[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

Synthesis of Potential Anticancer Agents. XV. Ribonucleosides of 2-Substituted Purines

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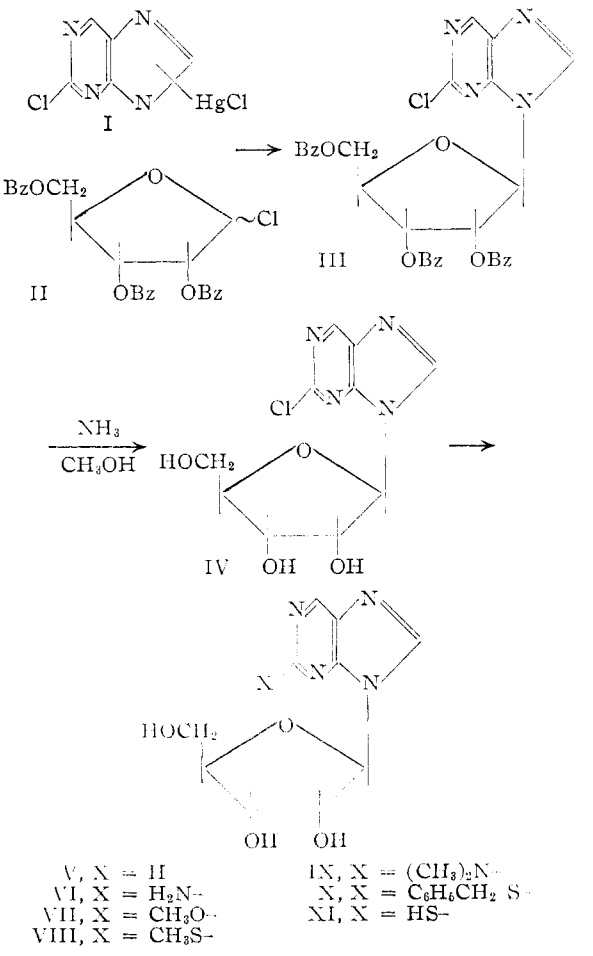
2-Chloro-9-β-D-ribofuranosylpurine has been prepared by a modification of the classical procedure. The structure of this key intermediate was established by conversion to 9-β-D-ribofuranosylpurine. The syntheses of several new 2-substituted 9-β-D-ribofuranosylpurines from 2-chloro-9-β-D-ribofuranosylpurine have been accomplished.

A search of the literature revealed that ribosylnucleosides of 2-substituted purines had not yet been prepared. Because of the potential usefulness that some 2-substituted purine ribonucleosides would have as anticancer agents, we extended our studies to include this important area. Since the value of 6-chloro-9-β-D-ribofuranosylpurine as an intermediate for the preparation of some 6-substituted-9-β-D-ribofuranosylpurines has been demonstrated,[2] we selected 2-chloropurine ribonucleoside (IV) as the key intermediate for the preparation of some new ribonucleosides in this area. By replacement of the chlorine atom of IV with different nucleophilic reagents, it should be possible to prepare a wide variety of 2-substituted purine ribonucleosides.

The preparation of 2-chloropurine ribonucleoside was accomplished by classical procedure[3] in which the recently published[4-6] improvements were employed. Thus, 2-chloropurine[7a] was converted into chloromercuri-2-chloropurine (I).[7b] Condensation of the chloromercuri derivative I with 2,3,5-tri-*O*-benzoylribofuranosyl chloride (II)[6] proceeded smoothly, and a good yield of the blocked nucleoside III was obtained. It was anticipated that the benzoyl blocking groups could be removed with methanolic ammonia from III without concomitant replacement of the chlorine atom, because a similar deblocking reaction was successful on the corresponding 6-chloropurine analog[2,8] even though the 6-chlorine atom of the corresponding 2,6-dichloropurine analog did undergo displacement when exposed to methanolic ammonia.[1] Indeed, when III was allowed to react with methanolic ammonia at 0°, a good yield of 2-chloropurine ribonucleoside (IV) was obtained.

