Registry No.—3a, 1428-11-2; **4a**, 33639-93-9; **5a**, 33639-91-7; **6a**, 65293-31-4; **6b**, 65293-32-5; **7a**, 65375-78-2; **8a**, 65292-96-8; **9a**, 65375-79-3; **9b**, 65292-94-6; **10a**, 65292-93-5; **10b**, 65292-95-7; sodium azide, 26628-22-8; formic acetic anhydride, 2258-42-6.

References and Notes

(1) Part 5: J. M. van der Eijk, R. J. M. Nolte, and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, **97**, 46 (1978).
(2) F. Millich, *Adv. Polym. Sci.*, **19**, 118 (1975).
(3) R. J. M. Nolte, A. J. M. van Beijnen, and W. Drenth, *J. Am. Chem. Soc.*, **96**, 5932 (1974).
(4) A. J. M. van Beijnen, R. J. M. Nolte, W. Drenth, and A. M. F. Hezemans, *Tetrahedron*, **32**, 2017 (1976).
(5) R. J. M. Nolte, R. W. Stephany, and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, **92**, 83 (1973).
(6) R. J. M. Nolte and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, **92**, 788 (1973).
(7) Polystyrene bounded sugars have been described in: (a) B. Helferich and H. J. Hofmann, *Chem. Ber.*, **85**, 175 (1952); (b) B. Helferich and K.-H. Jung, *Hoppe-Seyler's Z. Physiol. Chem.*, **311**, 54 (1958).
(8) L. Berrens, "The Chemistry of Atopic Allergens", Karger, Basel, 1971.
(9) P. Boullanger and G. Descotes, *Tetrahedron Lett.*, 3427 (1976); the ^{13}C-NMR resonance of the isocyano carbon in compound **2**, reported in this paper, is probably incorrect; see ref 22.
(10) F. Micheel and A. Klemer, *Adv. Carbohydr. Chem.*, **16**, 85 (1961).
(11) J. F. Sproviero, A. Salinas, and E. S. Bertiche, *Carbohydr. Res.*, **19**, 81 (1971).
(12) R. S. Tipson, A. S. Cerezo, V. Deulofeu, and A. Cohen, *J. Res. Natl. Bur. Stand., Sect. A*, **71**, 53 (1967).
(13) L. Dorland, B. L. Schut, J. F. G. Vliegenthart, G. Strecker, B. Fournet, G. Spik, and J. Montreuil, *Eur. J. Biochem.*, **73**, 93 (1977).
(14) I. Ugi and R. Meyr, *Angew. Chem.*, **70**, 702 (1958).
(15) H. M. Walborsky and G. E. Niznik, *J. Org. Chem.*, **37**, 187 (1972).
(16) R. Appel, R. Kleinstück, and K.-D. Ziehn, *Angew. Chem.*, **83**, 143 (1971).
(17) I. Ugi, "Isonitrile Chemistry", Academic Press, New York, N.Y., 1971.
(18) A. J. Naaktgeboren, R. J. M. Nolte, and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, in the press.
(19) A. J. M. van Beynen, R. J. M. Nolte, J. W. Zwikker, and W. Drenth, *J. Mol. Catal.*, in press.
(20) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *J. Am. Chem. Soc.*, **72**, 2200 (1950).
(21) D. E. Dorman and J. D. Roberts, *J. Am. Chem. Soc.*, **93**, 4463 (1971).
(22) R. W. Stephany, M. J. A. de Bie, and W. Drenth, *Org. Magn. Reson.*, **6**, 45 (1974).

Substituted Coumarins and Azacoumarins. Synthesis and Fluorescent Properties

Ronald L. Atkins* and Dan E. Bliss

Organic Chemistry Branch, Chemistry Division, Code 3856, Research Department
Naval Weapons Center, China Lake, California 93555

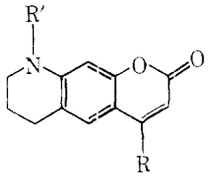
Received August 30, 1977

A number of new substituted 7-amino- and 8-aza-7-amino coumarins have been synthesized. Substituent effects on fluorescence properties (maxima and quantum yields) are reported. Substitution by fluorine in the 4-methyl position and by nitrogen in the benzo ring has been found to reduce fluorescence quantum yields. Nitrogen substitution in the benzo ring provides a blue shift in the fluorescence while fluorine substitution at the 4-methyl position gives pronounced red shifts.

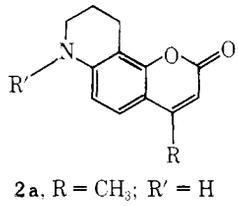
Recent synthesis programs in this laboratory have resulted in the preparation of a large number of substituted coumarins and azacoumarins for use as emission sources for dye laser applications. The effects of substituents on the lasing characteristics of these compounds have been reported.[1-4] This report describes the synthesis of several new laser dyes and the effects of substituents on their fluorescence maxima and fluorescence quantum yields.

The new coumarin dyes prepared in the present work are shown below. Results are summarized in Table I. The syntheses led to several new results of chemical interest.

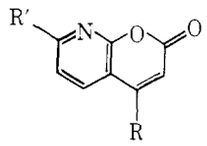
Synthesis. The preparation of 8-aza-7-hydroxy-4-methylcoumarin (**3c**) by the method of von Pechmann[5,6] from 2,6-dihydroxypridine (**4**) and ethyl acetoacetate gave in addition to the desired product small amounts of the bis addition product 10-aza-2,8-dioxo-4,6-dimethyl-2*H*,8*H*-benzo[1,2-*b*:5,4-*b*]dipyran (**5**) (detected by mass spectroscopy; M^+ ion at *m/e* 243). Merchant and co-workers[7] also noted the formation of trace amounts of a similar bis addition product in the reaction of ethyl acetoacetate with resorcinol. When the condensation of 2,6-dihydroxypyridine (**4**) is carried out in



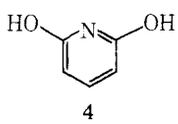
1a, R = CH_3; R′ = H
b, R = CF_3; R′ = H
c, R = CH_3; R′ = CH_3
d, R = CF_3; R′ = CH_3



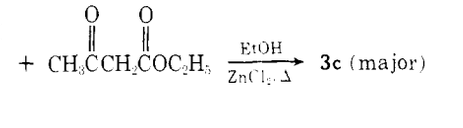
2a, R = CH_3; R′ = H
b, R = CF_3; R′ = H
c, R = CH_3; R′ = CH_3
d, R = CF_3; R′ = CH_3

