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On the Alkylation of Adenine (1)

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Much recent interest in the N-alkylation of purines and purine ribonucleosides and ribonucleotides is evident (2). In the course of our studies leading to the preparation of the nucleoside from pseudovitamin B_{12} (7-α-D-ribofuranosyladenine) (4e), we investigated the effect of substituents at N-1 and N-3 of purines on the position of attack on these purines by acylglycosyl halides and by alkyl halides (4d). Also, work in our laboratory (4a-e) and in others (3d, 4g, h) when examined together show the importance of solvent and the presence or absence of a proton acceptor in determining the position of alkylation. The present work deals with, among other things, the importance of the nature of the halides used in the alkylation of adenine (I) in determining the position of substitution (5).

To obtain an adenine with a substituent that might direct an entering group to N-7 and then be readily removed, we prepared 3-benzyladenine (4e, h) hydrochloride (II) by the reaction of adenine (I) with benzyl chloride in dimethylacetamide (7,8), and then converted the hydrochloride to the free base (VI) by treatment with aqueous ammonia (Scheme 1). The identity of VI was confirmed by its preparation from the reaction of 3-benzylpurine-6(3H)-thione (III) (4d) and alcoholic ammonia. Reaction of adenine (I) with benzyl chloride in dimethylacetamide in the presence of potassium carbonate gave an entirely different result - the only product isolated was 9-benzyladenine (V) (4a).

Although lengthy heating of adenine (I) with a large excess of benzyl chloride or benzyl bromide failed to produce any significant amount of a dibenzyladenine (9), treatment of the free base, 3-benzyladenine (VI), with an excess of benzyl bromide, but *not* benzyl chloride, gave 3, 7-dibenzyladenine hydrobromide (X) (4h), which was converted to 3,7-dibenzyladenine (IX) by treatment with methanolic sodium methoxide. These results establish that 3-benzyladenine hydrochloride (or hydrobromide) (II) is resistant to further alkylation and that a difference exists in the behavior of benzyl chloride and benzyl bromide, presumably resulting simply from the greater reactivity of benzyl bromide in dimethylacetamide.

The p.m.r. spectrum of 3,7-dibenzyladenine hydrobromide (X) in dimethylsulfoxide-d_6 shows the presence of two equivalent protons (10) attached to nitrogen and provides support for the structure X (11). The differences in the infrared spectrum of 3,7-dibenzyladenine (IX) and its hydrobromide (X) and similarity of the spectrum of the latter to that of 3-benzyladenine hydrochloride (II) also support the conclusion that protonation of IX takes place at the exocyclic imino group. The proof of the position of the second benzyl group in IX and X was provided by the preparation of X from the reaction of 7-benzyladenine (XI) (4a) with benzyl bromide in dimethylacetamide.

Reaction of 3-benzyladenine (VI) with excess benzyl chloride in dimethylacetamide in the presence of one equivalent of potassium carbonate gave a tribenzyladenine hydrochloride. This same tribenzyladenine resulted from 7-benzyladenine (XI) treated in the same way, thus establishing the positions of two of the benzyl groups as being at N-3 and N-7. The position of the third benzyl group was established by the preparation of the same tribenzyladenine from the reaction of N^6-benzyladenine (IV) (12) and benzyl chloride in the presence of potassium carbonate, although the major product of this reaction was 3,N^6-dibenzyladenine (VIII). Thus the tribenzyladenine is 3, 7, N^6-tribenzyladenine hydrochloride (VII). Since 3-benzyladenine (VI) failed to react with benzyl chloride in the absence of carbonate it would appear that it is necessary to remove hydrogen chloride in order to form any appreciable amount of 3, 7-dibenzyladenine. Furthermore, since 3, 7-dibenzyladenine hydrobromide (X) fails to react further with excess of the even more reactive benzyl bromide, it is necessary to produce the free 3, 7-dibenzylpurine (IX) (because of its great basic strength, see Table I) for further reaction with benzyl chloride. Thus the potassium carbonate serves a dual purpose in the conversion of 3-benzyladenine to 3, 7, N^6-tribenzyladenine hydrochloride (VII). The free base, 3, 7, N^6-tribenzyladenine (XII) was prepared by treatment of VII with aqueous ammonia.

