Alkylations at the Methyl or α-Methylene Group of 6- or 4-Alkyl-3-cyano-2(1)-pyridones through Dianions[1]

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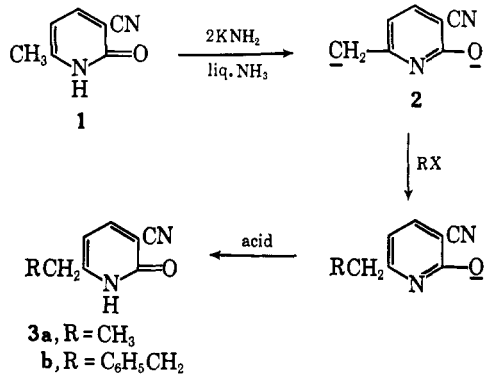
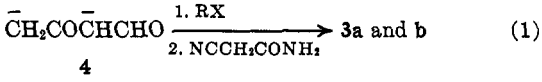
Received July 14, 1965

Alkylations were effected at the α-positions of 6- and 4-alkyl groups on 3-cyano-2(1)-pyridones through the dianions, which were prepared by means of 2 molecular equiv. of potassium amide in liquid ammonia. The yields are generally better than in the alternative alkylations of β-ketoaldehyde dicarbanions followed by cyclization with cyanoacetamide. Alkylation at both methyl groups of 4,6-dimethyl-3-cyano-2(1)-pyridone was effected through its trianion. Consideration is given to the theory of formation of intermediate dianions and to possible extensions of the method to certain other types of pyridones.

It seemed possible that 6-methyl-3-cyano-2(1)-pyridone (**1**) might undergo twofold ionization with 2 molecular equiv. of potassium amide in liquid ammonia to form dianion **2**, which could then be alkylated with alkyl halides to give the 6-methyl derivative.[2] This has been verified; also several related alkylations have been realized. Thus dianion **2** underwent alkylation with methyl and benzyl halides to afford **3a** and **b** in yields of 91 and 86%, respectively.[3]



Methyl alkylation structure **3b** was supported by the n.m.r. spectrum (see Table I). Both structures **3a** and **b** were confirmed by independent syntheses that involved alkylation of dicarbanion **4** with the appropriate alkyl halides followed by cyclization with cyanoacetamide (eq. 1).[4]



(1)

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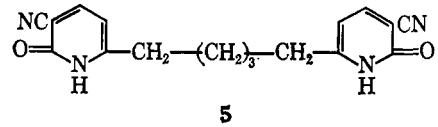
Dianion **2** underwent twofold alkylation with 1,3-dibromopropane to form coupled product **5** in 74% yield.



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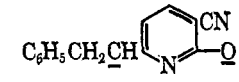
Benzylated pyridone **3b** from above was treated with 2 equiv. of potassium amide to form dianion **6**, which was alkylated with *n*-butyl bromide to give **7** in 64% yield.



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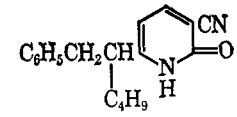

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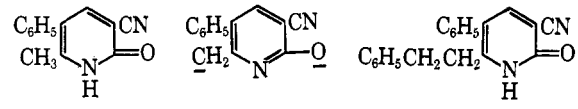
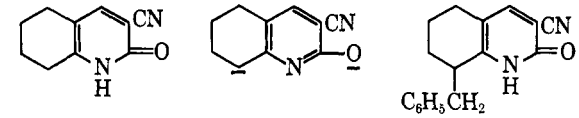
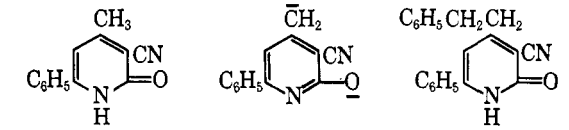
Similarly, alkylations at the 6-methyl group of pyridone **8**, at the 6-methylene group of pyridone **11**, and at the 4-methyl group of pyridone **14** were accomplished with benzyl chloride through dianions **9**, **12**, and **15** to afford derivativ es**10**, **13**, and **16**, respectively, in yields of 74–90%.



8 **9** **10**

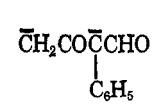


11 **12** **13**



14 **15** **16**

Structures **10** and **13** were confirmed by known independent syntheses from dianions **17**[5] and **18**,[6] respectively; the method is illustrated by eq. 1 (R = benzyl). The n.m.r. spectrum of **19** was consistent with the structure assigned (see Table I).



