action of 8 mmol of 2 with 2.2 g (12 mmol) of *n*-butyl iodide for 2.5 h gave a semisolid crude product which was chromatographed. Elution with dichloromethane–hexane (9:1, 700 mL) gave 0.32 g (10%) of **3h**.[19] Further elution with the same solvent mixture 1.2 L) gave 0.6 g (22%) of **3g**.

7-Chloro-3-(diphenylhydroxymethyl)-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (4a). To 4 mmol of anion 2 was added 0.73 g (4 mmol) of benzophenone in 5 mL of THF. The reaction was stirred for 2 h, decomposed with dilute HCl (pH of aqueous layer was 6–7), and extracted with ether. The oil obtained after evaporation of the dried extract was passed through a column of silica gel.

3-Acetyl-7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (6a). To 4 mmol of 2 was added 0.35 g (4 mmol) of ethyl acetate in 5 mL of THF, and the mixture was stirred for 1 h. The solution was treated with dilute HCl to pH 6–7. The reaction mixture was extracted with ether (500 mL). The oil, obtained after evaporation of the dried ethereal extract, was chromatographed. Elution with hexane–ethyl acetate (4:1, 200 mL) gave traces of an oil (unidentified). Further elution with the same solvent mixture (150 mL) gave a thick oil, which was crystallized from pentane to give 0.15 g (12%) of **6a**.

Reactions of Benzyl Chloride with LDA. To 4 mmol of LDA in THF was added 0.48 g (4 mmol) of benzyl chloride as a solution in 5 mL of THF. After 15 min at 25 °C the reaction was processed in the usual fashion to yield 1-chloro-1,2-diphenylethane (7) as a light yellow oil (homogeneous by TLC): ^{1}H NMR ($CDCl_3$) δ 7.61–7.15 (m, 10 H, aromatic), 4.96 (t, 1 H, CH), 3.24 (d, 2 H, CH_2).

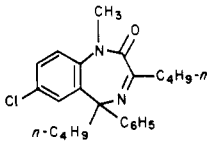
In a similar experiment employing 4 mmol of benzyl chloride and 8 mmol of LDA, *trans*-stilbene (8, mp 123–124 °C) was isolated as the major product. A mixture melting point with an authentic sample was not depressed. The ^{1}H NMR spectrum was identical with that of an authentic sample of 8.

Acknowledgment. We are grateful to Dr. W. E. Scott of Hoffman-La Roche Inc. for providing us with samples of diazepam (1) and racemic 3-methyldiazepam (**3a**) and to Mr. T. C. Glass for his help with the NMR experiments.

Registry No. 1, 439-14-5; 2, 78498-73-4; **3a**, 50882-52-5; **3b**, 40918-46-5; **3c**, 78498-74-5; **3d**, 29580-36-7; **3e**, 78498-75-6; **3f**, 78498-76-7; **3g**, 78498-77-8; **3h**, 78498-78-9; **4a**, 78498-79-0; **4b**, 78498-80-3; **4c**, 78498-81-4; **4d**, 78498-82-5; **4e**, 78498-83-6; **5a**, 78498-84-7; **5b**, 78498-85-8; **6a**, 78498-86-9; **6b**, 78498-87-0; 7, 4714-14-1; methyl iodide, 74-88-4; ethyl iodide, 75-03-6; isopropyl iodide, 75-30-9; benzyl chloride, 100-44-7; 4-methylbenzyl chloride, 824-94-2; 4-chlorobenzyl chloride, 104-83-6; butyl iodide, 542-69-8; diphenylmethanone, 119-61-9; 1-phenylethanone, 98-86-2; 2-propanone, 67-64-1; cyclohexanone, 108-94-1; benzaldehyde, 100-52-7; ethyl acetate, 141-78-6; methyl benzoate, 93-58-3.

Supplementary Material Available: ^{1}H NMR, IR, and analytical data for compounds **3a–h**, **4a–e**, **5a,b**, and **6a,b** (2 pages). Ordering information is given on any current masthead page.

(19) A referee has suggested that dibutyl derivative **3h** could have the 1,5-dihydro structure i. This alternative structure is ruled out by the observations that **3h** possesses the characteristic IR bands at 1680, 1610, and 1410 cm^{-1} for 1,3-dihydro-1,4-benzodiazepinones, while i would be expected to have strong absorption below 1650 cm^{-1}.[20]



i

(20) Ogata, M.; Matsumoto, H.; Hirose, K. *J. Med. Chem.* 1977, *20*, 776.

Pyrimidine Derivatives and Related Compounds. 39.[1] A Novel Cycloaromatization Reaction of 5-Formyl-1,3-dimethyluracil with Three-Carbon Nucleophiles. Synthesis of Substituted 4-Hydroxybenzoates

Kosaku Hirota,* Yukio Kitade, and Shigeo Senda

Gifu College of Pharmacy, 6-1, Mitahora-higashi 5 Chome, Gifu 502, Japan

Received April 13, 1981

Treatment of 5-formyl-1,3-dimethyluracil (1) with α-substituted acetone derivatives (C–C–C type nucleophiles) such as acetylacetone, acetoacetamide, ethyl acetoacetate, and phenylacetone in basic media affords the corresponding 4-hydroxybenzoates (4). On the other hand, treatment of 1 with cyanoacetamide, a C–C–N type nucleophile, gives the nicotinate 8. A mechanism for this cycloaromatization was proposed on the basis of reaction of 5-formyl-1,3-dimethyluracil-d_1 (6) with acetylacetone.

