developed with a 3:1:1 *n*-butyl alcohol–water–acetic acid mixture), and a comparison of the infrared spectra (KBr).

Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.55; H, 6.71. Found: C, 61.53; H, 7.07.

2-(*p*-Hydroxybenzyl)-2-nitropropane (4).—A mixture of 2.0 g (0.0132 mole) of N,N-dimethyl-*p*-hydroxybenzylamine (**1**), 1.21 g (0.0136 mole) of 2-nitropropane, and 20 mg of a 53% sodium hydride dispersion in mineral oil in 30 ml of toluene was heated at reflux under nitrogen for 18 hr. The cooled toluene solution was separated from an insoluble gum, washed with water, and dried over anhydrous sodium sulfate. After filtering, the solvent was removed under reduced pressure to give 1.03 g (40.2%) of **4**, mp 105–111°. Since recrystallizations from several solvents did not improve the melting point, the crude product was chromatographed on a silicic acid column and eluted with methylene chloride to give 0.65 g (25.3%) of product, mp 111.3–112.8°. The melting point was unchanged after recrystallization from an ethyl acetate–hexane mixture. The infrared spectrum ($CHCl_3$) contained strong absorption bands at 3580 (sharp) and 3320 (broad) (OH), 1530 and 1345 cm^{-1} (NO_2).[6b] Singlets were observed in the nmr spectrum at δ 1.58 ppm ($2CH_3$), 3.14 (CH_2), and 5.63, broad (OH); the four aromatic protons were observed as a multiplet centered at δ 6.85 ppm.

Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.82; H, 6.52; N, 7.51.

Reaction of N,N-Dimethyl-*p*-methoxybenzylamine (2) with Ethyl α-Nitropropionate.—A mixture of 2.0 g (0.0121 mole) of N,N-dimethyl-*p*-methoxybenzylamine,[16] 1.84 g (0.0125 mole) of ethyl α-nitropropionate,[13] and 20 mg of a 53% sodium hydride dispersion in mineral oil in 30 ml of toluene was heated at reflux under nitrogen for 20 hr. The absence of dimethylamine in the effluent nitrogen stream and thin layer chromatography (silica plate developed with a 5% methanol–chloroform mixture) indicated that no reaction had occurred. The toluene was replaced with 30 ml of xylene and the reaction was heated again at reflux for 36 hr. After washing with a dilute sodium hydroxide solution and water, the xylene extract was dried over anhydrous sodium sulfate, filtered, and concentrated to give 1.45 g (72.6%) of recovered N,N-dimethyl-*p*-methoxybenzylamine, identified by thin layer chromatography and infrared spectra.

Ethyl α-Nitropropionate Sodium Salt.—To a stirred solution of 1.0 g (6.8 mmoles) of ethyl α-nitropropionate[13] in 25 ml of dry benzene was added 0.38 g (8.08 mmoles) of a 51% sodium hydride–mineral oil dispersion. After stirring for 0.5 hr, excess sodium hydride was decomposed with a few drops of ethanol. The product was collected and dried to give a quantitative yield of the sodium salt, mp 196.0–197.5° dec, softening at 193°. A sample was recrystallized from absolute ethanol to give an analytical sample, mp 198.0–199.5° dec.

Anal. Calcd for $C_5H_8NaNO_4$: N, 8.28. Found: N, 8.19.

Ethyl 2-Nitro-2-(4-nitrobenzyl)propionate (8).—A solution of 1.0 g (5.84 mmoles) of *p*-nitrobenzyl chloride in 10 ml of dry dimethylformamide was added over 20 min to a stirred solution of 1.0 g (5.92 mmoles) of the sodium salt of ethyl α-nitropropionate in 20 ml of dimethylformamide at 50°. The reaction mixture was stirred at 80° for 5 hr, cooled, and diluted with water. The product was extracted into ethyl ether which was then washed with water and dried over anhydrous sodium sulfate. After filtering and removing the solvent under vacuum, the crude product was recrystallized twice from isopropyl alcohol to give 0.86 g (52.2%) of **8**, mp 78–80°. Further recrystallization gave an analytical sample, mp 79.5–80.8°. The infrared spectrum (KBr) contained strong absorption bands at 1755 (ester),[6a] 1545 (aliphatic NO_2), 1510 (aromatic NO_2), and 1350–1340 cm^{-1} (NO_2).[6b]

Anal. Calcd for $C_{12}H_{14}N_2O_6$: C, 51.06; H, 5.00; N, 9.93. Found: C, 51.03; H, 5.11; N, 9.97.

