***lin*-Benzoguanine (6-Aminoimidazo[4,5-*g*]quinazolin-8-(7*H*)-one, 7).** Similar conditions, but with a twofold excess of cyanamide (1.84 g, 44 mmol) and potassium *tert*-butoxide (4.92 g, 44 mmol) over crude **4a,b** from 5.00 g (21.7 mmol) of **3**, were used to obtain *lin*-benzoguanine (**7**) as a white powder from water: yield 2.62 g (59%); mp >300 °C (lit. mp >300 °C); ^{1}H NMR ($(CD_3)_2SO$) δ 6.46 (s, 2), 7.33 (s, 1), 8.16 (s, 1), 8.34 (s, 1), 11.5–12.5 (br s, 2); mass spectrum (10 eV), *m/e* (relative intensity) 201 (M^+, 100), 184 (11.9); high resolution mass spectrum, *m/z* 201.0651 (calcd for $C_9H_7N_5O$, 201.0652).

***lin*-Benzoadenine (8-Aminoimidazo[4,5-*g*]quinazoline, 8).** The previously described synthesis of *lin*-benzoadenine (**8**) required the conversion of **5** through the corresponding 8-thione.[2] In this sequence, compound **8** was obtained directly from the common precursor **4a,b** for **5**, **6**, and **7**. Anhydrous ammonia was bubbled into a suspension of **4a,b** obtained from 1.15 g (5 mmol) of **3** in 10 mL of anhydrous DMF at 10 °C for 30 min. The clear solution was degassed with dry N_2 to remove ammonia. After dropwise addition of 2 mL of phosphoryl chloride at 5–15 °C during 15 min the mixture was heated at 65–70 °C for 2 h and then cooled to 20 °C. Ice water (5 mL) was added, followed by concentrated NH_4OH to basicity (pH ~10.0). The resulting solution was filtered and then heated at 100 °C for 1 h. The solid that precipitated was collected by filtration and washed with 50 mL of water and then dried at 100 °C and 15 mmHg to afford **8**, as a cream powder: yield 0.52 g (56%); mp >320 °C (lit.[2] mp >320 °C); ^{1}H NMR (CD_3COOD) δ 8.45 (s, 1), 8.77 (s, 1), 8.89 (s, 1), 9.01 (s, 1); high resolution mass spectrum, *m/z* 185.0704 (calcd for $C_9H_7N_5$, 185.0701).

Acknowledgment. The work at the University of Illinois was supported by Research Grant GM 34125 from the National Institutes of Health, U.S. Public Health Service. NMR data were obtained in part with support from the University of Illinois NSF Regional Instrumental Facility, Grant NSF CHE 79-16100. High resolution mass spectra were obtained in the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois, supported in part by grant (GM 27029) from the National Institute of General Medical Sciences, National Institutes of Health.

Regioselective Synthesis of 1-Alkyl-3,6,8-trimethyl-2,7-naphthyridines

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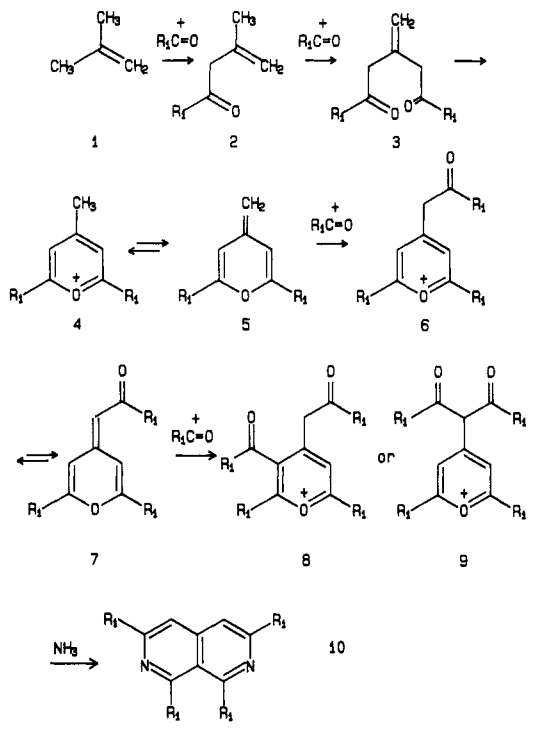
Received December 16, 1986