Uracil derivatives constituted of a urea part (N_1–C_2–N_3) and a three-carbon fragment (C_4–C_5–C_6) can be used as a source of formyl acetate.[2a] In fact, when uracils are allowed to react with the reagents containing two nucleophilic sites, various heterocyclic compounds are obtained.[2-5] For example, uracils are converted into the corresponding pyrazolones and isoxazolones by treatment with hydrazine and hydroxylamine, respectively.[3] Watanabe et al. and we[4] have also found that the reaction of 1,3-disubstituted uracils with 1,3-bifunctional nucleophiles such as guanidine

(1) For part 38, see M. Yogo, K. Hirota, and S. Senda, *J. Heterocycl. Chem.*, in press.
(2) (a) E. G. Lovett and D. Lipkin, *J. Org. Chem.*, 43, 3073 (1978); (b) *ibid.*, 42, 2574 (1977).
(3) F. Lingens and H. Schneider-Bernlöhr, *Justus. Liebigs Ann. Chem.*, 686, 134 (1965); D. H. Hayes and F. Hayes-Baron, *J. Chem. Soc. C*, 1528 (1967).
(4) K. Hirota, K. A. Watanabe, and J. J. Fox, *J. Heterocycl. Chem.*, 14, 537 (1977); *J. Org. Chem.*, 43, 1193 (1978); K Hirota, Y. Kitade, S. Senda, M. J. Halat, K. A. Watanabe, and J. J. Fox, *J. Am. Chem. Soc.*, 101, 4423 (1979); K. Hirota, Y. Kitade, and S. Senda, *Heterocycles*, 14, 407 (1980); K. Hirota, Y. Kitade, S. Senda, M. J. Halat, K. A. Watanabe, and J. J. Fox, *J. Org. Chem.*, 46, 846 (1981).
(5) K. Y. Zee-Cheng and C. C. Cheng, *J. Org. Chem.*, 33, 892 (1968).

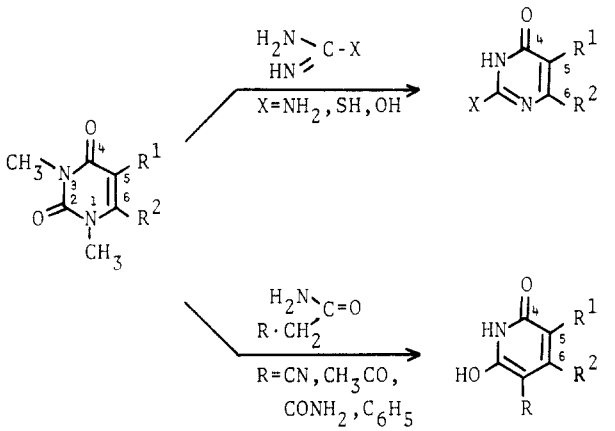
0022-3263/81/1946-3949$01.25/0

Table I. ^{1}H NMR Chemical Shifts of Substituted 4-Hydroxybenzoates 4 and 7[a]

compd	chemical shift,[c] δ				
	2-H	6-H	5-H	OH	other
4a	8.48 (d, $J_{2,6}$ = 2.0)	8.13 (dd, $J_{2,6}$ = 2.0, $J_{5,6}$ = 9.0)	6.99 (d, $J_{5,6}$ = 9.0)	12.64	4.39 (2 H, q, J = 7.0, OCH_2CH_3), 2.72 (3 H, s, $COCH_3$), 1.41 (3 H, t, J = 7.0, OCH_2CH_3)
4b	8.48 (d, $J_{2,6}$ = 2.0)	8.17 (dd, $J_{2,6}$ = 2.0, $J_{5,6}$ = 9.0)	7.00 (d, $J_{5,6}$ = 9.0)	12.65	3.92 (3 H, s, OCH_3), 2.70 (3, H, s, $COCH_3$)
4c[b]	8.54 (d, $J_{2,6}$ = 2.0)	7.98 (dd, $J_{2,6}$ = 2.0, $J_{5,6}$ = 8.6)	6.99 (d, $J_{5,6}$ = 8.6)	13.66	8.62 (1 H, br), 8.04 (1 H, br), 4.32 (2 H, q, J = 7.4, OCH_2CH_3), 1.33 (3 H, t, J = 7.4, CH_2CH_3)
4d	8.56 (d, $J_{2,6}$ = 2.0)	8.13 (dd, $J_{2,6}$ = 2.0, $J_{5,6}$ = 9.0)	7.00 (d, $J_{5,6}$ = 9.0)	11.29	4.45 (2 H, q, J = 7.0, OCH_2CH_3), 4.37 (2 H, q, J = 7.0, OCH_2CH_3), 1.46 (3 H, t, J = 7.0, CH_2CH_3), 1.40 (3 H, t, J = 7.0, CH_2CH_3)
4e	8.32 (d, $J_{2,6}$ = 2.0)	7.90 (dd, $J_{2,6}$ = 2.0, $J_{5,6}$ = 9.0)	7.00 (d, $J_{5,6}$ = 9.0)	11.12	4.44 (2 H, q, J = 7.0, OCH_2CH_3), 3.01 (3 H, d, J = 5.0, $NHCH_3$), 1.43 (3 H, t, J = 7.0, CH_2CH_3)
4f		8.70 (s, 2-H and 6-H)		12.23	3.99 (6 H, s, $2OCH_3$), 3.93 (3 H, s, OCH_3)
4g		8.09-7.85 (m, 2-H and 6-H)	6.99 (d, $J_{5,6}$ = 9.5)		4.33 (2 H, q, J = 7.0, OCH_2CH_3), 1.37 (3 H, t, J = 7.0, CH_2CH_3)
7		8.13 (d, $J_{5,6}$ = 9.0)	6.98 (d, $J_{5,6}$ = 9.0)	12.60	4.38 (2 H, q, J = 7.0, OCH_2CH_3), 2.68 (3, H, s, $COCH_3$), 1.39 (3 H, t, $J_{5,6}$ = 7.0, OCH_2CH_3)

