and purged under nitrogen. BF_3·OEt_2 (1 equiv, 1.14 mL, 92 mmol) was added and stirred for 15 min. Previously distilled CH_2N_2 (12.75 equiv, 210 mL each of 0.31 and 0.25 M dried over KOH for 1 h) was added over a 1.5-h period to the reaction mixture. After the addition the reaction was quenched with saturated aqueous $NaHCO_3$ (25 mL), filtered, washed with ether (100 mL), and diluted with H_2O (100 mL). The phases were separated and the aqueous layer extracted with more ether (two 25-mL portions). The combined ether extracts were dried over $MgSO_4$. Filtration followed by rotary evaporation gave an oily product which was chromatographed over silica gel (75 g, 80% CH_2Cl_2–hexane) to yield 0.97 g (50.4%) of V and 0.30 g (16.6%) of recovered IV: NMR V, δ 1.8–2.9 (m, 3 H), 2.36 and 2.44 (s, 3 H), 2.29 (m, 2 H), 3.74 and 4.12 (d, J = 9 Hz, 1 H), 5.77 (m, 1 H), 6.13 (m, 1 H), 6.8–7.3 (m, 3 H).

Methylbenzobullvalone Tosylhydrazone (VI). In a dry 50-mL flask purged with N_2, methylbenzobullvalone (V) (0.80 g, 3.8 mmol) and tosylhydrazine (0.70 g, 3.7 mmol) were stirred in dry ether (25 mL). After 57 h the product was filtered and washed with Et_2O (10 mL) to yield 0.428 g. Additional stirring of the filtrate for 36 h gave 10% more product. The total yield of crude VI was 0.478 g (34%), which was 90% one isomer VIa. The ether filtrates were concentrated on the rotary evaporator to give an additional 0.69 g of a puffy yellow solid. NMR indicated that 75% was probably VI. Estimated yield of VI was roughly 70%: mp, turns brown at 137 °C, 142–144 °C dec.

Methylbenzobullvalene (1, R = Me). Freshly distilled isopropylamine (3 equiv, 0.6 mL, 4.2 mmol) was dissolved in ether (100 mL) in a dry three-neck 300-mL flask equipped with a stirring bar and purged under N_2. After cooling the reaction in a dry ice–2-propanol bath, 3 equiv of n-BuLi (2.4 mL of 2.4 M in hexane) was added, and the mixture was warmed to 0 °C. Upon cooling the reaction flask to −78 °C, solid VI (0.217 g, 1.04 mmol) was added and the reaction was slowly warmed to room temperature. After several hours (3–8 h) the reaction was quenched with cold water (50 mL) and separated. The aqueous phase was extracted with ether (three 15-mL portions). The combined ether extracts were washed with 5% HCl (25 mL), saturated $NaHCO_3$ (25 mL), and saturated NaCl (25 mL), and dried over $MgSO_4$. Filtration followed by rotary evaporation gave a white solid: NMR δ 2.26 (s, 3 H); 2.82 (t, J = 9.5 Hz, 1 H), 2.17 (t, J = 9.5 Hz, 1 H), 3.5–4.6 (v br s, 4 H), 5.78 (complex t, 2 H), 6.75–7.20 (m, 3 H); IR (CCl_4) 685 (w), 700 (w), 730 (s), 750 (br s), 800 (s), 810 (sh), 815 (m), 875 (w), 915 (w), 975 (w), 1035 (w), 1095 (w), 1260 (w), 1375 (m), 1410 (w), 1450 (m), 1570 (s), 1580 (s), 1590 (w), 1650 (m), 2870 (w), 2970 (br m), 3030 (s), 3070 (sh) cm^{-1}; MS 195 (7.1), 194 (43.4), 193 (30.7), 192 (7.1), 191 (7.1), 189 (56.7), 180 (15.6), 179 (100), 178 (67.9), 177 (7.1), 176 (5.2), 166 (3.8), 165 (12.7), 153 (3.8), 152 (10.4), 151 (2.8), 142 (3.3), 141 (3.8), 139 (3.8), 129 (3.3), 128 (13.7), 127 (3.8), 115 (6.1), 96 (3.8), 89 (7.6), 77 (2.8), 76 (3.8), 63 (4.3), 51 (3.8), 39 (4.7).

Anal. Calcd for $C_{15}H_{14}$: C, 92.73; H, 7.26. Found: C, 92.44; H, 7.51.

