4H-Furo[3,4-d][1,3]oxazine-2(1H),4-dione. A Furan Analogue of Isatoic Anhydride

Jeffery B. Press,* Nancy H. Eudy, and Timothy O. Olagbemiro

Cardiovascular-CNS Disease Research Section, American Cyanamid Company, Medical Research Division, Lederle Laboratories, Pearl River, New York 10965

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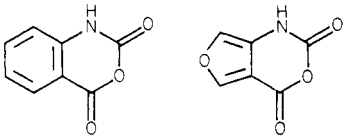
The title compound **2** was prepared in four steps from diethyl 3,4-furandicarboxylate. Reactions of **2** with nitrogen and oxygen nucleophiles occur exclusively at the nitrogen carbonyl to give ureido acids **6** or carbamato acids **8** under a variety of reaction conditions. The results are in contrast to the reactions of isatoic anhydride **1**. In order to achieve substitution at the carbonyl adjacent to the furan ring, carbamato acid **8a** was derivatized with subsequent deprotection of the amine. In this manner, furo[3,4-*d*][1,3]oxazines **14a–d** were prepared. Several possible reasons for the reactivity of **2** are presented.

Discussion

Isatoic anhydride (**1**) has been known in the literature since the late 19th century as a reactive intermediate used in the synthesis of agricultural, pharmaceutical, and industrial chemicals.[1] Although the chemistry of isatoic

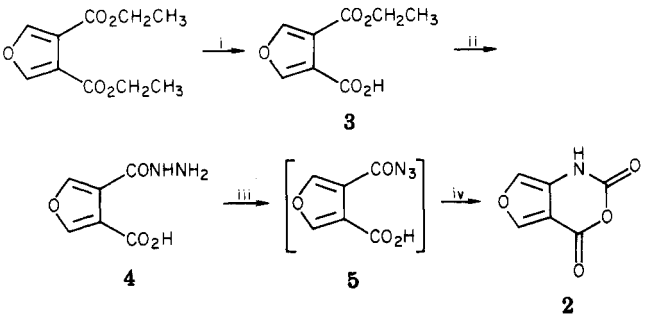


1 **2**

anhydride is well documented, only a few heterologues of **1** have been reported.[1] Because of our continuing interest in preparing novel heterotricyclic systems as potential CNS agents,[2] we were attracted to the development of new hetero analogues of **1** as possible intermediates to such systems. We describe herein the synthesis and some reactions of 4*H*-furo[3,4-*d*][1,3]oxazine-2(1*H*),4-dione (**2**), a novel furan analogue of **1**. Furan system **2** was chosen as a synthetic target because of its novelty, its potential anhydride-like activity with nucleophiles, and its 3,4-disubstitution which leaves the normally reactive 2 and 5 positions of furan systems available for other transformations.

The title compound **2** was prepared according to Scheme I. Commercially available diethyl 3,4-furandicarboxylate was converted most conveniently to monoacid **3** by using the procedure of Boyd et al.[3] Reaction of **3** with excess hydrazine hydrate in refluxing ethanol led to hydrazide **4** in high yield. Conversion of **4** to acylazide **5** with aqueous nitrous acid was straightforward; although **5** was crystalline and appeared stable, it was characterized only by an infrared absorption at 2158 cm^{-1} typical of acyl azides and was immediately converted to **2** in refluxing chloroform. Target anhydride **2** was crystalline and could be stored indefinitely without special precautions. The structure of **2** was supported by its complex absorptions in the infrared at 1786 and 1754 cm^{-1} typical of such anhydrides and the absence of absorption in the 2000–1800-cm^{-1} region of the infrared where azides and isocyanates appear. The overall yield of **2** from commercially available starting material was 45%, and there were no isolation or purification difficulties.

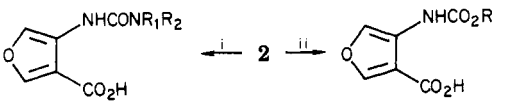
Scheme I[a]



3 **4** **5** **2**

[a] (i) NaOH, 0 °C/H_2O/CH_3CH_2OH, (ii) NH_2NH_2/CH_3CH_2OH/heat, (iii) HCl/$NaNO_2$, (iv) heat/$CHCl_3$.