Table I

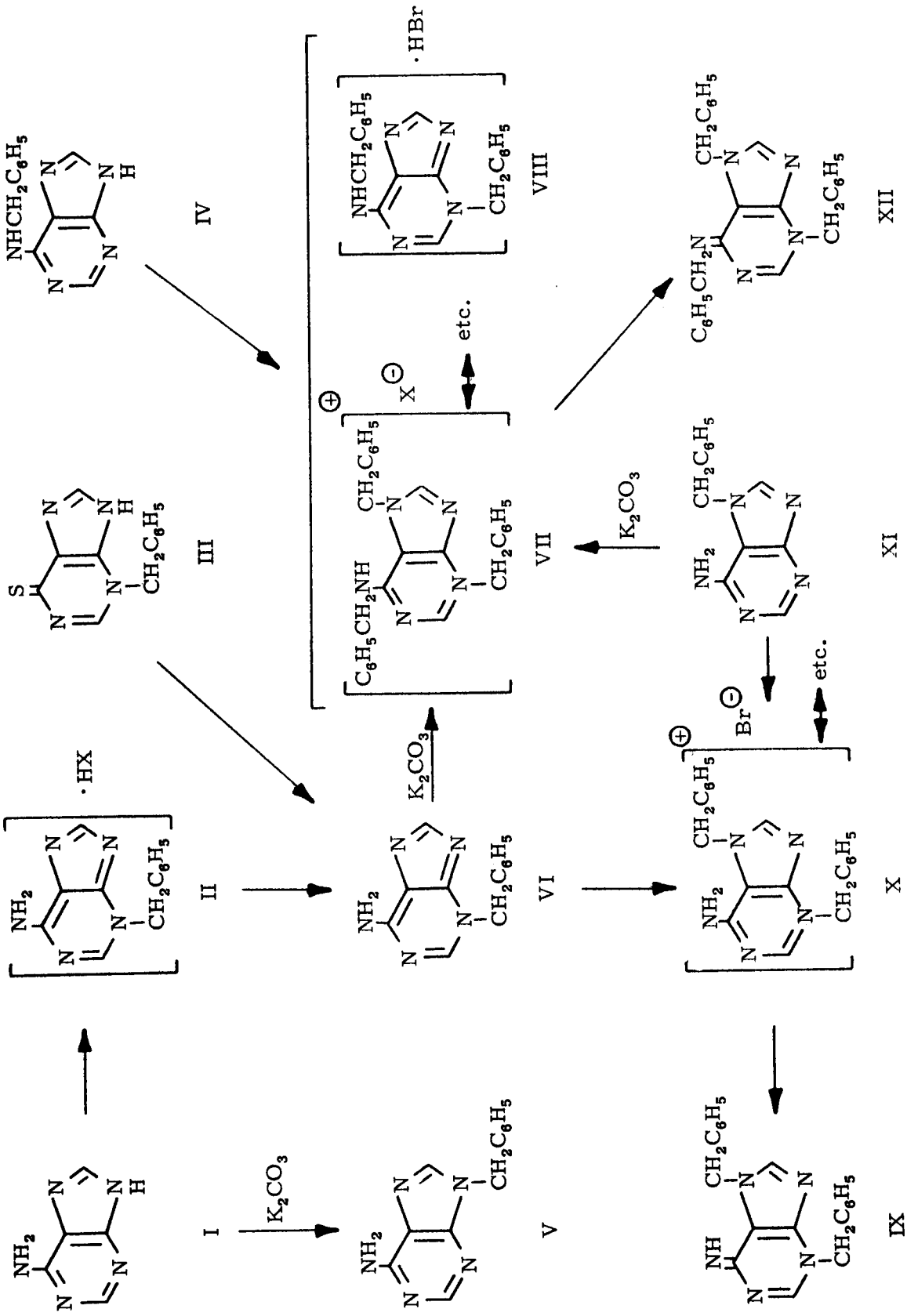
*p*Ka' Values for N-Substituted Adenines (a)

Substituents	pKa'_1	pKa'_2
none	4.22 (b)	9.8 (b)
3-Benzyl	5.1	-
7-Methyl	3.6 (c)	-
N^6-Methyl	4.18 (b)	9.99 (b)
3,7-Dibenzyl	9.6	-
3, 7, N^6-Tribenzyl	9.4	-