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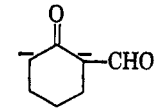

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The scope of such alkylations could presumably be extended considerably, as not only should other 4- and 6-alkyl-3-cyano-2(1)-pyridones undergo such alkylations, but other alkyl halides should also be

(1) This investigation was supported by National Science Foundation Research Grant No. NSF GP 2274 and by Public Health Service Research Grant No. USPHS CA 04455-06.

(2) The monoanion of **1** would presumably undergo N- or O-alkylation, as both modes of alkylation of the monoanion of 6-methyl-2(1)-pyridone have been effected under appropriate conditions: see E. Klingsberg, Ed., "The Chemistry of Heterocyclic Compounds," Part 3, Interscience Publishers Inc., New York, N. Y., 1962, p. 633.

(3) A preliminary report on the benzylation has appeared in a communication: T. M. Harris and C. R. Hauser, *J. Org. Chem.*, **27**, 2967 (1962).

(4) T. M. Harris, S. Boatman, and C. R. Hauser, *J. Am. Chem. Soc.*, **85**, 3273 (1963).

(5) T. M. Harris, S. Boatman, and C. R. Hauser, *ibid.*, **87**, 3186 (1965).

(6) S. Boatman, T. M. Harris, and C. R. Hauser, *ibid.*, **87**, 82 (1965).

TABLE I

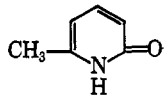
N.M.R. DATA FOR 6- AND 4-ALKYL-3-CYANO-2(1)-PYRIDONES

Compd.	Type of hydrogen	Peak character[a]	Peak center or over-all range, p.p.m.	No. of hydrogens (relative peak intensity)	Theoretical relative peak intensity
1	Methyl	Singlet	2.63	3 (1.0)	1.0
	4 and 5H of pyridone	Pair of doublets	6.72, 6.85 8.07, 8.20	2 (0.63)	0.67
3b	Methylene	Single peak (sharp)	3.07	4 (0.79)	0.80
	4 and 5H of pyridone	Pair of doublets	6.57, 6.70 8.03, 8.16	2 (0.39)	0.40
	Phenyl	Sharp peak with shoulders	7.23	5 (1)	1.0
8	Methyl	Singlet	2.48	3 (0.57)	0.60
	4H of pyridone	Singlet	8.06	1 (0.19)	0.20
	Phenyl	Complex group	7.14–7.61	5 (1.0)	1.0
10	Methylene	Collapsed A_2B_2 (like a triplet)	2.96	4 (0.38)	0.40
	4H of pyridone	Singlet	8.00	1 (0.10)	0.10
	Phenyl	Two complex groups	6.70–7.66	10 (1.0)	1.0
14	Methyl	Singlet	2.28	3 (0.60)	0.60
	5H of pyridone	Singlet	6.64	1 (0.20)	0.20
	Phenyl	Sharp peak with shoulders	7.17	5 (1)	1.0
16	Methylene	Collapsed A_2B_2 (like a triplet)	3.12	4 (0.80)	0.80
	5H of pyridone	Singlet	6.69	1 (0.20)	0.20
	Ring phenyl	One peak	7.12	5 (1)	1.0
	Side-chain phenyl	One peak	7.48	5 (1)	1.0
23	Methyl	Two singlets	2.59, 2.64	6 (1)	1.0
	5H of pyridone	Singlet	6.78	1 (0.17)	0.17
24 or 25	Methyl	Singlet	2.49	3 (0.60)	0.60
	Methylene	Collapsed A_2B_2 (like a triplet)	3.12	4 (0.80)	0.80
	5H of pyridone	Singlet	6.53	1 (0.20)	0.20
	Phenyl	Sharp peak with shoulders	7.23	5 (1)	1.0
27	Methylene	Sharp peak with shoulders	2.99	8 (0.82)	0.80
	5H of pyridone	Singlet	6.36	1 (0.10)	0.10
	Phenyl	Sharp peak with shoulders	7.23	10 (1)	1.0

[a] Generally, spectra were obtained with a sweep width of 500 c.p.s. A spectrum with a sweep width of 250 c.p.s. showed no fine structure for the single peak representing the methylene hydrogens of **3b**; the peak remained sharp. However, spectra of **10** and **16** at a sweep width of 250 c.p.s. showed slight splitting of each peak of the multiplets representing the methylene hydrogens. This was more pronounced for **10**.

suitable. This method has generally afforded better over-all yields than the previous method which involves alkylations of dicarbanions of β-ketoaldehydes or β-diketones such as **4**, **17**, **18**, and **28** followed by cyclizations with cyanoacetamide (see eq. 1). Moreover, certain of the cyclizations by the previous method have afforded mixtures of products, although this has been avoided in one case by use of the imine of the dicarbonyl compound.[7]