Scheme II[a]

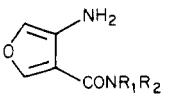


6a, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = Ph$; $R_2 = H$
d, $R_1 = R_2 = CH_3CH_2$
e, $R_1 = PhCH_2CH_2$; $R_2 = H$

8a, $R = CH_3CH_2$
b, $R = PhCH_2$

[a] (i) R_1R_2NH/THF/room temperature, (ii) ROH/room temperature.

With a convenient supply of **2** on hand, a brief study of its reactivity toward nucleophiles was undertaken (Scheme II). Reaction of **2** with a variety of aliphatic and aromatic amines at room temperature led to the exclusive formation of ureido acid derivatives **6**. The exclusivity of reaction was unaffected by elevated temperature, amine basicity, ionizing power of various solvents, amine concentration or stoichiometry, or by other basic catalysts. Amino amide **7**, the result of amine attack at the carbonyl adjacent to



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the furan ring of **2**, was not detected in the crude reaction mixtures. The fact that **6** is the only reaction product of **2** with amines is in contrast to the results reported for isatoic anhydride.[1,4] In these cases concentration, molar

(1) For a recent review of isatoic anhydride chemistry, see Coppola, G. M. *Synthesis* **1980**, 505.
(2) For examples of thiophene heterocycles recently reported from our laboratories, see Press, J. B.; Eudy, N. H.; Hofmann, C. M.; Safir, S. R. *J. Med. Chem.* **1981**, *24*, 154 and references contained therein.
(3) Boyd, M. R.; Harris, T. M.; Wilson, B. J. *Synthesis* **1971**, 545.
(4) Starger, R. P.; Wagner, E. C. *J. Org. Chem.* **1953**, *18*, 427.

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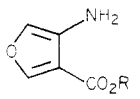
ratio, and basicity of the reactant amines affected the product ratio of anthranilamide and *o*-ureidobenzoic acid. Varying solvents also have a large effect upon these product ratios. The reactivity of **2** was similar to that reported for **1** in regard to reaction time and temperature.

Reaction of **2** with alcohols also gave rise to a single product, namely carbamate **8** (Scheme II). The quantitative formation of **8** was unaffected by base catalysts (such as sodium hydroxide or sodium ethoxide). Compound **2** reacted readily with alcohols at room temperature, in contrast to isatoic anhydride (**1**) which may be recrystallized from alcohols and which reacts only at elevated temperatures to give both anthranilate and isatoate products with ratios dependent on reaction conditions.[1,5,6] Attempts to thermally rearrange **8** to **9** caused decomposition of the furan ring although such rearrangements for the analogous benzene system have been reported.[6]



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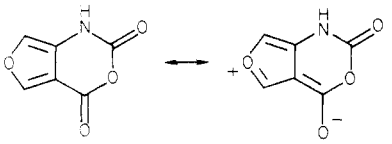
The increased reactivity of **2** toward alcohols, as compared to **1**, is probably a result of the increased ring strain of the [6.5] ring system of **2** compared to the [6.6] ring system of **1**. This increased strain is revealed in the infrared by the carbonyl absorption frequencies of **2** (1786 and 1754 cm^{-1}), which are higher than those of **1** (1760 and 1720 cm^{-1}). A possible cause for the exclusive formation of ureas **6** and carbamates **8** as products of reaction of **2** might be resonance deactivation of the carbonyl adjacent to the furan ring of **2** (i.e., **2b**). This effect would enhance the relative reactivity of the nitrogen carbonyl toward nucleophiles.