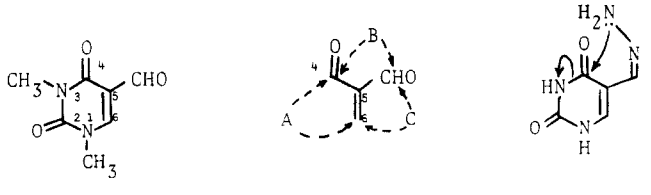
[a] Solvent $CDCl_3$. [b] Solvent Me_2SO-d_6. [c] J values given in hertz.

Scheme I



(N–C–N type) and α-substituted acetamides (C–C–N type) gives pyrimidines and pyridines, respectively (see Scheme I).

5-Formyl-1,3-dimethyluracil (1) is an interesting synthon providing a three-carbon fragment with three electrophilic sites (C_4, C_5 CHO, and C_6). According to their combination, recyclization of type A, B, or C with a bifunctional nucleophile would take place as shown in the drawing 2.



1 2 3

Cheng et al. reported[5] that the reaction of 5-formyluracil with hydrazine gave a B-type ring-transformation product, 4-(ureidomethyhlene)-1*H*-5-pyrazolone via intermediate 3.

However, treatment of 1 with α-substituted acetone derivatives containing two nucleophilic sites (C–C–C-type nucleophile) in a basic medium afforded C-type ring-transformation products, 4-hydroxybenzoates. This process is a novel method for synthesizing benzenes by the condensation of two three-carbon units—one with two electrophilic sites and the other with two nucleophilic ones. A preliminary paper[6] on this subject has appeared; we now report this cycloaromatization reaction in detail.

Results and Discussion

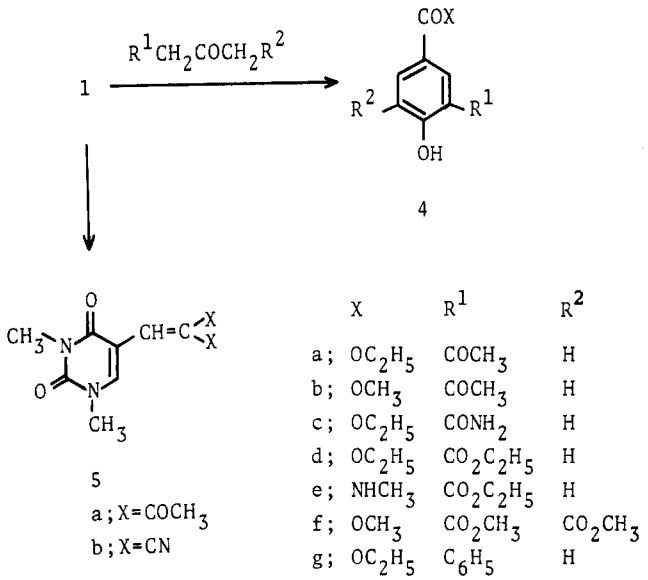
Refluxing of 1 with acetylacetone in ethanolic sodium ethoxide followed by neutralization of the reaction mixture gave ethyl 3-acetyl-4-hydroxybenzoate (**4a**)[7] in 55% yield and 1,3-dimethylurea (Scheme II). The use of sodium methoxide instead of sodium ethoxide resulted in the formation of the methyl benzoate (**4b**)[8] in 40% yield. Further evidence for the structure of **4a** was provided by conversion of 5-(2,2-diacetylvinyl)-1,3-dimethyluracil (**5a**) into the cycloaromatization product **4a** by treatment with ethanolic sodium ethoxide. Compound **5a** was synthesized by condensation of 1 and acetylacetone in the presence of piperidine–acetic acid with removal of the water formed as an azeotrope with benzene. Under the same cycloaromatization conditions, 1 and malononitrile, which lacks an active methyl group, gave the 5-vinyluracil derivatives **5b** in good yield.

Formation of the benzoate **4a** can be explained by two different reaction paths as shown in Scheme III. The ring transformation of uracil into 4-hydroxybenzoates probably takes place by an initial attack of a carbanion either at the C_5CHO position (path a) or at position C_6 (path b). Path a appears more likely on the basis of the isolation of **5b** described above.

