[CONTRIBUTION FROM THE LABORATORIES OF THE SLOAN-KETTERING DIVISION OF CORNELL UNIVERSITY MEDICAL COLLEGE]

Purine N-Oxides. VII. Reaction of Aminopurine 1-N-Oxides with Acetic Anhydride[1]

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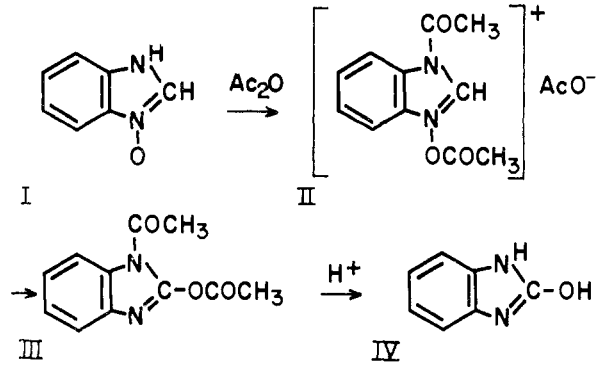
RECEIVED JUNE 1, 1959

Upon reaction with acetic anhydride, adenine 1-N-oxide and other aminopurine oxides behave in a manner different from other heterocyclic N-oxides in that no migration of the oxygen to an adjacent carbon takes place. The reaction of these oxides with acetic anhydride proceeds through 1-O-acetyl derivatives, followed by a cleavage of the pyrimidine ring to give imidazole compounds. Adenine N-oxide yields 5-methyl-3-[5′-(4′-acetamido)-imidazolyl]-1,2,4-oxadiazole, and the corresponding 4′-formamido derivative. Cleavage of 2,6-diaminopurine N-oxide to the same aminoimidazolyloxadiazole indicates that it, too, is a 1-N-oxide. The pyrimidine portion of 2-methyladenine 1-N-oxide is cleaved only to a small extent by prolonged reaction with acetic anhydride.

An attempt was made to convert the recently prepared[2] adenine 1-N-oxide to 2-hydroxyadenine (isoguanine), and 8-hydroxyadenine 1-N-oxide to 2,8-dihydroxyadenine, by the action of acetic anhydride. The analogous reactions of pyridine N-oxide and benzimidazole 1-N-oxide (I) with acetic anhydride yield 2-hydroxypyridine[3] and 2-hydroxybenzimidazole (IV),[4] respectively. The suggested[4] series of intermediates in the latter reaction is



I II III IV

In the pyridine series 2-methylpyridine N-oxide leads, with acetic anhydride, to 2-acetoxymethylpyridine, and a mechanism involving an intramolecular cyclic rearrangement is most favored,[5,6] although it had been thought previously that a free radical mechanism might be involved.[7] With 2-aminopyridine N-oxide the 2-acetamido derivative, but no rearrangement product, was obtained.[8]

The first product of the acetylation of adenine 1-N-oxide (V) (corresponding to II in the benzimidazole series) is O-acetyladenine 1-N-oxide acetate (VI). Acetic acid is slowly lost from VI under vacuum, and some decomposition to adenine 1-N-oxide occurs.

Compound VI can be isolated in 33% yield from an acetylation of adenine N-oxide at room temperature with a mixture of acetic anhydride and acetic acid. It reverts readily to V in warm glacial acetic acid, aqueous acid or, more rapidly, in base. It is unlikely that this acetyl derivative is the amino rather than the oxygen-acetyl derivative, since the former would be expected to have a spectrum in a neutral solution similar to that of adenine 1-N-oxide.[9] Compound VI has a characteristic spectrum with strong absorption at 240 mμ, and in weakly acid solutions also possesses peaks at 286 mμ and 315 mμ.

Compound VI (or V) in acetic anhydride at room temperature yields two products, both of which are shown by a Pauly test[10] to be imidazole derivatives. The major product, an imidazole derived from V by the addition of one acetyl group and loss of water, is, on the basis of hydrolytic, synthetic and analytical evidence, 5-methyl-3-[5′-(4′-formamido)-imidazolyl]-1,2,4-oxadiazole (IX). At elevated temperatures a second product, obtained in greater yield, is the acetamido derivative, 5-methyl-3-[5′-(4′-acetamido)-imidazolyl]-1,2,4-oxadiazole (X). A paper chromatographic study of the change of adenine N-oxide into the 5′-formamido and acetamido compounds (IX and X) in cold acetic anhydride shows that the formamido derivative is formed first and is then converted into the acetamido derivative. Thus, mechanisms for the acetylation which involve addition of acetyl to the 3-nitrogen of the adenine oxide ring, before cleavage of the pyrimidine ring, are contraindicated.