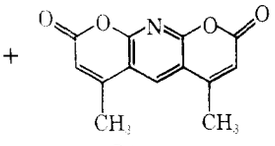


3a, R = CH_3; R′ = NH_2
b, R = CH_3; R′ = $N(CH_3)_2$
c, R = CH_3; R′ = OH
d, R = CF_3; R′ = 
e, R = CH_3; R′ = 



4





5 (trace)

Table I. Substituted Amino-, Hydroxy-, 8-Aza-7-amino-, and 8-Aza-7-hydroxycoumarins

Compd	Registry no.	Yield %	Mp °C	Recrystallization solvent	Fluores max in ethanol, (exc., nm)	Quantum yield ϕ_{fluor}	Molecular formula	Anal. % (theory) C	H	N	F
1a	62669-73-2	55	236–238	Ethanol	450 (380)	0.92	$C_{13}H_{13}NO_2$	72.27 (72.54)	5.96 (6.09)	6.35 (6.51)	
1b	53518-16-4	76	229–230	Ethanol	522 (406)	0.85	$C_{13}H_{10}F_3NO_2$	57.92 (58.00)	3.59 (3.74)	5.08 (5.20)	21.09 (21.17)
1c	65292-83-3	67	145–148	Acetonitrile	458 (378)	1.00	$C_{14}H_{15}NO_2$	72.99 (73.34)	6.37 (6.59)	6.06 (6.11)	
1d	53518-19-7	87	197–198	Acetonitrile	522 (413)	0.75	$C_{14}H_{12}F_3NO_2$	59.46 (59.36)	4.25 (4.24)	5.13 (4.95)	19.94 (20.14)
2a	65292-84-4	78	148–151	Methanol	455 (372)	0.67	$C_{13}H_{13}NO_2$	72.39 (72.54)	5.90 (6.08)	6.47 (6.51)	
2b	53518-17-5	39	187–188	Ethanol	537 (405)	0.64	$C_{13}H_{10}F_3NO_2$	57.89 (58.00)	3.69 (3.74)	5.15 (5.20)	21.34 (21.17)
2c	65292-85-5	50	126–128	Methanol	468 (375)	0.73	$C_{14}H_{15}NO_2$	73.03 (73.34)	6.38 (6.59)	6.14 (6.11)	
2d	65292-86-6		134–136	Methanol	537 (410)	0.33	$C_{14}H_{12}F_3NO_2$	58.96 (58.95)	4.45 (4.95)	4.95 (4.90)	20.00 (19.98)
3a	65292-87-7	63	330–340	Me_2SO	370 (340)		$C_9H_8N_2O_2$	61.33 (61.36)	4.61 (4.58)	16.07 (15.90)	
3b	57980-06-0	13	157–160	Benzene/ Hexane	422 (365)	0.60	$C_{11}H_{12}N_2O_2$	64.61 (64.69)	6.03 (5.92)	13.71 (13.72)	
3c	57980-05-9	15	295–297	Me_2SO	412 (356)	0.76	$C_9H_7NO_3$	60.90 (61.01)	4.00 (3.98)	8.03 (7.91)	
3d	58721-73-6	95	218–220	Acetonitrile	478 (380)	0.20	$C_{13}H_{11}F_3N_2O_3$	52.33 (52.01)	3.77 (3.69)	9.30 (9.33)	19.14 (18.98)
3e	57980-07-1	99	188–189	Benzene	425 (358)	0.54	$C_{13}H_{14}N_2O_3$	66.34 (63.41)	5.69 (5.73)	11.22 (11.38)	

the presence of excess ethyl 4,4,4-trifluoroacetoacetate, 10-aza-2,8-dioxo-4,6-bis(trifluoromethyl)-2*H*,8*H*-benzo[1,2-*b*:5,4-*b*]dipyran, (**6**), the bis addition compound, is the principal product (50% yield).

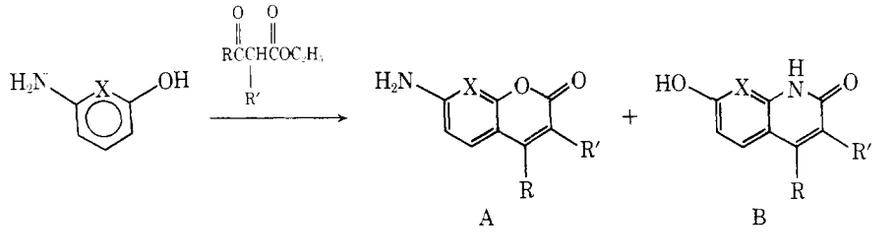
In the preparation of 7-amino-4-methylcoumarin (**7**) from

6

ethyl acetoacetate and *m*-aminophenol, a second strongly fluorescing coumarin was isolated. This material had also been prepared by von Pechmann and was reported to be 2-keto-4,6,6,8-tetramethyl-6,7-dihydro-2*H*-pyrano[3,2-*g*]quinoline (**10**).[8]

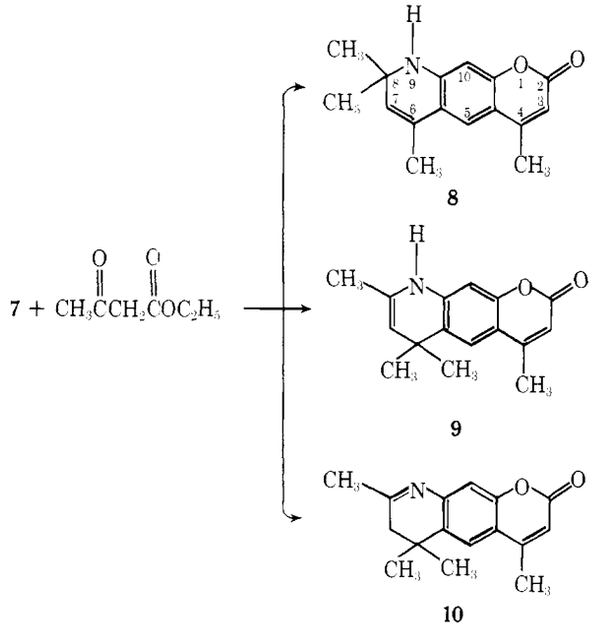
This assignment is incorrect. The product exhibits a sharp absorption in the IR at 3310 cm^{-1} indicative of the secondary amine moiety. The ^1H-NMR spectrum (see Experimental Section) which eliminates **10** does not allow a definitive choice between **8** and **9**. NMR analysis employing the shift reagent $Eu(fod)_3$ which associates with the carbonyl oxygen made possible the assignment of all proton absorptions. However,

Table II. Reaction of β-Ketoesters with *m*-Aminophenol and 6-Amino-2-pyridinol



A B

Experiment	X	R	R′	Reaction conditions	Coumarin (A) No. (%)	Quinolone (B) No. (%)
(1)	C	CH_3	CH_3	Neat	**11** (46)	**12** (trace)
(2)	C	CH_3	H	Neat	**7** (trace)	**13** (60)
(3)	C	CF_3	H	Neat	**14** (major)	**15** (10)
(4)	C	CH_3	H	$ZnCl_2$/EtOH	**7** (16)	**13** (25)
(5)	C	CF_3	H	$ZnCl_2$/EtOH	**14** (42)	**15** (trace)
(6)	N	CF_3	H	Neat	**16** (61)	**17** (15)
(7)	N	CH_3	CH_3	Neat	**18** (major)	**19** (20)



8 **9** **10**

a choice between **8** and **9** still could not be made since the geminal dimethyl group and vinylmethyl (the 6-methyl in **8** or the 8-methyl in **9**) are essentially equidistant from the site of Eu(fod)$_3$ association.