Variable Temperature Carbon-13 NMR Spectra. Proton square wave decoupled[15] carbon-13 spectra were recorded on a modified Varian XL-100-15 spectrometer operating in the Fourier transform mode. The 25.16-MHz excitation frequency was supplied by a Hewlett-Packard Model 8660A frequency synthesizer. Data were collected and calculated on a Nicolet 1080-20 computer. Field-frequency lock was provided by a sample of acetone-d_6 contained in the annulus of a 12-mm tube. The sample itself was placed in a 10-mm tube inside the 12-mm tube. Data points (8K) were collected with a 5-KHz window resulting in 4K real data points after transformation. The excitation pulse length varied from 70 μs (pulse angle 52°) at low temperature to 30 μs (pulse angle 23°) at high temperature. The pulse repetition rate was 1.1 s, and a receiver recovery delay of 200 μs was employed. A minimum of 8192 scans was accumulated in each case. Chemical shifts were calculated from internal tetramethylsilane using the computer calculated frequency separation between peak maxima.

Temperature control was provided by a flow of precooled nitrogen gas using the Varian V4341 temperature controller. Temperature was measured with a Wilmad 5-mm low temperature thermometer and/or a chromel–alumel thermocouple. The temperature sensors were placed at the level of the observation coil immersed in a 12-mm tube containing $CHCl_2CHCl_2$ filled to the same level as the sample. Calibration studies both inside and outside the spectrometer showed that a substantial stem correction (over 10° at low temperature) was required for the thermometer, which varied with the ambient temperature. The thermocouple was used for all reported temperature measurements. Temperatures were recorded before and after data accumulation and were held constant within ±0.5 °C. The absolute temperature is presumed to be accurate to ±1 °C. The samples were prepared by dissolving 0.35 mg of benzobullvalene (0.121 mg of o-toluobullvalene) in 2.5 mL of $CHCl_2CHCl_2$ together with 2–3 drops of tetramethylsilane. No corrections for the temperature dependence of chemical shifts were applied in the calculations.

Registry No.—Ia, 61990-59-8; Ib, 61990-60-1; II, 61990-61-2; III, 61990-64-5; IVa, 61990-62-3; IVb, 61990-63-4; V, 61990-91-8; VIa, 61990-65-6; VIb, 61990-66-7; VIIa, 61990-67-8; VIIb, 62015-28-5; VIII, 34886-96-9; IX, 61990-68-9; X, 61990-69-0; benzobullvalene, 50653-71-9; methylbenzobullvalene, 61990-70-3; 3-methylanthranilic acid, 4389-45-1; tropone, 539-80-0; bullvalene, 1005-51-2.

Supplementary Material Available. An expanded Experimental Section, Tables III–V (11 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) G. Schröder and J. F. M. Oth, *Angew. Chem., Int. Ed. Engl.*, **6**, 414 (1967); (b) P. Ahlberg, J. B. Grutzner, D. L. Harris, and S. Winstein, *J. Am. Chem. Soc.*, **92**, 3478 (1970); (c) J. C. Barborak, S. Chari, and P. v. R. Schleyer, *ibid.*, **93**, 5275 (1971); (d) R. Hoffmann and W. D. Stohrer, *ibid.*, **93**, 6941 (1971); (e) M. J. S. Dewar and D. H. Lo, *ibid.*, **93**, 7201 (1971); (f) J. F. M. Oth, E. Machens, H. Röttelle, and G. Schröder, *Justus Liebigs Ann. Chem.*, **745**, 112 (1971); (g) L. G. Griefenstein, J. B. Lambert, M. J. Broadhurst, and L. A. Paquette, *J. Org. Chem.*, **38**, 1210 (1973); (h) B. D. Reverend and P. Goudmand, *Bull. Soc. Chim. Fr.*, 389 (1973); (i) A. K. Cheng, F. A. L. Anet, J. Miodyski, and J. Meinwald, *J. Am. Chem. Soc.*, **96**, 2887 (1974); (j) A. G. Invernizzi, R. Gandolfi, and M. Strigazzi, *Tetrahedron*, **30**, 3717 (1974); (k) L. A. Paquette and W. E. Volz, *J. Am. Chem. Soc.*, **98**, 2910 (1976); (l). G. R. Krow, J. Reilly, D. M. Fan, J. Markowski, and K. C. Ramey, *J. Am. Chem. Soc.*, **98**, 3636 1976); (m) C. B. Chapleo and A. S. Dreiding, *Helv. Chim. Acta*, **59**, 765 (1976).