When *p*-nitrobenzyl bromide was substituted for *p*-nitrobenzyl chloride, **8**, mp 77–79°, was isolated in 30.6% yield.

Reaction of Ethyl α-Nitropropionate with Benzyl Chloride.—The reaction of 25.4 g (0.20 mole) of benzyl chloride with 29.4 g (0.20 mole) of ethyl α-nitropropionate[13] and 9.06 g (0.20 mole) of a 53% suspension of sodium hydride in mineral oil in 150 ml of dimethylformamide was carried out as described for *p*-nitrobenzyl chloride. The crude product was distilled through an 18-in. Vigreux column to give a series of fractions which were analyzed by gas chromatography on a fluorosilicone column. The infrared spectrum of the product distilling at 77–80° (27 mm), 7.07 g, was identical with that of an authentic sample of benzaldehyde. However, since gas chromatography indicated that it contained only 92.6% benzaldehyde, the adjusted yield is 30.9%.

(16) E. Stedman, *J. Chem. Soc.*, 1904 (1927).

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Determination of the Anomeric Configuration of 9-α-D-Mannofuranosyladenine and Preparation of 9-α-D-Lyxofuranosyladenine[1a]

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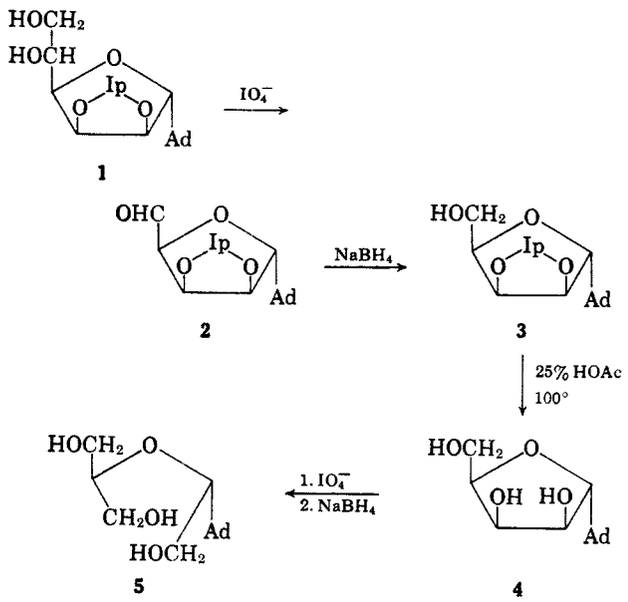
Recently the preparation of a 9-D-mannofuranosyladenine was reported.[2] The nucleoside was prepared by the condensation of 2,3:5,6-di-O-isopropylidene-D-mannofuranosyl chloride with 6-benzamidochloromercuripurine, which resulted in a product presumed to have an α configuration. The only evidence for this aspect of the structure was the molecular rotation (+22, 280°), which suggested an α configuration on the basis of comparison with a number of glycofuranosides of known anomeric configuration. The *trans* rule could not be relied on for further suggestive evidence inasmuch as the blocking isopropylidene group does not participate in the condensation reaction and therefore has no directive effect. Because of the lack of evidence pertaining to this structural feature of the nucleoside, it was decided to reinvestigate the compound in order to obtain more direct evidence as to its nature. For this purpose the reactions shown in Scheme I were carried out.

