. (0.119 mole) of sodium methoxide in 56 ml. of reagent methanol. After 4 days in a stoppered flask at about 5°, the mixture was treated with 4 g. of Celite and filtered. The insoluble materials were washed with methanol (3 × 25 ml.). The combined filtrate and washings were neutralized with 3 ml. of acetic acid, then evaporated to dryness *in vacuo.* The residue was dissolved in water, and the solution was extracted with chloroform (7 × 80 ml.). After being dried over magnesium sulfate, the combined extracts were evaporated to dryness *in vacuo.* Distillation of the residue through a short Vigreux column gave two easily separable fractions.

Fraction I, b.p. 48–70° (5 μ) (mainly at 48°), was a colorless oil with $n^{20}D$ 1.4578 and $[\alpha]^{25}_{589}$ −109° (1.98% in H_2O); λ^{film}_{max} 2.88 μ (OH), 3.26 μ (epoxide CH), 11.60 μ (epoxide); yield 6.81 g.

Fraction II, b.p. 70–90° (2 μ) (mainly at 87–90°), was also a colorless oil with $n^{20}D$ 1.4714 and $[\alpha]^{29}_{589}$ +13.1° (2.29% in H_2O); λ^{film}_{max} 2.86 μ (OH), 3.27 μ (epoxide CH), 11.62 μ (epoxide); yield 5.05 g.

There were distinct differences in the infrared spectra of these two fractions and, in addition, fraction II was considerably more viscous than fraction I. The rotations clearly show that fraction I was the β-anomer and fraction II the α-anomer. The combined fractions represented a 78% yield from XII or a 47% over-all yield from I.

Anal. Calcd. for $C_6H_{10}O_4$: C, 49.3; H, 6.90. Found: (fraction I), C, 49.5; H, 7.13; (fraction II), C, 49.2; H, 7.19.

(B).—Treatment of 15.18 g. (40.4 mmoles) of XIII in 25 ml. of methanol with 2.49 g. (46 mmoles) of sodium methoxide in 23 ml. of methanol, as described in preparation A above, gave 2.82 g. (48%) of fraction I, b.p. 45–56° (2 μ) (mainly 45–46°), $n^{20}D$ 1.4581, and 0.77 g. (13%) of fraction II, b.p. 56–80° (2 μ) (mainly at 80°), $n^{20}D$ 1.4708. The two fractions each had infrared spectra identical with the corresponding fractions in preparation A.

A large scale run starting with 101.5 g. of recrystallized II and proceeding through IV, VIII and XIII, without purification of these intermediates, afforded a 47% yield of distilled XI over-all from I. This was collected in two fractions whose refractive indices and infrared spectra were in complete agreement with those of the corresponding fractions described above.

Methyl 5-*O*-Acetyl-2,3-anhydro-β-D-ribofuranoside (XVb).—A solution of 5.22 g. (35.8 mmoles) of XIb in 10.5 ml. of reagent pyridine and 4.07 ml. of acetic anhydride was allowed to stand at room temperature for 27 hr., then processed in the usual manner; yield 6.22 g. (92%) of a colorless oil, b.p. 66° (8 μ), $n^{20}D$ 1.4476, $[\alpha]^{23}_{589}$ −112° and $[\alpha]^{23}_{546}$ −131° (2.23% in $CHCl_3$); λ^{film}_{max} 3.27 μ (epoxide CH), 5.73, 8.09 μ (acetate).

Similarly, **methyl 5-*O*-acetyl-2,3-anhydro-α-D-ribofuranoside (XVa)** was prepared; b.p. 80–82° (35 μ), $n^{20}D$ 1.4553, $[\alpha]^{23}_{589}$ −2.1° and $[\alpha]^{23}_{546}$ −2.9° (2.28% in $CHCl_3$); λ^{film}_{max} 3.30 μ (epoxide CH), 5.75, 8.08 μ (acetate).

Anal. Calcd. for $C_8H_{12}O_5$: C, 51.1; H, 6.42. Found: (β-anomer), C, 51.0; H, 6.53; (α-anomer), C, 50.7; H, 6.49.