Although 2-picoline is readily converted to its anion by amide ion in liquid ammonia, the monoanion of 6-methyl-2(1)-pyridone was insufficiently activated for methyl ionization to be effected by potassium amide. Thus, treatment of **19** with 2 equiv. of the reagent followed by benzyl chloride afforded stilbene, which arose through self-condensation of the halide.[8] This condensation was presumably effected by amide ion with which benzyl chloride is known to react readily.[8] The dianion of **19** would have been expected to undergo alkylation with the halide-like dianion **2**. Apparently conversion of the monoanion of **19** to the dianion was far from complete, and the halide reacted preferentially with amide ion present in equilibrium.



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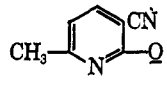

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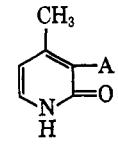
In cyanopridone monoanion **1′**, the cyano group located *para* to the methyl group provided sufficient additional activation[9] so that secondary ionization of the methyl group was essentially complete. Alternative nucleophilic attack of amide ion on the cyano group or on the ring was not observed.

The present method involving dianion intermediates might be applicable to various compounds of types **20** and **21** and to the corresponding 5-substituted 6- and 4-alkyl-2(1)-pyridones, in which A is not only CN but also carbonyl substituents such as COC_6H_5, COOR, $CONR_2$, etc.[10]



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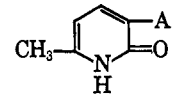

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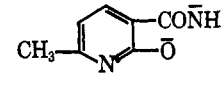

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However, an attempt to extend the method to pyridone **21** (A = $CONH_2$), in which a trianion would pre-

(7) U. Basu, *J. Indian Chem. Soc.*, **12**, 299 (1935).

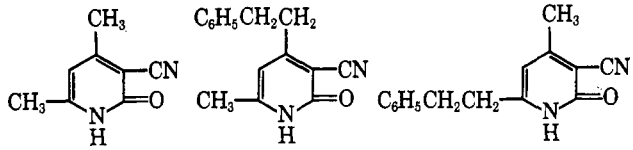
(8) See D. R. Bryant, S. D. Work, and C. R. Hauser, *J. Org. Chem.*, **29**, 235 (1964).

(9) We have observed the activating influence of a *p*-cyano group in a homoaromatic system. *p*-Tolunitrile was found to be attacked by amide ion mainly at the methyl group in preference to the nitrile group; this result will be published later.

(10) Although amide ion might attack the carbonyl group of certain of these compounds, this could presumably be minimized by use of a sterically hindered carbonyl substituent, such as *t*-butyl or higher tertiary alkyl ester.

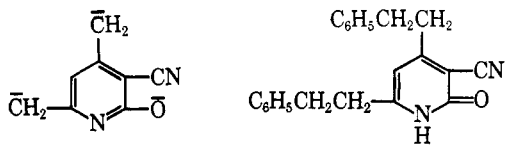
sumably be required for alkylation at the 6-methyl group, was unsuccessful. Thus, treatment of the compound with 3 molecular equiv. of potassium amide in liquid ammonia followed by benzyl chloride afforded stilbene. This is not surprising, as the activating effect of the carbonyl group of substituent A was diminished considerably in the intermediate dianion **22**, which was not alkylated under the conditions employed. Apparently a dianion with negative charge on the methyl group was not formed to any large extent, since such a dianion would be expected to undergo alkylation at the methyl position.

Finally, a study was made of pyridone **23**, with which alkylation might occur at either the 4- or 6-methyl group. Treatment of **23** with 2 equiv. of potassium amide apparently afforded a single dianion, as subsequent addition of benzyl chloride seemed to produce a single product, either **24** or **25** (see Experimental Section). However, its structure has not been established.

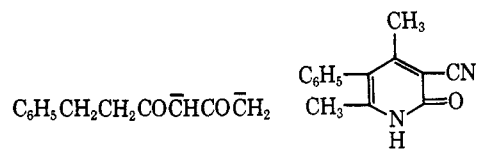


23 **24** **25**

Treatment of pyridone **23** with 3 equiv. of amide ion evidently formed some of trianion **26** (and the dianion), as subsequent addition of excess benzyl chloride produced dibenzyl derivative **27** and monobenzyl derivative **24** (or **25**) each in 35% yield; however, considerable amide ion was apparently in equilibrium, because much (30%) stilbene also was obtained (see Experimental Section). Structure **27** was supported by the n.m.r. spectrum, which showed no methyl hydrogens (see Table I), and was established by independent synthesis from dicarbanion **28**, benzyl chloride, and cyanoacetamide (see eq. 1).