9-(2′,3′-O-Isopropylidene-D-mannofuranosyl)adenine (**1**),[2] an intermediate in the previously described preparation of 9-D-mannofuranosyladenine, was treated with sodium periodate and the resultant aldehyde product (**2**) was passed over an anion-exchange resin to remove iodate and excess periodate. The effluent from the column was collected in a flask containing sodium borohydride, bringing about an immediate reduction to 9-(2′,3′,-O-isopropylidene-α-D-lyxofuranosyl)adenine (**3**). The isopropylidene group was removed by hydrolysis with acetic acid to yield 9-α-D-lyxofuranosyladenine (**4**).

(1) (a) Supported in part by U. S. Public Health Service Grant No. CA-07960. (b) To whom requests for reprints should be addressed.

(2) L. M. Lerner and P. Kohn, *J. Org. Chem.*, **31**, 339 (1966).

SCHEME I



Recently, Reist, *et al.*,[3] described the preparation of 9-(2′,3′-O-isopropylidene-β-D-lyxofuranosyl)adenine and 9-β-D-lyxofuranosyladenine. Comparison of the physical properties of their compounds with the corresponding compounds described in this report showed marked differences in most instances.[4] Only the mobility of the anomeric monoisopropylidene derivatives was the same when thin layer chromatography on silica gel was carried out using 5% aqueous disodium hydrogen phosphate as the developing solvent. This lack of identity of the compounds indicates that the lyxose derivatives prepared from mannose were the α anomers, inasmuch as those prepared by Reist, *et al.*,[3] were the β anomers. The properties of these substances are summarized in Table I.

TABLE I
PHYSICAL CONSTANTS OF ANOMERIC LYXOFURANOSYLADENINE NUCLEOSIDES AND THEIR MONOISOPROPYLIDENE DERIVATIVES

	9-D-Lyxofuranosyladenine		9-(2′,3′-O-Isopropylidene-D-lyxofuranosyl)adenine	
	α	β	α	β
Mp	248–250°	123–131°	182–183°	267.5–268.5°[a]
$[\alpha]_D$	+93.8°	−21°[a]	−28°	+17.8°[a]
R_{Ad}	1.31	1.22	0.84	0.84

[a] Cited in ref 3.

To establish further the anomeric configuration of the lyxofuranosyladenine prepared from mannofuranosyladenine, the lyxose derivative was treated with sodium periodate and the product of the reaction was reduced with sodium borohydride as described by Davoll, *et al.*,[5a] and Wright, *et al.*,[5b] to give 2-O-[1-(9-adenyl)-2-(hydroxy)ethyl]glycerol (**5**). This product had a specific rotation of −65°. When authentic adenosine was treated in the same manner, the product was found to have a specific rotation of +68.1°. These findings constitute unequivocal evidence that the lyxofuranosyladenine had an α configuration, and, therefore, the mannofuranosyladenine from which it was prepared must have been 9-α-D-mannofuranosyladenine.

It is of interest to note that Lee and Nolan[6] recently reported the preparation of a 9-D-mannofuranosyladenine by essentially the same route we had used earlier.[2] Their synthesis differed primarily in the means whereby the intermediate 2,3:5,6-di-O-isopropylidenemannofuranosyl chloride was prepared. On the basis of nmr studies, Lee and Nolan conclude that the 2,3:5,6-di-O-isopropylidenemannofuranose and the glycosyl halide prepared from it have an α configuration. As shown in this report, the adenine nucleoside derived from the halogenose also has an α configuration. Lee and Nolan conclude, as we did earlier,[2] that this retention of configuration implies an SN1 reaction mechanism, with the formation of a single anomer resulting from steric hindrance due to the bulky isopropylidene group. The mannofuranosyl nucleoside obtained by Lee and Nolan is probably identical with that which we obtained, although they report a melting point some 12° lower than we obtained.