In order to clarify which of these two routes is involved, we investigated reaction of a deuterium labeled compound (**6**) with acetylacetone. Thus, 5-formyl-1,3-dimethyluracil-d_1 (**6**) was synthesized by reaction of 1,3-dimethyluracil and *N*,*N*-dimethylformamide-d_7 in the presence of phosphorus oxychloride. When **6** was treated with acetylacetone in ethanolic sodium ethoxide only the 2-deuteriobenzoate (**7**) was formed (Scheme III). The product (**7**) was characterized by NMR spectroscopy and mass spectrometry. The aromatic protons of **7** appeared

(6) K. Hirota, Y. Kitade, and S. Senda, *J. Heterocycl. Chem.*, **17**, 413 (1980).
(7) D. N. Shah and N. M. Shah, *J. Indian Chem. Soc.*, **26**, 235 (1949).
(8) C. Rohmann and H. D. Wilm, *Arch. Pharm.*, **280**, 76 (1942).

Scheme II



	X	R^1	R^2
a;	OC_2H_5	$COCH_3$	H
b;	OCH_3	$COCH_3$	H
c;	OC_2H_5	$CONH_2$	H
d;	OC_2H_5	$CO_2C_2H_5$	H
e;	$NHCH_3$	$CO_2C_2H_5$	H
f;	OCH_3	CO_2CH_3	CO_2CH_3
g;	OC_2H_5	C_6H_5	H

as two doublets ($J_{5,6}$ = 9.0 Hz) at δ 6.98 and 8.13 (see Table I). The molecular ion of **7** was m/e 209 with the base peak at m/e 164. The fragmentation pattern of **7** was similar to that of **4a**.

On the basis of the above reaction in which **7** was formed, we concluded that the reaction proceeded by path a as shown in Scheme III.

Compound **1** was readily converted into ethyl 3-carbamoyl-4-hydroxybenzoate (**4c**)[9] by treatment with acetoacetamide in ethanolic sodium ethoxide. When ethyl acetoacetate was used as a 1,3-bifunctional nucleophile under the same conditions, the cycloaromatization did not occur cleanly. However, the reaction in the presence of potassium hydroxide proceeded smoothly to give two aromatic compounds **4d**[10] and **4e** in 37% and 12% yields, respectively. Formation of the benzoate (**4e**) suggests that the nitrogen–carbon bond breakage must occur between position C_2 and N_3 in the uracil ring. Also, treatment of **1** with dimethyl acetonedicarboxylate in methanolic sodium methoxide produced 2,4,6-tris(methoxycarbonyl)-phenol (**4f**).[11] Then, the use of phenylacetone and dibenzyl ketone as three-carbon fragments containing two nucleophilic sites was studied. Thus, **1** was treated with phenylacetone in the same way as above to afford the biphenyl compound **4g**.[12] On the contrary, reaction of **1** with dibenzyl ketone did not proceed.

When cyanoacetamide, a C–C–N-type nucleophile, was employed as a compound with two nucleophilic sites in the cycloaromatization reaction, ethyl 5-cyano-6-hydroxynicotinate (**8**) was obtained in 46% yield (Scheme IV). Compound **8** was also prepared in 77% yield by treating the Knoevenagel product (**9**) with ethanolic sodium ethoxide. Thus, **9** was prepared from **1** and cyanoacetamide in a similar manner for the preparation of **5a**. Treatment of **1** with malonamide, however, did not give the corresponding nicotinate.

Subsequently, we have investigated the reactivity of 5-formyl-1,3,6-trimethyluracil (**10**) toward a C–C–C-type nucleophile such as acetylacetone. The expected benzoate (**11**)[13] was not obtained in ethanolic sodium ethoxide, but in the presence of piperidine–acetic acid the quinazoline derivative **12** was formed in 46% yield (Scheme V).

Experimental Section

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Elemental analyses were carried out at the Microanalytical Laboratory of our college. Proton magnetic resonance spectra (60 MHz) were recorded on a Hitachi Perkin-Elmer R-20B spectrometer, with tetramethylsilane (Me_4Si) as an internal reference. Chemical shifts are reported in parts per million (δ), the J values are given in hertz, and signals are quoted as s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet), or br (broad); J values are first order. Infrared spectra were taken on a Hitachi 215 instrument as KBr pellets. Mass spectra were obtained in a JEOL JMS-D300 machine operating at 70 eV. Ultraviolet spectra were obtained from ethanol on a Hitachi 323 spectrophotometer. Column chromatography was carried out on silica gel (Wakogel C-200).

Ethyl 3-Acetyl-4-hydroxybenzoate (4a) and 1,3-Dimethylurea. (a) A mixture of **1** (0.504 g, 0.003 mol) and acetylacetone (1.20 g, 0.12 mol) in ethanolic sodium ethoxide [prepared by dissolving Na (0.230 g, 0.010 mol) in 40 mL of absolute EtOH] was heated at reflux for 2 h. The solvent was removed in vacuo, and the residue was dissolved in cold water (20 mL). Upon acidification of the solution with concentrated HCl, the product precipitated and was collected by filtration: 0.345 g (55%);[15] mp 61–63 °C. Recrystallization from petroleum ether gave analytically pure **4a**: mp 63–64 °C (lit.[7] mp 71 °C) mass spectrum, m/e 208 (M^+); UV λ_{max} 322, 256, 234 (ϵ 3100, 11 600, 35 800). Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.46; H, 5.81. Found: C, 63.43; H, 5.83.