Since the condensation of metal derivatives of purines with *O*-acylated glycosyl halides may yield either a 9- or a 7-ribosyl derivative, and since an α- or a β-nucleoside[9] may be obtained, it is necessary to establish for each condensation reaction the position of substitution and the stereochemistry of the nucleoside. The proof of structure of 2-chloropurine ribonucleoside (IV) was effected by

CHART I



the removal of the chlorine atom by catalytic hydrogenolysis with a palladium-on-charcoal catalyst in the presence of magnesium oxide as the acid acceptor; the resulting purine nucleoside was shown by physical and optical methods of analysis to be 9-β-D-ribofuranosylpurine (V).[10] Therefore, the structure of the nucleoside obtained from condensa-

(1) Affiliated with Sloan-Kettering Institute. This work was supported by funds from the C. F. Kettering Foundation and the National Institutes of Health, Grant Number CY-2942. Part XIV, H. J. Schaeffer and H. Jeanette Thomas, THIS JOURNAL, **80**, 3738 (1958).

(2) J. A. Johnson, Jr., H. J. Thomas and H. J. Schaeffer, *ibid.*, **80**, 699 (1958).

(3) E. Fischer and B. Helferich, *Ber.*, **47**, 210 (1914).

(4) J. Davoll, B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, 967 (1948).

(5) J. Davoll and B. A. Lowy, THIS JOURNAL, **73**, 1650 (1951).

(6) H. M. Kissman, C. Pidacks and B. R. Baker, *ibid.*, **77**, 18 (1955).

(7) (a) J. A. Montgomery, *ibid.*, **78**, 1928 (1956). (b) J. J. Fox and co-workers of Sloan-Kettering Institute have devised a procedure for the preparation of chloromercuri derivatives in excellent yield in which an inverse order of addition of reactants is employed. See the Experimental section.

(8) B. R. Baker, K. Hewson, H. J. Thomas and J. A. Johnson, Jr., *J. Org. Chem.*, **22**, 954 (1957).

(9) A rule has been proposed which states that for this type of condensation reaction, the nucleoside will possess a C_1-C_2-*trans* configuration. See B. R. Baker, J. P. Joseph, R. E. Schaub and J. H. Williams, *ibid.*, **19**, 1786 (1954).

(10) G. B. Brown and V. S. Weliky, *J. Biol. Chem.*, **204**, 1019 (1953).

tion of chloromercuri-2-chloropurine (I) and 2,3,5-tri-*O*-benzoylribofuranosyl chloride (II) is 2-chloro-9-β-D-ribofuranosylpurine (IV).

The reaction of 2-chloro-9-β-D-ribofuranosylpurine (IV) with methanolic ammonia at 87° proceeded, for the most part, with decomposition, and the desired product 2-amino-9-β-D-ribofuranosylpurine (VI) was isolated in low yield. Therefore, 2-aminopurine ribonucleoside was prepared by the condensation of chloromercuri-2-benzamidopurine and 2,3,5-tri-*O*-benzoylribofuranosyl chloride. A comparison of this product with 2-amino-9-β-D-ribofuranosylpurine (VI), revealed that the two products were identical. The replacement of the chlorine atom of IV by the amino group, although not of preparative value, established that for the condensation of chloromercuri-2-benzamidopurine and 2,3,5-tri-*O*-benzoylribofuranosyl chloride, substitution occurred at the 9-position and that the nucleoside had the β-configuration.[11]

Recently, Montgomery and Holum[12] have shown that there are wide differences in the reactivity of the chlorine atom at the 2- and 6-position of the purine nucleus. In the case of the monochloropurines, the 6-chlorine atom is more reactive than the 2-chlorine atom. In fact, under similar reaction conditions, the 2-chlorine atom was not replaced in the majority of reactions studied.