Measurement of the nuclear Overhauser effect enhancements of the ring protons proved definitive. Saturation of the geminal dimethyl resonance resulted in the enhancement of the N–H integral and the dihydro ring vinyl proton integrals. Saturation of the 4-methyl absorption revealed enhancement of H-3 and H-5, while saturation of the dihydro ring vinyl methyl absorption resulted in observation of enhanced absorption of H-5 and the dihydro ring vinyl hydrogen. These data are consistent only with structure **8**.

Product **8** is most likely formed by the Michael-type addition of the intermediate 7-amino-4-methylcoumarin (**7**) to mesityl oxide. The mesityl oxide most likely is formed under the reaction conditions employed from acetone (the acetone derived by retrogression from ethyl acetoacetate). Knoevenagel[9] has reported a similar 1,4-Michael addition of aniline to mesityl oxide (formed *in situ* from acetone) giving 1,2-dihydro-2,2,4-trimethylquinoline. This mechanistic path is further supported by the reaction of mesityl oxide with **7** to yield **8**.

A convenient method for preparation of courmarins and quinolones is to omit catalyst and solvent and simply heat the precursor aminophenol with the β-keto ester.[10,11] This method, however, can lead to mixtures of coumarins and quinolones in contrast to von Pechmann's procedure which provides primarily coumarins. While the reaction is regiospecific in that ring formation is ortho to the reacting functional group and para to the second giving 7-substituted products, no 5-substituted products are obtained, it is nonselective with respect to the functional groups.

Several examples illustrate this reaction feature (Table II). When *m*-aminophenol is heated in the presence of ethyl 2-methylacetoacetate, Table II, reaction 1, the major product is 7-amino-2,3-dimethylcoumarin (**11**) formed in 46% yield. A trace amount of the isomeric 7-hydroxy-2,3-dimethylquinolone (**12**) was isolated from the base-soluble extract of the reaction mixture.[12] However, when *m*-aminophenol is heated in the presence of an equimolar amount of ethyl acetoacetate, the only isolable addition product is 7-hydroxy-4-methylquinolone (**13**). Only a trace amount of coumarin **7** (detected by TLC analysis of the reaction mixture) was formed.

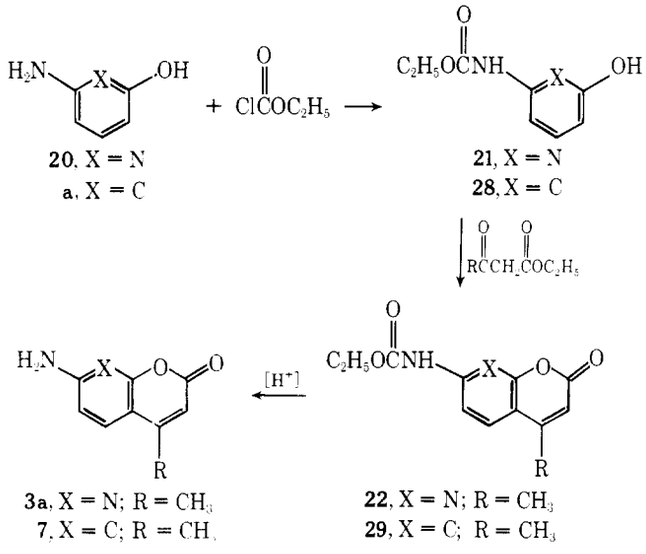
When the condensation of *m*-aminophenol and ethyl 4,4,4-trifluoroacetoacetate is carried out in absolute ethanol at reflux in the presence of anhydrous zinc chloride (von Pechmann conditions) the addition occurs at the hydroxyl group giving **14**. Only a trace of quinolone is observed (Table II, reaction 5). Evidently the zinc chloride complexes with the amino group and thus facilitates condensation via the hydroxyl group. However, when the condensation of *m*-aminophenol with ethyl 4,4,4-trifluoroacetoacetate is carried out in the absence of solvent (Table II, reaction 3), the major product is the coumarin **14**. A 10% yield of quinolone **15** was recovered from the base-soluable extract.[12]

Similar results are obtained with 6-amino-2-pyridinol (**20**). When **20** is heated in the presence of ethyl 4,4,4-trifluoroacetoacetate a 76% yield of addition products is obtained giving approximately a 4:1 ratio of quinolone to coumarin, Table II, reaction 6.[12] A similar product distribution is realized when **20** is allowed to react with ethyl 2-methylacetoacetate,[12] Table II, reaction 7.

Since reaction of **20** with β-keto esters gives mixtures of quinolones and coumarins, it was necessary to modify the reaction sequence in order to obtain pure 7-aminocoumarins in good yields. This was accomplished by first deactivating the amino substituent through formation of its urethane derivative. Reaction of this intermediate gives exclusively the coumarin derivative (Scheme I). The free amino compound is then liberated by mild acid hydrolysis.[13]

While urethane derivative **21** gave reasonable yields of coumarin upon reaction with β-keto esters, 6-acetamido-2-

Scheme I



pyridinol (**23**) fails to give the desired product. Prolonged heating of **23** in the presence of excess ethyl acetoacetate resulted in the recovery of starting material.

A convenient procedure for the methylation of functional groups (amino, hydroxyl, amide) in these systems has been developed. Where other procedures such as reductive methylation with sodium cyanoborohydride or hydrogen (platinum catalyst) failed, simply heating the precursor in the presence of excess trimethyl phosphate gives the desired product in good to excellent yields,[14] see for example the prepartion of **1c** and **1d.**

In the preparation of 7-hydroxy- and 5-hydroxy-5,6,7,8-tetrahydroquinolines it was found that when the hydrogenation of the heteroring was carried out in neutral media, no acid catalyst,[15] uptake of hydrogen was quantitative (although longer reaction times were required) and a cleaner product resulted.