Isolation of 1,3-dimethylurea: the aqueous filtrate obtained above was extracted with chloroform to remove the excess acetylacetone, and the aqueous layer was evaporated to dryness. The residue was dissolved in chloroform, and the chloroform solution was dried over $MgSO_4$ and was evaporated to dryness to give 0.120 g of 1,3-dimethylurea.

(b) A solution of **5a** (0.500 g, 0.002 mol) in ethanolic sodium ethoxide [prepared by dissolving Na (0.230 g, 0.01 mol) in 40 mL of absolute EtOH] was heated at reflux for 30 min. The mixture was evaporated to dryness, and the residue was dissolved in cold water (20 mL). The solution was acidified with concentrated HCl to give **4a**: 0.295 g (71%); mp 61–63 °C. The NMR and IR spectra were identical with those of the compound prepared above.

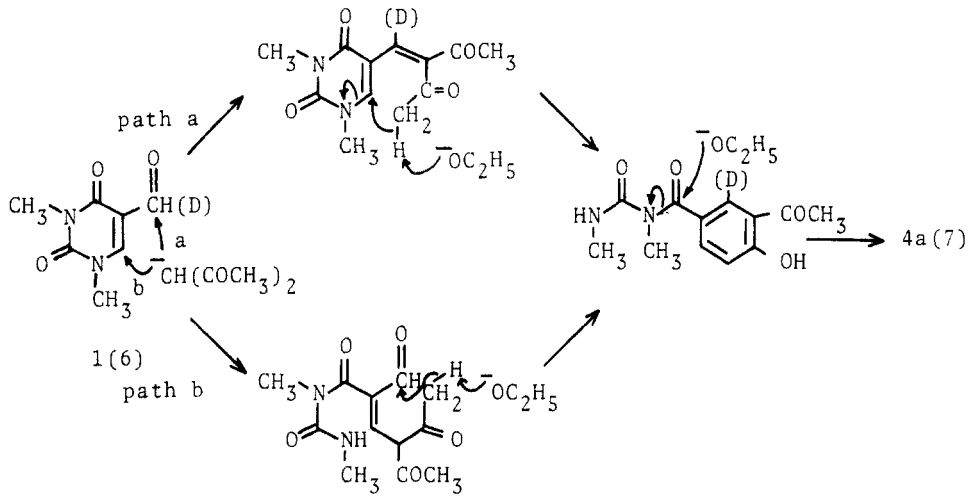
Methyl 3-Acetyl-4-hydroxybenzoate (4b). A mixture of **1** (0.504 g, 0.003 mol) and acetylacetone (1.20 g, 0.12 mol) in methanolic sodium methoxide [prepared by dissolving Na (0.138 g, 0.006 mol) in 40 mL of absolute MeOH] was heated at reflux for 3 h. The reaction mixture was treated as described above to give crude product **4b**: 0.230 g (40%);[15] mp 91–93 °C. Recrystallization from petroleum ether gave analytically pure **4b**: mp 93–94 °C (lit.[8] mp 98 °C); mass spectrum, m/e 194 (M^+); UV λ_{max} 322, 256, 233 (ϵ 2900, 11 100, 33 600). Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 62.20; H, 5.28.

Ethyl 3-Carbamoyl-4-hydroxybenzoate (4c). A mixture of **1** (0.850 g, 0.005 mol) and acetoacetamide (0.650 g, 0.005 mol) in ethanolic sodium ethoxide [prepared by dissolving Na (0.700 g, 0.030 mol) in 50 mL of absolute EtOH] was heated at reflux for 2 h. The reaction mixture was treated as described above to give crude product: 0.640 g (61%);[15] mp 210–214 °C. Recrystallization from ethanol gave analytically pure **4c**: mp 216–217 °C (lit.[9] mp 225–226 °C); mass spectrum, m/e 209 (M^+); UV λ_{max} 302, 258, 219 (ϵ 3200, 13 100, 29 100). Anal. Calcd for $C_{10}H_{11}O_4N$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.48; H, 5.17; N, 6.81.

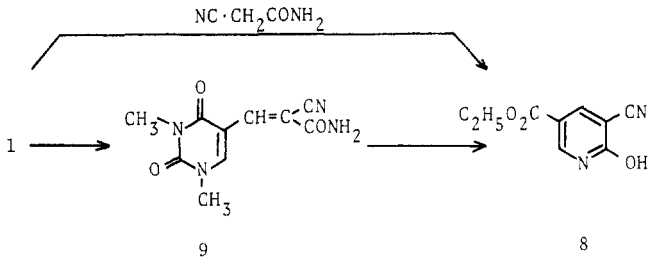
Ethyl 3-(Ethoxycarbonyl)-4-hydroxybenzoate (4d) and 3-(Ethoxycarbonyl)-4-hydroxy-*N*-methylbenzamide (4e). A

(9) J. M. Z. Gladych, A. S. Lindsey, and E. P. Taylor, *J. Chem. Soc.*, 4834 (1957).
(10) S. E. Hunt, J. I. Jones, and A. S. Lindsey, *Chem. Ind. (London)*, 417 (1955).
(11) O. B. Maximov and V. E. Shapovalov, *J. Chromatogr.*, **66**, 29 (1972).
(12) K. H. Slotta and A. E. Nold, *Chem. Ber.*, **68**, 2226 (1935).
(13) In this reaction, cycloaddition similar to that previously reported[14] proceeded to give quinazoline derivative. It will be described later in detail.
(14) S. Senda, T. Asao, I. Sugiyama, and K. Hirota, *Tetrahedron Lett.*, 531 (1980).
(15) The NMR spectrum of this compound showed it to be in a high state of purity.