Methyl 2,3-Anhydro-5-*O*-(*p*-nitrobenzoyl)-D-ribofuranoside (XVIa and b). (A) α-Anomer.—Methyl 2,3-anhydro-α-D-ribofuranoside (XIa) (604 mg.) was allowed to react with excess *p*-nitrobenzoyl chloride in pyridine at room temperature for 3.5 hr., yielding 1.14 g. of crude XVIa, m.p. 130–133° with preliminary softening. Recrystallization from benzene–hexane afforded 989 mg. (81%) of product collected in several crops, m.p. 130–133° to 132–134.5°. The product of a preliminary preparation, recrystallized twice from ethanol and once from benzene, had a constant m.p. 134–136° and $[\alpha]^{26}_{589}$ −26.4° and $[\alpha]^{26}_{546}$ −32.8° (2.01% in $CHCl_3$); λ^{KBr}_{max} 3.21 and 3.27 μ (aromatic and epoxide CH) 5.78 μ (ester C=O), 6.56 (NO_2), 11.60 μ (shoulder, epoxide).

Anal. Calcd. for $C_{13}H_{13}NO_7$: C, 52.9; H, 4.44; N, 4.74. Found: C, 53.1; H, 4.47; N, 4.98.

(B) β-Anomer.—Similarly, 519 mg. of XIb afforded 997 mg. of crude XVIb, m.p. 96–98°. Recrystallization from benzene–hexane yielded 910 mg. (87%) of product, m.p. 97–98.5°. A second recrystallization from benzene–hexane gave material of m.p. 98.5–99.5° and $[\alpha]^{25}_{589}$ −95.8° and $[\alpha]^{26}_{546}$ −114° (2.00% in $CHCl_3$).

Anal. Calcd. for $C_{13}H_{13}NO_7$: C, 52.9; H, 4.44; N, 4.74. Found: C, 53.0; H, 4.48; N, 4.73.

The pyranoside isomer, methyl 2,3-anhydro-4-*O*-(*p*-nitrobenzoyl)-β-D-ribopyranoside,[13] has m.p. 159–160° and $[\alpha]^{24}D$ +24.6° (0.33% in $CHCl_3$).

Methyl 3-Amino-3-deoxy-β-D-xylopyranoside (XIV).—A solution of 12.0 g. (36.8 mmoles) of III in 310 ml. of 1% methanolic hydrogen chloride was refluxed for 15 hr., then processed as described for the sequence VII → XII → XI. The resulting mixed anhydropentosides readily were separated by distillation into two fractions, representing a 60% yield (based on III). Fraction I had b.p. 50° (2 μ) and $n^{20}D$ 1.4660; yield 2.48 g. of a colorless oil which was a

mixture of XIb with IX and/or X. Fraction II had b.p. 80–83° (2 μ) and $n^{20}D$ 1.4732; yield 0.75 g. of colorless oil which was mainly XIa, but its infrared spectrum indicated other contaminants.

Anal. Calcd. for $C_6H_{10}O_4$: C, 49.3; H, 6.90. Found: (fraction I), C, 49.5; H, 6.97; (fraction II), C, 49.5; H, 7.16.

Ammonolysis of 2.57 g. of fraction I by the procedure described for the preparation of XVIIb (see below) gave 2.80 g. (98%) of crude product. Recrystallization from 15 ml. of 95% ethanol afforded 557 mg. of white crystals, m.p. 196–199°; a second crop of 82 mg. (total 22%) of product was obtained with m.p. 193–195°. Recrystallization from 95% ethanol gave white crystals of XIV, m.p. 195–197° cor., $[\alpha]^{28}_{589}$ −63° (0.76% in H_2O); λ_{max}^{KBr} 2.95, 3.01 μ (OH, NH); 6.29 μ (NH). For paper chromatographic data see Table I.

Anal. Calcd. for $C_6H_{13}NO_4$: C, 44.2; H, 8.03; N, 8.58. Found: C, 44.2; H, 8.17; N, 8.48.

This compound consumed 1.95 moles of periodate in 15 minutes and was constant at 2.07 moles after 2–16 hours when oxidized by the procedure of Fleury and Lange.[22] This aminopyranoside (XIV) is enantiomorphic with methyl 3-amino-3-deoxy-β-L-xylopyranoside,[14] m.p. 192–193° dec., $[\alpha]^{24}D$ +61° (1% in H_2O).