Fluorescence. Substituent effects on the fluorescence maxima of these systems parallel those observed in other coumarin dyes. A large bathochromic shift of 82 nm is seen in changing the 4-methyl group in **2a** to a trifluoromethyl group in **2b.** Similar shifts are observed in other pairs, i.e., **1a–b, 1c–d.** The red shift is not of the same magnitude in the azacoumarins. A shift of 53 nm is obtained with **3d** compared to **3e.**

Varying the substituent in the 7 position does not result in large shifts in these compounds and does not seem to follow a predictable pattern. Compounds **2b** and **2d** for example both have fluorescence maxima at 537 nm. The alkylation seemingly has no effect. However, compound **1a** exhibits a red shift of 8 nm upon methylation of the nitrogen to give **1c,** and methylation of **2a** results in a 13-nm red shift in **2c.** The azacoumarins all exhibit pronounced hypsochromic shifts when compared to their carbon analogues.

The quantum yields of fluorescence are generally high for the substituted 7-amino-4-methylcoumarins. In all cases substitution by fluorine at the 4-methyl position results in a diminished quantum yield of fluorescence. In the azacoumarin series the quantum yields are less than in the carbon series, and again substitution of fluorine in the 4-methyl group lowers the quantum yield still further, i.e., compounds **3e** and **3d.**

These factors work in concert in the 4-trifluoromethyl-8-azacoumarins and these compounds exhibit low quantum yields of fluorescence. The fluorinated bis adduct **6** shows very poor fluorescence and at liquid nitrogen temperature in absolute ethanol exhibits strong phosphorescence. To the contrary, the pseudo-bis adduct **8** fluoresces strongly at 470 nm with high stability and exhibits lasing action over a 25-nm range (455–480 nm). Surprisingly, **8** also shows strong phosphorescence in ethanol at liquid nitrogen temperature indicating efficient intersystem crossing to the triplet state, a process generally regarded to be highly deleterious to lasing.

Experimental Section

Proton and ^{13}C-NMR spectra were obtained with a Varian XL-100 FT spectrometer and are referenced to tetramethylsilane as an internal standard. IR spectra (KBr discs) were obtained with a Perkin-Elmer 137 spectrometer. UV absorbance data were measured on a Cary-14 spectrometer. Fluorescence spectra and quantum yields were determined using a Turner Model 210 spectrofluorometer utilizing quinine sulfate as a quantum yield standard. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6E spectrometer. Melting points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

7-Hydroxyquinoline (23). This compound was prepared from *m*-aminophenol via the Skraup quinoline synthesis using the procedure of Bradford *et al.*[16]

7-Hydroxy-1,2,3,4-tetrahydroquinoline (24). 7-Hydroxyquinoline (4.0 g, 27.6 mmol) and PtO_2 (0.3 g) were suspended in 150 mL of 95% ethanol containing 1 mL of concentrated HCl. Hydrogenation (Parr apparatus, room temperature, 50 lb H_2 pressure) was continued until the theoretical amount of H_2 was absorbed (4 h). Filtration and concentration gave 5.04 g of red oil. Water (50 mL) was added and the resulting suspension was made basic (dilute NH_3). Extraction with ether (4 × 75 mL), drying ($CaCl_2$), and concentration gave 3.5 g of oil (90%) which solidified upon standing (mp 70–80 °C): NMR ($CDCl_3$) δ 1.8–2.4 (m, 2H, $CH_2\mathbf{CH_2}CH_2$), 2.76 (t, 2, J = 7 Hz, $\mathbf{NCH_2}CH_2$), 3.38 (t, 2, J = 6 Hz, $CH_2\mathbf{CH_2}Ar$), 4.8 (bs, 2, **OH** and **NH**), 6.16 (d, 1, J_{para} = 2 Hz, H-8), 6.33 (d of d, 1, J_{para} = 2 Hz, J_{ortho} = 8 Hz, H-5), 7.05 (d, 1, J_{ortho} = 8 Hz, H-6). In subsequent preparations the HCl was omitted. While the hydrogenation generally took two or three times longer, the product (obtained in quantitative yield) was of sufficient purity for use without further purification.

2-Keto-4-methyl-6,7,8,9-tetrahydro-2*H*-pyrano[3,2-*g*]quinoline (1a). Ethyl acetoacetate (7.78 g, 60 mmol), **24** (7.9 g, 53 mmol), and anhydrous zinc chloride (11 g, 80 mmol) were added to absolute ethanol (100 mL). The resulting mixture was heated at reflux 15 h. A yellow solid had precipitated. More solid was deposited upon cooling to room temperature. Filtration gave 5.62 g. Pouring the mother liquors into ice water (100 mL) yielded an additional 0.75 g of yellow solid. The crude yield was 55%. Two recrystallizations from ethanol gave yellow needles, mp 236–238 °C; NMR (Me_2SO-d_6): δ 2.78 (m, 2, $CH_2\mathbf{CH_2}CH_2$), 2.30 (s, 3, 4-Me), 2.72 (t, 2, J = 6.2 Hz, $CH_2\mathbf{CH_2}Ar$), 3.29 (t, 2, J = 6.2 Hz, N-$\mathbf{CH_2}CH_2$), 5.82 (s, 1, H-3), 6.31 (s, 1, H-5), 6.81 (bs, 1, N-**H**), 7.21 (s, 1, H-10); IR: 3425 cm^{-1} (N-H); 1710 cm^{-1} (C=O).

2-Keto-4-trifluoromethyl-6,7,8,9-tetrahydro-2*H*-pyrano[3,2-*g*]quinoline (1b). 7-Hydroxy-1,2,3,4-tetrahydroquinoline (2.38 g, 16 mmol), ethyl 4,4,4-trifluoroacetoacetate (2.9 g, 16 mmol), anhydrous zinc chloride (6.0 g), and dry ethanol (50 mL) were mixed and the resulting mixture was heated at reflux for 18 h under a dry N_2 atmosphere with stirring. A solid deposited on cooling. Filtration gave yellow crystals: 3.5 g (76%); mp 229–230 °C; NMR ($CDCl_3$) δ 1.64–1.88 (m, 2, $CH_2\mathbf{CH_2}CH_2$), 2.62 (t, 2, J = 6 Hz, $CH_2\mathbf{CH_2}Ar$), 3.23 (t, 2, J = 6 Hz, $\mathbf{NCH_2}CH_2$), 6.23 (bs, 2, C-5 and C-8), 7.06 (bs, 1, H-3); IR 3450 (NH), 1720 cm^{-1} (C=O), mass spectrum m/e 269, M^+.