26 **27**



28 **29**

Similarly, treatment of pyridone **29** with 3 equiv. of the reagent followed by benzyl chloride apparently afforded a mixture of the mono- and dibenzyl derivatives (corresponding to **24** or **25** and **27**) and stilbene (40%) (see Experimental Section). Incidentally, pyridone **29**, which melted unusually high (about 350°), was surprisingly difficult to liberate from its alkali metal salt. For this reason **29** was prepared more satisfactorily from the imine of 3-phenyl-2,4-pentanedione and cyanoacetamide in the absence of a base than from the monoalkali salt of the β-diketone and cyanoacetamide by the usual procedure.

Experimental Section[11]

Starting Alkyl-3-cyanopyridones.—Pyridone **1** was obtained by cyclization of sodioformylacetone with cyanoacetamide by the method of Mariella[12] and pyridone **3b** by benzylation of the dianion of **1** (see below).

Pyridone 8 was prepared by refluxing a mixture of 16.2 g. (0.1 mole) of 2-phenyl-1,3-butanedione,[13] 11 g. of sodium carbonate, and 9.0 g. of cyanoacetamide in 100 ml. of water. After 4 hr., the mixture was cooled and acidified with acetic acid. The resulting oily precipitate (obtained after cooling in an ice bath) was collected on a funnel and washed with water and ether. The solid was recrystallized from ethanol to give 15.9 g. (75%) of 6-methyl-5-phenyl-3-cyano-2(1)-pyridone, m.p. 296–297°. The infrared spectrum showed strong absorption characteristic of pyridones at 6.18 and 6.38 μ and a peak for the CN group at 4.51 μ. The ultraviolet spectrum exhibited maxima at 346 and 247 mμ.

Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.80; N, 13.33. Found: C, 74.17; H, 4.82; N, 13.26.

Pyridone 11 was prepared in 50% yield from sodioformylcyclohexanone and cyanoacetamide as described for **1**[12]; after recrystallization from glacial acetic acid it melted at 251–252°, lit.[14] m.p. 248–249°. Because of our slightly higher melting point, the compound was analyzed for nitrogen.

Anal. Calcd. for $C_{10}H_{10}N_2O$: N, 16.08. Found: N, 15.98.

Pyridone 13 was prepared in 70% yield by heating an equimolar mixture of the ketoimine[15] of benzoylacetone and cyanoacetamide at 150° for 30 min. The resulting solid was recrystallized from glacial acetic acid to give **13**, m.p. 310–311°, lit.[7] m.p. 310°.

N.m.r. Results.—N.m.r. spectra are summarized in Table I for certain of the starting cyanopyridones and products. The spectra were consistent with the structural assignments. They were obtained on a Varian A-60 spectrometer using trifluoroacetic acid as solvent and tetramethylsilane as an external reference.

Conversion of 6- and 4-Alkyl-3-cyanopyridones to Dianions.—To a stirred solution of 0.108 mole of potassium amide in 700 ml. of commercial, anhydrous, liquid ammonia[16] was added 0.05 mole of the appropriate pyridone. After stirring for 1 hr., the reaction mixture was assumed to contain 0.05 mole of the corresponding pyridone dianion, which was employed in the alkylations described below.

Alkylations of Dianions.—To a stirred suspension of 0.05 mole of the dianion was added a solution of 0.06 mole of the appropriate alkyl halide[17] in 25 ml. of anhydrous ether. After 1–3 hr., the reaction mixture was worked up as described below.

In the preparation of alkyl derivatives **3a** and **b**, excess ammonium chloride was added to the reaction mixture, and the ammonia was then evaporated. The residue was stirred with water and the mixture was filtered. The filter cake was washed with ether, ethanol, and water and then recrystallized from ethanol.

In the preparation of alkyl derivatives **5**, **7**, **10**, **13**, and **16** the ammonia was evaporated from the reaction mixtures, and ice, water, and ether were then cautiously added. After stirring to dissolve the salt, the layers were separated. The aqueous layer was acidified with 6 *M* hydrochloric acid and cooled. The solid was collected, washed with water, and recrystallized from ethanol or glacial acetic acid.