In contrast, we have found that the chlorine atom of 2-chloro-9-β-D-ribofuranosylpurine (IV) is much more reactive than the chlorine atom of 2-chloropurine. Furthermore, the 2-chlorine atom in the ribonucleoside series is, in certain reactions, only slightly less reactive than the 6-chlorine atom in 6-chloro-9-β-D-ribofuranosylpurine. For example, we have found that when two equivalents of sodium methoxide was allowed to react with 2-chloro-9-β-D-ribofuranosylpurine (IV) in refluxing methanol, the reaction was complete within one hour, as shown by paper chromatograms prepared from aliquots of the reaction mixture. With 6-chloro-9-β-D-ribofuranosylpurine[2] under similar conditions, the reaction was complete in 30 minutes, whereas 2-chloropurine failed to react even under more drastic conditions.[13] Thus, from the reaction of 2-chloro-9-β-D-ribofuranosylpurine with sodium methoxide in refluxing methanol we have isolated 2-methoxy-9-β-D-ribofuranosylpurine (VII) in a 48% yield.

The synthesis of 2-methylthio-9-β-D-ribofuranosylpurine (VIII) from 2-chloro-9-β-D-ribofuranosylpurine (IV) has been carried out in a 74% yield. The reaction, which was followed by paper chromatography in a pilot run, was complete in 30 minutes at 65° when two equivalents of sodium methyl mercaptide were employed.

Treatment of 2-chloro-9-β-D-ribofuranosylpurine (IV) with dimethylamine at 87° for 15 hours resulted in the formation of 2-dimethylamino-9-β-D-ribofuranosylpurine (IX). Similar treatment of IV with *n*-butylamine resulted in decomposition, possibly by cleavage of the imidazole ring, and the desired product could not be isolated.

The synthesis of 2-benzylthio-9-β-D-ribofuranosylpurine (X) was effected by allowing IV to react with two equivalents of a methanolic solution of sodium benzyl mercaptide. The crude product was obtained as a tan glass; an attempt was made to purify the crude product by partition and absorption chromatography, but the partially purified product could not be induced to crystallize. The analytical sample was obtained as a glass, however, by several precipitations of the crude product from water.

Several attempts were made to prepare 2-mercapto-9-β-D-ribofuranosylpurine (XI) by a reaction similar to the one used for the preparation of 6-mercapto-9-β-D-ribofuranosylpurine, *i.e.*, treatment of 2-chloropurine ribonucleoside (IV) with a methanolic solution of sodium hydrogen sulfide at 65°—but the desired product was not obtained. From this reaction mixture, we obtained a good yield (55%) of 2-methoxy-9-β-D-ribofuranosylpurine. An examination of the literature[14] revealed that, for similar nucleophilic displacement reactions by hydroxide anion in which ethanol was used as the solvent, a mixture of the hydroxy and ethoxy derivatives was produced. The formation of the mixture of products is caused by the equilibration reaction

$$KOH + C_2H_5OH \rightleftharpoons C_2H_5OK + H_2O$$

In our experiments we prepared a sodium hydrogen sulfide solution in methanol by saturating a 1 *N* sodium methoxide solution in methanol with hydrogen sulfide. Since an equilibration exists,

$$NaSH + CH_3OH \rightleftharpoons CH_3ONa + H_2S$$

then an explanation of the results obtained from 2-chloro- and 6-chloro-9-β-D-ribofuranosylpurine is at hand. The preparation of 6-mercaptopurine ribonucleoside from the 6-chloro analog by reaction with methanolic sodium hydrogen sulfide was a relatively rapid reaction—seven minutes at 65°. In this short time, the excess hydrogen sulfide which was present in the reaction mixture caused a high concentration of hydrosulfide anion to be maintained. However, the rate of displacement of the 2-chlorine atom from 2-chloro-9-β-D-ribofuranosylpurine was much slower (16 hours). Consequently, the volatile hydrogen sulfide which was gradually lost from the reaction mixture caused the formation of methoxide anions and, ultimately, 2-methoxy-9-β-D-ribofuranosylpurine. It was, therefore, obvious that if 2-mercaptopurine ribonucleoside was to be prepared by this procedure the reaction mixture would have to be kept saturated with hydrogen sulfide by continuous addition of hydrogen sulfide throughout the reaction period. When this was done, the formation of the 2-methoxy analog VII was eliminated, and the desired 2-mercapto-9-β-D-ribofuranosylpurine (XI) was obtained.