2-Keto-4,9-dimethyl-6,7,8,9-tetrahydro-2*H*-pyrano[3,2-*g*]quinoline (1c). Trimethyl phosphate (1.0 g, 7.1 mmol) and **1a** (1.0 g, 4.65 mmol) were heated in an oil bath at 200 °C for 30 min. The resulting dark oil set to a solid mass upon cooling. Crystallization from acetonitrile (10 mL) gave yellow-green plates (0.7 g, mp 145–148 °C) of the desired product (67% yield): NMR ($CDCl_3$) δ 1.75–2.2 (m, 2, $CH_2\mathbf{CH_2}CH_2$), 2.32 (d, 3, J = 0.6 Hz, 4-Me), 2.81 (t, 2, J = 7 Hz, $CH_2\mathbf{CH_2}Ar$), 3.40 (t, 2, J = 6.5 Hz $\mathbf{NCH_2}CH_2$), 2.98 (s, 3, NMe), 6.0 (q, 1, J = 0.6 Hz, H-3), 6.48 (s, 1, H-5), 7.18 (s, 1, H-6); IR 1724 cm^{-1} (C=O), N-H absent.

2-Keto-4-trifluoromethyl-9-methyl-6,7,8,9-tetrahydro-2*H*-pyrano[3,2-*g*]quinoline (1d). Trimethyl phosphate (30 mL) and **1b** (2.5 g) were heated at reflux for 4 h. Cooling gave yellow crystals (2.3 g, 87%) which recrystallized from acetonitrile gave golden needles (mp 197–198 °C): NMR ($CDCl_3$) δ 1.86–2.10 (m, 2, $CH_2\mathbf{CH_2}CH_2$), 2.80 (t, 2, J = 6 Hz, $CH_2\mathbf{CH_2}Ar$), 3.01 (s, 3, $\mathbf{NCH_3}$), 3.41 (t, 2, J = 6 Hz, $\mathbf{NCH_2}CH_2$), 6.36 and 6.44 (two s, each 1 H, C-5 and C-10), 7.20 (bs, 1, H-3); mass spectrum m/e 283, M^+.

5-Hydroxy-1,2,3,4-tetrahydroquinoline, (25). 5-Hydroxyquinoline (5.0 g, 35 mmol) suspended in 100 mL of 95% ethanol con-

taining 6 mL of concentrated HCl was hydrogenated in the presence of PtO_2 (0.5 g) in a Parr apparatus (room temperature, 50 lb H_2) until the theoretical amount of H_2 was absorbed. Filtration and concentration gave a dark oil. Water (100 mL) was added and the resulting solution was neutralized by addition of 1 N NaOH (70 mL). The solution was extracted with ether (5 × 100 mL) and dried ($CaSO_4$). Filtration and concentration gave 5 g of a brown oily solid. The brown solid was washed with $CHCl_3$ (100 mL) and dried to give 4.8 g of a tan solid (95%): mp 110–112 °C; IR 3180 cm^{-1} (NH); NMR ($CDCl_3$) δ 1.92 (m, 2, $CH_3CH_2CH_2$), 2.65 (6, 2, J = 7 Hz, NCH_2CH_2), 3.22 (t, 2, J = 5.5 Hz, CH_2CH_2Ar), 4.76 (bs, 2, NH and OH), 6.09 (d, 2, J = 8 Hz, H-6 and H-8), 6.80 (t, 1, J = 8 Hz, H-7).

2-Keto-4-methyl-7,8,9,10-tetrahydro-2*H*-pyrano[2,3-*f*]-quinoline (2a). Ethyl acetoacetate (5.2 g, 40 mmol), **25** (5.5 g, 37 mmol), and anhydrous zinc chloride (6.8 g, 50 mmol) were added to 50 mL of absolute ethanol. The resulting mixture, protected from moisture with a positive dry N_2 atmosphere, was heated at reflux for 20 h. The cooled reaction solution was poured onto 100 g of crushed ice. A viscous oil separated and gave 1.4 g of yellow solid upon rubbing with a glass rod. The remaining organic phase was dissolved in hot ethanol and gave a second crop of product (2.1 g). A third crop of yellow solid (3.1 g) was recovered from the combined aqueous phase extracts and acetone washings of the gummy solids adhering to the reaction flasks. Yield of crude product was 78%. Two recrystallizations (MeOH) gave yellow needles (mp 149–151 °C); NMR ($CDCl_3$) δ 1.9 (m, 2, $CH_2CH_2CH_2$), 2.3 (s, 3, 4-Me), 2.9 (t, 2, J = 6.4 Hz, CH_2CH_2Ar), 3.38 (t, 2, J = 5.8 Hz, NCH_2CH_2), 4.5 (bs, 1, NH), 6.0 (s, 1, H-3), 6.41 (d, 1, J = 8.5 Hz, H-5), 7.27 (d, 1, J = 8.5 Hz, H-6); IR 3436 (NH), 1724 cm^{-1} (C=O).

2-Keto-4-trifluoromethyl-7,8,9,10-tetrahydro-2*H*-pyranol [2,3-*f*]quinoline (2b). Ethyl 4,4,4-trifluoroacetoacetate (6.63 g, 36 mmol), **25** (6.36 g, 36 mmol), anhydrous $ZnCl_2$ (10 g), and absolute ethanol (75 mL) were heated at reflux for 20 h (dry N_2 atmosphere). The cooled solution was concentrated, taken up in 75 mL of $CHCl_3$, washed with 1 N NaOH (2 × 50 mL) and water (50 mL), and dried ($MgSO_4$). Filtration and concentration gave 4.0 g (39%) of yellow solid, mp 187–188 °C (ethanol): IR 3310 (NH), 1710 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 1.84 (p, 2, J = 6 Hz, $CH_2CH_2CH_2$), 2.73 (t, 2, J = 6 Hz, NCH_2CH_2), 3.31 (t, 2, J = 6 Hz, CH_2CH_2Ar), 3.54 (bs, 1, NH), 6.29 (s, 1, H-3), 6.58 (d, 1, J_{ortho} = 9 Hz, H-6), 7.19 (d of q, 1, J_{ortho} = 9 Hz, J_{CF_3} = 1.8 Hz, H-5).