The mother liquor from the crude XIV described above was evaporated, and the residual gum was treated with acetic anhydride in water to convert the amino sugar(s) present to the N-acetyl derivatives. The crude product traveled as a single spot in solvents D (R_f 0.47), E (R_f 0.80 ± 0.01) and F (R_f 0.90), indicating that it was the acetamidofuranoside XXb (*cf.* Table II).

Methyl 3-Acetamido-2,4-di-*O*-acetyl-3-deoxy-β-D-xylopyranoside (XVIII).—Acetylation of 330 mg. of XIV with acetic anhydride in pyridine according to the procedure described for the enantiomer[14] gave 505 mg. (86%), m.p. 172–173° cor. Recrystallization from benzene–hexane gave 423 mg. of white needles, m.p. 171–172° cor., $[\alpha]^{26}_{589}$ −59.3° and $[\alpha]^{26}_{546}$ −71.6° (1.43% in $CHCl_3$); λ_{max}^{KBr} 2.97 μ (NH), 5.74, 5.81 μ (acetate C=O), 5.94 μ (amide C=O), 6.47 μ (amide NH).

Anal. Calcd. for $C_{12}H_{19}NO_7$: C, 49.8; H, 6.62; N, 4.85. Found: C, 50.1; H, 6.79; N, 4.65.

The enantiomer[14] has m.p. 170–171° and $[\alpha]^{23}D$ +60.7° (2% in $CHCl_3$).

Methyl 3-Acetamido-3-deoxy-β-D-xylopyranoside (XXI).—A solution of 320 mg. (1.11 mmoles) of XVIII in 6 ml. of absolute methanol containing 0.12 ml. of 1.0 *N* methanolic sodium methoxide was refluxed for 0.5 hr. Evaporation of the methanol *in vacuo* left a tan solid which was dissolved in 5 ml. of water. The solution was stirred with 0.2 g. of Amberlite IRC-50 (H)[18] until neutral. Filtration and evaporation *in vacuo* afforded 292 mg. of crystalline XXI, m.p. 196–199° cor. Recrystallization from ethyl acetate gave 189 mg. (83%) of white needles, $[\alpha]^{24}_{589}$ −65.1° and $[\alpha]^{24}_{546}$ −78.1° (1.39% in H_2O), in two crops, both having the m.p. 198–199° cor.; λ_{max}^{KBr} 3.0 μ (broad, OH and NH), 6.14 μ (amide C=O), 6.39–6.45 μ (amide NH).

Anal. Calcd. for $C_8H_{15}NO_5$: C, 46.8; H, 7.37; N, 6.83. Found: C, 46.9; H, 7.45; N, 6.56, 6.81.

This material moved as a single spot in solvents D, E and F (see Table II). A 5-γ spot was detectable but a 1-γ spot was not. The enantiomer[14] of XXI has m.p. 194–195° and $[\alpha]^{24}D$ +64.4° (2% in H_2O).

Methyl 3-Amino-3-deoxy-α-D-xylofuranoside (XVIIa).—A solution of 3.24 g. (22.2 mmoles) of XIa in 24 ml. of concentrated ammonium hydroxide was heated in a steel bomb at 100° for 15.5 hours. The solution was treated with Norit A, filtered through Celite, then evaporated *in vacuo*. Two portions of benzene were evaporated from the yellowish residue (finally at 40° and 0.4 mm.), which then weighed 4.01 g. (111%). It showed no epoxide absorption at 11.6 μ. A 1.10-g. portion was evaporatively distilled at 100° (bath temperature) and 0.10 mm., leaving a 75-mg. residue. The colorless, waxy distillate was dissolved from the condenser with methanol and the solution evaporated (finally at 40° and 0.8 mm.) to leave 1.04 g. (103%) of product.

Anal. Calcd. for $C_6H_{13}NO_4$: C, 44.2; H, 8.03; N, 8.58. Found: C, 44.3, 44.2; H, 8.01, 8.01; N, 7.31, 7.37.

(22) P. Fleury and J. Lange, *J. pharm. chim.*, **17**, 107 (1933).