Acknowledgment.—The authors are indebted to Mr. J. P. Holmquist and Mr. J. W. Murphy for the micro-analytical results reported, to Mr. W. A. Rose for the infrared spectral determinations, and to Mr. L. D. Norton for the optical rotations and

(11) Dr. J. J. Fox of the Sloan-Kettering Institute recently informed us that he has prepared 2-amino-9-β-D-ribofuranosylpurine by a different procedure. See J. J. Fox, I. Wempen, A. Hampton and I. L. Doerr, THIS JOURNAL, **80**, 1669 (1958).

(12) J. A. Montgomery and L. B. Holum, *ibid.*, **79**, 2185 (1957).

(13) J. A. Montgomery, personal communication.

(14) J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, **49**, 273 (1951).

the ultraviolet spectral determinations. The authors wish to express their appreciation to Dr. J. A. Montgomery for his encouragement of this research. Some of the analyses reported were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

Experimental[15]

Chloromercuri-2-chloropurine (I).—To a stirred suspension of 5.00 g. (32.0 mmoles) of 2-chloropurine and 12.0 g. of Celite in 600 ml. of 50% aqueous ethanol containing 8.70 g. (32.0 mmoles) of mercuric chloride, there was added slowly 11.6 ml. of 10% sodium hydroxide solution (32.0 mmoles). After the suspension was cooled overnight, the solid was collected by filtration, washed with cold water, with ethanol and finally with ether, and dried *in vacuo* for 16 hours over phosphorus pentoxide; yield 22.8 g. including 12.0 g. of Celite (87%). In other experiments, yields as high as 94% were obtained.

The analytical sample of the chloromercuri derivative was obtained from a pilot run in which the Celite was not added.

Anal. Calcd. for $C_5H_2N_4Cl_2Hg$: N, 14.39. Found: N, 13.88.

2-Chloro-9-β-D-ribofuranosylpurine (IV).—A solution of 2,3,5-tri-*O*-benzoylribofuranosyl chloride, which was prepared[6] from 13.6 g. (27.0 mmoles) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose in 50 ml. of xylene, was added to an azeotropically dried suspension of 10.5 g. (27.0 mmoles) of chloromercuri-2-chloropurine (I) and 11.7 g. of Celite in 400 ml. of xylene. The mixture, protected with a calcium chloride tube, was refluxed with stirring for two hours and then filtered; the filter cake was washed with hot chloroform (3 × 100 ml.). The xylene filtrate was evaporated *in vacuo;* the residue was dissolved in chloroform (300 ml.), and the solution was combined with the chloroform washings. The resulting solution was washed with 30% aqueous potassium iodide (2 × 200 ml.) and water (2 × 250 ml.), then dried with magnesium sulfate and filtered. Concentration of the filtrate gave the crude nucleoside III, which was then dissolved in 300 ml. of methanol saturated with ammonia at 0°. The solution was refrigerated overnight and then filtered. After the filtrate was concentrated *in vacuo,* the residue was dissolved in water (50 ml.) and extracted with chloroform (2 × 25 ml.). Concentration of the aqueous solution caused the precipitation of the product; yield, 3.55 g. (46.0%), m.p. 153–156°. One recrystallization from water gave the pure product, which was dried at 100° (0.8 mm.) over phosphorus pentoxide for 5 hours before analysis; m.p. 154–156°, $[\alpha]^{26}D$ −30.0 ± 1.2° (0.38% in water); λ_{max} in mμ (ε × 10^{-3}): *p*H 1, 271 (8.20); *p*H 7, 271 (8.10); *p*H 13, 272 (8.50); $\bar{\nu}$ in cm.$^{-1}$ (KBr): 3450–3200 (OH); 1595, 1570 and 1500 (C=N, C=C); 1105, 1085 and 1045 (C–O–). The yields of IV from other experiments were 60 and 56%.