Scheme III



Scheme IV



mixture of 1 (0.504 g, 0.003 mol), ethyl acetoacetate (0.390 g, 0.003 mol), and KOH (0.336 g, 0.006 mol) in 40 mL of ethanol was heated at reflux for 2 h. The reaction mixture was treated as described above to give a mixture of **4d** and **4e** (0.370 g). The mixture was dissolved in hot ether, and insoluble matter was filtered. The filtrate gave analytically pure **4d** [0.264 g (37%); mp 53–54 °C (lit.[10] mp 54–55 °C)], while the insoluble matter was recrystallized from ligroin to give analytically pure **4e**: 0.83 g (12%); mp 191–192 °C.

4d: mass spectrum, m/e 238 (M^+); UV λ_{max} 306, 256, 223 (ϵ 3000, 11 400, 35 600). Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.71; H, 6.01.

4e: mass spectrum, m/e 223 (M^+): UV λ_{max} 308, 243 (sh), 220 (ϵ 2900, 10 900, 37 200). Anal. Calcd for $C_{11}H_{13}O_4N$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.03; H, 5.90; N, 6.06.

2,4,6-Tris(methoxycarbonyl)phenol (4f). A mixture of 1 (0.504 g, 0.003 mol) and dimethyl acetonedicarboxylate (2.09 g, 0.12 mol) in methanolic sodium methoxide [prepared by dissolving Na (0.230 g, 0.010 mol) in 40 mL of absolute MeOH] was heated at reflux for 30 min. The precipitate was filtered and dissolved in cold water (20 mL). The solution was acidified with concentrated HCl to give **4f**: 0.475 g (59%); mp 134–136 °C. Recrystallization from ethanol gave analytically pure **4f**: 0.285 g (35%); mp 138–139 °C; mass spectrum, m/e 268 (M^+). Anal. Calcd for $C_{12}H_{12}O_7$: C, 53.73; H, 4.51. Found: C, 53.53; H, 4.51.

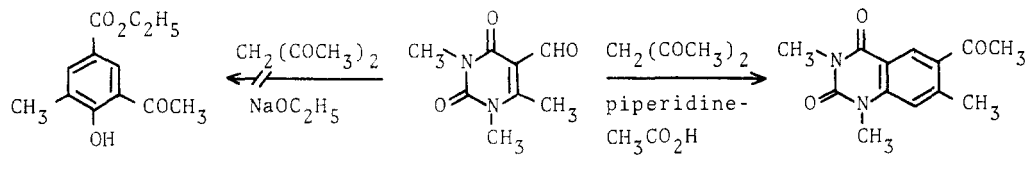
Ethyl 4-Hydroxy-3-phenylbenzoate (4g). A mixture of 1 (0.504 g, 0.003 mol) and phenylacetone (0.800 g, 0.006 mol) in ethanolic sodium ethoxide [prepared by dissolving Na (0.136 g, 0.006 mol) in 40 mL of absolute EtOH] was heated at reflux for 3 h. The solvent was removed in vacuo and the residue was dissolved in cold water. The solution was acidified with concentrated HCl and extracted with $CHCl_3$, and the extract was dried over $MgSO_4$ and evaporated to dryness. The residue was subjected to column chromatography. Elution with chloroform and benzene (1:5) gave analytically pure **4g**: 0.130 g (18%); mp 111–112 °C (lit.[12] mp 112–114 °C; mass spectrum, m/e 242 (M^+); UV λ_{max} 262 (sh), 242 (ϵ 15 300, 31 500). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.31; H, 5.85.

5-(2,2-Diacetylvinyl)-1,3-dimethyluracil (5a). A mixture of 1 (1.68 g, 0.01 mol), acetylacetone (1.20 g, 0.012 mol), piperidine (1 drop), and acetic acid (1 drop) in 80 mL of benzene was refluxed with separation of water as benzene azeotrope for 4 h. The reaction mixture was evaporated to dryness. The residue was triturated with ether, and the resulting precipitate was collected by filtration and recrystallized from ethanol to give 1.84 g (74%) of **5a**: mp 162–164 °C; NMR ($CDCl_3$) δ 2.34 (3 H, s, CH_3) 2.44 (3 H, s, CH_3), 3.38 (3 H, s, CH_3), 3.47 (3 H, s, CH_3), 7.45 (1 H, s, CH=C), 7.90 (1 H, s, C_6H); mass spectrum, m/e 250 (M^+); UV λ_{max} 320, 286 (sh) (ϵ 19 300, 7000). Anal. Calcd for $C_{12}H_{14}O_4N_2$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.61; H, 5.61; N, 11.16.