A solution of crude XVIIa (2.00 g., prepared in 103% yield in another run) in 100 ml. of water was applied to an 8.7 × 2.2 cm. column containing 20 g. of Amberlite IRC-50 (H) resin.[17,18] The column was washed with 500 ml. of water. No ninhydrin-positive substance was detected in the resulting eluate. The first 220 ml. was evaporated *in vacuo*, leaving 262 mg. of colorless sirup, possibly methyl α-D-xylofuranoside, which was not investigated further. The aminofuranoside XVIIa was eluted with 2 *N* ammonium hydroxide in 50% aqueous methanol, 20-ml. fractions being collected. Detection was done by spotting aliquots on a paper strip and developing with ninhydrin. The combined ninhydrin-positive fractions 33–40 yielded, on evaporation *in vacuo*, 1.72 g. (88% from XIa) of pale sirup which became a waxy solid on standing. Paper chromatographic results are included in Table I. A 0.30-g. portion was evaporatively distilled at 100° and 0.10 mm., leaving only 5 mg. of residual brown gum. The colorless distillate (XVIIa) was a hygroscopic, waxy solid which could not be crystallized from the usual solvents and had $[\alpha]^{25}_{589}$ +134° (1.82% in H_2O); $[\alpha]^{27}_{589}$ +131° and $[\alpha]^{27}_{546}$ +154° (2.00% in $CHCl_3$); λ_{max}^{KBr} 2.99 μ (OH, NH); 6.17, 6.26 μ (NH_2).

Anal. Calcd. for $C_6H_{13}NO_4$: C, 44.2; H, 8.03; N, 8.58. Found: C, 43.8; H, 8.02; N, 8.27, 8.36.

Methyl 3-Acetamido-3-deoxy-α-D-xylofuranoside (XXa).—Distilled crude methyl 3-amino-3-deoxy-α-D-xylofuranoside (XVIIa) (508 mg., 3.12 mmoles, shown by nitrogen analysis to contain 86% methyl aminopentoside) dissolved in 2.5 ml. of water was treated with 0.40 ml. of acetic anhydride, while the temperature was kept from rising above 35°. After 7 minutes in a 35° water-bath, the solution was evaporated *in vacuo*. The residual brown gum was covered with acetone and seeded with some crystals (m.p. 75–128°) obtained in 60% yield by Florisil[23] chromatography of the product of a preliminary run. The gum then largely crystallized. Evaporation of the acetone, finally at 25° and 0.4 mm., left 616 mg. of crudely crystalline XXa, which melted completely by 85°. Trituration in acetone followed by centrifugation afforded 435 mg. (79%) of white, apparently crystalline solid, m.p. 65–85° with preliminary softening. On repeated recrystallization from benzene–acetone and other solvents, it melted erratically over the range 60–156°. The sample used for analysis had m.p. 103–156° and $[\alpha]^{25}_{589}$ +104° and $[\alpha]^{25}_{546}$ +119° (0.200% in H_2O); λ_{max}^{KBr} 3.04 μ (OH, NH), 6.06 μ (amide C=O), 6.44 μ (amide NH). Results of paper chromatography are given in Table II.

Anal. Calcd. for $C_8H_{15}NO_5$: C, 46.8; H, 7.37; N, 6.83. Found: C, 47.0; H, 7.51; N, 7.08.

The residue from the combined mother liquors from the purification of the above product also traveled as a single spot in solvents D (R_f 0.55), E (R_f 0.77 ± 0.01) and F (R_f 0.94 ± 0.02) (*cf.* Table II).

Methyl 3-Deoxy-3-(*p*-nitrobenzamido)-2,5-di-*O*-(*p*-nitrobenzoyl)-α-D-xylofuranoside (XIX).—To a solution of 557 mg. (3.42 mmoles) of XVIIa (shown to contain 86% methyl aminopentoside by purification on Amberlite IRC-50) in 40 ml. of pyridine containing 2.4 ml. (17.1 mmoles) of triethylamine, cooled in an ice-bath, was added 2.86 g. (15.4 mmoles) of *p*-nitrobenzoyl chloride. After being stirred at 0° for 1 hr. and standing at room temperature for 46 hr., the mixture was worked up in the usual way, affording 2.05 g. of partially crystalline product. Recrystallization from ethyl acetate–hexane yielded 0.87 g. (42%) of XIX as an ethyl acetate solvate, m.p. 94–99° with gas evolution. A similar experiment using distilled crude XVIIa (467 mg.) gave a 45% yield of crude product, m.p. 98–101° with gas evolution. Three recrystallizations from ethyl acetate–hexane afforded 0.41 g. of pure XIX solvate having the constant m.p. 101–103° with gas evolution and $[\alpha]^{26}_{589}$ −24.7° and $[\alpha]^{26}_{546}$ −32.4° (2.00% in $CHCl_3$); λ_{max}^{KBr} 5.78 μ (ester C=O), 6.00 μ (amide C=O), 6.25 μ (phenyl), 6.54 μ (NO_2 and amide NH).