Anal. Calcd. for $C_{10}H_{11}N_4O_4Cl$: C, 41.88; H, 3.86; N, 19.54. Found: C, 42.26; H, 3.98; N, 19.63.

9-β-D-Ribofuranosylpurine (V) from 2-Chloro-9-β-D-ribofuranosylpurine (IV).—To a solution of 500 mg. (1.75 mmoles) of 2-chloro-9-β-D-ribofuranosylpurine (IV) in 75 ml. of water were added 170 mg. of 5% palladium-on-charcoal catalyst and 70 mg. of magnesium oxide. The mixture was hydrogenated at room temperature and atmospheric pressure; the theoretical amount of hydrogen was absorbed in 29 minutes. The catalyst was removed by filtration, and the filtrate was evaporated *in vacuo* to dryness. The residual oil was crystallized from ethanol; yield 278 mg. (63%), m.p. 176–178° in agreement with the literature.[16] The ultraviolet and infrared spectra and a paper chromatogram of this sample were identical to those of an authentic sample of 9-β-ribofuranosylpurine.[17]

2-Benzamidopurine.—A mixture of 1.87 g. (13.8 mmoles) of 2-aminopurine and 9.35 g. (41.4 mmoles) of benzoic anhydride was heated in an oil-bath at 180° for 15 minutes. The cooled reaction mixture was heated with ethanol (85 ml.) for 10 minutes; after the mixture was cooled, it was filtered, and the solid was washed well with ethanol; yield 1.61 g. (49%), m.p., 312–315° dec. Two recrystallizations from methyl Cellosolve gave the analytical material, m.p. 317–318° dec.; λ_{max} in mμ (ε × 10^{-3}): *p*H 1, 243 (26.0), 270 (19.2); *p*H 7, 237 (19.8); *p*H 13, unstable; $\bar{\nu}$ in cm.$^{-1}$ (KBr): 3410 and 3140 (NH); 2800–1800 (acidic hydrogen); 1690 (C=O); 1620 (phenyl); 1605, 1525 and 1505 (C=N, C=C); 740 and 715 (monosubstituted benzene).

Anal. Calcd. for $C_{12}H_9N_5O$: C, 60.24; H, 3.79; N, 29.28. Found: C, 60.30; H, 3.95; N, 29.17.

Chloromercuri-2-benzamidopurine.—To a stirred suspension of 1.55 g. (6.50 mmoles) of 2-benzamidopurine and 3.08 g. of Celite in 150 ml. of 50% aqueous ethanol containing 1.78 g. (6.50 mmoles) of mercuric chloride slowly was added 2.34 ml. of 10% sodium hydroxide solution (6.50 mmoles). The cooled suspension was filtered, and the product was washed with water, ethanol and ether, and then dried *in vacuo* for 16 hours over phosphorus pentoxide; yield 5.84 g. including 3.08 g. of Celite (90%). The analytical sample of the chloromercuri compound was obtained from a pilot run in which the Celite was not added.

Anal. Calcd. for $C_{12}H_8N_5OClHg$: N, 14.80. Found: N, 14.32.

2-Amino-9-β-D-ribofuranosylpurine (VI) was synthesized by the general procedure used for the preparation of 2-chloro-9-β-D-ribofuranosylpurine (IV). Condensation of 5.80 mmoles of chloromercuri-2-benzamidopurine with 5.80 mmoles of 2,3,5-tri-*O*-benzoylribofuranosyl chloride followed by deacylation of the blocked nucleoside with methanolic ammonia gave the desired product; yield 367 mg. (24%), m.p. 122°. One recrystallization from isopropyl alcohol gave the pure product, which was dried at 100° (0.8 mm.) over phosphorus pentoxide for 16 hours before analysis; m.p. 123°, $[\alpha]^{26}D$ −29.8 ± 1.5° (0.952% in water); λ_{max} in mμ (ε × 10^{-3}): *p*H 1, 245 (shoulder) (4.28); 312 (3.90); *p*H 7, 244 (5.70), 305 (6.60); *p*H 13, 243 (shoulder) (5.40), 304 (6.80); $\bar{\nu}$ in cm.$^{-1}$ (KBr): 3450–3250 (broad OH, NH); 3170 and 1615 (NH); 1580 and 1510 (C=N, C=C); 1080 and 1045 (C–O–).