5-(2,2-Dicyanovinyl)-1,3-dimethyluracil (5b). A mixture of 1 (0.504 g, 0.003 mol) and malononitrile (0.792 g, 0.012 mol) in ethanolic sodium ethoxide [prepared by dissolving Na (0.460 g, 0.02 mol) in 40 mL of absolute EtOH] was heated at reflux for 30 min. The reaction mixture was evaporated to dryness, and the residue was dissolved in cold water (20 mL). The solution was acidified with concentrated HCl to give crystals: 0.545 g (84%);[15] mp 170–171 °C. Recrystallization from ethanol gave analytically pure **5b**: mp 179.5–180.5 °C; NMR (Me_2SO-d_6) δ 3.22 (3 H, s, CH_3), 3.44 (3 H, s, CH_3), 7.92 (1 H, s, CH=C) 8.65 (1 H, s, C_6H); mass spectrum, m/e 216 (M^+); UV λ_{max} 355, 267, 240 (ϵ 19 800, 6400, 5500). Anal. Calcd for $C_{10}H_8O_2N_4$: C, 55.55; H, 3.73; N, 25.92. Found: C, 55.27; H, 3.72; N, 25.63.

Ethyl 3-Acetyl-2-deuterio-4-hydroxybenzoate (7). 1,3-Dimethyluracil (1.68 g, 0.012 mol) was dissolved in a mixture of *N,N*-dimethylformamide-d_7 (1 mL) and phosphorus oxychloride (1.84 g, 0.012 mol). The reaction mixture was heated at 80 °C for 1 h. The reaction mixture was evaporated in vacuo, and the residue was dissolved in cold water (20 mL). The solution was extracted with chloroform. The extract was dried over $MgSO_4$ and evaporated to dryness to give a mixture (1.36 g) of **6** and 1,3-dimethyluracil (ratio, 3:1): mp 125–126 °C. NMR ($CDCl_3$) of **6**: 3.37 (3 H, s, CH_3), 3.53 (3 H, s, CH_3), 8.11 (1 H, s, C_6H). This was used in the following step without purification. Thus, the mixture (0.40 g) and acetylacetone (0.50 g, 0.005 mol) were

Scheme V



dissolved in ethanolic sodium ethoxide [prepared by dissolving Na (0.06 g) in 30 mL of absolute EtOH]. The mixture was heated at reflux for 3 h. The solvent was removed by evaporation in vacuo, and the residue was dissolved in cold water. The resulting precipitate was collected by filtration to give 0.115 g of 7,[15] mp 58–60 °C. Recrystallization from petroleum ether gave pure 7: mp 65–67 °C; mass spectrum, m/e 209 (M^+); UV λ_{max} 322, 256, 234 (ϵ 3000, 11300, 34900).

Ethyl 5-Cyano-6-hydroxynicotinate (8). (a) A mixture of 1 (0.504 g, 0.003 mol) and cyanoacetamide (0.84 g, 0.01 mol) in ethanolic sodium ethoxide [prepared by dissolving Na (0.23 g, 0.01 mol) in 40 mL of absolute EtOH] was heated at reflux for 1 h. The solvent was removed in vacuo, and the residue was dissolved in cold water (20 mL). Upon acidification with concentrated HCl, the crystalline product precipitated and was collected by filtration: 0.233 g (46%);[15] mp 218–221 °C. Recrystallization from water gave analytically pure 8: mp 223–225 °C; NMR (Me_2SO-d_6) δ 1.30 (3 H, t, J = 7, CH_3), 4.24 (2 H, q, J = 7, CH_2), 8.29 (1 H, d, J = 2, C_6H), 8.42 (1 H, d, J = 2, C_4H), 13.08 (1 H, br, OH); mass spectrum, m/e 192 (M^+); UV λ_{max} 332, 261, 218 (sh), (ϵ 7200, 15100, 14000). Anal. Calcd for $C_9H_8O_3N_2$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.26; H, 4.16; N, 14.79.

(b) A solution of 9 (0.702 g, 0.003 mol) in ethanolic sodium ethoxide [prepared by dissolving Na (0.138 g, 0.006 mol) in 40 mL of absolute EtOH] was heated at reflux for 3.5 h. The reaction solution was evaporated to dryness, and the residue was dissolved in cold water (20 mL). The solution was acidified with concentrated HCl to give 8: 0.445 g (77%); mp 220–222 °C. The IR spectrum was identical with that of the compound prepared above.

5-(2-Carbamoyl-2-cyanovinyl)-1,3-dimethyluracil (9). A mixture of 1 (1.68 g, 0.01 mol), cyanoacetamide (1.01 g, 0.012 mol), piperidine (1 drop), and acetic acid (1 drop) was refluxed in 80 mL of benzene with separation of water as a benzene azeotrope for 2 h. The reaction mixture was evaporated to dryness. The residue was triturated with ether, and the resulting precipitate was collected by filtration to give 2.19 g (94%) of 9, mp 244–246 °C. Recrystallization from water gave analytically pure 9: 1.26 g (54%); mp 256–257 °C; NMR (Me_2SO-d_6) 3.23 (3 H, s, CH_3), 3.44 (3 H, s, CH_3), 8.05 (1 H, s, CH=C), 8.63 (1 H, s, C_6H); mass spectrum, m/e 234 (M^+); UV λ_{max} 344, 265, 234 (ϵ 16700, 7500, 5800). Anal. Calcd for $C_{10}H_{10}O_3N_4$: C, 51.28; H, 4.30; N, 23.92. Found: C, 50.98; H, 4.18; N, 23.71.