A possible mechanism by which adenine N-oxide is converted, in the cold, to the oxadiazoles IX and X could involve the intermediate VII. A nucleophilic attack by acetate ion at position 2, with simultaneous heterolytic fission of the 2C–1N bond of the pyrimidine and closure of the oxadiazole, would lead to the enol-acetate VIII.[11] Cleavage of VIII leads to the formamido derivative IX. The formamido derivative IX is then converted slowly, by amide interchange, into the acetamido derivative X.

If adenine 1-N-oxide is refluxed with acetic anhydride, both imidazoles IX and X are formed

(1) This investigation was supported in part by funds from the American Cancer Society (Grant E-8), National Cancer Institute, National Institutes of Health, Public Health Service (Grant #CY-3190), and from the Atomic Energy Commission (Contract #AT(30-1)-910).

(2) M. A. Stevens, D. I. Magrath, H. W. Smith and G. B. Brown, THIS JOURNAL, **80**, 2755 (1958).

(3) M. Katada, *J. Pharm. Soc. Japan*, **67**, 51 (1947).

(4) F. Montanari and A. Risalti, *Gazz. chim. ital.*, **83**, 278 (1953).

(5) I. J. Pachter, THIS JOURNAL, **75**, 3026 (1953).

(6) V. J. Traynelis and R. F. Martello, *ibid.*, **80**, 6590 (1958).

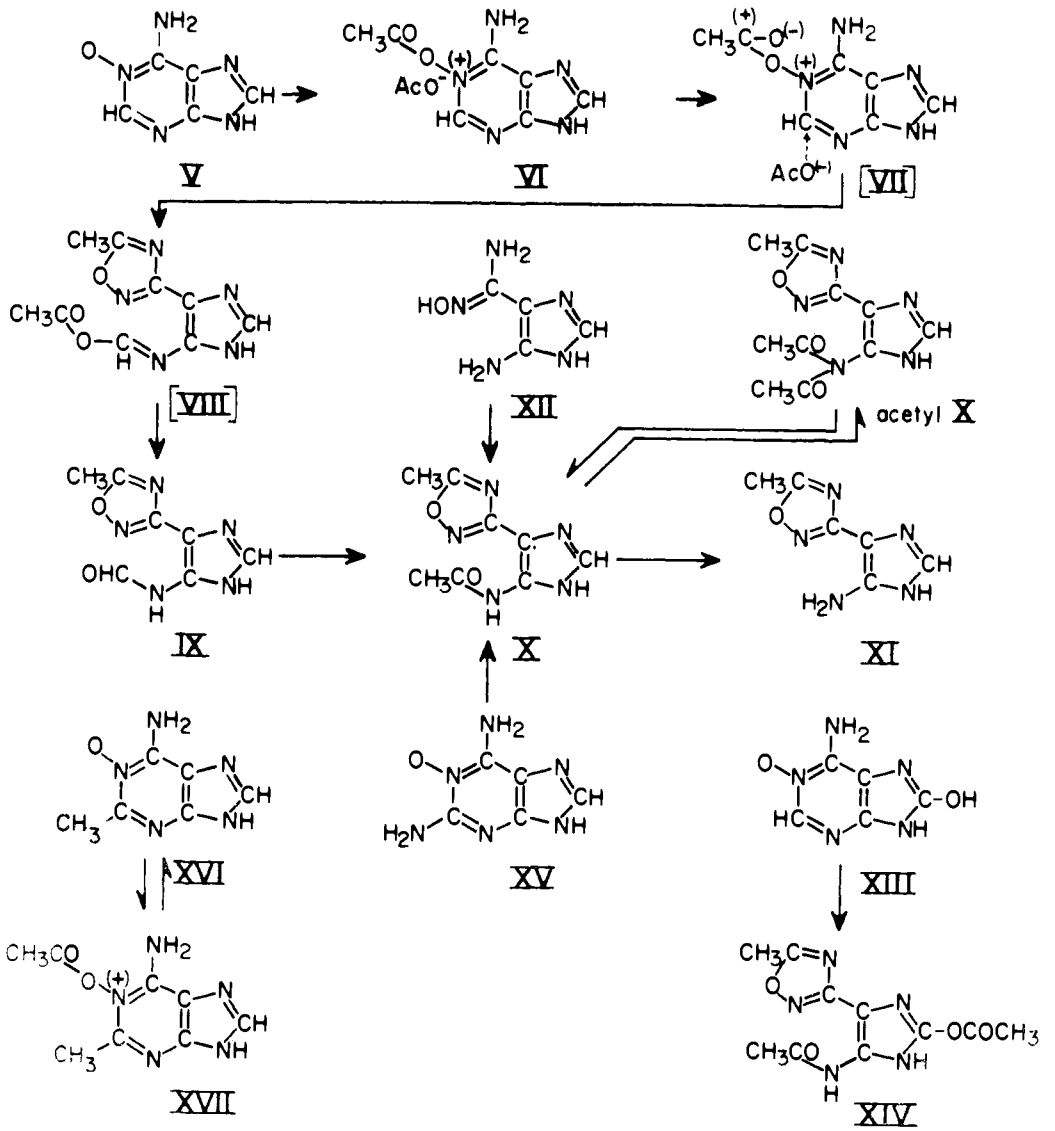
(7) (a) V. Boekelheide and W. J. Linn, *ibid.*, **76**, 1288 (1954); (b) V. Boekelheide and D. L. Harrington, *Chemistry & Industry*, 1423 (1955).