Anal. Calcd. for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.32. Found: C, 45.05; H, 5.29; N, 25.79.

The melting point of this compound is a poor criterion of purity, since wide variations in the melting point were observed when different recrystallization solvents were employed. Thus, when methanol–ethyl acetate was used, a melting point of 166–171° was observed. However, when ethyl alcohol or isopropyl alcohol was used as the recrystallization solvent, a product was obtained that melted near 123°.

2-Methoxy-9-β-D-ribofuranosylpurine (VII).—To a solution of 573 mg. (2.00 mmoles) of 2-chloro-9-β-D-ribofuranosylpurine (IV) in 20 ml. of methanol was added 4 ml. of 1 *N* sodium methoxide in methanol. The solution was heated under reflux for two hours; the cooled solution was neutralized with 2 ml. of 1 *N* hydrochloric acid and evaporated *in vacuo.* The residue was triturated with water (3 ml.), and the product was collected by filtration; yield 407 mg. (72.0%), m.p. 172–174°. Two recrystallizations from ethyl acetate gave the analytical sample, which was dried at 100° (0.8 mm.) over phosphorus pentoxide for 12 hours; m.p. 174–176°, $[\alpha]^{26}D$ −15.8 ± 1.9° (0.73% in water); λ_{max} in mμ (ε × 10^{-3}): *p*H 1, 282 (6.80); *p*H 7, 235 (shoulder) (2.99), 281 (8.65); *p*H 13, 235 (shoulder) (2.80), 281 (8.80); $\bar{\nu}$ in cm.$^{-1}$ (KBr): 3420 (OH); 1610 and 1585 (C=N, C=C); 1065, 1050 and 1035 (C–O–).

Anal. Calcd. for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 5.00; N, 19.85. Found: C, 47.21; H, 5.23; N, 19.62.

2-Methylthio-9-β-D-ribofuranosylpurine (VIII).—A solution of 500 mg. (1.74 mmoles) of 2-chloro-9-β-D-ribofuranosylpurine (IV) and 3.48 ml. of 1 *N* sodium methyl mercaptide[1] in 80 ml. of methanol was heated under reflux for 0.5

(15) The ultraviolet spectra were determined in aqueous solution with a Beckman model DK-2 spectrophotometer, and the optical densities were determined with a Beckman model DU spectrophotometer, the infrared spectra with a Perkin-Elmer model 21 spectrophotometer, and the optical rotations with a standard polarimeter model D attachment to the Beckman DU spectrophotometer calibrated with standard sucrose solutions.[18] Melting points were determined on a Kofler Heizbank and are corrected.

(16) A. Keston, Abst. 127th Meeting, Am. Chem. Soc., 1955, p. 18c.

(17) This material was furnished by Dr. G. Brown of the Sloan Kettering Institute.

hour; the cooled solution was neutralized with 1 *N* hydrochloric acid and evaporated *in vacuo*. The residue was crystallized from water and the product was collected by filtration: yield 384 mg. (74%), m.p. 208–210°. One recrystallization from water gave the analytical sample, which was dried at 100° (0.8 mm.) over phosphorus pentoxide for 48 hours; m.p. 208–210°, $[\alpha]^{26}D$ +8.2 ± 2.7° (0.51% in water); λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 246 (12.8), 306 (4.60); *p*H 7, 233 (15.0), 260 (9.75), 303 (7.05); *p*H 13, 234 (13.4), 259 (9.15), 303 (7.10) $\tilde{\nu}$ in cm.$^{-1}$ (KBr): 3400 and 3250 (OH); 1610 and 1570 (C=N, C=C); 1070, 1050 and 1020 (C–O–).