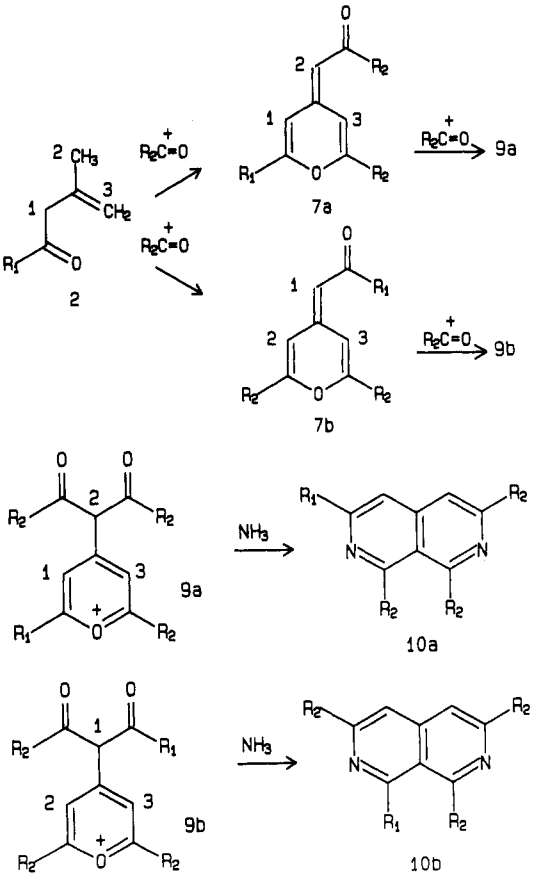
The chemistry of 2,7-naphthyridine derivatives has been little explored, partly due to the difficult and multistep synthesis of these compounds.[1,2] Some of the syntheses reported are not applicable to the preparation of polyalkyl derivatives. We recently reported a short and general synthesis of 1,3,6,8-tetralkyl-2,7-naphthyridines by a one-pot tetraacylation of 2-methyl-1-propene or 2-methyl-1-propene precursors followed by treatment with liquid ammonia (Scheme I).[3,4]

The reaction goes through a monoacylation step, producing the kinetic nonconjugated keto olefin **2**, which is further acylated to give **3**. Ring closure of **3** gives the pyrylium salt **4**. Acylation of **3** followed by ring closure or acylation of **5**, the conjugate base of the pyrylium **4**,

Scheme I



Scheme II



results in the formation of the 4-ketonyl-2,6-dialkylpyrylium salt **6**, which is in equilibrium with its unprotonated form **7**. We have proposed **7** as a possible intermediate for the last acylation, which can occur either in positions 3 or 5 of the methylenepyran framework to give **8** or, preferentially according to calculated electronic charges,[8] on the exocyclic carbon atom leading to **9**. We

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0022-3263/87/1952-2935$01.50/0

believe that acylation stops after that step for steric reasons. **8** or **9**, which are in equilibrium, give, by ring opening and double ring closures, the 2,7-naphthyridine **10** under treatment with liquid ammonia.

It is clear that any of the postulated intermediates on the naphthyridine route can be used as a possible starting material for naphthyridine synthesis. We have already shown that the use of monoacylated olefins **2** as starting material provides a new synthesis of tetraalkyl-2,7-naphthyridines **10**, when the same alkyl group is attached to the acid chloride and **2**.[5] Furthermore, when the acylation is performed with an acid chloride bearing a R_2 alkyl group different from that of **2**, isomeric naphthyridines **10a** and **10b** are obtained, **10a** being in a majority (Scheme II).[5] The occurence of **10a** and **10b** is easily accounted for if one considers the isomeric analogues of **7**, **7a** and **7b**, which are obtained by a double acylation of **2** at carbons 2 and 3 and further ring closure. Acylation of **7a** on carbon 2 gives **9a**, whereas **9b** is obtained by acylation of **7b** on carbon 1. By ring opening and double ring closure under treatment with ammonia, **9a** and **9b** give **10a** and **10b**, respectively. It is worth noting that acylation of **7a** at carbon 3 or acylation of **7b** at carbons 2 or 3 lead to **10a**, whereas acylation of **7a** at carbon 1 lead to **10b** through isomeric analogues of **8**. These routes are not depicted in Scheme II for sake of clarity.

According to this reaction scheme, it is clear that starting from **7** (Scheme I), the same naphthyridine should be obtained whether the site of acylation is at carbon 1, 2 or 3, since isomeric intermediates **15a** and **15b** would give the same naphthyridine by ring opening and double ring closure under treatment with ammonia. Furthermore it can be inferred that the incoming alkyl residue will be regioselectively situated at position 1 of the naphthyridine nucleus (Scheme III).