(8) A. R. Katritsky, *J. Chem. Soc.*, 191 (1957).

(9) M. A. Stevens and G. B. Brown, THIS JOURNAL, **80**, 2759 (1958).

(10) H. Pauly, *Z. physiol. Chem.*, **42**, 508 (1904).

(11) If the reaction were to proceed in a manner similar to the classical pyridine N-oxide rearrangement, the substance VI would undergo nuclear attack by acetate without ring scission, and regain its aromatic character. This would lead to 2-hydroxyadenine upon hydrolysis.



rapidly. If reflux is continued, another substance is formed which is apparently the result of further acetylation of the 4'-amino group of X to give a 5-methyl-3-[5'-(4'-diacetimido)-imidazolyl]-1,2,4-oxadiazole (acetyl X). Though this substance is readily hydrolyzed back to the acetamido derivative X, it is stable enough in neutral solvents to permit its R_f to be determined (Table I). An acetylation of the 4-amino group to a diacetimido group, with hot acetic anhydride, has also been observed with 4-aminoimidazole-5-carboxamide.[12] Both IX and X are hydrolyzed in 1 *N* hydrochloric acid to 5-methyl-3-[5'(4'-amino)-imidazolyl]-1,2,4-oxadiazole (XI) without cleavage of the oxadiazole ring.

Additional support for the oxadiazole structure is afforded by synthesis of X from 4-aminoimidazole-5-carboxamidoxime (XII),[9] a reaction analogous to that of benzamidoxime[13] with acetic anhydride, to yield 5-methyl-3-phenyl-1,2,4-oxadiazole. Compound X synthesized from XII is identical in spectral properties and R_f in four solvents with X derived directly from adenine 1-N-oxide; its hydrolysis leads to XI.

It has not been possible to detect any 2-hydroxyadenine (isoguanine) among the rearrangement products of adenine 1-N-oxide. This chemical behavior is paralleled by the observation[14] that xanthine oxidase, the enzyme effecting biological hydroxylation of purines, is also unable to convert adenine 1-N-oxide to a 2-hydroxylated adenine. The enzyme hydroxylates only the 8-position, to yield 8-hydroxyadenine 1-N-oxide. This adds further weight to the view[15] that the basic process in hydroxylation by xanthine oxidase is a direct entry of hydroxyl on the carbon involved.

The 8-hydroxyadenine 1-N-oxide reacts as does adenine 1-N-oxide. The definition of the products is more difficult because the 8-hydroxy group is readily acetylated and the progress of the reaction

(12) M. E. Balis and B. R. Baker, personal communications.

(13) F. Tiemann and P. Kruger, *Ber.*, **17**, 1696 (1884). That reaction proceeds through an O-acetyl derivative of the amidoxime.

(14) G. B. Brown, M. A. Stevens and H. W. Smith, *J. Biol. Chem.*, **233**, 1513 (1958).

(15) F. Bergmann and S. Dikstein, *ibid.*, **223**, 765 (1956).

cannot be followed by the Pauly color test. The main product of the reaction in hot acetic anhydride is, by analogy, probably 5-methyl-3-[5′(2′-acetoxy-4′-acetamido)-imidazolyl]-1,2,4-oxadiazole (XIV). Hydrolysis of this product with acid gives 5-methyl-3-[5′(2′-hydroxy-4′-amino)-imidazolyl]-1,2,4-oxadiazole.