Anal. Calcd. for $C_{27}H_{22}N_4O_{13}\cdot C_4H_8O_2$: C, 53.3; H, 4.33; N, 8.02; *O*-acetyl, 6.16. Found: C, 53.5; H, 4.45; N, 7.97, 8.18; *O*-acetyl, 6.38.

Methyl 3-Amino-3-deoxy-β-D-xylofuranoside (XVIIb).—Methyl 2,3-anhydro-β-D-ribofuranoside (XIb) (2.53 g.) was

(23) A synthetic magnesium aluminum silicate adsorbent manufactured by the Floridin Company, Warren, Pennsylvania.

ammonolyzed as described for the α-anomer XIa, affording crude XVIIb as a slightly yellowish, viscous oil weighing 3.54 g. (125%). It showed no epoxide absorption at 11.6 μ. A 435-mg. portion was dried at 100° and 0.15 mm. until the decrease in weight was less than 1% per hour. The final weight was 316 mg. (91%).

The crude product of an ammonolysis performed at 90° for 17 hr. (showing weak absorption at 11.6 μ) was purified on Amberlite IRC-50 (H)[18] as described for the α-anomer XVIIa. This afforded a 21% yield of neutral material, mainly recovered XIb, and a 73% yield of XVIIb as a pale oil. A 239-mg. portion of the latter was heated at 100° and 0.10 mm. until the weight loss remained constant at about 7 mg./hour. This sample had $[\alpha]^{24}_{589}$ −66.1° (2.51% in H_2O); $[\alpha]^{27}_{589}$ −74.4° and $[\alpha]^{27}_{546}$ −92.3° (0.34% in $CHCl_3$); and λ^{film}_{max} 2.99 μ (OH, NH), 6.27 μ (NH_2).

Anal. Calcd. for $C_6H_{13}NO_4$: C, 44.2; H, 8.03; N, 8.58. Found: C, 44.1; H, 8.04; N, 8.45.

Methyl 3-Acetamido-3-deoxy-β-D-xylofuranoside (XXb).—Crude methyl 3-amino-3-deoxy-β-D-xylofuranoside (XVIIb) was treated with acetic anhydride in water as described for the α-anomer XXa. The crude derivative crystallized on trituration in ethyl acetate, affording 549 mg. (107% based on XIb) of white crystals, m.p. 97–104°. Three recrystallizations from ethyl acetate–ethanol yielded 243 mg. of white crystals, m.p. 105–106°; $[\alpha]^{25}_{589}$ −31.2° and $[\alpha]^{25}_{546}$ −37.0° (1.16% in H_2O); λ^{KBr}_{max} 2.96, 3.05 μ (OH, NH), 6.06 μ (amide C=O); 6.47 μ (amide NH). Paper chromatographic results are given in Table II.

Anal. Calcd. for $C_8H_{15}NO_5$: C, 46.8; H, 7.36; N, 6.83. Found: C, 46.9, 46.9; H, 7.50, 7.28; N, 6.59, 6.44.

The residue from the combined mother liquors from the purification of the analytical sample also moved as a single spot in solvents D (R_f 0.47 ± 0.02), E (R_f 0.79 ± 0.01) and F (R_f 0.90) (*cf.* Table II).