Yields, spectral data, and analyses are summarized in Table II. Alkylation products **3a**,[4] **3b**,[4] **10**[5], and **13**[6] were independently synthesized by a previous method. In each case the product was shown to be the same as the compound obtained by alkylation

(11) Melting points (taken on a Mel-Temp capillary melting point apparatus) are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 137 or 237 Infracord with potassium bromide pellets. Ultraviolet spectra were obtained with a Cary 14 recording spectrophotometer, using approximately 10^{-4} *M* solutions in 95% ethanol. When nonaqueous solvent layers were dried, the drying agent was anhydrous magnesium sulfate. Elemental analyses were by Galbraith Laboratories, Knoxville, Tenn., and by Janssen Pharmaceutica, Beerse, Belgium.

(12) R. P. Mariella, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p. 365.

(13) L. M. Roch, *Ann. chim.* (Paris), **6**, 105 (1961).

(14) A. Dornov and E. Neuse, *Arch. Pharm.*, **288**, 174 (1955).

(15) E. Knoevenagel, *Ber.*, **36**, 2188 (1903).

(16) See C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958).

(17) In the case of **5**, 0.025 mole of 1,3-dibromopropane was added.

TABLE II

ALKYLATIONS OF 6- AND 4-ALKYL-3-CYANO-2(1)-PYRIDONES THROUGH THEIR DIANIONS

Starting cyanopyridone	Alkyl halide	Alkylation product	Yield,[a] %	M.p.,[b] °C.	Ultraviolet λ_{max}, mμ	Ultraviolet Log ε
1	CH_3I	6-Ethyl-3-cyano-2(1)-pyridone (**3a**)[c]	91	246–248	...	...
1	$C_6H_5CH_2Cl$	6-(β-Phenylethyl)-3-cyano-2(1)-pyridone (**3b**)	86	204–205[d]	337, 237	4.12, 3.89
1	$Br(CH_2)_3Br$	Pentamethylenedi-6-(3-cyano-2(1)-pyridone) (**5**)[e]	74	269–270	338, 237	4.03, 3.83
3b	n-C_4H_9Br	6-(1-Phenyl-2-hexyl)-3-cyano-2(1)-pyridone (**7**)[f]	64	127–128	339, 238	4.10, 3.82
8	$C_6H_5CH_2Cl$	5-Phenyl-6-(β-phenylethyl)-3-cyano-2(1)-pyridone (**10**)	74	284–286[g]	349, 246	4.10, 4.23
11	$C_6H_5CH_2Cl$	1,2;5,6,7,8-Hexahydro-3-cyano-8-benzyl-2-quinolone (**13**)	75	292–294[h]	348, 238	4.12, 3.97
14	$C_6H_5CH_2Cl$	4-(β-Phenylethyl)-6-phenyl-3-cyano-2(1)-pyridone (**16**)[i]	90	241–242	354, 253	4.22, 4.07

[a] Yields were based on product of slightly lower melting point than recorded. [b] All compounds but **11** were recrystallized from ethanol; **11** was recrystallized from glacial acetic acid. [c] *Anal.* Calcd. for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 65.01; H, 5.38; N, 19.03. [d] S. N. Joshi, R. Kaushal, and S. S. Deshapande [*J. Indian Chem. Soc.*, **18**, 479 (1941)] reported m.p. 198°. [e] *Anal.* Calcd. for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.04; H, 5.28; N, 17.95. Infrared absorption at 6.00, 6.22, 6.42 μ for pyridone, 4.50 μ for CN. [f] *Anal.* Calcd. for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.20; H, 7.27; N, 10.20. Infrared absorption at 6.08, 6.27, 6.39 μ for pyridone, 4.53 μ for CN. [g] Lit.[5] m.p. 285–286°. [h] Lit.[6] m.p. 293–294°. [i] *Anal.* Calcd. for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33. Found: C, 79.95; H, 5.34; N, 9.34. Infrared absorption at 6.07, 6.23, 6.35 μ for pyridone, 4.53 μ for CN.

of a cyanopyridone by undepressed mixture melting point and identical infrared spectra.

Attempt to Alkylate 6-Methyl-2(1)-pyridone (19).—To 0.054 mole of potassium amide in liquid ammonia was added 2.7 g. (0.025 mole) of 6-methyl-2(1)-pyridone (**19**).[18] After 1 hr., 3.3 g. (0.026 mole) of benzyl chloride in 10 ml. of ether was added. The reaction mixture became violet and remained so throughout the addition, indicating the formation of stilbene. After 3 hr. the ammonia was evaporated, and ether, ice, and water were added. The ether layer, dried and evaporated, afforded 2.1 g. (91%) of stilbene, m.p. 119–123°, which was identified by a mixture melting point with an authentic sample. The aqueous layer was acidified with 6 *M* hydrochloric acid, cooled, and extracted with methylene chloride. The extract was dried and evaporated, affording 2.6 g. (96%) of the starting material (identified by a mixture melting point with an authentic sample), m.p. 159–163°.