It was not possible to utilize hydrolysis to determine the structure of 2,6-diaminopurine N-oxide[2] because of its stability to hydrolysis. In the light of its spectral resemblance to adenine 1-N-oxide, this substance was considered to be either a 1- or 3-N-oxide.[9] The conversion of an aminopurine N-oxide to an imidazolyl-oxadiazole is, however, a reaction that can be used to determine the structure of this N-oxide since it is susceptible to attack by acetic anhydride. The 1-N-oxide XV of 2,6-diaminopurine might be expected to lead to 5-methyl-3-[5′-(4′-ureido)-imidazolyl]-1,2,4-oxadiazole (N-carbamyl XI), while the 3-N-oxide would lead to an entirely different type of oxadiazole derivative. The main product of the prolonged reaction of acetic anhydride at 140° with 2,6-diaminopurine N-oxide was found to be the acetamido compound X rather than an N-carbamyl derivative of XI, although the latter is an expected intermediate.[16] Thus 2,6-diaminopurine N-oxide has a 1-N-oxide structure. When the crude product of its acetylation is hydrolyzed, only XI is formed, and there is no evidence of the formation of an alternative oxadiazole between the 1-N-oxide and the 2-amino group.

By analogy with adenine 1-N-oxide it might be expected that 2-methyladenine 1-N-oxide (XVI) would react with acetic anhydride to give only X. 2-Methyladenine 1-N-oxide was obtained in 56% yield from 2-methyladenine, and could be hydrogenated to the parent purine. The 1-N-oxide structure was proved by hydrolysis with hydrochloric acid to 4-aminoimidazole-5-carboxamidoxime (XII).

The reaction of a mixture of acetic anhydride and acetic acid at room temperature with 2-methyladenine 1-N-oxide first gives the 1-O-acetyl derivative as an acetate (XVII). Unlike VI, XVII does not precipitate from solution in the pure state, but is contaminated with XVI. Purification by recrystallization was not possible, but XVII can be purified in small quantities by paper chromatography. The similarity of the spectrum of material so purified to that of VI suggests that XVII is also the O-acetyl derivative. On treatment with dilute ammonia this is reconverted to XVI.

Refluxing 2-methyladenine 1-N-oxide with acetic anhydride gives first the O-acetyl derivative which rapidly disappears. The main product detected by paper chromatography has a strong yellow fluorescence in ultraviolet light, and decomposes to a tar when attempts are made at isolation. The small extent of cleavage of the pyrimidine ring is evident from the failure to yield more than a trace of an imidazole responding to the Pauly test.

On the basis of the mechanism suggested for the ring opening of adenine 1-N-oxide an attack of acetate ion on the 2-carbon of O-acetyl-2-methyladenine 1-N-oxide would be necessary. Such attack is probably discouraged by the steric influence of the 2-methyl substituent. With the pyrimidine cleavage blocked, perhaps the reaction proceeds by an alternative pathway to 2-acetoxymethyladenine,[17] which then decomposes further.

Experimental

Except where otherwise stated all chromatographic analyses were performed, ascending, with Whatman No. 1 paper, at 25°: solvent A (1% ammonium sulfate–isopropyl alcohol, 1:2 vol./vol.),[18] solvent B (5% disodium phosphate–isoamyl alcohol, 3:2 vol./vol.),[19] solvent C (ethanol–30% ammonia-water, 20:1:4)[20] and solvent D (1-butanol–acetic acid–water, 5:4:1).[20]

Measurements of ultraviolet absorption were made with a Beckman DK-2 recording spectrophotometer. Spectral data and R_f's are given in Table I.

Preparation of O-Acetyladenine 1-N-Oxide.—Adenine oxide (900 mg.) was stirred with 80 ml. of 2:1 acetic acid–acetic anhydride. After 3 minutes at room temperature the oxide dissolved to give a pale yellow-green solution. After 30 minutes a heavy slurry formed. This was collected and the filtrate was stirred for 15 minutes until it was again a thick slurry. The filtering and stirring were repeated four times. This stepwise process is necessary since the first product, if left in the reaction medium, slowly reacts further and goes into the solution. The four precipitates were combined and washed with a little acetic acid. The product at this stage was chromatographically pure and was analyzed directly, since it is unstable in most solvents. The product, O-acetyladenine 1-N-oxide acetate, decomposed at 220–224°. The crystals slowly lose acetic acid upon drying, and after 36 hours in vacuum over phosphorus pentoxide amounted to 497 mg. (33% yield). The analysis corresponded to approximately 0.9 molecule of acetic acid per molecule of *O*-acetyladenine 1-N-oxide.

Anal. Calcd. for $C_7H_7N_5O_2 \cdot CH_3COOH$: C, 42.68; H, 4.38; N, 27.65. Found: C, 43.31; H, 4.34; N, 28.50.