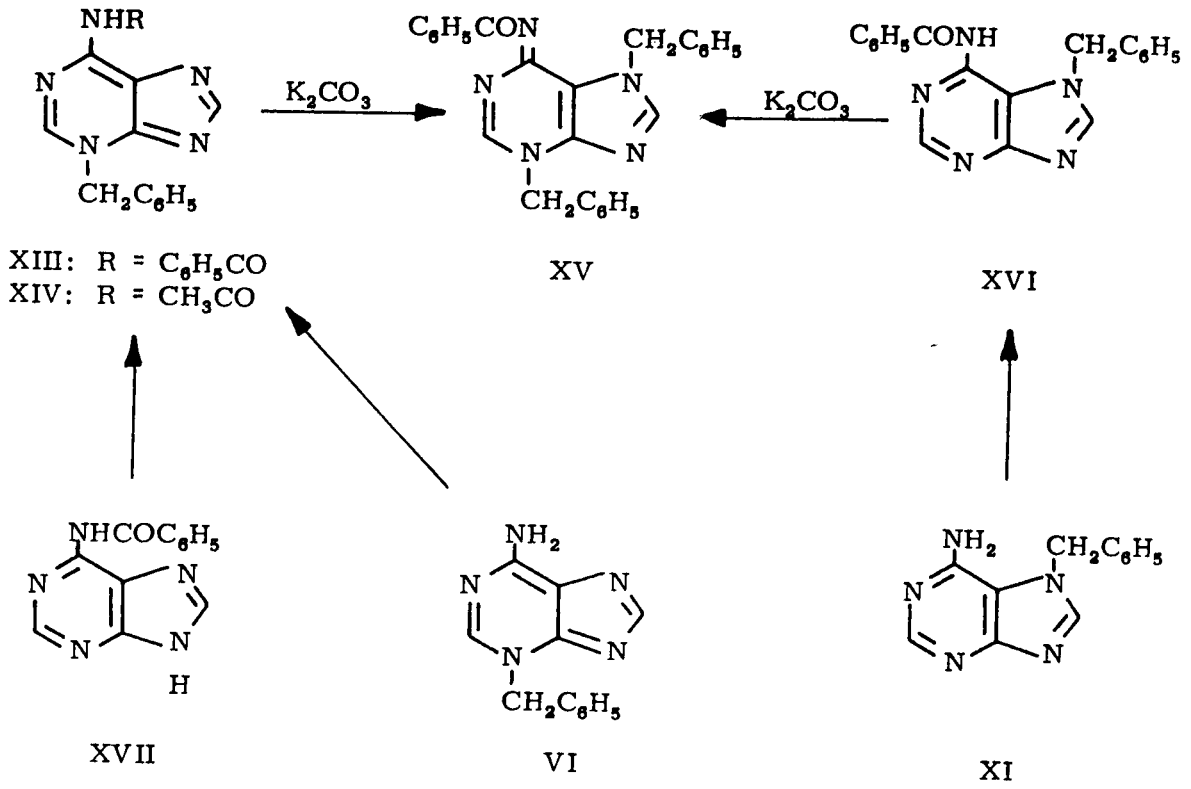
(a) Determined in 95% ethanol. (b) In water, A. Albert and D. J. Brown, *J. Chem. Soc.*, 1341 (1954). (c) In 50% DMF - 50% water, see Reference (4g).

To determine the effect of an acyl group at N^6 on alkylation and to provide a suitably blocked adenine for the synthesis of 7-glycosyladenines, we studied the benzylation of N^6-benzoyladenine (13) and found that alkylation in the usual manner, in the absence of potassium carbonate, gave N^6-benzoyl-3-benzyladenine (XIII) (Scheme 2). Proof that alkylation took place at N-3 was provided by the preparation of XIII by the