Experimental Section[7]

Melting points were obtained on a Kofler hot stage and correspond to corrected values. Thin layer chromatography was carried out using Brinkmann TLC plates precoated with silica gel F_{254}, developed with 5% aqueous disodium hydrogen phosphate.[8] Spots were located with a Mineralight lamp which produced ultraviolet radiation at 254 mμ, and assigned R_{Ad} values which correspond to the ratio of the distance the nucleoside traveled to that which adenine traveled. Optical rotations were determined in 100-mm semimicro tubes using a Rudolph polarimeter, Model 70. Ultraviolet spectra were obtained in a Perkin-Elmer 202 spectrophotometer and the molar extinction coefficients (ε) were determined on a Gilford multiple sample recorder utilizing the optical system of a Beckman DU spectrophotometer.

9-(2′,3′-O-Isopropylidene-α-D-lyxofuranosyl)adenine (3).—9-(2′,3′-O-Isopropylidene-α-D-mannofuranosyl)adenine[2] (506 mg, 1.5 mmoles) was dissolved in 90 ml of water by heating. The solution was cooled to about 15° and 4 ml of 0.5 *M* sodium periodate was added. The reaction mixture was allowed to stand at room temperature in the dark for 2 hr, then passed over a column containing 12 g of Amberlite IR-45 (20 × 1.2 cm). The effluent and water eluent were collected in a flask containing 1.1 g of sodium borohydride and allowed to stand at room temperature for 1 hr. At the end of that time, acetone was added to decompose excess sodium borohydride; the solution was cooled in an ice bath and brought to neutrality by dropwise addition of glacial acetic acid. The solution was concentrated to a volume of 10 ml under reduced pressure at 40° and extracted six times with 10-ml portions of chloroform. The combined chloroform extracts were dried over anhydrous sodium sulfate and concentrated to a glass under reduced pressure at 40°. The glass was dissolved in a small volume of 1-butanol, from which **3** crystallized as white needles which melted at 181–182° (293 mg; 63.5%). Recrystallization from 1-butanol yielded the pure material (216 mg), which began to shrink at 164–166°, mp 182–183°; $[\alpha]^{23}D$ −28° (*c* 0.52, pyridine); $\lambda_{max}^{H_2O}$ 262 mμ (ε 14,600).

Anal. Calcd for $C_{13}H_{17}N_5O_4$: C, 50.81; H, 5.58; N, 22.79. Found: C, 50.77; H, 5.60; N, 23.02.

9-α-D-Lyxofuranosyladenine (4).—To 160 mg of 9-(2′,3′-O-isopropylidene-α-D-lyxofuranosyl)adenine (**3**) was added 6 ml of 25% acetic acid. The solution was stirred at 100° in an oil bath for 3.5 hr; the solvent was removed under reduced pressure at 45°, leaving a syrupy, solid mass which was dissolved in a

(3) E. J. Reist, D. F. Calkins, and L. Goodman, *J. Org. Chem.*, **32**, 169 (1967).

(4) The authors wish to thank Dr. E. J. Reist for gifts of samples of the β derivatives, enabling comparison of properties and behavior.

(5) (a) J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 833 (1946); (b) R. S. Wright, G. M. Tener, and H. G. Khorana, *J. Am. Chem. Soc.*, **80**, 2004 (1958).

(6) J. B. Lee and T. J. Nolan, *Tetrahedron*, **23**, 2789 (1967).

(7) Elementary analyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich.

(8) C. E. Carter, *J. Am. Chem. Soc.*, **72**, 1466 (1950).

small amount of hot water. The solution was placed in the refrigerator and crystallization occurred, yielding 88 mg (63%) of crude product, mp 233–242°, in three crops. The combined solids were dissolved in a small amount of hot water, the solution was decolorized with Norite A, and the product was allowed to crystallize, first at room temperature then in the refrigerator. After a second recrystallization, pure 9-α-D-lyxofuranosyladenine (**4**) was obtained as irregular white crystals (46 mg, 33%), mp 248–250°; $[\alpha]^{23}D$ +93.8° (*c* 0.3, water); $\lambda_{max}^{H_2O}$ 260 mμ (ε 14,600).

Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.20. Found: C, 44.82; H, 4.95; N, 26.25.