6-Methyl-2(1)-pyridone-3-carboxamide (21, A = $CONH_2$).—To 65 g. of polyphosphoric acid (PPA), heated at 115°, was added 7.0 g. (0.052 mole) of 6-methyl-3-cyano-2(1)-pyridone (**1**), with manual stirring.[19] The mixture was heated for 1.5 hr. Water and ice were added to dilute the PPA, and the yellow solid was collected and washed with water, saturated sodium bicarbonate solution, and water to afford 5 g. (60%) of **21** (A = $CONH_2$), m.p. 300–305°. Recrystallization from ethanol raised the melting point to 305–306°. The infrared spectrum showed strong absorption at 5.98, 6.13, and 6.39 and at 2.90 and 3.08 μ, characteristic of a primary amide. The ultraviolet spectrum exhibited maxima at 329 (log ε 4.30) and 237 (log ε 4.12) mμ.

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.29; H, 5.24; N, 18.25.

Attempt to Alkylate Pyridone 21 (A = $CONH_2$).—To 0.077 mole of potassium amide in liquid ammonia was added 3.8 g. (0.025 mole) of pyridoneamide **21** (A = $CONH_2$); after 1 hr. 3.4 g. (0.027 mole) of benzyl chloride in 10 ml. of ether was added. The reaction mixture became violet and remained so throughout the addition, indicating the formation of stilbene. After 5 min. an additional 3.2 g. (0.025 mole) of benzyl chloride in 10 ml. of ether was added; after addition of a few drops of the solution, the stilbene color disappeared (indicating presence of dianion **22**). After 3 hr. the ammonia was evaporated, and ether, ice, and water were added. The ethereal layer, dried and evaporated, afforded 5.4 g. of a residue, which was shown by v.p.c. to consist of benzyl chloride and stilbene in the ratio of 2:1. The aqueous layer was acidified with 6 *M* hydrochloric acid. The solid was collected, washed with water, and dried to afford 3.8 g. (100%) of the starting material (identified by mixture melting point), m.p. 302–304°.

Alkylation of 4,6-Dimethyl-3-cyano-2(1)-pyridone (23). A. Using 2 Equiv. of Potassium Amide.—Cyanopyridone **23**[19] (0.05 mole) was converted to its dianion (a green slurry) and alkylated with benzyl chloride according to the general method described above. Examination of the crude product by thin layer chromatography indicated that it was a single compound, either **24** or **25**.[20] The product, m.p. 220–225°, weighed 10.2 g. (87%) after one recrystallization from ethanol. Another recrystallization gave 9.5 g. (81%), m.p. 227–229°. A further recrystallization from ethanol raised the melting point to 232–233°. The infrared spectrum showed strong absorption at 6.06 and 6.13 μ characteristic of a pyridone and absorption at 4.51 μ for CN. The ultraviolet spectrum exhibited maxima at 332 (log ε 3.97) and 233 (log ε 3.91) mμ.

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.62; H, 5.88; N, 11.76. Found: C, 75.66; H, 5.88; N, 12.03.

B. Using 3 Equiv. of Amide Ion.—To 0.18 mole of potassium amide in liquid ammonia was added 7.4 g. (0.05 mole) of cyanopyridone **23** to form a reddish brown solution. After 1 hr., 25 g. (0.2 mole) of benzyl chloride in 25 ml. of ether was added and the reaction mixture was stirred for 3 hr. The ammonia was evaporated; ether, ice, and water were added, and, when the salts had dissolved, the layers were separated. The ethereal layer, dried and evaporated, afforded 5.4 g. (30%) of stilbene (identified by mixture melting point with an authentic sample). The aqueous layer was acidified with 6 *M* hydrochloric acid, and the oily precipitate, which hardened on standing, was collected[21] and recrystallized from ethanol to afford 4.0 g. (35%) of monobenzyl derivative **24** (or **25**), m.p. 225–230°, and, after recrystallization from ethanol, m.p. 231–233°. A mixture melting point with the product from the preceding reaction was undepressed. Concentration and chilling of the initial crystallization solvent afforded 6.0 g. (35%) of dibenzyl derivative **27**, m.p. 160–175°, and m.p. 178–179° after two recrystallizations from ethanol. The infrared spectrum of **27** showed strong absorption at 6.03, 6.16, and 6.22 μ characteristic of a pyridone and absorption at 4.51 μ for CN. The ultraviolet spectrum exhibited maxima at 334 (log ε 4.30) and 236 (log ε 3.98) mμ.