6-Acetyl-1,3,7-trimethylquinazoline-2,4(1*H*,3*H*)-dione (12). A mixture of 10 (0.546 g, 0.003 mol), acetylacetone (0.360 g, 0.0036 mol), piperidine (1 drop), and acetic acid (1 drop) in 80 mL of benzene was refluxed with separating water as a benzene azeotrope for 12 h. The reaction mixture was evaporated to dryness. The residue was triturated with ether, and the resulting precipitate was collected by filtration and recrystallized from ethanol to give 0.340 g (46%) of 12: mp 210–211 °C; NMR ($CDCl_3$) δ 2.67 (3 H, s, $COCH_3$), 2.70 (3 H, s, C_7CH_3), 3.49 (3 H, s, NCH_3), 3.62 (3 H, s, NCH_3), 7.04 (1 H, s, C_8H), 8.62 (1 H, s, C_5H); UV λ_{max} 284, 241 (ϵ 15200, 42300); mass spectrum, m/e 246 (M^+), 231 ($M^+ - 15$). Anal. Calcd for $C_{13}H_{14}O_3N_2$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.28; H, 5.80; N, 11.13.

Registry No. 1, 4869-46-9; **4a**, 57009-53-7; **4b**, 57009-12-8; **4c**, 74442-95-8; **4d**, 5985-25-1; **4e**, 74442-97-0; **4f**, 36727-23-8; **4g**, 74442-96-9; **5a**, 74442-98-1; **5b**, 78515-04-5; **6**, 78515-05-6; **7**, 78515-06-7; **8**, 74443-00-8; **9**, 74442-99-2; **10**, 23941-84-6; **12**, 78515-07-8; acetylacetone, 123-54-6; 1,3-dimethylurea, 96-31-1; acetoacetamide, 5977-14-0; ethyl acetoacetate, 141-97-9; dimethyl acetonedicarboxylate, 1830-54-2; phenylacetone, 103-79-7; malononitrile, 109-77-3; 1,3-dimethyluracil, 874-14-6; cyanoacetamide, 107-91-5.

Neber Rearrangement of Amidoximesulfonates. Synthesis of 2-Amino-1-azirines

John A. Hyatt

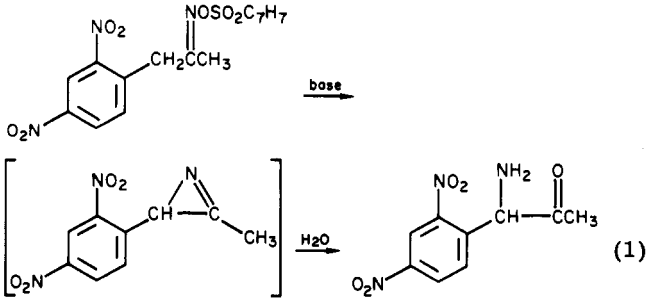
Research Laboratories, Tennessee Eastman Company, Eastman Chemicals Division, Eastman Kodak Company, Kingsport, Tennessee 37662

Received December 24, 1980

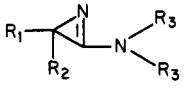
Amidoximes prepared from α-cyanoacetanilides and (phenylsulfonyl)acetonitrile were converted to the corresponding *O*-tosyl derivatives. Upon treatment with base, these amidoxime-*O*-sulfonates afforded 2-amino-1-azirines instead of the expected 3-amino-2-pyrazolin-5-ones. This transformation can be viewed as a new variant of the Neber rearrangement. Azirines bearing unsubstituted amino groups have not been reported previously; structure proof and reactions of these compounds are discussed.

Introduction

The Neber rearrangement of ketoxime-*O*-sulfonates to amino ketones, shown in its classic form in eq 1, proceeds via 1-azirine intermediates but has not been a generally useful preparation method for 1-azirines.[1,2] Other routes to 1-azirines are available,[3] however, and in recent years syntheses of 2-(*N*,*N*-dialkylamino)-1-azirines have been reported.[4,5] A considerable body of work, principally by Ghosez[6] and by Heimgartner[7] and their co-workers, has demonstrated that compounds of the type 1 are remarkably useful intermediates for the synthesis of a large array of heterocyclic compounds.



(1)



1, R_1 = H or alkyl or aryl; R_2 = alkyl or aryl; R_3 = alkyl

(1) O'Brien, C. *Chem. Rev.* **1964**, *64*, 81.
(2) Hassner, A.; Fowler, F. *J. Am. Chem. Soc.* **1968**, *90*, 2869.
(3) F. Fowler In "Advances in Heterocyclic Chemistry"; Academic Press: New York, 1971; Vol. 13, p 45.
(4) Rens, M.; Ghosez, L. *Tetrahedron Lett.* **1970**, 3765.
(5) de Voghel, G.; Eggerichs, T.; Clamot, B.; Viehe, H. *Chimia* **1976**, *30*, 191.
(6) Demoulin, A.; Gorissen, H.; Hesbain-Frisque, A. M.; Ghosez, L. *J. Am. Chem. Soc.* **1975**, *97*, 4409.
(7) For leading references, see Heimgartner, H. *Chimia* **1979**, *33*, 111.

0022-3263/81/1946-3953$01.25/0