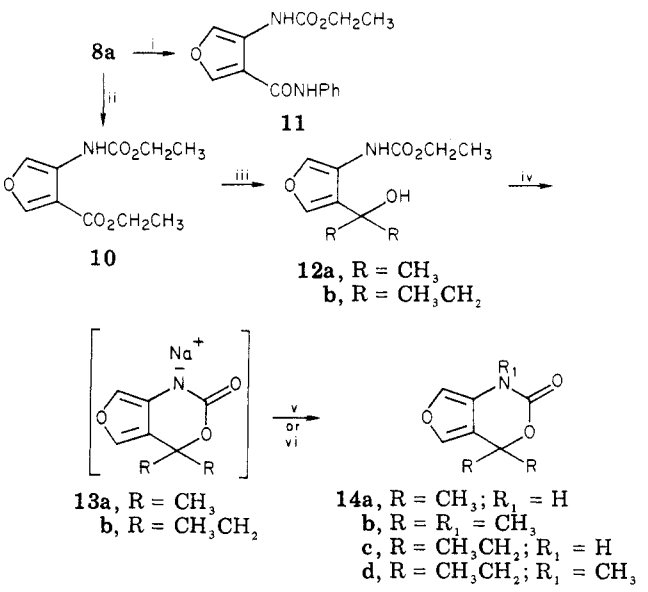


2a **2b**

Reactions of **2** with other reagents did not give useful results. Attempts to react **2** with water in tetrahydrofuran, dioxane, or dimethyl sulfoxide led to complete decomposition of the system. When **2** was treated with thiols with or without base catalysis, no characterizable product could be isolated. Attempts to N-alkylate **2** using standard conditions, including those used to prepare N-substituted isatoic anhydrides,[1] also resulted in extensive decomposition without formation of the desired products. Reaction of **2** with electrophiles (such as SO_2Cl_2 or Br_2) in a variety of solvents also gave intractable mixtures.

Since we initiated our investigation to prepare a furan anhydride that would react at either carbonyl depending upon reaction conditions, in a manner similar to **1**, the surprising observed product exclusivity was disappointing. The carbamate **8**, however, could be treated as a protected form of aminofuran **9**, which was probably advantageous since aminofurans are generally unstable.[7,8] In this regard, **8a** reacted in ethanol with acid catalysis to give the carbamato ester **10** (Scheme III). Acid **8a** also condensed with aniline with activation by dicyclohexylcarbodimide to give carbamato amide **11**. Ester **10** reacted with methyl or ethyl magnesium bromide in ether to give carbamato alcohols **12a** and **12b**, respectively. These in turn ring closed in refluxing toluene by the action of sodium hydride and azeotropic removal of ethanol to form the sodium salts of furo[3,4-*d*][1,3]oxazine **13a** and **13b**.

Scheme III[a]



13a, R = CH_3
b, R = CH_3CH_2

14a, R = CH_3; R_1 = H
b, R = R_1 = CH_3
c, R = CH_3CH_2; R_1 = H
d, R = CH_3CH_2; R_1 = CH_3

[a] (i) DCC/$PhNH_2$/THF, (ii) CH_3CH_2OH/H^+, (iii) >3-RMgBr, (iv) NaH/PhMe/heat, (v) H^+, (vi) CH_3I/DMF.

Protonation of **13** led to oxazinones **14a** and **14c**, while alkylation with methyl iodide led to *N*-methyl derivatives **14b** and **14d** in high yield. It is interesting that N-alkylation occurred readily for these dialkyl oxazine systems but failed for the title compound **2**. The overall result of these processes is that substitution at the carbonyl adjacent to the furan ring could be effected despite the preferential reaction of nucleophiles at the nitrogen carbonyl initially observed.

In summary, a convenient synthesis of a furan analogue of isatoic anhydride has been developed, and several reaction products have been characterized. The fact that **2** reacts with high selectivity with use of milder reaction conditions than are required for similar reactions with isatoic anhydride suggests that **2** might be a useful intermediate for the preparation of novel furan systems with interesting chemical and pharmaceutical properties.

Experimental Section

Melting points were determined on a Mel-Temp capillary block melting point apparatus and are uncorrected. All compounds are homogeneous by thin-layer chromatographic analysis, using Whatman KIF or K5F (5 × 10cm) silica gel analytical plates. ^1H NMR measurements were obtained on a Varian Associates HA-100A or CFT 20 spectrometer with tetramethylsilane as the internal standard.

3,4-Furandicarboxylic Acid Monoethyl Ester (3). Diethylfuran-3,4-dicarboxylic acid (20.25 g, 0.0955 mol) was treated in the manner described by Boyd et al.[3] to give the product as a white crystalline solid (12.2 g, 85%), mp 136–137 °C (lit.[3] mp 139–140 °C).