Isomerization of Methyl 3-Amino-3-deoxy-D-xylofuranoside (XVII) to Methyl 3-Amino-3-deoxy-β-D-xylopyranoside (XIV). (A) α-Anomer.—A solution of 1.56 g. of crude XVIIa (86% pure) in 50 ml. of 1% methanolic hydrogen chloride was refluxed for 22 hr. (protected from moisture) and evaporated to dryness *in vacuo*. The residue, dissolved in 25 ml. of water, was neutralized by being stirred with 12 g. of Dowex 2 (CO_3)[24] for 1 hr. at 60–70°. The resin was removed by filtration and the combined filtrate and water washings (3 × 10 ml.) were again treated with 10 g. of Dowex 2 (CO_3). The filtered solution was evaporated to dryness *in vacuo*. Several recrystallizations of the residue from 95% ethanol gave a total of 72 mg. (5.4%) of pure XIV, m.p. 193–195° cor. A mixture with authentic XIV melted at 193–196° cor., and a comparison of their infrared spectra confirmed this identity.

(B) β-Anomer.—Isomerization of 1.53 g. of crude XVIIb (76% pure) as described for the α-anomer gave 147 mg. (13%) of pure XIV, m.p. 193–196° cor. A mixture with authentic XIV melted at 194–196° cor., and the two samples had identical infrared spectra.

Paper Chromatography.—The paper chromatograms were run by the descending technique on Whatman No. 1 paper in these several solvent systems: A, 1-butanol/acetic acid/water (5/2/3)[25]; B, ethyl acetate/pyridine/water (2/1/2)[26]; C, 1-butanol/ethanol/water (4/1/5)[27]; D, water-saturated 1-butanol[28]; E, methyl Cellosolve/water (9/1)[29]; and F, 5% disodium hydrogen phosphate[30] (without the usual organic phase). For the aminoxylosides, 250-γ applications were used; for the acetamidoxylosides, 100-γ.

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(24) An anion-exchange resin purchased from Microchemical Specialties Company, Berkeley, California.

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MENLO PARK, CALIFORNIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEW MEXICO]

The Synthesis of 1-Methyl-3,4-benzpyrene and 1,8-Dimethyl-3,4-benzpyrene[1-3]

BY WILLIAM CARTER DOYLE, JR.,[4] AND GUIDO H. DAUB

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Condensation of anthrone (I) with ethyl methacrylate in the presence of potassium *t*-butoxide followed by acid hydrolysis and reduction gave β-(9-anthranyl)-isobutyric acid (II) in 71% yield. Reduction of II with sodium in *n*-amyl alcohol gave β-(9,10-dihydro-9-anthranyl)-isobutyric acid (III) (87% yield) which was cyclized to 2-methyl-3-keto-1,2,3,11b-tetrahydro-7H-*meso*-benzanthracene (IV) in 81% yield. The Stobbe condensation of IV with dimethyl succinate using W. S. Johnson's procedure for hindered ketones gave a 95% yield of crude oily half-ester. Saponification of the half-ester with alcoholic potassium hydroxide yielded a mixture of isomeric unsaturated dibasic acids. Decarboxylation of the dibasic acids yielded a mixture from which β-(2-methyl-1,11b-dihydro-7H-*meso*-benzanthracene-3)-propionic acid (VII) was isolated in 40% yield. Reduction of the entire crude mixture of acidic material from the decarboxylation with sodium in *n*-amyl alcohol followed by cyclization with anhydrous hydrogen fluoride gave a mixture of neutral and acidic ketonic material. The neutral fraction (36.5% yield from IV) was shown to contain 8-keto-1-methyl-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene (VIII) and 8-keto-1-methyl-1,2,8,9,10,10a-hexahydro-3,4-benzpyrene (IX). This neutral fraction was readily converted into 1-methyl-3,4-benzpyrene (XII) *via* Wolff–Kishner reduction and then by dehydrogenation, and into 1,8-dimethyl-3,4-benzpyrene (XIII) *via* a Grignard reaction with subsequent dehydration and dehydrogenation. The over-all yield for each of these two hydrocarbons from anthrone was 9%.

Previous papers in this series have reported the synthesis of the 10-,[5] 2-[6] and 9-[7] monomethyl-3,4-benzpyrenes, the 8,10-,[5] 2,8-,[6] 8,9-,[7] 5,8-[8] and 5,10-[8] dimethyl-3,4-benzpyrenes and 5,8,10-trimethyl-3,4-benzpyrene.[8] We are now reporting the synthesis of two more new 3,4-benzpyrenes, namely, 1-methyl-3,4-benzpyrene and 1,8-dimethyl-3,4-benzpyrene.

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(4) Graduate Research Assistant, February, 1952, to December, 1955.

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