In order to verify this hypothesis, we began with the 4-ketonylidene-2,6-dialkylpyran **7**, which comes, as depicted in Scheme I, from triacylation of the starting 2-methyl-1-propene and which is one acylation step away from the direct precursors of the naphthyridine nucleus. We have already shown that it is impossible to stop the acylation sequence after the first three acylations and that tetraacylation gives the unavoidable intermediates **8** or **9**.[4,5] However, these compounds are easily deacylated under hydrolysis of the crude reaction mixture with water and then treatment with cold aqueous ammonia to give **7**.[4]

4-Acetonylidene-2,6-dimethyl-4*H*-pyran (**7**, R_1 = Me) has been studied by various authors.[6,7] Recently Balaban et al.[8] calculated by CNDO/2 the electronic charges on carbon atoms in *S*-cis and *S*-trans forms and, as expected, carbons 1, 2, and 3 are negatively charged. The largest negative charge is located on the exocyclic carbon atom.

We treated 4-acetonylidene-2,6-dimethyl-4*H*-pyran (**7**, R_1 = Me) with an excess of R_2COCl (R_2 = Me, Et, Pr, *i*-Pr) in the presence of aluminium chloride at 35 °C for half an hour and poured the crude reaction mixture into liquid ammonia. In all cases, the conversion of the starting material was complete and 1-R_2-3,6,8-trimethylnaphthyridines **11–14** were regioselectively obtained.[9] The identification of these compounds is straightforward by conventional methods, NMR is particularly useful since alkyl substituents in the peri positions are strongly deshielded; the results are given in the Experimental Section.

It follows that the synthetic strategy which involves a tetracylation step of 2-methyl-1-propene (or 2-methyl-1-propene precursors), followed by hydrolysis and then further acylation with a different acyl halide, is a promising one to regioselectively obtain alkylnaphthyridines which were not previously obtainable.

Experimental Section

General Procedures. Aluminium chloride (Fluka Puriss) was used without further purification. Acid chlorides were purified by distillation before use. GLC was performed on a stainless steel column packed with Chromosorb P AW 80/100, 5% KOH, 20% Apiezon L (1.5 m × $^1/_8$ in. i.d.). TLC was performed on Merck Silica 60 F_{204} plates, using a mixture methyl *tert*-butyl ether/heptane (70–30 v/v) as eluent. Flash chromatography was performed on Merck Kieselgel 60 (230–400 mesh) using the same eluent. Mass spectra were obtained on a Ribermag R-10-10, and NMR spectra were obtained on a Brüker AM-200. The homogeneity of the reported compounds was checked by capillary GC, TLC, and microanalysis.

Synthesis Procedure. The preparation and the characteristics of 4-acetonylidene-2,6-dimethyl-4*H*-pyran **7** have already been reported.[4,6-8] In a double-jacketed glass reactor (500 mL) equipped with a bottom outlet valve, a vibromixer, an efficient cooled condenser (−40 °C) connected to an HCl trap and a dropping funnel, 2 equiv (0.2 mol) of $AlCl_3$ was diluted with 16 equiv of R_2COCl (1.6 mol) at 15 °C. After dissolution, solid **7** was added in 1 min, and the reaction mixture was warmed at 35 °C for 30–45 min. The crude reaction mixture was poured into a flask containing liquid ammonia being stirred and cooled with a dry ice–acetone mixture. The reaction is highly exothermic (protective hood). The resulting heterogenous mixture was allowed to stand until all the excess ammonia was evolved by evaporation, further treated with chloroform, and washed with water. Continuous extraction was performed for 12–24 h. Evaporation of the dried organic phase afforded a mixture of amide in excess and naphthyridine which are separated by flash-chromatography. Byproducts from **7** are not extracted during the procedure.