Anal. Calcd. for $C_{11}H_{14}N_4O_4S$: C, 44.29; H, 4.73; N, 18.78. Found: C, 44.09; H, 4.71; N, 18.62.

2-Dimethylamino-9-β-D-ribofuranosylpurine (IX).—A solution of 500 mg. (1.74 mmoles) of 2-chloro-9-β-D-ribofuranosylpurine (IV) in 17 ml. of a 25% aqueous solution of dimethylamine was diluted with 40 ml. of methanol and heated in a stainless steel bomb at 87° for 15 hours. The resulting dark orange reaction solution was evaporated *in vacuo* to dryness. Crystallization of the residue from water gave the crude product; yield 175 mg. (34%), m.p. 179–185°. The analytical sample was prepared by recrystallization from water and was dried over phosphorus pentoxide at 110° (0.8 mm.) for 72 hours; m.p. 190–191°, $[\alpha]^{32}D$ +9.1 ± 2.9° (0.48% in methanol); λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 232 (32.0); *p*H 7, 226 (22.5), 257 (12.1), 331 (5.65); *p*H 13, 228 (20.8), 257 (11.5), 330 (5.80); $\tilde{\nu}$ in cm.$^{-1}$ (KBr): 3360 (OH); 1610, 1575 and 1550 (C=N, C=C); 1105 and 1050 (C–O–).

Anal. Calcd. for $C_{12}H_{17}N_5O_4$: C, 48.80; H, 5.80; N, 23.72. Found: C, 49.07; H, 5.67; N, 23.34.

2-Benzylthio-9-β-D-ribofuranosylpurine (X).—A solution of 510 mg. (1.78 mmoles) of 2-chloro-9-β-D-ribofuranosylpurine (IV) and 3.56 ml. of 1 *N* sodium benzyl mercaptide[2] in 80 ml. of methanol was heated under reflux for 1.25 hours; the cooled reaction solution was neutralized with 1 *N* hydrochloric acid and evaporated *in vacuo*. The residue was extracted several times with diethyl ether (4 × 75 ml.); concentration of the combined ether extracts gave the crude product. This compound could not be induced to crystallize but was purified by two precipitations from water, and then drying over phosphorus pentoxide at 100° (0.07 mm.) for 24 hours before analysis; m.p. 112–113°, $[\alpha]^{26}D$ +24.2 ± 2.2° (0.63% in methanol); λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 232 (14.6), 253 (11.6), 304 (5.61); *p*H 7, 232 (17.4), 261 (10.3), 303 (7.60); *p*H 13, 259 (9.94), 303 (7.65); $\tilde{\nu}$ in cm.$^{-1}$ (KBr): 3420 (OH); 1605 and 1580 (C=N, C=C); 1105, 1080 and 1045 (C–O–).

Anal. Calcd. for $C_{17}H_{18}N_4O_4S$: C, 54.50; H, 4.87; N, 14.94. Found: C, 54.42; H, 5.09; N, 14.90.

2-Mercapto-9-β-D-ribofuranosylpurine (XI).—To a solution of 570 mg. (1.99 mmoles) of 2-chloro-9-β-D-ribofuranosylpurine (IV) in 100 ml. of methanol was added 10 ml. of 1 *N* methanolic sodium hydrogen sulfide; the solution was heated under reflux for 10 hours during which time a slow stream of hydrogen sulfide was passed through the reaction mixture. The cooled reaction mixture was neutralized with 1 *N* hydrochloric acid and filtered. The filtrate was evaporated *in vacuo* to dryness, and the residue was triturated with chloroform (4 × 50 ml.) to remove free sulfur. The residue was extracted with hot *n*-propyl alcohol (5 × 20 ml.), and the crude product was obtained by concentration of the alcoholic extracts; yield 351 mg. (62%). Several recrystallizations from methanol gave the pure material, which was dried at 110° (0.07 mm.) for 24 hours over phosphorus pentoxide before analysis; m.p. 200° dec.; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 247 (11.5), 291 (22.1); *p*H 7, 238 (12.6), 281 (12.8); *p*H 13, 238 (14.1), 273 (13.7), 329 (5.73); $\tilde{\nu}$ in cm.$^{-1}$ (KBr): 3400 (broad OH); 2800–2200 (acidic hydrogen); 1645 (unassigned); 1590 and 1520 (C=N, C=C); 1110, 1080 and 1055 (C–O–).