Anal. Calcd. for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53. Found: C, 80.46; H, 6.30; N, 8.63.

Independent synthesis of dibenzylated pyridone **27** was accomplished by treating 1,7-diphenyl-3,5-heptanedione[22] with cyanoacetamide in water adjusted to pH 8 with piperidine and acetic acid. The mixture was heated on a steam bath for 2 hr., acidified with acetic acid, and cooled. The crystals were collected, washed with water, and recrystallized from ethanol to give **27**, m.p. 179–180°. The melting point was undepressed on admixture with **27** from above.

(18) R. Adams and A. W. Schrecker, *J. Am. Chem. Soc.*, **71**, 1186 (1949).

(19) J. P. Wibaut, J. H. Uhlenbroek, E. C. Kooyman, and D. K. Kettenes, *Rec. trav. chim.*, **79**, 481 (1960).

(20) A spot of the crude product dissolved in dimethyl sulfoxide (DMSO) was applied to a film of silica gel G according to Stahl (from Merckag, Darmstadt, Germany) and developed with acetone or absolute ethanol. Exposure of the dry film to iodine vapor showed two spots, one of which was combined starting material (**23**) and DMSO (determined from a known sample). The other spot was found to be the same obtained from purified **24** or **25**.

(21) A sample of the crude product was examined by thin layer chromatography as described above.[20] Three spots were observed: the first was combined starting material and DMSO; the second was dibenzylation product **27**; and the third was monobenzylation product **24** or **25** (determined from known samples).

(22) T. M. Harris and C. R. Hauser, *J. Am. Chem. Soc.*, **81**, 1160 (1959).

4,6-Dimethyl-5-phenyl-3-cyano-2(1)-pyridone (29).—To a solution of 3-phenyl-2,4-pentanedione[23] in anhydrous ethanol was added anhydrous liquid ammonia until the flask remained cold. The resulting slurry was concentrated, cooled, and filtered, affording 70% of the imine.[24]

An equimolar mixture of this imine and cyanoacetamide was heated at 150° for 2 hr. The resulting solid was cooled and recrystallized from glacial acetic acid to afford, after washing with ether, 50% of 4,6-dimethyl-4-phenyl-3-cyano-2(1)-pyridone (29), m.p. 354–356°.[25] The infrared spectrum showed strong absorption at 6.01, 6.21, and 6.50 μ characteristic of a pyridone and absorption at 4.50 μ for CN. The ultraviolet spectrum exhibited maxima at 337 (log ε 4.01) and 242 (log ε 4.01) mμ.

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.88; H, 5.45; N, 12.50.

In an earlier attempt to prepare 29, 3-phenyl-2,4-pentanedione was converted to its salt by aqueous sodium hydroxide, treated with cyanoacetamide, and heated on a steam bath for 2 hr. The resulting slurry was cooled, acidified with acetic acid, and filtered, and the solid was washed thoroughly with water. When a sample of the solid was ignited, a basic residue was left, and an infrared spectrum indicated that the salt of pyridone 29 was present. A residue was no longer obtained on ignition only after several recrystallizations of the solid from acetic acid. Attempts to liberate neutral pyridone 29 by single treatments of the salt with hot, aqueous mineral acids, with hot, concentrated sulfuric acid, and with ammonium chloride in liquid ammonia failed.

Alkylation of Pyridone 29.—To a solution of 0.025 mole of potassium amide in liquid ammonia was added 2.0 g. (0.008 mole) of 29. After 1 hr. 2.7 g. (0.017 mole) of benzyl chloride in 20 ml. of ether was added. When the ammonia had evaporated, ether and cold water were added. The ether layer was dried and evaporated, a residue of 0.65 g. (40%) of stilbene was recovered (identified by mixture melting point with an authentic sample). The aqueous layer (actually a slurry of solid and liquid) was cooled, acidified with 6 *M* hydrochloric acid, and filtered; the product, washed with water and dried, weighed 2.1 g. and left a residue on ignition. An n.m.r. spectrum of this solid indicated that it contained mono- and dibenzylation product in approximately 3:1 ratio (also a very small amount of starting material).

(23) C. R. Hauser and R. M. Manyik, *J. Org. Chem.*, **18**, 588 (1953).
(24) See ref. 15.
(25) This compound was quite insoluble in ethanol, acetone, and water.