To 10.90 mg of 9-α-D-lyxofuranosyladenine, 1.5 ml of 0.08 *M* sodium periodate was added, and the mixture was allowed to stand at room temperature for 30 min. To the solution 40 mg of sodium borohydride was added and, after 30 min, 0.5 ml of 10% acetic acid was slowly added. When gas evolution ceased (90–120 min), the specific rotation of the solution was obtained, $[\alpha]^{23}D$ −65.0°. Authentic adenosine treated in the same manner showed $[\alpha]^{23}D$ +68.1° (lit.[5b] +66° for 9-β-D-ribofuranosyladenine, −66° for 9-α-D-ribofuranosyladenine). These results indicate that the lyxofuranosyladenine had an α configuration.

1-Substituted Estrone 3-Methyl Ethers

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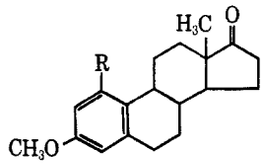
We wish to report the preparation of some 1-substituted derivatives (**5**–**13**) of estrone 3-methyl ether from 1-aminoestrone 3-methyl ether (**1**).[1a]

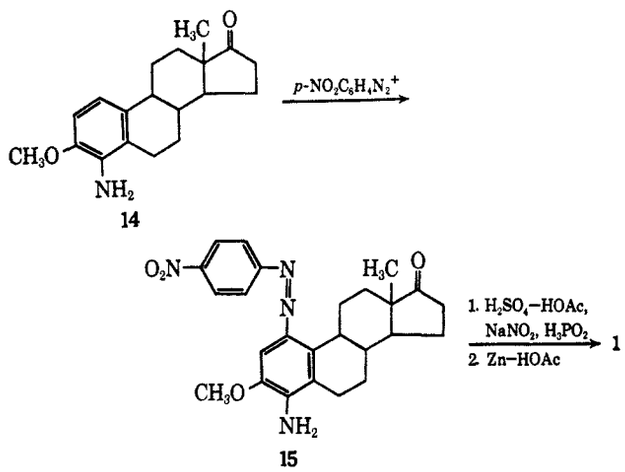


1, R = NH_2	**8**, R = OCH_3
2, R = $N{\equiv}N^+$	**9**, R = $OCOCH_3$
3, R = OH	**10**, R = F
4, R = N_3	**11**, R = Cl
5, R = $NHCH_3$	**12**, R = Br
6, R = $N(CH_3)_2$	**13**, R = I
7, R = $N{=}CHC_6H_5$	

In the aromatic substitution reactions of estrone the attacking species is directed, in a normal way, *ortho* to the C-3 hydroxyl group.[2] It is not surprising, therefore, that while a variety of 2- and 4-substituted derivatives of estrone have been reported,[2] relatively few 1-substituted compounds have been prepared.[3]

With few exceptions,[3d] the only 1-substituted estra-1,3,5(10)-trienes are those derived, either directly or indirectly, from the dienone–phenol[3a,b] or related[3c] rearrangements. Of these compounds only the 1-hydroxy[3a] and 1-methyl[3a] derivatives are oxygenated at the 3 position. Hence this approach was not considered to be readily adaptable[4] to the general preparation of 1-substituted estrone 3-methyl ethers.

Previously we reported on the coupling of 4-aminoestrone 3-methyl ether (**14**) with *p*-nitrobenzene diazonium chloride to give the 1-azo-4-amino derivative (**15**) in good yield.[1a,b] This reaction provided the key to the successful preparation of 1,11-iminoestrones[1a] *via* the intermediate 1-aminoestrone 3-methyl ether (**1**).



14

15

Because of the synthetic utility of arylamines, the 1-amino compound (**1**) proved to be a valuable intermediate for the preparation of a variety of other 1-substituted derivatives of estrone 3-methyl ether, as exemplified by the following syntheses.