As pointed out before,[3,4] treatment of the crude reaction mixture with other sources of ammonia (e.g., ammonium acetate in methanol) results in complex reaction mixtures. For instance, the mixture resulting from the reaction **7** + *i*-PrCOCl, under treatment with 200 mL of a saturated solution of ammonium acetate in anhydrous methanol, afforded a mixture of 1-(2,6-dimethyl-4-pyridyl)propane-2-one [MS, *m/e* (relative intensity) 163, 121 (100%, $-CH_2CO$)], 1-(2,6-dimethyl-4-pyridyl)-3-methylbutane-2-one [MS, *m/e* (relative intensity) 191, 121, (100%, $-Me_2CCO$)], naphthyridine **14**, and two isomeric compounds that were unprotonated forms of **15a** and **15b** [MS, *m/e* (relative intensity) 234 (11), 219 (5), 192 (7), 191 (58), 149 (14), 43 (100) and 234 (25), 219 (9), 192 (22), 191 (99), 150 (23), 149 (100), 43 (97)]. Since the relative proportions of all these strongly related compounds vary dramatically with the treatment conditions (time, temperature, solvent, source and proportion of ammonia, amount of water, mode of extraction), they were not representative of the initial mixture of acylation, and thus further analyses were not carried out. Direct analysis of the crude reaction medium before any treatment except elimination of the excess of acyl chloride was not a simple task since the compounds were in the form of pyrylium tetrachloroaluminate salts together with tars and the excess of aluminium chloride. The classical way of analysis of pyrylium salts by treatment with water and crystallization was not possible since deacylation occurs very rapidly in these conditions, precluding in our hands direct analysis. An attempt was performed with trifluoromethanesulfonic acid as acylation catalyst to avoid the presence of aluminium chloride; no acylation was observed since the equilibrium **6** ⇄ **7** was completely shifted toward **6**.

Products. 1,3,6,8-Tetramethyl-2,7-naphthyridine[3-5] (**11**): mp 62 °C; yield 49%[9]; R_f 0.15 (diethyl ether/pentane, 1/1); 1H NMR ($CDCl_3$) δ 2.6 (s, 6 H), 3.05 (s, 6 H), 7.1 (s, 2 H). ^{13}C NMR

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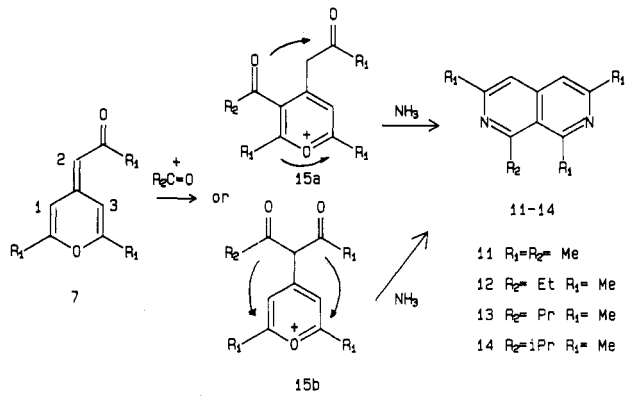
(9) The yields are not optimized, but differences with the tetraacylation route, in which **7** is consumed as soon as it is formed, might account for the lower yields obtained with direct introduction of the preformed **7**.

Scheme III



($CDCl_3$) δ 24.1 (3,6-CH_3), 29.1 (1,8-CH_3), 116.2 (4,5-C), 120.9 (8a-C), 142.5 (4a-C), 153.5 (3,6-C), 159 (1,8-C); MS (70 eV), *m/e* (relative intensity) 187 (16.2), 186 (100), 185 (48), 171 (12), 144 (7), 115 (8), 77 (8), 53 (6), 51 (8), 42 (8), 39 (11).

1-Ethyl-3,6,8-trimethyl-2,7-naphthyridine (12): mp 36–37 °C; yield 39%; R_f 0.47 (diethyl ether). Anal. Calcd for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99. Found: C, 77.92; H, 8.01; N, 13.95. ^1H NMR ($CDCl_3$) δ 1.4 (t, 3 H), 2.6 (s, 6 H), 3.06 (s, 3 H), 3.4 (q, 2 H), 7.14 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.61 (CH_2CH_3), 24.02 (3-CH_3), 24.13 (6-CH_3), 28.56 (8-CH_3); 32.71 (CH_2CH_3); 116.02 (4-C), 116.38 (5-C), 119.5 (8a-C), 142.66 (4a-C), 153.06 (3-C), 153.82 (6-C), 158.25 (8-C), 163.60 (1-C); MS (70 eV), *m/e* (relative intensity) 201 (8), 200 (49), 199 (30), 186 (13), 185 (100), 172 (16).