Preparation of 5-Methyl-3-[5′-(4′-formamido)-imidazolyl]-1,2,4-oxadiazole.—Adenine 1-N-oxide (100 mg.) was stirred in a mixture of acetic acid (6 ml.) and acetic anhydride (3 ml.) for 23 hours. The solution of the oxide in the solvent mixture was followed by a rapid precipitation of the O-acetyl derivative, which later went into solution. A chromatogram of the solution, developed in solvent A at 6 hours, showed it contained equal amounts of the product and of the O-acetyl derivative; at 23 hours it contained the product plus a little of the corresponding 4′-acetamido derivative. The solution was evaporated to dryness *in vacuo* at room temperature after 23 hours, and the light yellow solid was recrystallized from ethanol–ethyl acetate to give white crystals (62.5 mg., 50%), m.p. 193–195° (dec.).

Anal. Calcd. for $C_7H_7N_5O_2$: C, 43.50; H, 3.64; N, 36.27. Found: C, 43.87; H, 3.91; N, 36.39.

Preparation of the 5-Methyl-3-[5′-(4′-acetamido)-imidazolyl]-1,2,4-oxadiazole.—Adenine 1-N-oxide (500 mg.) was suspended in acetic anhydride (25 ml.) and the mixture was heated under reflux for 5 minutes. The brown solution that resulted was poured into water (100 ml.) and the aqueous solution was evaporated to dryness at room temperature *in vacuo*. The evaporation yielded 700 mg. of a light yellow solid, mainly the acetamido derivative, but containing appreciable quantities of the corresponding formamido deriva-

(16) If 2,6-diaminopurine N-oxide is acetylated with acetic anhydride at 140° for 10 minutes, the main product is an imidazole (R_f 0.75 in A and 0.56 in B) which gives a pink Pauly[10] color. As the reaction proceeds, this imidazole disappears and X appears. Since the intermediate rapidly decomposes if attempts are made to isolate it, it is probably not N-carbamyl XI, but may be 5-methyl-3-[5′-(4′-N-acetyl-4′-N-carbamylamino)-imidazolyl]-1,2,4-oxadiazole.

(17) With 6-methylpurine 1-N-oxide a rearrangement to a 6-acetoxymethyl derivative can occur; A. Giner-Sorolla, I. Zimmerman and A. Bendich, Abstracts, 135th Meeting Am. Chem. Soc., Boston, Mass., 1959, p. 6-N.

(18) N. Anand, V. M. Clark, R. H. Hall and A. R. Todd, *J. Chem. Soc.*, 3665 (1952). Controls are particularly necessary with this solvent[9] because of its poor buffering capacity.

(19) C. E. Carter, THIS JOURNAL, **72**, 1466 (1950).

(20) V. M. Clark, A. R. Todd and J. Zussman, *J. Chem. Soc.*, 2953 (1951).

TABLE I

Substance	R_f A[a]	R_f B[a]	U.v. spectrum max. at particular pH	M.p., °C.	Pauly color
Adenine 1-N-oxide	0.48	0.48	258 at 1 231 and 262.5 at 7 233 and 275 at 13	297–307 d.	Transient pink
O-Acetyladenine 1-N-oxide (acetate)	.51	Dec.	243 and 287 312 shoulder } at 2	226–230 d.	None
5-Methyl-3-[5′-(4′-formamido)-imidazolyl]-1,2,4-oxadiazole	.77	.57	257 at 2.0 265 at 7.0 278 at 12.0	193–195 d.	Orange red
5-Methyl-3-[5′-(4′-acetamido)-imidazolyl]-1,2,4-oxadiazole	.78	.66	252 at 2.0 259.5 at 7.0 276 at 12.0	219 d.	Orange
5-Methyl-3-[5′-(4′-diacetimido)-imidazolyl]-1,2,4-oxadiazole	.85	Dec.	248 at 7 247 at 2	.....	Orange
8-Hydroxyadenine 1-N-oxide	.45	.52	218 and 273 at 1.5 242 and 298 at 12.4	325 d.	None
5-Methyl-3-[5′-(2′-hydroxy-4′-amino)-imidazolyl]-1,2,4-oxadiazole	.54[b]	.45	272 at 2 272 at 7 282 at 12	205 d. (20°/min.)	None
2,8-Dihydroxyadenine		.08	232 and 304 at 2.3 237 and 302 at 9.2	335–340 d.	None
5-Methyl-3-[5′-(4′-amino)-imidazolyl]-1,2,4-oxadiazole	.70[b]	.51	271.5 at 1.5 276.5 at 7.0 292 at 12.5	HCl, 204–210°	Orange-red
2-Methyladenine 1-N-oxide	.49	.53	228 and 257 at 2.6 229 and 260 at 7.0 229 and 271 at 12.5	306 d.	Transient light yellow
O-Acetyl-2-methyladenine 1-N-oxide	.70	.53	234 and 287 at 6	.....	None