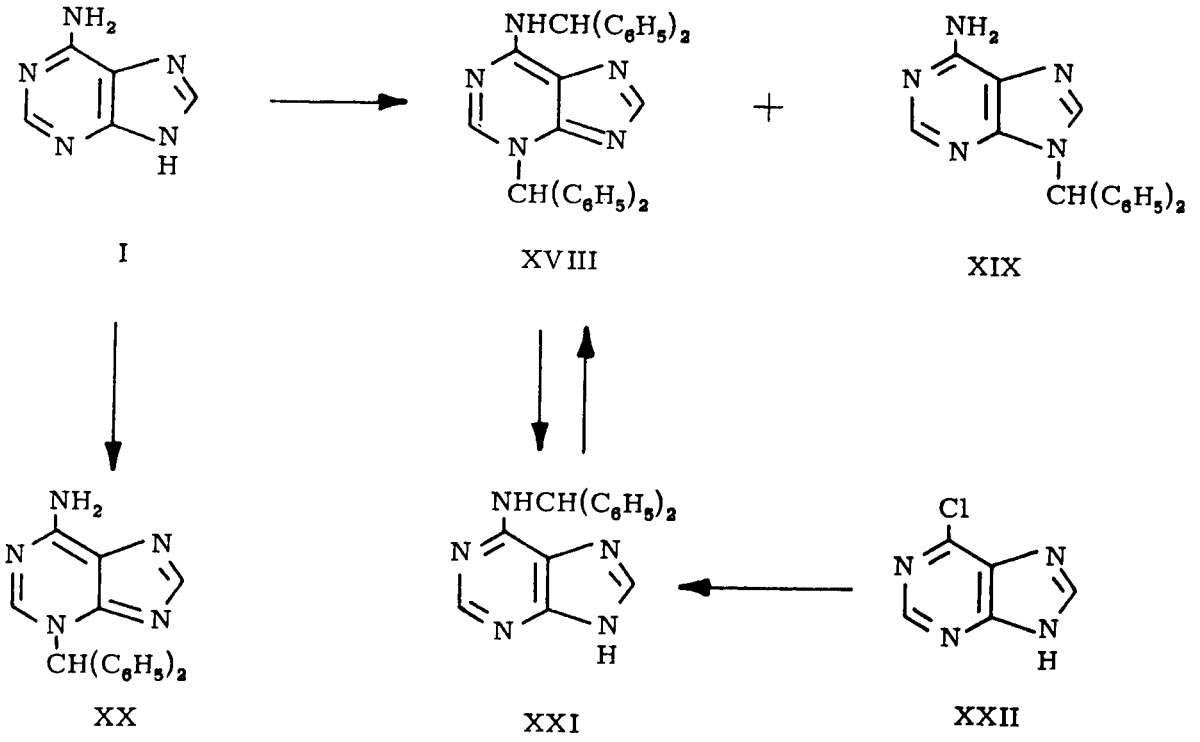
SCHEME 1



SCHEME 2



SCHEME 3



benzoylation of 3-benzyladenine (VI) with benzoic anhydride and, in fact, this method proved superior for the preparation of XIII. N^6-Acetyl-3-benzyladenine was prepared from VI and acetic anhydride in a similar manner. Treatment of XIII with benzyl chloride in the presence of potassium carbonate gave N^6-benzoyl-3,7-dibenzyladenine XV. The identity of this material was established by its preparation from 7-benzyladenine (XI) via N^6-benzoyl-7-benzyladenine (XVI), since we have so far been unsuccessful in our efforts to debenzoylate XV to 3,7-dibenzyladenine (IX). We can find no ready explanation for the unusual stability of this amide linkage other than the fact that 3,7-dibenzyl adenine (IX) is a much stronger base than other adenines (see Table I).

In view of the difficulties that were encountered in attempted catalytic hydrogenolysis of certain 3-benzylpurine nucleosides (4d), we decided to prepare 3-benzhydryladenine for further nucleoside work. Reaction of adenine (I) with an excess of benzhydryl chloride in the usual manner gave, quite unexpectedly, a dibenzhydryladenine hydrochloride (Scheme 3), the identity of which was not immediately apparent in that its ultraviolet spectrum was not compatible with that to be expected from 3,7-dibenzhydryladenine. A second minor product of this reaction was tentatively identified as 9-benzhydryladenine (XIX) on the basis of its spectra. This compound (XIX) was also prepared by the reaction of adenine with benzhydryl chloride in dimethylacetamide in the presence of potassium carbonate. We were able to prepare the desired 3-benzhydryladenine (XX) by reducing the ratio of benzhydryl chloride to adenine employed in the reaction, but the per cent conversion to XX was low. The dibenzhydryladenine was catalytically hydrogenolyzed to a monobenzhydryladenine that was different from XX. Identification of this compound as N^6-benzhydryladenine (XXI) was made by its preparation from the amination of 6-chloropurine with benzhydrylamine. Final identification of the dibenzhydryladenine as XVIII was made by its preparation from the reaction of benzhydryl chloride and N^6-benzhydryladenine (XXI). The difference in the behavior of adenine towards benzyl bromide or benzyl chloride (Scheme 1) and benzhydryl chloride (Scheme 3) may be due simply to steric interference by the bulky benzhydryl group with attack at N-7 or, since attack of the second mole of benzhydrylchloride is on 3-benzhydryladenine hydrochloride, protonation at N-7 could interfere; this point has as yet not been resolved.

Dissociation Constants.

Table I shows a comparison of the apparent *p*Ka value of a number of substituted adenines. Although monosubstitution does not greatly alter the basic strength of adenine, 3,7-disubstitution produces a compound 10^5 times as basic. Further substitution on N^6 does not cause any significant further change in basic strength. This great difference in basic strength between 3-benzyladenine and 3,7-dibenzyladenine is probably a reflection of the necessary imino group at C-6, and may be considered good evidence that 3-benzyladenine does, in fact, exist in the amino form.

EXPERIMENTAL

The melting points reported were determined on a Kofler Heizbank and are corrected. The ultraviolet spectra were determined in aqueous solution with a Cary Model 14 Spectrophotometer. The infrared spectra were determined in pressed potassium bromide disks with a Perkin-Elmer Model 221 Spectrophotometer.

3-Benzyladenine (VI). Method A.

A solution of 242 mg. of 3-benzylpurine-6(3H)-thione in 24 ml. of ethanolic ammonia (sat. at 0°) was heated for 48 hr. in a Parr bomb at 160°. The resulting solution was taken to dryness *in vacuo*, and the residue was recrystallized from ethanol; yield 56 mg. (24%). One more recrystallization gave a material melting at 275-277° (mixture melting point with 3-benzyladenine from Method B, 275-277°) and identical in all respects with 3-benzyladenine prepared by Method B.

Method B.

A solution of 5.00 g. (37.0 mmoles) of adenine and 13.55 g. (108 mmoles) of benzyl chloride in 100 ml. of N,N-dimethylacetamide was heated at 115° for 18 hr. The residue from evaporation of the solution to dryness *in vacuo* was crystallized from 700 ml. of ethanol as a white solid; yield 5.82 g. (60% yield as the hydrochloride).

A solution of the hydrochloride II in 50 ml. of water was neutralized by the addition of 0.9 ml. of concentrated ammonium hydroxide. The white precipitate that formed was removed by filtration and dried; yield 2.62 g. (60%).

The analytical sample, obtained by recrystallization from ethanol, was dried at 78°/0.07 mm. over phosphorus pentoxide for 18 hr.; m.p. 275-277°; λ max in mμ ($\epsilon \times 10^{-3}$): *p*H 1-275 (17.5), *p*H 7-272 (12.5), *p*H 13-272 (12.2).