2-Keto-4,7-dimethyl-7,8,9,10-tetrahydro-2*H*-pyrano[2,3-*f*]-quinoline (2c). Trimethyl phosphaste (1.0 g, 7 mmol) and **2a** (0.83 g, 3.8 mmol) were mixed and heated at 195 °C for 1 h in an oil bath. The resulting dark oil was dissolved in 20 mL of methylene chloride and chromatographed on a 15 × 3 cm alumina column ($MeCl_2$ eluant). The first yellow band (0.7 g) was recrystallized from MeOH (10 mL) to give 0.44 g (50%) of the desired product: mp 126–128 °C; NMR ($CDCl_3$) δ 1.78 (m, 2, $CH_2CH_2CH_2$), 2.34 (d, 3, J = 0.6 Hz, 4-Me), 2.7–3.1 (m, 2, CH_2CH_2Ar), 3.2 (s, 3, NMe), 3.39 (t, 2, J = 6 Hz, NCH_2CH_2), 6.1 (bs, 1, H-3), 6.62 (d, 1, J = 9.4 Hz, H-5), 7.38 (d, 1, J = 9.4 Hz, H-6); IR 1740 cm^{-1} (C=O), NH absent.

2-Keto-7-methyl-4-trifluoromethyl-7,8,9,10-tetrahydro-2*H*-pyrano[2,3-*f*]quinoline (2d). The methylation of **2b** was carried out as in preparation **2c** to give the desired product as yellow needles (mp 134–136 °C): NMR ($CDCl_3$) δ 2.0 (m, 2, $CH_2CH_2CH_2$), 2.92 (t, 2, J = 7 Hz, CH_2CH_2Ar), 3.08 (s, 3, NMe), 3.36 (t, 2, J = 7 Hz, NCH_2CH_2), 6.44 (s, 1, H-3), 3.65 (d, 1, J_{ortho} = 9 Hz, H-8), 7.44 (d of q, 1, J_{ortho} = 9 Hz, J_F = 1.0 Hz, H-7); IR 1738 cm^{-1} (C=O), N–H absent.

3-Hydroxyphenylurethane (28). Ethyl chloroformate (10 g, 92 mmol) was added in one portion to a stirred suspension of *m*-aminophenol (10 g, 92 mmol) in 400 mL of dry diethyl ether. A white precipitate (the amine hydrochloride) formed immediately. The reaction mixture was stirred an additional 2 h at room temperature. The hydrochloride was removed by filtration. Evaporation of the solvent left 8 g of grey solid. Crystallization from benzene/cyclohexane (200 and 400 mL, respectively) gave upon cooling (0 °C) 7.0 g (84% yield) of colorless needles: mp 94–95 °C; IR 3260 (NH), 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.30 (t, 3, J = 7 Hz, OCH_2CH_3), 4.21 (q, 2, J = 7 Hz, OCH_2CH_3), 6.59 (bm, 4, NH, OH, H-4, and H-6), 7.06 (t, 1, J = 8 Hz, H-7), 7.30 (s, 1, H-2).

7-Carbethoxyamino-4-methylcoumarin (29). Ethyl acetoacetate (5.62 g, 43 mmol) and **28** (6.5 g, 36 mmol) suspended in 88 mL of 70% H_2SO_4 were stirred 4 h at room temperature. The clear yellow solution was poured into 400 mL of ice water, giving a voluminous white crystalline precipitate. The solid filtered and crystallized from 400 mL of absolute ethanol to give 7.4 g (83% yield) of colorless needles: mp 186–188 °C; NMR (Me_2SO-d_6) δ 1.39 (t, 3, J = 7 Hz, CH_2CH_3), 2.32 (d, 3, J = 1.4 Hz, 4-Me), 3.83 (q, 2, J = 7 Hz, CH_2CH_3), 5.54 (q, 1, J = 1.4 Hz, H-3), 6.52 (d of d, 1, J_{ortho} = 7.4 Hz, J_{para} = 2 Hz, H-5), 6.65 (d, 1, J_{para} = 2 Hz, H-8), 6.76 (d, 1, J_{ortho} = 7.4 Hz, H-6), 8.80 (bs, 1, NH). Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 62.95; H, 5.29; N, 5.65.

7-Amino-4-methylcoumarin (7). 7-Carbethoxyamino-4-methylcoumarin (**29**) (7.0 g, 28 mmol) was heated at reflux 4 h in 25 g of concentrated H_2SO_4 and 25 g of glacial acetic acid. On cooling a yellow precipitate was deposited. The mixture was poured into 100 mL of ice water and let stand overnight. The resulting suspension was made slightly basic with 50% NaOH with cooling by addition of ice chips. The yellow precipitate was filtered and washed with ice water (3 × 50 mL). Crystallization from ethanol yielded three crops of yellow needles (4.9 g, 99%), mp 220–224 °C (lit.[18] mp 223 °C).

6-Carbethoxyamino-2-pyridinol (26). 2-Amino-6-hydroxypyridine (11 g, 100 mmol) and ethyl chloroformate were stirred at room temperature for 20 h in a solution of 400 mL of dry ether and 100 mL of dry tetrahydrofuran containing 10 g (100 mmol) of triethylamine. Filtration of the reaction mixture gave 12.5 g of grey solid which was identified as a mixture of triethylamine hydrochloride and unreacted 2-amino-6-hydroxypyridine by TLC. Evaporation of the mother liquors gave 6.7 g (37%) of small colorless needles (mp 70–72 °C) which darkened appreciably upon exposure to light: IR 3420 (OH), 3310 and 3205 (NH), 1755 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.34 (t, 3, J = 7 Hz, CH_2CH_3), 4.37 (q, 2, J = 7 Hz, CH_2CH_3), 4.69 (bs, 2, NH and OH), 6.45 (d, 1, J = 8 Hz, H-3 or H-5), 6.48 (d, 1, J = 8 Hz, H-3 or H-5), 7.50 (t, 1, J = Hz, H-4). Anal. Calcd for $C_8H_{10}N_2O_2$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.67; H, 5.56; N, 15.32.

8-Aza-7-amino-4-methylcoumarin (3a). Ethyl acetoacetate (4.55 g, 35 mmol) and **26** (5.0 g, 27.5 mmol) were mixed and heated at 130 °C with stirring for 16 h. After 15 min of heating a clear solution resulted. A yellow solid formed as heating was continued. After cooling the excess ester was removed by rotoevaporation. The resulting yellow solid was crystallized from Me_2SO to give 2.3 g of yellow solid (mp 230–235 °C). The mother liquors were diluted with 200 mL of distilled water to give an additional 2 g of yellow solid. The combined material, isolated in 63% yield, was 8-aza-7-amino-4-methylcoumarin as confirmed from spectral data. Apparently the reaction conditions were sufficient to effect hydrolysis of the carbethoxy group: IR 1670 cm^{-1} (C=O). The NH absorption bands are not evident in KBr nor do they appear in a Nujol mull. The carbamate carbonyl is absent. NMR (Me_2SO-d_6) δ 2.33 (s, 3, 4-Me), 6.12 (s, 1, H-3), 6.26 (d, 1, J_{ortho} = 8.5 Hz, H-5), 7.77 (d, 1, J_{ortho} = 8.5 Hz, H-6); upon addition of D_2O the 7-amino protons appeared as a broad singlet at 3.50; MS *m/e* 231, M^+.