When the amine (**1**) was refluxed with methyl iodide and potassium carbonate in methanol for 4 hr, a 1:5 mole ratio of the mono- (**5**) and dimethyl (**6**) derivatives was obtained. After being refluxed for 21 hr the amine (**1**) was completely converted to its dimethyl derivative. No evidence of any quaternary salt was found after this time. The absence of quaternization is probably due to steric hindrance with the 11-methylene group. In this connection, Nagata and coworkers[5] have shown by nuclear magnetic resonance (nmr) studies that appreciable interaction exists between the C-1 and C-11α protons.

The benzylidene derivative (**7**) of 1-aminoestrone 3-methyl ether (**1**) was obtained in 80% yield by refluxing a solution of **1** and benzaldehyde in benzene with azeotropic removal of water during the reaction.

Previously it was noted[1a] that the 1-diazonium salt

(1) (a) E. W. Cantrall, R. B. Conrow, and S. Bernstein, *J. Am. Chem. Soc.*, **86**, 2943 (1964). For the full paper, see E. W. Cantrall, R. B. Conrow, and S. Bernstein, *J. Org. Chem.*, **32**, 3445 (1967). (b) This coupling reaction was also successfully applied to 4-amino-2,3-dimethoxyestra-1,3,5(10)-trien-17-one in the preparation of 1,2,3-trimethoxyestra-1,3,5(10)-trien-17β-ol [R. B. Conrow, E. W. Cantrall, and S. Bernstein, *Steroids*, **9**, 307 (1967)].

(2) For examples of some aromatic substitution reactions of estrone and estrone 3-methyl ether, see: (a) nitration, A. J. Tomson and J. P. Horwitz, *J. Org. Chem.*, **24**, 2056 (1959); (b) halogenation, E. Schwenk, C. G. Castle, and E. Joachim, *ibid.*, **28**, 136 (1963); (c) dialkylaminomethylation, T. L. Patton, *ibid.*, **25**, 2148 (1960); (d) chloromethylation, W. F. Johns, *ibid.*, **30**, 3993 (1965); (e) thiomethoxymethylation, M. G. Burdon and J. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 4656 (1965).

(3) (a) R. H. Shapiro, "Steroid Reactions," C. Djerassi, Ed., Holden-Day Inc., San Francisco, Calif., 1963, pp 373–402. (b) In an adaptation of Scherrer's procedure (R. A. Scherrer, Abstracts of Papers, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 1963, p 33Q), Morrow and Butler converted 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one to 1-amino-4-methylestra-1,3,5(10)-trien-17-one and then to the 1-bromo and 1-fluoro derivatives *via* the diazo reaction [D. F. Morrow and M. E. Butler, *J. Org. Chem.*, **29**, 1893 (1964)]. (c) Androsta-1,4-diene-3,17-dione was converted by Moersch, *et al.*, to 3-chloro- and 3-bromoandrosta-1,3,5-trien-17-one which underwent a dienone–phenol type of rearrangement to give the corresponding 1-chloro- and 1-bromo-4-methylestra-1,3,5(10)-trien-17-one [G. W. Moersch, W. A. Neuklis, T. P. Culbertson, D. F. Morrow, and M. E. Butler, *J. Org. Chem.*, **29**, 2495 (1964)]. (d) H. Dannenberg, D. D. von Dresler, and T. Köhler [*Arzneimittel-Forsch.*, **14**, 780 (1964)] report the nitration of 17-acetoxy-4-methylestra-1,3,5(10)-triene to give the 1-, 2-, and 3-nitro derivatives which were reduced to the corresponding amino compounds.

(4) Possibly 1,3-diacetoxyestra-1,3,5(10)-trien-17-one [A. M. Gold and E. Schwenk, *J. Am. Chem. Soc.*, **80**, 5683 (1958)] could be converted to 1-hydroxyestrone 3-methyl ether and then to 1-substituted estrone 3-methyl ethers *via* the procedure of Morrow and Butler.[3b] However, the starting diacetate is only obtainable in poor over-all yield from estrone.

(5) W. Nagata, T. Terasawa, and K. Tori, *ibid.*, **86**, 3746 (1964).