Anal. Calcd. for $C_{12}H_{11}N_5$: C, 63.98; H, 4.92; N, 31.08. Found: C, 63.96; H, 5.02; N, 31.21.

In another reaction the hydrochloride of 3-benzyladenine was obtained in 56% yield. The analytical sample, obtained by recrystallization from ethanol, was dried for 16 hr. at 78°/0.07 mm. over phosphorus pentoxide; m.p. 265°, with sublimation; λ max in mμ ($\epsilon \times 10^{-3}$): *p*H 1-275 (17.2), *p*H 7-273 (12.4), *p*H 13-273 (12.1).

Anal. Calcd. for $C_{12}H_{11}N_5 \cdot HCl$: C, 55.14; H, 4.62; N, 26.80. Found: C, 54.99; H, 4.63; N, 26.65.

9-Benzyladenine (V).

A solution of 135 mg. (1.00 mmoles) of adenine and 253 mg. (2.00 mmoles) of benzyl chloride in 10 ml. of N,N-dimethylacetamide containing 138 mg. (1.00 mmole) of dry potassium carbonate as a suspension was heated with stirring for 16 hr. at 110°. After filtration the solution was evaporated to dryness *in vacuo*, and the residue was cyrstallized from ethanol to give a white solid; yield 82 mg. (27%); m.p. 230°; λ max in mμ ($\epsilon \times 10^{-3}$): *p*H 1-259 (14.8), *p*H 7-261 (14.9), *p*H 13-261 (15.1).

This material was found to be identical to an authentic sample of 9-benzyladenine (4a).

3,7-Dibenzyladenine (IX). Method A.

A solution of 2.25 g. (10.0 mmoles) of 3-benzyladenine and 5.13 g. (30.0 mmoles) of benzyl bromide in 200 ml. of N,N-dimethylacetamide was heated in an oil bath at 70° for 28 hr. and then evaporated to dryness *in vacuo*. The residue became a white solid after trituration with ether (2 x 350 ml.); yield, 3.92 g. (89%) of the hydrobromide X, which was found to be 91% pure by its ultraviolet spectra.

The analytical sample, obtained by crystallization from ethanol, was dried 16 hr. at 100°/0.07 mm. over phosphorus pentoxide; λ max in mμ ($\epsilon \times 10^{-3}$): *p*H 1-278 (15.2), *p*H 7-278 (15.2), *p*H 13-281 (12.4).

Anal. Calcd. for $C_{19}H_{17}N_5 \cdot HBr$: C, 57.58; H, 4.58; N, 17.68. Found: C, 57.70; H, 4.54; N, 17.57.

The free base IX was obtained by treatment of a methanol solution of the hydrobromide with a slight excess of sodium methoxide in methanol. The addition of water precipitated the free base an an oil that crystallized on standing.

Anal. Calcd. for $C_{19}H_{17}N_5$: C, 72.35; H, 5.43; N, 22.20. Found: C, 72.51; H, 5.28; N, 21.87.

Method B.

A solution of 200 mg. (0.89 mmoles) of 7-benzyladenine and 456 mg. (2.67 mmoles) of benzyl bromide in 20 ml. of N,N-dimethylacetamide was heated in an oil bath at 65° for 16 hr. and was then evaporated to dryness *in vacuo*. The gummy residue, after trituration with 200 ml. of ether, became a yellow solid (327 mg.). This material was found by its ultraviolet spectrum to be 91% pure. Recrystallization of this material from 5 ml. of ethanol gave a white, crystalline solid; yield 252 mg. (81%), m.p. 145° (mixture melting point with 3,7-dibenzyladenine hydrobromide prepared by Method A showed no depression). The ultraviolet and infrared spectra and the chromatographic behavior of this

material were identical to those of the compound prepared by Method A.

3,7,N^6-Tribenzyladenine Hydrochloride (VII). Method A.

A mixture of 225 mg. of 7-benzyladenine and 138 mg. of potassium carbonate in 10 ml. of N,N-dimethylacetamide containing 0.23 ml. of benzyl chloride was heated at 110° with stirring overnight. The volatiles were removed *in vacuo* with additions of ethanol, and the residue was recrystallized from ethanol; yield 93 mg. (30%), m.p. 236-244°. A small sample was again recrystallized from ethanol for analysis. λ max in mμ (ε x 10^{-3}): *p*H 1-289 (21.3), *p*H 7-289 (21.2), *p*H 13-287 (unstable).

Anal. Calcd. for $C_{26}H_{23}N_5 \cdot HCl$: C, 70.49; H, 5.47; N, 15.81. Found: C, 70.87; H, 5.84; N, 15.42.