(2) J. F. M. Oth, K. Mullen, J. M. Gilles, and G. Schröder, *Helv. Chim. Acta*, **57**, 1415 (1974).

(3) H. Günther and J. Ulmen, *Tetrahedron*, **30**, 3781 (1974).

(4) W. E. Doering, B. M. Ferrier, E. T. Fossel, J. H. Hartenstein, M. Jones, G. Klumpp, P. M. Rubin, and M. Saunders, *Tetrahedron*, **23**, 3943 (1967).

(5) J. Ciabattoni, J. E. Crowley, and A. S. Kende, *J. Am. Chem. Soc.*, **89**, 2778 (1967).

(6) A. Eisenstadt, *Tetrahedron*, **30**, 2353 (1974).

(7) N. K. Wilson and J. B. Stothers, *Top. Stereochem.*, **8**, 1 (1974).

(8) J. F. M. Oth, H. Kwee, U. Prange, and G. Schröder, *Tetrahedron Lett.*, 1565 (1976).

(9) I. O. Sutherland, *Annu. Rep. NMR Spectrosc.*, **4**, 71 (1971). We thank Dr. J. Lambert of Northwestern University for providing this program.

(10) More complete details may be found in R. O. Carlsen, Ph.D. Thesis, Purdue University, 1976.

(11) (a) P. Radlich, *J. Org. Chem.*, **29**, 960 (1964). (b) An improved procedure is available from Dr. K. Harmon, Oakland University. We thank Dr. Harmon for providing us with details of the preparation prior to publication.

(12) T. Tsuji, H. Ishitobi, and H. Tanida, *Bull. Chem. Soc. Jpn.*, **44**, 2447 (1971).

(13) J. S. Blair, J. Clark, and G. V. Meehan, *Tetrahedron Lett.*, 3097 (1972).

(14) E. Vedejs, M. F. Solomon, and P. H. Weeks, *J. Am. Chem. Soc.*, **95**, 6770 (1973).

(15) J. B. Grutzner and R. E. Santini, *J. Magn. Reson.*, **19**, 173 (1975).

Preparation of Uracil

Ralph J. De Pasquale

PCR, Inc., Gainesville, Florida 32602

Received October 26, 1976

Over the last seven decades, uracil, a molecule of interest to organic and biochemists alike, and its derivatives have been prepared by a variety of reactions. Methods of synthetic utility as well as chemical curiosity include synthesis from 2-thiouracil and chloroacetic acid followed by hydrolysis,[1] malic acid and urea in oleum,[2] maleic or fumaric acid and urea in PPA,[3] cyclization of substituted ureiodopropionic acid to dihydrouracil followed by bromination–dehydrobromination,[4] treatment of β-alkoxy acrylamides with ammonia or amines followed by dilute alkali,[5] and palladium salt catalyzed oxidative cyclization of acryloylurea.[6]

This report describes the preparation of uracil by condensing urea and propiolic acid[7] under acid catalysis in refluxing benzene. Uracil-forming reactions run in acidic solvents present formidable problems on plant scale; in this case, the use of organic solvents provides an acceptable alternate. Compared to commercial uracil processes,[1,2] the reaction is

Table I. Uracil and Derivatives

Urea, mol	Acid,[a] mol	Solvent, mL, temp, h	HMDS (mL), h reflux	Product, % yield[b]
Urea, 0.071	P, 0.071	C_6H_6, 120, reflux, 18	40, 5	III, 45–65
Urea, 0.071	P, 0.071	DMF, 60, 80, 18	40, 5	III, 8
Urea, 0.071	P, 0.071	H_2O, 60, 80, 18		III, trace
Methylurea, 0.071	P, 0.071	C_6H_6, 120, reflux, 18	40, 18	V, 20 VI, 7
Thiourea, 0.071	P, 0.071	C_6H_6, 120, reflux, 48	40, 18	No 2-thiouracil
Urea, 0.061	T, 0.060	C_6H_6, 120, reflux, 96	50, 18	IV, 33

[a] P = propiolic acid, T = tetrolic acid. [b] GLC yields of the trimethylsilyl derivatives III, uracil; IV, 6-methyluracil; V, 3-methyluracil; VI, 1-methyluracil.

simple to perform, potentially inexpensive,[8] and offers minimal chemical disposal problems.