8-Aza-7-hydroxy-4-methylcoumarin (3c). Ethyl acetoacetate (2.60 g, 20 mmol), **4** (2.22 g, 20 mmol), and anhydrous $ZnCl_2$ were mixed and heated at reflux in 25 mL of anhydrous methanol under a dry N_2 atmosphere with stirring for 8 h. After standing at room temperature a red-orange solid was deposited (0.48 g), 15%: mp 295–297 °C (Me_2SO); NMR (Me_2SO-d_6) 2.40 (d, 3, J = 0.8 Hz, 4-Me), 3.22 (bs, 1, OH), 6.18 (q, 1, J = 0.8 Hz, H-3), 6.66 (d, 1, J_{ortho} = 4 Hz, H-5), 8.04 (d, 1, J_{ortho} = 4 Hz, H-6); IR 1750 cm^{-1} (C=O).

2-Hydroxy-6-morpholinopyridine (27). 2-Chloro-6-hydroxypyridine (4.0 g, 31 mmol) was heated at reflux (87 °C) in 25 mL of morpholine for 96 h. Upon cooling morpholine hydrochloride, 3.5 g (mp 160–165 °C (lit.[17] mp 175 °C)) precipitated. The hydrochloride was filtered and the green mother liquors were concentrated to give a green solid. The solid was dissolved in 100 mL of benzene, treated with decolorizing charcoal, and filtered. The emerald green solution deposited crystals upon cooling (10 °C), 5.1 g (mp 136–140 °C, 91% yield). Recrystallization from acetonitrile did not improve the melting point: NMR (Me_2SO-d_6) δ 3.35 (m, 4, CH_2OCH_2), 3.69 (m, 4, CH_2NCH_2), 5.92 (d, 1, J = 4 Hz, H-2 or H-4), 6.09 (d, 1, J = 4 Hz, H-2 or H-4), 7.39 (t, 1, J = 4 Hz, H-3); MS *m/e* 180, M^+; IR NH absent.

8-Aza-7-morpholino-4-trifluoromethylcourmarin (3d). Ethyl 4,4,4-trifluoroacetoacetate (5 mL) and **27** (2.0 g, 11 mmol) were heated at reflux for 60 h. The volatile material was removed by rotoevaporation to give crystalline material. Recrystallization from acetonitrile (75 mL) gave gold needles: 3.2 g (95%, mp 218–220 °C); NMR (acetone-d_6) δ 3.02 (s, 8, morpholine protons), 6.57 (s, 1, H-3), 6.94 (d, J_{ortho} = 4.5 Hz, H-6), 7.90 (d of q, 1, J_{ortho} = 4.5 Hz, J_F = 1.0 Hz, H-5); IR 1728 cm^{-1} (C=O).

8-Aza-7-dimethylamino-4-methylcoumarin (3b). 2-Dimethylamino-6-hydroxypyridine (1.1 g, 8 mmol) was heated at 150 °C in the presence of excess ethyl acetoacetate (10 mL) for 66 h. The excess ethyl acetoacetate was removed by rotoevaporation to give a dark oil. Addition of methanol (5 mL) gave a yellow solid. The solid was crystallized from benzene/hexane to give 210 mg (13%) of the desired product as yellow crystals (mp 157–160 °C): NMR ($CDCl_3$) δ 2.24 (d, 1, J = 0.6 Hz, 4-Me), 3.12 (s, 6, NMe_2), 5.94 (q, 1, J = 0.6 Hz, H-3), 6.38 (d, 1, J_{ortho} = 4 Hz, H-5), 7.62 (d, 1, J_{ortho} = 4 Hz, H-6).

Table III. NOE Enhancement Factors

Saturated group	Enhancement[a] H-5	N-H	H-10	H-3	H-7
Geminal dimethyl	1.00	1.16	1.00	0.95	1.23
6-Me	1.19	1.04	0.92	1.00	1.17
4-Me	1.34	0.97	0.97	1.54	1.00

[a] The enhancement ratio was determined from the ratio of the integral obtained with the secondary irradiation frequency on to the integral obtained with the secondary irradiation frequency off, both values being the average value obtained for at least five integrations.

8-Aza-4-methyl-7-morpholinocoumarin (3e). Ethyl acetoacetate (5.1 g, 40 mmol) and **27** (2.0 g, 11 mmol) were mixed and heated at reflux for 60 h to give a dark oil. The volatile materials were removed by rotoevaporation giving 3.6 g of semicrystalline black solid. This solid was washed with ether (100 mL) and twice recrystallized from benzene to give tan needles: mp 188–189 °C; IR 1735 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.36 (d, 3, J = 0.7 Hz, 4-Me), 3.76 (m, 8, morpholino protons), 6.04 (d. 1, J = 07 Hz, H-3), 6.54 (d, 1, J = 4.2 Hz, H-5), 7.69 (d, 1, J = 4.2 Hz, H-6).

10-Aza-2,8-dioxo-4,6-bis(trifluoromethyl)-2*H*,8*H*-benzo-[1,2,-*b*:5,4-*b*]dipyran (6). 2,6-Dihydroxypyridine was heated at 135 °C in excess ethyl 4,4,4-trifluoroacetoacetate (66 h). The product crystallized as colorless needles: mp 280–282 °C (Me_2SO); 5.36 g (50% yield); IR 1780 cm^{-1} (C=O); MS m/e 351, M^+; NMR (Me_2SO-d_6) δ 7.10 (s, 2, H-3 and H-7), 8.32 (broad s, 1, H-5). Anal. Calcd for $C_{13}H_3F_6NO_4$: C, 44.47; H, 0.86; F, 32.18; N, 3.99. Found: C, 44.42; H, 0.82; F, 32.18; N, 3.99.

2,6-Dihydroxypyridine (4). 2,6-Dihydroxypyridine hydrochloride (10.0 g, 68 mmol) was suspended in 400 mL of water and the pH was adjusted to 3.5 by addition of concentrated aqueous ammonia. The flocculent white solid was filtered, dried in vacuo, and used immediately without further purification.

6-Acetamido-2-pyridinol (30). This compound was prepared by the method of Buo-Hoi, Gauthier, and Xuong[18] in 50% overall yield starting from 6-amino-2-pyridinol.