An aqueous solution of 3,7,N^6-tribenzyladenine hydrochloride was taken to *p*H 9 with ammonium hydroxide. The free base XII, which immediately precipitated, was collected by filtration and dried for 16 hr. at 110°/0.07 mm. over phosphorus pentoxide; m.p. 128-130°; λ max in mμ (ε x 10^{-3}): *p*H 1-289 (21.1), *p*H 7-289 (21.1), *p*H 13-287 (unstable).

Method B.

In a similar manner 3-benzyladenine was benzylated to give a tribenzyladenine hydrochloride identical in all respects (*i.e.*, spectra, chromatographic behavior) to the compound prepared by Method A. Mixture melting point of A and B, 232-240°.

Benzylation of 6-Benzylaminopurine.

A solution of 1.00 g. (4.45 mmoles) of 6-benzylaminopurine and 4.56 g. (26.7 mmoles) of benzyl bromide in 40 ml. of N,N-dimethylacetamide was heated for 16 hr. at 120° and then evaporated to dryness *in vacuo*. The gummy residue was triturated with water and the water removed by evaporation *in vacuo*; the process was repeated. To remove traces of water, the residue was dissolved in ethyl alcohol and the solution evaporated to dryness. Crystallization of the residue from 50 ml. of ethyl alcohol gave 3-benzyl-N^6-benzylaminopurine hydrobromide (VIII) as a white solid weighing 1.13 g. This material was recrystallized from 75 ml. of ethanol and dried for 16 hr. at 100°/0.07 mm. over phosphorus pentoxide; yield 979 mg. (56%); m.p. 212-214°; λ max in mμ (ε x 10^{-3}): *p*H 1-287 (24.7), *p*H 7-290 (17.7), *p*H 13-290 (17.3).

Anal. Calcd. for $C_{19}H_{17}N_5 \cdot HBr$: C, 57.58; H, 4.58; N, 17.68. Found: C, 57.73; H, 4.50; N, 17.69.

The filtrate was evaporated to dryness, and the residue was triturated with acetone. This treatment gave 3,7,N^6-tribenzyladenine hydrobromide (VII) as a crystalline solid; yield 124 mg. (6%); m.p. 204-205°. The free base XII was obtained by treating an aqueous solution of the compound with enough 1N ammonium hydroxide to give a *p*H of 9. The precipitate that formed was recrystallized from ethanol as a white solid; m.p. 128-130°; λ max in mμ (ε x 10^{-3}): *p*H 1-289 (22.1), *p*H 7-289 (21.9), *p*H 13-287 (unstable). This compound was identical in all respects (*i.e.*, spectra, chromatographic behavior) to the compound prepared by benzylation of both 3- and 7-benzyladenine with base.

Anal. Calcd. for $C_{26}H_{23}N_5$: C, 77.06; H, 5.72; N, 17.27. Found: C, 77.09; H, 5.75; N, 17.36.

3-Benzyl-6-benzamidopurine Hydrochloride (XIII). Method A.

A solution of 239 mg. (1.00 mmole) of 6-benzamidopurine and 378 mg. (3.00 mmoles) of benzyl chloride in 10 ml. of N,N-dimethylacetamide was heated at 110° for 16 hr. After cooling, the reaction deposited a crystalline solid, yield 75 mg. (21%); m.p. 255-257°.

This material was found to be identical to that obtained from treatment of 3-benzyladenine hydrochloride with benzoic anhydride. Base treatment of this material gave 3-benzyladenine as the only product.

Method B.

A mixture of 225 mg. of 3-benzyladenine and 678 mg. of benzoic anhydride was heated in an oil bath at 180-185° for 15 min., and the resulting solid was recrystallized from 15 ml. of ethanol; wt., 323 mg. This material was recrystallized again from ethanol: yield, 239 mg. (73%); m.p. 218° (softened at 180°). A small amount of this material, recrystallized a third time from ethanol, was dried *in vacuo* over phosphorus pentoxide; m.p. 216° (softened at 180°); λ max in mμ (ε x 10^{-3}): *p*H 1-300 (28.2), *p*H 7-240 (sh) (17.1) and 301 (17.1), *p*H 13-231 (sh) (17.0) and 333 (17.9).

Anal. Calcd. for $C_{19}H_{15}N_5O \cdot 1/4H_2O$: C, 68.36; H, 4.68; N, 21.03. Found: C, 68.36; H, 4.68; N, 20.99.

Treatment of 3-benzyladenine hydrochloride with benzoic anhydride, followed by ether trituration and recrystallization from ethanol gave 3-benzyl-6-benzamidopurine hydrochloride; yield 52 mg. (16%); m.p. 258°. λ max in mμ (ε x 10^{-3}): *p*H 1-299 (26.4), *p*H 7-242 (16.0) and 300 (16.0), *p*H 13-232 (15.8) and 332 (16.9).

Anal. Calcd. for $C_{19}H_{15}N_5O \cdot HCl$: C, 62.39; H, 4.41; N, 19.15. Found: C, 62.18; H, 4.35; N, 19.00.

3-Benzyl-6-acetamidopurine (XIV).