3,4-Furandicarboxylic Monohydrazide (4). 3,4-Furandicarboxylic acid monoethyl ester (**3**; 24.5 g, 0.133 mol) and hydrazine hydrate (20 mL) were refluxed in ethanol (75 mL) for 18 h. The cooled reaction mixture was filtered and the collected solid was dissolved in water (300 mL). After filtration the aqueous layer was acidified with 1 N hydrochloric acid and allowed to stand

(5) Starger, R. P.; Miller, E. B. *J. Org. Chem.* **1959**, *24*, 1214.
(6) Heyman, D. A. *J. Heterocycl. Chem.* **1978**, *15*, 113.
(7) Acheson, R. M. "An Introduction to the Chemistry of Heterocyclic Compounds", 3rd ed.; Wiley: New York, 1976; pp 141–142.
(8) Bosshard, P.; Eugster, C. H. "Advances in Heterocyclic Chemistry"; Katritzky, A. R., Boulton, A. J., Ed.; Academic Press: New York, 1966, Vol. 7, pp 378–490.

at room temperature for several hours, and the product was collected by filtration (22.2 g, 98%). The analytical sample was prepared by recrystallization from methanol and melted at 251–252 °C: ^{1}H NMR (Me_2SO-d_6) δ 8.32 (s, 2 H, furan H), 8.00 (br s, 4 H, NH and OH). Anal. Calcd for $C_6H_6N_2O_4$: C, 42.36; H, 3.55; N, 16.47. Found: C, 42.18; H, 3.59; N, 16.22.

4-(Azidoformyl)-3-furoic Acid (5). 3,4-Furandicarboxylic acid monohydrazide (4; 5.0 g, 0.03 mol) was dissolved with difficulty in 3 N hydrochloric acid (30 mL), chloroform (120 mL) was added, and the mixture was cooled to 5 °C. Sodium nitrite (2.25 g, 0.032 mol) in water (10 mL) was added dropwise with stirring so that the reaction temperature was maintained at 5–8 °C. After the mixture warmed to room temperature, the layers were separated, and the chloroform layer was dried over sodium sulfate and concentrated to a fine white crystalline solid (4.2 g, 81%): mp 115–160 °C (gas evolution); IR (KBr) 2158 cm^{-1}.

4H-Furo[3,4-d][1,3]oxazine-2(1H),4-dione (2). 4-(Azidoformyl)-3-furoic acid (5; 8.0 g, 0.044 mol) in chloroform (250 mL) was refluxed for 18 h and cooled. The precipitate (4.8 g, 66%) was collected by filtration and purified by recrystallization from ethyl acetate/hexanes: mp 204–205 °C; IR (KBr) 1786, 1754, 1653 cm^{-1}; UV (CH_3OH) 205, 255, 325 nm; mass spectrum, m/e 153 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 11.25 (br s, 1 H, NH), 8.64 (s, 1 H), 7.68 (s, 1 H, both furan H). Anal. Calcd for $C_6H_3NO_4$: C, 47.04; H, 1.97; N, 9.14. Found: C, 47.27; H, 2.08; N, 9.19.

4-Ureido-3-furoic Acid (6a). A suspension of 4H-furo[3,4-d][1,3]oxazine-2(1H),4-dione (2; 0.5 g, 0.0033 mol) in tetrahydrofuran (25 mL) was treated with concentrated ammonium hydroxide (5 mL) added dropwise. The reaction mixture was stirred for 4 h and concentrated. The solid residue was washed with water and dried to give the product (0.52 g, 93%), which was crystallized from ethyl acetate/petroleum ether to give the analytical sample: mp 200–205 °C dec; IR (KBr) 1695 cm^{-1}; UV (CH_3OH) 205, 230, 265 nm; mass spectrum, m/e 170 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 9.60 (br s, 1 H, OH), 8.26 (s, 1 H), 8.00 (s, 1 H, both furan H), 7.86 (br s, 1 H), 6.40 (br s, 2 H, all NH). Anal. Calcd for $C_6H_6N_2O_4$: C, 42.36; H, 3.55; N, 16.67. Found: C, 42.30; H, 3.83; N, 16.30.