Results

The reactants were stirred in refluxing benzene containing several drops of concentrated sulfuric acid[9] for 18 h. Uracil can be isolated by filtration and repeated recrystallization; however, it was more convenient to convert uracil to its bis(trimethylsilyl) derivative[10] which was isolated by distillation. Yields of uracil as high as 65% (based on propiolic acid) have been detected by GLC, but the range of 45–55% was more common. Propiolic acid was completely consumed after the 18-h reflux period. During silylation unreacted urea was quantitatively converted to its easily isolable bis(trimethylsilyl) derivative.[11] Thus, interrupting the reaction by silylation after 3, 7, and 18 h showed 30, 52, and 79% consumption of urea, respectively. At these intervals the product ratio essentially was unchanged; attempts at intermediate isolation or detection of intermediate buildup were unsuccessful.

The reaction was extended to the synthesis of uracil derivatives by appropriate substitution of reactants (see Table I). Reaction between thiourea and propiolic acid afforded no 2-thiouracil probably owing to ynylation at sulfur.[12] Compounds prepared were characterized by comparison of their physical and spectral properties with those of authentic samples.

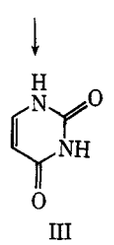
Discussion

In this uracil-forming reaction, the failure to detect or isolate intermediates is consistent with a two-step reaction where the second step is considerably faster than the first. A reasonable sequence follows.

$H_2NCONH_2 + HC{\equiv}CCO_2H$

$\longrightarrow$ [$H_2NCONHCH{=}CHCO_2H$ or $HC{\equiv}CCONHCONH_2$]

I II



III

Based on literature references[5,13,14] on related reactions the intervention of I[15] is preferred over II.

In an attempt to qualitatively determine which functional group (triple bond or acid) is the first to react, model reactions were investigated. Reaction between urea and model acids (e.g., p-$NO_2C_6H_4CO_2H$) or acetylenes (e.g., $C_8F_{17}C{\equiv}CH$) under simulated uracil reaction conditions gave >95% recovery of starting materials. In retrospect, this is reconcilable; reactions involving urea performed in nonpolar aprotic solvents are rare[16] presumably owing to the heterogeneity of the system. The success of the uracil forming reaction then suggests an intimacy between the reacting partners. Thus, admixing urea and propiolic acid in warm benzene followed by cooling quantitatively deposits an isolable 1:1 crystalline adduct. In the uracil forming reaction, benzene probably serves not as a solvent but rather as a medium for water removal and heat transfer.

Experimental Section

Materials. Urea (USP crystals) was supplied by Mallinckrodt; propiolic acid and substituted ureas were purchased from Aldrich. Commercial grade hexamethyldisilazane (HMDS), PCR, Inc., was used throughout. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrometer while a Hewlett-Packard 5712 instrument using a 6 ft × 0.125 in. 10% UCL-45:8% OV-7 (50:50 mix) on Gas Chrom 2 (80–100 mesh) column at 170 °C was used to obtain GLC data.

Uracil from Urea and Propiolic Acid. Urea (4.3 g, 0.071 mol) and anhydrous benzene (120 mL) were stirred together at 25 °C when propiolic acid (5.0 g, 0.071 mol) was introduced rapidly. Solids underwent a change in crystal size shortly after the acid was added. Three drops of concentrated sulfuric acid were added and the solution was heated to reflux. After ca. 6 h, water began to separate (Dean-Stark trap) and was removed as formed. After 18 h of reflux, the reaction mixture was allowed to cool to 25 °C. At this time ca. 0.6–0.8 mL of water had been removed; the solid product (ca. 8–9 g) was insoluble in C_6H_6. TLC of the solids (dissolved in water, eluted with a 70:40:10 by volume mixture of ethyl acetate–acetone–water and visualized by UV) showed uracil as the major component accompanied by two slower and one faster moving minor components. The benzene was decanted and 40 mL of HMDS added. The resulting mixture was refluxed for 5 h (ammonia evolved), cooled, and pressure filtered (coarse frit) with care taken to avoid atmospheric moisture. The crystalline solid was washed with HMDS (10 mL) and dried under vacuum affording 3.4 g of bis(trimethylsilyl)urea (79% consumption of urea), mp 218–220 °C (lit.[11] 222–224 °C). At this point the filtrate containing bis(trimethylsilyl)uracil could either be mixed with a known quantity of n-amylbenzene (internal standard) and analyzed by GLC (for yields, see Table I) or distilled. On distillation the fraction of bp 76–81 °C (2 mm) [lit.[10] bp 123 °C (18 mm)] was >97% bis(trimethylsilyl)uracil. TLC of the silylated uracil derivative was identical with that of uracil; evidently, hydrolysis occurs during analysis. This silyl derivative was easily converted to uracil in quantitative yield by treatment with aqueous acetone at 25 °C.