A solution of 100 mg. (0.44 mmole) of 3-benzyladenine in 4 ml. of acetic anhydride was refluxed for 3 hr. The dark crystalline solid that formed in the cooled reaction solution was collected and recrystallized from ethanol with charcoal treatment; yield 30 mg. (26%) of a white solid.

The analytical sample, obtained by another recrystallization from ethanol, was dried at 78°/0.07 mm. over phosphorus pentoxide; m.p. 218°; λ max in mμ (ε x 10^{-3}): *p*H 1-275 (18.6), *p*H 7-272 (13.4), *p*H 13-272 (10.1).

Anal. Calcd. for $C_{14}H_{13}N_5O$: C, 62.90; H, 4.91; N, 26.21. Found: C, 62.72; H, 4.89; N, 26.35.

N^6-Benzoyl-3,7-dibenzyladenine (XV). Method A.

A mixture of 329 mg. of N^6-benzoyl-3-benzyladenine, 138 mg. of potassium carbonate, and 0.35 ml. of benzyl chloride in 10 ml. of N,N-dimethylacetamide was heated at 100° for 16 hr. After the usual work-up, the crude product was recrystallized from ethanol; yield 190 mg. (45%); m.p. 217-218°. λ max in mμ (ε x 10^{-3}): *p*H 1-225 (sh) (20.8) and 303 (18.3), *p*H 7-238 (14.1) and 336 (21.0), *p*H 13-238 (13.8) and 336 (19.0).

Anal. Calcd. for $C_{26}H_{21}N_5O$: C, 74.45; H, 5.05; N, 16.70. Found: C, 74.17; H, 5.17; N, 16.61.

Method B.

In the same manner benzylation of the N^6-benzoyl-7-benzyl-adenine gave a 30% yield of a compound identical in all respects with the product from Method A above, m.p. 217-218°.

N^6-Benzoyl-7-benzyladenine (XVI).

A mixture of 450 mg. of 7-benzyladenine and 1.36 g. of benzoic anhydride was heated at 185° for 15 min. The crude product was recrystallized twice from ethanol; yield 563 mg. (86%), m.p. 238°; λ max in mμ (ε x 10^{-3}): *p*H 1-240 (10.3), 280 (12.7), and 330 (19.7); *p*H 7-237 (11.2), 279 (11.9), and 333 (2.81); *p*H 13-298 (11.3).

Anal. Calcd. for $C_{19}H_{15}N_5O$: C, 69.14; H, 4.59; N, 21.32. Found: C, 68.84; H, 4.81; N, 21.54.

3,N^6-Dibenzhydryladenine Hydrochloride (XVIII). Method A.

To a stirred, heated (110°) suspension of adenine (1.0 g.) in 17 ml. of N,N-dimethylacetamide was added 5.3 ml. of benzhydryl chloride. The resulting solution was heated overnight at 110°. An additional 5.3 ml. of benzhydryl chloride was added and heating at 110° continued for another day. The volatiles were removed *in vacuo*, the residue extracted with hot water, dried, and triturated with ether. The resulting solid was recrystallized from ethanol; yield 1.37 g. (37%), m.p. 195-200°. A mmole sample was recrystallized again from alcohol for analysis, m.p. 202-204°; λ max in mμ (ε x 10^{-3}): *p*H 1-280 (25.9) and 294 (sh) (20.8), *p*H 7-283 (30.0) and 292 (sh) (28.8), *p*H 13-281 (28.6) and 291 (sh) (25.0).

Anal. Calcd. for $C_{13}H_{25}N_5 \cdot HCl$: C, 73.87; H, 5.20; N, 13.90. Found: C, 73.69; H, 5.31; N, 13.99.

From the ethanol filtrate upon addition of ether there was obtained 9-benzhydryladenine hydrochloride (XIX) as a white crystalline solid; yield 314 mg. (13%); m.p. 186-187°; λ max in mμ (ε x 10^{-3}): *p*H 1-258 (17.3), *p*H 7-263 (17.0), *p*H 13-263 (17.4).

Anal. Calcd. for $C_{18}H_{15}N_5 \cdot HCl$: C, 64.00; H, 4.77; N, 20.73. Found: C, 63.94; H, 4.80; N, 20.75.

Method B.

The reaction of N^6-benzhydryladenine (200 mg.) with benzhydryl-chloride (405 mg.) in dimethylacetamide (5 ml.) gave 229 mg. (68%) of impure N^6,3-bisbenzhydryladenine. Recrystallization from alcohol gave material whose ultraviolet and infrared spectra are in good agreement with those of the compound prepared by Method A. Thin-layer chromatography revealed the presence of a small amount of impurity, probably a trisbenzhydryladenine.

9-Benzhydryladenine (XIX). Method B.