4-(3-Methylureido)-3-furoic Acid (6b). A suspension of 4H-furo[3,4-d][1,3]oxazine-2(1H),4-dione (2; 0.46 g, 0.003 mol) in tetrahydrofuran was treated with 40% aqueous methyl amine (0.22 mL, 0.003 mol *or* 2.2 mL, 0.03 mol) and the mixture was stirred at room temperature overnight. The solvents were removed in vacuo, and the solid residue was triturated with water and dried in a vacuum oven at 80 °C to give a tan foam (0.52 g, 95%). The analytical sample was crystallized as white crystals from ethyl acetate and melted 181–183 °C: IR (KBr) 1695 cm^{-1}; UV (CH_3OH) 207, 230, 275 nm; mass spectrum, m/e 184 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 9.75 (br s, 1 H, OH), 8.04 (t, 2 H, NH and furan H), 7.88 (d, 1 H, furan H), 7.14 (br s, 1 H, NH), 2.64 (d, 3 H, CH_3). Anal. Calcd for $C_7H_8N_2O_4$: C, 45.65; H, 4.38; N, 15.21. Found: C, 45.83; H, 4.47; N, 15.45.

4-(3-Phenylureido)-3-furoic Acid (6c). Aniline (0.28 g, 0.003 mol) and 4H-furo[3,4-d][1,3]oxazine-2(1H),4-dione (2; 0.46 g, 0.003 mol) were stirred in tetrahydrofuran (15 mL) overnight. The reaction mixture was concentrated in vacuo and the residue was triturated with water. The solid (0.75 g, 100%) was recrystallized from methylene chloride/petroleum ether to give the analytical sample: mp 181–183 °C dec; IR (KBr) 1695 cm^{-1}; UV (CH_3OH) 205, 250, 290 nm; mass spectrum, m/e 246 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 9.68 (br s, 1 H, OH), 8.49 (br s, 1 H, NH), 8.04 (d, 2 H, NH and furan H), 7.22 (br m, 6 H, furan H and aromatic H). Anal. Calcd for $C_{12}H_{10}N_2O_4$: C, 58.54; H, 4.09; N, 11.38. Found: C, 58.48; H, 4.21; N, 11.37.

4-(3-Diethylureido)-3-furoic Acid (6d). Diethylamine hydrochloride (1.10 g, 0.01 mol), triethylamine (1 mL), and 4H-furo[3,4-d][1,3]oxazine-2(1H),4-dione (2; 1.53 g, 0.01 mol) were combined in tetrahydrofuran (50 mL), and the mixture was stirred overnight. After filtration the solution was concentrated and the residue was recrystallized from ethanol to give the analytical sample (1.20 g, 53%): mp 159–161 °C dec; IR (KBr) 1705 cm^{-1}; UV (CH_3OH) 200, 224, 265 nm; mass spectrum, m/e 226 (M^+); ^{1}H NMR ($CDCl_3$) δ 11.00 (br s, 1 H, OH), 8.54 (br s, 1 H, NH), 7.92 (d, 2 H, furan H), 3.40 (q, 2 H, CH_2), 1.22 (t, 3 H, CH_3). Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.90; H, 6.20; N, 12.03.

4-(3-Phenethylureido)-3-furoic Acid (6e). Phenethylamine (1.21 g, 0.01 mol) and 4H-furo[3,4-d][1,3]oxazine-2(1H),4-dione (2; 1.53 g, 0.01 mol) were combined in tetrahydrofuran (50 mL), and the mixture was stirred overnight. The solvent was removed in vacuo and the residue (2.73 g, 100%) was recrystallized from ethanol to give the white crystalline analytical sample: mp 167–168 °C dec; IR (KBr) 1660 cm^{-1}; UV (CH_3OH) 200, 263 nm; mass spectrum, m/e 274 (M^+); ^{1}H NMR ($CDCl_3$) δ 8.20 (br s, 1 H, NH), 8.00 (s, 1 H, furan H), 7.86 (s, 1 H, furan H), 7.25 (br s, 7 H, NH, furan H, aromatic H), 3.46 (t, 2 H, NCH_2), 2.83 (t, 2 H, CH_2CH_2). Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.30; H, 5.14; N, 10.21. Found: C, 60.90; H, 5.21; N, 10.10.