The same procedure was used to prepare the substituted uracil derivatives; for details see Table I.

Complex Isolation. Urea (2.6 g, 0.043 mol) and propiolic acid (3.0 g, 0.043 mol) were placed in a flask with benzene (16 mL). The mixture was heated with stirring to 64 °C over a 25-min period, then cooled to 40 °C and pressure filtered. The resulting white solid was dried at 1 mm for 3 h and weighed 5.35 g, mp 60–63 °C. Infrared (KBr) showed bands at 2.95, 4.72, 6, 6.2, 6.95, 7.35, 7.85, 11.1, 11.6, 12.9, 13.2, and 14.25 μ.

Anal. Calcd for $C_4H_6N_2O_3$: C, 36.9; H, 4.6; N, 21.5. Found: C, 36.7; H, 4.7; N, 21.7.

Acknowledgment. The author gratefully acknowledges Mr. W. A. Martin for his capable technical assistance and Dr. P. D. Schuman for his interest in this work.

Registry No.—I, 62076-97-5; III, 66-22-8; IV, 626-48-2; V, 608-34,4; VI, 615-77-0; urea, 57-13-6; methylurea, 598-50-5; thiourea, 62-56-6; propiolic acid, 471-25-0; tetrolic acid, 590-93-2.

References and Notes

(1) H. L. Wheeler and L. M. Liddle, *Am. Chem. J.*, **40**, 547 (1908).
(2) D. Davidson and O. Baudisch, *J. Am. Chem. Soc.*, **48**, 2379 (1926).
(3) K. Takemoto and Y. Yanamoto, *Synthesis*, **3**, 143 (1971).
(4) N. W. Gabel and S. B. Binkley, *J. Org. Chem.*, **23**, 643 (1958).
(5) M. R. Atkinson, M. H. Maguire, R. K. Ralph, G. Shaw, and R. N. Warrener, *J. Chem. Soc.*, 2363 (1957).
(6) A. Kasahara and N. Fukuda, *Chem. Ind. (London)*, 485 (1976).
(7) After our experimental work had been completed, a communication described the preparation of uracil and 1,3-dimethyluracil from the corresponding urea and propiolic acid in H_2SO_4 or PPA. See K. Harada and S. Suzuki, *Tetrahedron Lett.*, 2321 (1976).
(8) Propiolic acid has been prepared in high yields from acetylene, carbon dioxide, sodium, and ferrous salts in liquid ammonia: I. J. Pachter, U.S. Patent 2 799 793; *Chem. Abstr.*, **52**, 1206*a* (1958).
(9) Without the addition of sulfuric acid the reaction proceeds at a much reduced rate.
(10) The bis(trimethylsilyl) derivative, formed from uracil and HMDS in >95% yield, is frequently used to prepare uracil nucleosides; see E. Whittenburg, *Z. Chem.*, **4**, 303 (1964); U. Niedballa and H. Vorbrüggen, *J. Org. Chem.*, **41**, 2084 (1976).
(11) V. U. Wannagat, H. Bürger, C. Krüger, and J. Pump, *Z. Anorg. Allg. Chem.*, **321**, 208 (1963).
(12) E. G. Kataev, L. K. Konovalova, and E. G. Yarkova, *Zh. Org. Khim.*, **5**, 621 (1969); *Chem. Abstr.*, **71**, 21667 (1969).
(13) H. S. Rhinesmith, *J. Org. Chem.*, **40**, 1773 (1975); A. R. Butler and E. Leitch, *J. Chem. Soc., Perkin Trans 2*, 832 (1976).
(14) J. E. Baldwin, J. Cutting, W. DuPont, L. Kruse, L. Silbermane, and R. C. Thomas, *J. Chem. Soc., Chem. Commun.*, 737 (1976).
(15) If I intervenes it must exist in the cis conformation for conversion to II; this requires trans addition of urea to the propiolic acid triple bond. Reactions between amines and activated acetylenes predominantly proceed in a trans fashion (kinetic control); see W. E. Truce and D. W. Onken, *J. Org. Chem.*, **40**, 3200 (1975); W. Bottomley, *Tetrahedron Lett.*, 1997 (1967).
(16) To the best of our knowledge, only extremely facile reactions (acetylation, silylation) involving urea proceed under these conditions.