[a] For solvent constitutions see Experimental. [b] Figure is variable due to weak buffering power of ammonium sulfate.

tive. Solution of the light yellow solid in hot methanol (25 ml.), treatment with charcoal, and cooling, gave white crystals, m.p. 219°, (dec.) (225 mg., 33%), of chromatographically pure 5-methyl-3-[5′-(4′-acetamido)-imidazolyl]-1,2,4-oxadiazole.

Anal. Calcd. for $C_8H_9N_5O_2$: C, 46.40; H. 4.35; N, 33.80. Found: C, 46.32; H, 4.37; N, 33.72.

Preparation of 5-Methyl-3-[5′-(4′-amino)imidazolyl]-1,2,-4-oxadiazole.—Adenine 1-N-oxide (1.0 g.) was dissolved in acetic anhydride (15 ml.). The solution was brought to reflux, cooled, and poured into water (40 ml.). The resulting solution was evaporated to dryness *in vacuo*, the residue was refluxed with 1 *N* HCl (50 ml.) for 3 hours, and the solution was again evaporated to dryness. The product (1.0 g. 75%) was recrystallized three times from acetic acid to give 5-methyl-3-[5′-(4′-amino)-imidazolyl]-1,2,4-oxadiazole as the hydrochloride, m.p. 204–210° dec.

Anal. Calcd. for $C_6H_7N_5O\cdot HCl$: C, 35.73; H, 3.97; N, 34.73. Found: C, 36.03; H, 3.88; N, 35.34.

Reaction of 4-Aminoimidazole-5-carboxamidoxime with Acetic Anhydride.—4-Aminoimidazole-5-carboxamidoxime dihydrochloride (200 mg.) was dissolved in water (20 ml.), then run through a column of Dowex 1 (OH^- form) to convert the carboxamidoxime to the free base. The resulting solution was evaporated to dryness *in vacuo*, the residue was dissolved in acetic anhydride (5 ml.), and the solution was allowed to stand for one day. The acetic anhydride was removed *in vacuo* and the brown residue (160 mg.), was recrystallized from ethanol–ethyl acetate to give buff crystals, m.p. 168° dec. This material is identical with 5-methyl-3-[5′-(4′-acetamido)imidazolyl]-1,2,4-oxadiazole in spectrum at various *p*H's and in R_f in solvents A and B. The melting point of this material was lower than that of 5-methyl-3-[5′-(4′-acetamido)-imidazolyl]-1,2,4-oxadiazole obtained from adenine 1-N-oxide and acetic anhydride. However, when this latter material was treated with acetic acid it gave a product with a melting point of 174° dec., which gave no depression of decomposition point upon admixture with the product of the reaction of 4-aminoimidazole-5-carboxamidoxime and acetic anhydride. This latter product, after hydrolysis with 1 *N* hydrochloric acid, gave a product with an ultraviolet spectrum and R_f's in solvents A and B which are identical with those of 5-methyl-3-[5′-(4′-amino)-imidazolyl]-1,2,4-oxadiazole.

Further Acetylation of Adenine-1-N-Oxide.—A solution of adenine 1-N-oxide (1.0 g.) in acetic anhydride (50 ml.) was refluxed for 3 hours. The solution was evaporated *in vacuo* at 60–65° to a viscous consistency. A solid was obtained by repeated evaporation from methyl alcohol, the bulk of which behaved chromatographically like the product obtained by refluxing 5-methyl-3-[5′-(4′-acetamido)-imidazolyl]-1,2,4-oxadiazole for one hour, or 5-methyl-3-[5′-(4′-formamido)-imidazolyl]-1,2,4-oxadiazole for 1.5 hours in acetic anhydride. Attempts to obtain the 5-methyl-3′-[5′-(4-diacetimido)-imidazolyl]-1,2,4-oxadiazole (R_f 0.85 in solvent A) by recrystallization from such reactions were unsuccessful; only the acetamido derivative was obtained. Hydrolysis of the crude product from the acetylation of adenine 1-N-oxide with water at 80° for one hour gave only the acetamido derivative (R_f 0.78 in solvent A). Solutions for spectral determination of 5-methyl-3-[5′-(4′-diacetimido)-imidazolyl]-1,2,4-oxadiazole were obtained by elution from chromatograms developed in solvent A.