4-Carboxy-3-furancarbamic Acid 3-Ethyl Ester (8a). 4H-Furo[3,4-d][1,3]oxazine-2(1H),4-dione (2; 10.0 g, 0.065 mol) was suspended in ethanol (100 mL) and stirred overnight. The solvent was removed in vacuo, the residue was dissolved in ether (500 mL), and the ethereal solution was filtered through diatomaceous earth. The filtrate was concentrated in vacuo to give the product as a yellow oil, which slowly crystallized (13.0 g, 100%). The analytical sample was prepared from ethyl acetate: mp 170–171 °C; IR (KBr) 1709, 1563 cm^{-1}; UV (CH_3OH) 205, 225, 260; mass spectrum, m/e 199 (M^+); ^{1}H NMR ($CDCl_3$) δ 13.18 (br s, 1 H, OH), 8.21 (br s, 1 H, NH), 8.10 (s, 1 H), 7.48 (s, 1 H, both furan H), 4.18 (q, 2 H, CH_2), 1.28 (t, 3 H, CH_3). Anal. Calcd for $C_8H_9NO_5$: C, 48.24; H, 4.55; N, 7.03. Found: C, 48.10; H, 4.69; N, 7.00.

4-Carboxy-3-furancarbamic Acid 3-Benzyl Ester (8b). In a like manner, 4H-furo[3,4-d][1,3]oxazine-2(1H),4-dione (2; 1.0 g, 0.0065 mol) was reacted with benzyl alcohol (10 mL). The reaction was quenched with water (100 mL) and the crystalline product was collected by filtration (1.50 g, 88%). The analytical sample was prepared from ether: mp 155–156 °C; IR (KBr) 1724, 1700, 1530 cm^{-1}; UV (CH_3OH) 207, 257 nm; mass spectrum, m/e 261 (M^+); ^{1}H NMR ($CDCl_3$) δ 11.20 (br s, 1 H, OH), 8.40 (br s, 1 H, NH), 8.16 (s, 1 H), 7.90 (s, 1 H, both furan H), 7.40 (br s, 5 H, aromatic H), 5.22 (s, 2 H, CH_2). Anal. Calcd for $C_{13}H_{11}NO_5$: C, 59.77; H, 5.27; N, 14.53. Found: C, 59.80; H, 5.17; N, 14.51.

4-(Phenylcarbamoyl)-3-furancarbamic Acid Ethyl Ester (11). Aniline (0.7 g, 0.0075 mol), dicyclohexylcarbodiimide (1.60 g, 0.0077 mol), and 4-carboxy-3-furancarbamic acid 3-ethyl ester (8a) were combined in tetrahydrofuran (25 mL), and the solution was stirred for 18 h. The dicyclohexyl urea was removed by filtration and the filtrate was concentrated to a viscous oil which slowly crystallized (1.50 g, 71%). Recrystallization from methylene chloride/hexanes gave the analytical sample: mp 123–124 °C; IR (KBr) 1724, 1653 cm^{-1}; UV (CH_3OH) 205, 263 nm; mass spectrum, m/e 274 (M^+); ^{1}H NMR ($CDCl_3$) δ 8.60 (br s, 1 H, NH), 7.90 (br s, 1 H, NH), 7.80 (s, 1 H), 7.47 (s, 1 H, both furan H), 7.32 (m, 5 H, aromatic H), 4.20 (q, 2 H, CH_2), 1.26 (t, 3 H, CH_3). Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.12; H, 5.15; N, 10.45.