Site of Alkylation of N^6,N^6-Dialkyl-9-Substituted Adenines. Synthesis and Alkaline Degradation of 6-Diethylamino-3,9-dimethylpurinium Iodide

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Received May 5, 1965

N^6,N^6-Diethyl-9-methyladenine (1) was methylated with methyl iodide in ethanol to give 6-diethylamino-3,9-dimethylpurinium iodide (2). Alkaline degradation of 2 at room temperature afforded 1-methyl-5-methylamino-4-(N,N-diethyl)imidazolecarboxamidine hydriodide (6), whereas, at 100°, the degradation proceeded further to produce 1-methyl-5-methylamino-4-imidazolecarbonitrile (5) and then 1-methyl-5-methylamino-4-imidazolecarboxamide (4). The degradation product 4 was synthesized by formylation of 5-amino-1-methyl-4-imidazolecarboxamide (7) and subsequent selective reduction of the formamido group of 8 with lithium aluminum hydride.

Alkylation of purine bases of nucleic acid and their nucleosides has been studied extensively in recent years, both because of intrinsic chemical interest, and to provide information relative to certain biochemical problems.[1,2] Since N^6,N^6-dimethyladenosine has been found to be a minor base occurring in the RNA of several bacteria,[3] it was of interest to determine the position of alkylation. Such evidence would be useful in the identification of fragments derivable from alkylated RNA which contains N^6,N^6-dimethyladenine as one of its constituent bases.

Methylation of N^6,N^6-dimethyladenine with dimethyl sulfate produced the 1-, 3-, and 9-methyl derivatives[4,5]; no studies have been described of alkylation of N^6,N^6-dialkyl-3-, -7-, or -9-substituted adenines. We chose N^6,N^6-diethyl-9-methyladenine (1), available from another investigation, for methylation study.

N^6,N^6-Diethyl-9-methyladenine (1)[6] was synthesized in the classical manner from 4,6-dichloro-5-nitropyrimidine.[7] Monosubstitution was readily accomplished by reaction with 2 equiv. of diethylamine in ether at −40° to give 4-chloro-6-diethylamino-5-nitropyrimidine. Reaction of the latter with aqueous methylamine at room temperature for 2 hr. gave 73% (from dichloronitropyrimidine) of pure 6-diethylamino-4-methylamino-5-nitropyrimidine as a viscous oil, which was further characterized as its crystalline picrate. Reduction of the diaminonitropyrimidine with hydrogen and Raney nickel gave 79% of 5-amino-4-diethylamino-6-methylaminopyrimidine. Cyclization in refluxing ethyl orthoformate–acetic anhydride[8,9] afforded the hydrochloride **1a** of the desired purine in 69% yield.

Reaction of N^6,N^6-diethyl-9-methyladenine (1) with methyl iodide in boiling ethanol for 24 hr. gave, in addition to 17% of recovered 1, 41% of a crystalline water-soluble methiodide. Based on ultraviolet spectral properties (see Experimental Section) and alkaline degradation, the structure of this quaternary iodide was unequivocally shown to be 6-diethylamino-3,9-dimethylpurinium iodide (2). Thus the site of alkylation of 1 is N-3 and this same alkylation site is expected with N^6,N^6-dimethyladenosine and 2′-deoxy-N^6,N^6-dimethyladenosine. This is in contradistinction to

(1) *Cf.* G. Schmidt, *Ann. Rev. Biochem.*, **33**, 674 (1964).
(2) J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.*, **85**, 193 (1963).
(3) J. W. Littlefield and D. B. Dunn, *Biochem. J.*, **70**, 642 (1958).
(4) L. B. Townsend, R. K. Robins, R. N. Loeppky, and N. J. Leonard [*J. Am. Chem. Soc.*, **86**, 5320 (1964)] have shown that the 6-dimethylamino-"7"-substituted purines of B. R. Baker, R. E. Schaub, and J. P. Joseph [*J. Org. Chem.*, **19**, 638 (1954)] are, in reality, 6-dimethylamino-3-substituted purines.
(5) B. C. Pal and C. A. Horton, *J. Chem. Soc.*, 400 (1964).
(6) Previously prepared by R. K. Robins and H. H. Lin [*J. Am. Chem. Soc.*, **79**, 490 (1957)] by displacement of chloride from 6-chloro-9-methylpurine with diethylamine.
(7) W. R. Boon, W. G. M. Jones, and G. R. Ramage, *J. Chem. Soc.*, 96 (1951).
(8) L. Goldman, J. W. Marsico, and A. L. Gazzola, *J. Org. Chem.*, **21**, 599 (1956).
(9) J. A. Montgomery, *J. Am. Chem. Soc.*, **78**, 1928 (1956).