Reaction of 2,6-Diaminopurine 1-N-Oxide with Acetic Anhydride.—A solution of 2,6-diaminopurine 1-N-oxide[2] (5 mg.) in acetic anhydride (2 ml.) was refluxed for 3 hours. The resulting dark brown solution was cooled, treated with water (2 ml.) and evaporated to dryness *in vacuo* at 45–55°. Chromatograms run on the resulting dark brown solid in solvents A, B, C and D showed it to contain, as the major component, a material with the same R_f as 5-methyl-3-[5′-(4′-acetamido)-imidazolyl]-1,2,4-oxidiazole in solvents A and B, and R_f's of 0.57 and 0.71 in C and D. The spot on a chromatogram representing this major product gave a Pauly color (orange-yellow) similar to that given by a spot of authentic 5-methyl-3-[5′-(4′-acetamido)-imidazolyl]-1,2,4-oxadiazole.

The main impurity in the acetylation mixture after a 3-hour reflux was an imidazole (R_f 0.75 in A and 0.56 in B) which gave a pink color with Pauly reagent. By chromatographic study of the acetylation of 2,6-diaminopurine 1-N-oxide at various time intervals, it was found that this decreased with the increase of 5-methyl-3-[5′-(4′-acetamido)-imidazolyl]-1,2,4-oxadiazole. The imidazole intermediate, which was the chief product of the 10-minute acetylation,

was not isolated because of its instability. It is either 5-methyl-3-[5'-(4'-ureido)-imidazolyl]-1,2,4-oxidiazole or its 4'-acetyl derivative. The fact that it is closely related to the final product, the 4'-acetamido derivative, is demonstrated by hydrolyzing the solid mixture of the two imidazoles obtained from a 3-hour acetylation. After heating one hour in 1 *N* HCl, chromatographic analysis of the hydrolyzate shows it to contain only 5-methyl-3-[5'-(4'-amino)-imidazolyl]-1,2,4-ozadiazole. The 5-methyl-3-[5'-(4'-acetamido-, and 5-methyl-3-[5'-(4'-amino)imidazolyl]-1,-2,4-oxadiazoles prepared from 2,6-diaminopurine 1-N-oxide were spectrally identical with those from adenine 1-N-oxide.

Preparation of a 2-Methyladenine 1-N-Oxide.—2-Methyladenine (1 g.) was suspended in a mixture of acetic acid (100 ml.) and 30% hydrogen peroxide (10 ml.). After 4 hours at room temperature the solid dissolved. The solution was kept 6 days at room temperature, at which time chromatographic analysis showed that the material in solution was mainly 2-methyladenine N-oxide. The hydrogen peroxide was destroyed by adding 10% palladium-on-charcoal (150 mg.) and stirring the solution overnight. The palladium-on-charcoal was removed by filtration and the filtrate was evaporated to 7 ml. when pure 2-methyladenine 1-N-oxide (165 mg.) crystallized. After evaporation to 4 ml. a further 275 mg. of the oxide crystallized. Further crops (356 mg.) were not pure, and were recrystallized from water. A total of 623 mg. (56%) was obtained as white crystals, decomposing at 306° (some initial decomposition at 230°). Analysis was performed on a sample after drying at 78° for 24 hours over phosphorus pentoxide.

Anal. Calcd. for $C_6H_7N_5O\cdot H_2O$: C, 39.34; H, 4.95; N, 38.23. Found: C, 39.31; H, 5.33; N, 38.83.

Hydrolysis of 2-Methyladenine 1-N-Oxide.—2-Methyladenine 1-N-oxide (36 mg.) was dissolved in 2 *N* HCl (6.0 ml.) and the solution was refluxed for 20 minutes. At the end of this time aliquots of the solution were chromatographed in solvents A and B. The main spot observed on the chromatograms was at R_f 0.22 in A, and 0.55 in B, identical with 4-aminoimidazole-5-carboxamidoxime.[9] This hydrolysis product had the same ultraviolet spectrum as 4-aminoimidazole-5-carboxamidoxime and gave the same orange color with Pauly reagent.

Hydrogenation of 2-Methyladenine 1-N-Oxide.—2-Methyladenine 1-N-oxide (50 mg.) was dissolved in acetic acid (25 ml.). Raney nickel (10 mg.) was added and the mixture was shaken with hydrogen for 21 hours, at which time 6.0 ml. (theory 6.7 ml.) of hydrogen had been absorbed. Chromatograms run on the solution showed that it still contained 2-methyladenine 1-N-oxide but that most had been reduced to a material with R_f's in solvents A (0.39) and B (0.38), and spectra which were identical with those of 2-methyladenine.