Attempted Preparation of 7-Acetamido-8-aza-4-methylcoumarin (31). Ethyl acetoacetate (1.72 g; 13.2 mmol) and **30** (2.0 g; 13.2 mmol) were heated at 170 °C (oil bath) for 16 h. The pyridinol had not gone into solution. Mesytelene (5 mL) was added and the reaction mixture was heated an additional 20 h at 170 °C. Upon cooling, 2.1 g of solid separated. NMR and IR showed this to be recovered **24**, contaminated with a small amount of mesytelene.

2-Keto-4,6,8,8-tetramethyl-8,9-dihydro-2*H*-pyrano[3,2-*g*]-quinoline (8). *m*-Aminophenol (10 g; 92 mmol) and ethyl acetoacetate were mixed. Upon heating to 150 °C a clear solution was obtained. As heating continued a yellow precipitate formed. Heating was continued for a total of 6 h. The precipitate was filtered from the hot solution and washed with cyclohexane. A further 2.2 g of yellow solid was obtained from the cooled filtrate. Crystallization from methanol gave beautiful golden needles (mp 270–274 °C (lit.[8] mp 268 °C)): NMR (Me_2SO-d_6) δ 1.68 (s, 6, 8-*gem*-dimethyls), 2.29 (d, 3, J = 2 Hz, 6-Me), 2.72 (d, 3, J = 1.6 Hz, 4-Me), 5.8 (bs, 1, H-7), 6.25 (q, 1, J = 1.6 Hz, H-3), 6.71 (s, 1, H-10), 7.1 (bs, 1, NH), 7.48 (s, 1, H-5); IR 3311 (NH), 1695 cm^{-1} (C=O); MS m/e 255, M^+. Anal. Calcd: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.67; H, 6.87; N, 5.45. The nuclear Overhauser effect enhancements[19] are given in Table III. The spectra were obtained at 80 °C from a 100% Me_2SO-d_6 sample degassed by five freeze cycles and sealed under vacuum.

Registry No.—**4**, 626-06-2; **6**, 65292-88-8; **7**, 26093-31-2; **8**, 65392-09-8; **23**, 580-20-1; **24**, 58196-33-1; **25**, 61468-43-7; **26**, 65292-89-9; **27**, 65292-90-2; **28**, 7159-96-8; **29**, 58632-48-7; **30**, 770-20-7; ethyl acetoacetate, 141-97-9; ethyl 4,4,4-trifluoroacetoactate, 372-31-6; trimethyl phosphate, 512-56-1; 5-hydroxyquinoline, 578-67-6; *m*-aminophenol, 591-27-5; 2-amino-6-hydroxypyridine, 5154-00-7; 2-chloro-6-hydroxypyridine, 16879-02-0; morpholine, 110-91-8; 2-dimethylamino-6-hydroxypyridine, 65292-91-3; 2,6-dihydroxypyridine·HCl, 10357-84-3; ethyl chloroformate, 541-41-3; ethyl 2-acetopropionate, 609-14-3.

References and Notes

(1) E. J. Schimitschek, J. A. Trias, P. R. Hammond, and R. L. Atkins, *Opt. Commun.*, **11**, 352 (1974).
(2) P. R. Hammond, A. N. Fletcher, R. A. Henry, and R. L. Atkins, *Appl. Phys.*, **8**, 311 (1975).
(3) P. R. Hammond, A. N. Fletcher, R. A. Henry, and R. L. Atkins, *Appl. Phys.*, **8**, 315 (1975).
(4) E. J. Schimitschek, J. A. Trias, P. R. Hammond, R. A. Henry, and R. L. Atkins, *Opt. Commun.*, **16**, 313 (1976).
(5) H. von Pechmann and C. Duisberg, *Chem Ber.*, **16**, 2119 (1883).
(6) S. M. Sethna and R. Phadke, *Org. React.*, **7**, 1 (1953).
(7) J. R. Merchant, J. R. Patell, and S. M. Thakkar, *Indian J. Chem.*, **12**, 657 (1974).
(8) H. von Pechmann and O. Schwarz, *Chem. Ber.*, **32**, 3699 (1899).
(9) E. Knoevenagel *et al.*, *Chem. Ber.*, **56**, 2414 (1923).
(10) R. A. Henry and P. R. Hammond, *J. Heterocycl. Chem.*, **14**, 1109 (1977).
(11) L. L. Woods and M. M. Fooladi, *J. Chem. Eng. Data*, **13**, 440 (1968).
(12) Experiment was performed by Dr. R. A. Henry of this Laboratory. Details are available in Naval Weapons Center Technical Publications 5768, Part 1, September 1975.
(13) J. E. Pretka, U. S. Patent 3 008 969 (1961).
(14) P. R. Hammond and R. L. Atkins, *J. Heterocycl. Chem.*, **12**, 1061 (1975).
(15) C. J. Cavallito and T. H. Haskell, *J. Am. Chem. Soc.*, **66**, 1166 (1944).
(16) L. Bradford, T. J. Elliot, and F. M. Reese, *J. Chem. Soc.*, 437 (1947).
(17) L. Knorr, *Justus Liebigs Ann. Chem.*, **301**, 1 (1898).
(18) N. P. Buo-Hoi, M. Gauthier, and M. Dat Xuong, *Bull. Soc. Chim. Fr.*, 52 (1965).
(19) F. A. L. Anet and R. Anet, "Determination of Organic Structures by Physical Methods", Vol. 3, F. C. Nachod and J. J. Zuckerman, Ed., Academic Press, New York, N.Y., 1973, pp 344–420.

Syntheses of [1-(Alkylthio)]- and (1-Mercapto)cycloalkanephosphonic Esters by the Reactions of Cycloalkanethiones with Trialkyl Phosphites

Shigeo Yoneda, Tokuzo Kawase, and Zen-ichi Yoshida*

Department of Synthetic Chemistry, Kyoto University, Yoshida, Kyoto 606, Japan

Received September 29, 1977

Cycloalkanethiones reacted with trialkyl phosphites to give [1-(alkylthio)]- and/or (1-mercapto)cycloalkanephosphonic esters. The reaction mechanism is discussed in terms of a concerted one via the betaine intermediate. These sulfur-containing esters are easily converted to cycloalkanephosphonic esters in good yields by Raney nickel treatment.

The chemistry of thiocarbonyl compounds[1] has attracted much attention owing to their interesting reactivities and preparative significance. Especially, the reactions of thiocarbonyl compounds with organophosphorus compounds such as phosphites and phosphines have been the focus of interest in the past several years, because phosphines and phosphites

0022-3263/78/1943-1980$01.00/0