1-Propyl-3,6,8-trimethyl-2,7-naphthyridine (13): mp 50 °C; molecular distillation, 110 °C (1.5 mbar); yield 23%; R_f 0.65 (diethyl ether). Anal. Calcd for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.51; H, 8.46; N, 13.02. ^1H NMR ($CDCl_3$) δ 1.07 (t, 3 H), 1.81 (m, 2 H), 2.6 (s, 6 H), 3.09 (s, 3 H), 3.35 (m, 2 H), 7.14 (s, 2 H); ^{13}CNMR ($CDCl_3$) δ 14.25 ($CH_2CH_2CH_3$); 24.10 (3-CH_3), 24.23 (6-CH_3), 28.56 (8-CH_3), 24.73 ($CH_2CH_2CH_3$), 41.8 ($CH_2CH_2CH_3$), 116.10 (4-C), 116.40 (5-C), 119.65 (8a-C), 142.77 (4a-C), 153.12 (3-C), 153.82 (6-C), 158.4 (8-C), 162.78 (1-C); MS (70 eV), *m/e* (relative intensity) 214 (5), 200 (14.4), 199 (100), 186 (67), 185 (10).

1-Isopropyl-3,6,8-trimethyl-2,7-naphthyridine (14): colorless oil; molecular distillation 90 °C (1 mbar); yield 27%; R_f 0.90 (diethyl ether). Anal. Calcd for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.36; H, 8.47; N, 13.00. ^1H NMR ($CDCl_3$) δ 1.37 (d, 6 H), 2.58 (s, 3 H), 3.12 (s, 3 H), 4.09 (q, 2 H), 7.05 (s, 1 H), 7.09 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ 23.13 ($CHCH_3$), 24.0 (3-CH_3), 24.25 (6-CH_3), 29.06 (8-CH_3), 33.64 (1-$CHCH_3$), 115.54 (4-C), 116.40 (5-C), 119.14 (8a-C), 142.71 (4a-C), 152.59 (3-C), 153.62 (6-C), 157.81 (8-C), 167.13 (1-C); MS (70 eV), *m/e* (relative intensity) 214 (19), 200 (13.8), 199 (100), 186 (15.3), 183 (9.5), 172 (10.9).

Registry No. 7, 39588-76-6; 11, 88300-52-1; 12, 88300-64-5; 13, 108418-80-0; 14, 98929-07-8; CH_3COCl, 75-36-5; CH_3CH_2COCl, 79-03-8; $CH_3CH_2CH_2COCl$, 141-75-3; $(CH_3)_2CHCOCl$, 79-30-1.

Molecular Mechanics Parameters for Organophosphines

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Received November 25, 1986

The molecular mechanics technique has been successfully applied to model numerous classes of organic compounds.[1] Most common functional groups can currently be handled by the MM2 force field,[2] which has replaced its MM1 predecessor.[3] However, some functional groups that were parameterized for MM1 were not updated and transferred to MM2 until recently. Since the two force fields are substantially different, it is not a very good approximation to use the older MM1 parameters with the MM2 force field. We wish to report here the MM2 parameter set for organophosphines. The latest version of the MM2 program has these values already incorporated.[2] The new parameters, listed in Table I, can be read directly into older program versions. It should be pointed out that using MM1 parameters[4] instead may lead to errors. For example, recent work by Rithner and Bushweller[5] found some significant discrepancies between experimental and calculated energy barriers by using the MM1 values in the MM2 force field.

In general, we have found good agreement between the available experimental data and our calculations. Table II displays the more important compounds which were used to derive our parameters.[6-12] Where experimental

Table I. Parameters

atom type				V1	V2	V3
Torsional						
3	1	1	25	0.000	0.000	0.400
1	25	2	2	0.000	0.000	0.400
1	1	25	2	−0.050	−0.100	0.300
2	25	1	5	0.050	0.000	0.200
1	1	1	25	0.000	0.000	0.400
5	1	1	25	0.000	0.000	0.330
1	1	25	5	−0.530	−0.400	0.600
5	1	25	5	0.000	0.000	0.428
5	1	25	1	0.050	0.000	0.420
2	2	25	2	0.000	0.000	0.330
2	2	2	25	0.000	16.250	0.000
5	2	2	25	0.000	16.250	0.000
1	1	25	1	−0.150	0.000	0.500

Bond Stretching and Dipole Bond Moment

bond type	K_s	l_o	μ
5–25	3.33	1.4370	0.50
1–25	2.91	1.8560	0.83
2–25	2.91	1.8280	1.04

Bending

atom types			K_b	θ_o
	2	25	0.500	
2	25	2	0.480	93.200
1	25	2	0.480	92.500
5	25	5	0.438	93.400
5	1	25	0.360	111.000
1	25	5	0.480	95.000
1	1	25	0.480	111.500
1	25	1	0.576	96.000
2	2	25	0.380	120.000

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