Preparation of O-Acetyl-2-methyladenine 1-N-Oxide.—2-Methyladenine 1-N-oxide (62 mg.) was suspended in a 1:1 mixture of acetic acid and acetic anhydride (4 ml.). After 5 minutes the solid went into solution and the resulting solution was lyophilized to a yellow solid (59 mg.). Partial purification of the O-acetyl derivative could be effected by suspending the solid in ethyl acetate, adding methyl alcohol, and warming to obtain a clear solution. O-Acetyl-2-methyladenine 1-N-oxide, contaminated with minor amounts of starting material, crystallized when the solution was cooled. The O-acetyl derivative had a spectrum similar to O-acetyladenine 1-N-oxide with peaks at 234 and 287 mμ. Upon hydrolysis, the O-acetyl-2-methyladenine 1-N-oxide was reconverted to 2-methyladenine 1-N-oxide.

Further Acetylation of 2-Methyladenine 1-N-oxide.—2-Methyladenine 1-N-oxide was refluxed with an acetic anhydride–acetic acid mixture for 2 hours, then chromatographed. The main product, separated by chromatography, was a material (R_f in A of 0.61; in B of 0.67) which exhibits a yellow fluorescence in ultraviolet and is negative to Pauly's reagent. The product could be isolated from solution, but soon became tarry, and resisted purification.

Reaction of 8-Hydroxyadenine 1-N-Oxide with Acetic Anhydride.—8-Hydroxyadenine 1-N-oxide (2.1 g.) was suspended in a solution of acetic anhydride (110 ml.) and acetic acid (10 ml.). The suspension was heated and dissolution of suspended material occurred on approach to reflux temperature. The brown solution obtained was refluxed for 12 hours and contained, as determined by paper chromatography, a major product (R_f 0.83 in solvent A and R_f 0.61 in solvent B). The solution was evaporated to a viscous residue and the residue obtained was refluxed with 3 *N* HCl (25 ml.) for 2 hours. Evaporation of the hydrochloric acid solution yielded 1.1 g. of a pale brown solid. The solid was recrystallized from glacial acetic acid (60 ml.) yielding 0.2 g. of chromatographically pure 5-methyl-3-[5'-(2'-hydroxy-4'-amino)-imidazolyl]-1,2,4-oxadiazole monohydrochloride, decomposition point 205°.

Anal. Calcd. for $C_6H_7N_5O_2\cdot HCl$: N, 32.18. Found: N, 31.85.

Halogen was present, and no 2,8-dihydroxyadenine was detected by chromatography.

NEW YORK 21, N. Y.

[CONTRIBUTION NO. 1049 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Synthesis of Nitrogen-containing Ketones. IX. The Acylation of 1-(2-Pyridyl)-3-dimethylaminopropane and 1-(2-Pyridyl)-1-phenyl-3-dimethylaminopropane[1-3]

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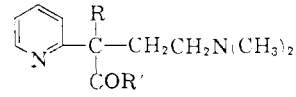
RECEIVED JUNE 22, 1959

A study has been made of the acylation of 1-(2-pyridyl)-3-dimethylaminopropane (I) and 1-(2-pyridyl)-1-phenyl-3-dimethylaminopropane (II) using phenylsodium and/or phenyllithium as the condensing agents to give ketones of the type $2\text{-}C_5H_4NCR(COR^1)CH_2CH_2N(CH_3)_2$, where R = H and C_6H_5 and R^1 = alkyl and phenyl. Comments are made concerning the molar proportions of I and II:condensing agent:ester which are required to give maximum yields of the ketones. The acylation of 1-(2-pyridyl)-1-phenyl-3-(N-pyrrolidino)-propane is also described.

In the first paper of this series, we reported[5] the synthesis of a series of 2-picolyl ketones, $2\text{-}C_5H_4NCH_2COR$ (where R is an alkyl, aryl or heterocyclic radical) by the acylation of 2-picoline with esters using phenyllithium as the condensing agent.

The present paper is concerned with the synthesis of two series of ketones of the formula



series I: R = H and R′ = alkyl and phenyl
series II: R = C_6H_5 and R′ = alkyl and phenyl

(1) For paper VIII in this series, see S. Raynolds and R. Levine, THIS JOURNAL, **82**, 472 (1960).

(2) Part of this work was performed under Contract No. AT(30-1)-670 between the U. S. Atomic Energy Commission and the University of Pittsburgh.

(3) This paper is based on part of the thesis presented by S. Raynolds to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements for the Ph.D. degree.

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(5) N. N. Goldberg, L. B. Barkley and R. Levine, THIS JOURNAL, **73**, 4301 (1951).