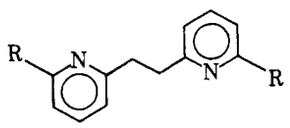
Synthesis of Hexahydroquino[8,7-*h*]quinolines. Cis and Trans Isomers of 3,9-Dimethyl-4b,5,6,10b,11,12-hexahydroquino[8,7-*h*]quinoline

M. Josefina Vitolo and Victor E. Marquez*

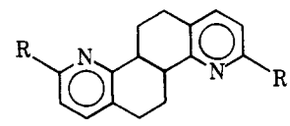
Departamento de Investigacion, Laboratorio de Quimica
Laboratorios Cosmos S.A.,
Apartado 62419-Chacao, Caracas 106, Venezuela

Received November 29, 1976

Preliminary findings suggestive of the biological importance of some 1,2-di(2-pyridyl)ethane derivatives (I) prompted a research program aimed at the synthesis of some steroidal



I

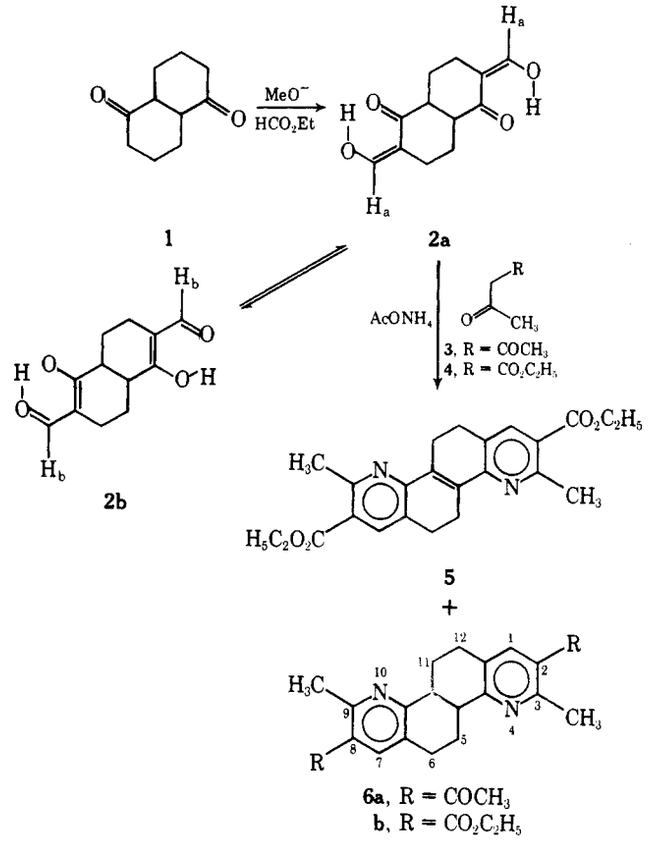


II

analogues which could be regarded as their rigid counterparts (II). The synthetic sequence leading to these type of medicinally interesting compounds started with pure *trans*-decalin-1,5-dione (1)[1] (Scheme I). Treatment of 1 with ethyl formate in pyridine utilizing sodium methoxide as catalyst afforded compound 2 in good yields. NMR spectral data of 2 seem to indicate that the compound exists as a mixture of rapidly equilibrating tautomers with an average signal for the H_a and H_b protons at δ 9.00. According to the formula proposed by Garbisch[2] for this type of equilibrium the mixture is 92% in favor of tautomer **2b.** In addition, a singlet at δ 14.5, accounting for two protons, underwent easy exchange with D_2O.

Heating 2 with either acetylacetone (3) or ethyl acetoacetate (4), without solvent and in the presence of ammonium acetate, afforded **6a** and **6b,** respectively, in fair yields. Along with **6b,**

Scheme I



it was possible to isolate after chromatography a fluorescent material for which all available data indicated to have structure **5.** Structures of these compounds are in agreement with the appearance of singlets between δ 7.72 and 8.20, in the NMR spectra, which correspond to γ protons of a pyridine nucleus. This synthetic procedure is similar to the one employed by Breitmaier et al.[3] for the synthesis of cycloalkeno(*b*)pyridines from the corresponding α-(aminomethylene)cycloalkanones with either 3 or 4 in the presence of catalytic amounts of ammonium acetate.

An objective was to functionalize both α-methyl groups of the pyridine rings and later to eliminate the carbomethoxy group of **6b.** The functionalization step was successful when

Scheme II