A suspension of 1.35 g. (10.0 mmoles) of adenine and 1.38 g. (10.0 mmoles) of anhydrous potassium carbonate in 60 ml. N,N-dimethylacetamide was treated with 4.05 g. (20.0 mmoles) of benzhydryl chloride and heated with vigorous stirring in an 115° oil bath for 18 hr. After filtration the solution was evaporated to dryness *in vacuo*. The orange syrupy residue became a solid upon ether trituration. This solid was dissolved in ethanol, and the solution was made acid by the addition of concentrated hydrochloric acid. Seeding gave a white solid precipitate (985 mg.). Recrystallization of this material from ethanol gave pure 9-benzhydryladenine hydrochloride (XIX); yield 598 mg. (18%); m.p 187-188°. A mixed melting point with the monobenzhydryladenine obtained in Method A showed no depression. This material was identical in all respects (*i.e.* spectra, chromatographic behavior) to the compound obtained in Method A.

3-Benzhydryladenine (XX).

To a hot solution (110°) of 1 g. of adenine in 20 ml. of N,N-dimethylacetamide was added 1.33 ml. of benzhydryl chloride and the resulting solution heated overnight. The solution was evaporated *in vacuo*, and the residue was dissolved in hot ethanol. On cooling adenine (559 mg.) deposited and was removed by filtration. The addition of 4 volumes of ether to the filtrate caused a gum to precipitate. This gum was dissolved in hot water, the solution cooled and then neutralized with ammonium hydroxide. The precipitate that formed was recrystallized from ethanol; yield 248 mg. (10%); m.p. 262-267°; λ max in mμ (ε x 10^{-3}): *p*H 1-274 (16.8), *p*H 7-269 (12.8), *p*H 13-270 (12.5).

Anal. Calcd. for $C_{18}H_{15}N_5 \cdot C_2H_5OH$: C, 69.14; H, 6.10; N, 20.16. Found: C, 69.68; H, 6.11; N, 20.57.

Drying overnight at 110°/0.07 mm. over phosphorus pentoxide gave the unsolvated material.

Anal. Calcd. for $C_{18}H_{15}N_5$: C, 71.74; H, 5.02; N, 23.24. Found: C, 71.41; H, 4.96; N, 23.09.

N^6-Benzhydryladenine Hydrochloride (XXI). Method A.

A solution of 200 mg. (0.4 mmole) of dibenzhydryladenine hydrochloride in 20 ml. of ethanol containing a suspension of 50 mg. of 5% palladium-on-charcoal catalyst was hydrogenated at 748 mm. and 27° for 72 hr. The uptake of hydrogen was 22.9 ml. (theory, 20.0 ml.). The catalyst was removed and the solution evaporated to dryness *in vacuo*. The gummy residue, which became a partial solid after trituration with ether, was crystallized from 7 ml. of ethanol; yield 41 mg. (30%). The analytical sample was obtained by recrystallization from ethanol; m.p. 210°; λ max in mμ (ε x 10^{-3}): *p*H 1-280 (21.6), *p*H 7-271 (21.4), *p*H 13-276 (20.4) and 284 (sh) (16.0).

Anal. Calcd. for $C_{18}H_{15}N_5 \cdot HCl$: C, 64.00; H, 4.77; N, 20.73. Found: C, 64.30; H, 4.90; N, 20.62.

Method B.

A solution of 500 mg. (3.23 mmoles) of 6-chloropurine and 5.92 g. (32.3 mmoles) of benzhydrylamine was refluxed for 6 hr. and evaporated to dryness *in vacuo*. Ether trituration of the syrupy residue produced a white solid, benzhydrylamine hydrochloride. The ether solution was filtered and then evaporated to dryness. A solution of the residue, in water, was acidified with concentrated hydrochloric acid and extracted with ether. The ether extract gave another crop of benzhydrylamine hydrochloride. The aqueous solution was neutralized with ammonium hydroxide and again extracted with ether. The ether extract gave 427 mg. of the desired 6-benzhydrylaminopurine as the free base. Recrystallization of the material from 10 ml. of ethanol gave a crystalline solid; yield 317 mg. (33%); m.p. 225-227°; λ max in mμ (ε x 10^{-3}): *p*H 1-280 (22.0), *p*H 7-271 (21.5), *p*H 13-276 (20.8) and 284 (sh) (16.3).

A solution of 67 mg. of this compound in 3 ml. of absolute ethanol was taken to *p*H 1 with concentrated hydrochloric acid. Seeding produced N^6-benzhydryladenine hydrochloride as a crystalline solid; yield 55 mg., m.p. 210°. A mixture melting point with material prepared by Method A showed no depression. The ultraviolet and infrared spectra of this sample are identical with those of the sample prepared by Method A.

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(2) This interest stems partly from a desire to help elucidate the mechanism of action of the biological alkylating agents (3) and partly from the synthetic utility of such procedures (4).

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(7) The preparation of 3-methyladenine tosylate by a similar procedure was first described by R. K. Robins (3g).

(8) Although other monobenzyl isomers were detectable by thin-layer chromatography none was isolated.

(9) The product was, of course, 3-benzyladenine hydrohalide.

(10) The appearance of a small sharp water band distinct from the NH absorption in this spectrum tends to eliminate exchange as an explanation of this equivalence.

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