Anal. Calcd. for $C_{10}H_{12}N_4O_4S$: C, 42.23; H, 4.26; N, 19.72. Found: C, 42.01; H, 4.25; N, 19.89.

BIRMINGHAM 5, ALA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF IOWA STATE COLLEGE]

A Novel Conversion of Derivatives of Oxindoles to Indoles[1]

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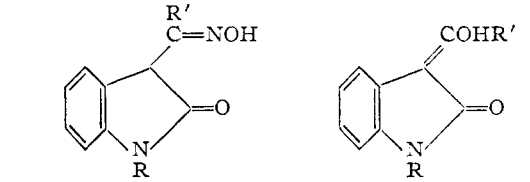
Catalytic hydrogenation of 3-acyloxindole oximes leads to 3-(α-aminoalkylidene)-oxindoles and 2-alkylindoles. Acetate treatment of the oximes also leads to indoles. The mechanisms of the reactions and their influence on the interpretation of intramolecular reaction processes in the oxindole field are discussed.

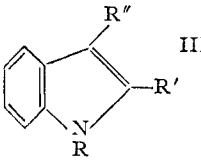
As part of continuing studies in the chemistry of oxindole[2] we have investigated the reported conversion of 3-phenylacetyloxindole oxime (Ia) into 3-(β-phenylethyl)-indole (IIIa).[2c] In order to ascertain the generality of such a transformation, several 3-acyloxindole oximes were exposed to hydrogenation with platinum in acetic acid. The starting materials were obtained by standard oximination of 3-(α-hydroxyalkylidene)-oxindoles (II) which, in turn, had been produced by base-catalyzed condensation of oxindole or N-methyloxindole with ethyl phenylacetate or ethyl acetate.

Whereas the catalytic hydrogenation of the oximes proceeded readily, it initially yielded exclusively 3-(α-aminoalkylidene)-oxindoles (IV). Even though this was not necessarily an unexpected result, being interpretable on the basis of hydrogenolysis of the N–O single bond followed by tautomeric change of the resulting imine, the uptake



Ia, R = H, R′ = $CH_2C_6H_5$
b, R = H, R′ = CH_3
c, R = CH_3, R′ = $CH_2C_6H_5$
d, R = CH_3, R′ = CH_3

II



IIIa, R = R′ = H, R″ = $CH_2CH_2C_6H_5$
b, R = H, R′ = $CH_2C_6H_5$, R″ = CH_3
c, R = R″ = H, R′ = $CH_2C_6H_5$
d, R = R″ = H, R′ = CH_3
e, R = CH_3, R′ = $CH_2C_6H_5$, R″ = H

of more than one mole of hydrogen, later erratic yields of products and the general dependence of

(1) Presented before the 133rd Meeting of the American Chemical Society, San Francisco, Calif., April 13–18, 1958.

(2) (a) E. Wenkert, A. K. Bose and T. L. Reid, THIS JOURNAL, **75**, 5514 (1953); (b) E. Wenkert and T. L. Reid, *Chemistry and Industry*, 1390 (1953); (c) E. Wenkert and T. L. Reid, *Experientia*, **10**, 417 (1954); (d) E. Wenkert, N. K. Bhattacharyya, T. L. Reid and T. S. Stevens, THIS JOURNAL, **78**, 797 (1956).