4-Carboxy-3-furancarbamic Acid Diethyl Ester (10). A solution of 4-carboxy-3-furancarbamic acid 3-ethyl ester (8; 12.58 g, 0.063 mol) in ethanol (320 mL) was treated with 3.2 mL of concentrated sulfuric acid and refluxed from 2 to 4 days through 3Å molecular sieves until thin-layer chromatographic analysis revealed complete disappearance of starting acid. The reaction mixture was concentrated to quarter volume, quenched with water, and extracted with methylene chloride (4 × 150 mL). The combined organic layer was dried over sodium sulfate, decolorized with activated charcoal, filtered, and concentrated to give the product as a yellow viscous liquid (13.5 g, 94%). Molecular distillation gave the analytical sample as a clear liquid: bp 109–111 °C (0.3 mmHg); IR (neat) 1740, 1709 cm^{-1}; UV (CH_3OH) 203, 260 nm; mass spectrum, m/e 227 (M^+); ^{1}H NMR ($CDCl_3$) δ 8.08 (br s, 1 H, NH), 7.94 (s, 1 H), 7.84 (s, 1 H, both furan H), 4.33 (dq, 4 H, CH_2), 1.35 (dt, 6 H, CH_3). Anal. Calcd for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.77; N, 6.11. Found: C, 52.93; H, 5.86; N, 6.04.

4-(1-Hydroxy-1-methylethyl)-3-furancarbamic Acid Ethyl Ester (12a). Methylmagnesium bromide (3 N in ether, 40 mL, 0.12 mol) was added dropwise with vigorous stirring to a cooled (0 °C) solution of 4-carboxy-3-furancarbamic acid diethyl ester (10; 5.03 g, 0.022 mol) in ether (55 mL). After the mixture was stirred for 4 days at room temperature, water (65 mL) and 3 N hydrochloric acid (20 mL) were added and the layers were separated. The aqueous layer was extracted with methylene chloride (3 × 50 mL). The combined organic layers were dried over sodium

sulfate and concentrated to give the product as a dark yellow oil (4.51 g, 96%). The analytical sample was prepared by molecular distillation: bp 105–110 °C (0.05 mmHg); IR (neat) 3390, 1709 cm^{-1}; mass spectrum, m/e 213 (M^+); ^1H NMR ($CDCl_3$) δ 7.80 (br s, 1 H), 7.70 (br s, 1 H, OH, NH), 7.30 (m, 1 H), 7.15 (m, 1 H, both furan H), 4.25 (q, 2 H, CH_2), 1.60 (s, 6 H, CH_3COH), 1.30 (t, 3 H, CH_3CH_2). Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.30; H, 7.09; N, 6.57. Found: C, 55.85; H, 8.13; N, 6.20.

4-(1-Ethyl-1-hydroxypropyl)-3-furancarbamic Acid Ethyl Ester (12b). In a similar manner to the above, ethylmagnesium bromide (0.16 mol) was reacted with 4-carboxy-3-furancarbamic acid diethyl ester (**10**; 7.99 g, 0.035 mol) for 18 h. Upon workup, the product was obtained as a yellow solid (7.60 g, 90%). The analytical sample was prepared from methylene chloride/petroleum ether as buff crystals: mp 70–71 °C; IR (KBr) 3450, 3350, 1700 cm^{-1}; mass spectrum, m/e 241 (M^+); ^1H NMR ($CDCl_3$) δ 7.84 (br s, 2 H, NH, furan H), 6.98 (s, 1 H, furan H), 4.20 (q, 2 H, OCH_2), 1.97 (br s, 1 H, OH), 1.74 (q, 4 H, $C(OH)CH_2$), 1.28 (t, 3 H, CH_3CH_2O), 0.87 (t, 6 H, $CH_3CH_2C(OH)$. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.53; H, 7.95; N, 5.75.

4,4-Dimethyl-4*H*-furo[3,4-*d*][1,3]oxazin-2(1*H*)-one (14a). A mixture of sodium hydride (0.23 g, 0.01 mol) and 4-(1-hydroxy-1-methylethyl)-3-furancarbamic acid ethyl ester (**12a**; 2.13 g, 0.01 mol) was refluxed for 18 h in toluene (50 mL), using a Dean–Stark water separator and 4Å molecular sieves. The reaction mixture was cooled to room temperature and the sodium salt of the product was collected by filtration (1.83 g, 97%). The solid was triturated with methylene chloride (50 mL) and treated with 1 N hydrochloric acid (5 mL) in water (45 mL). The organic layer was separated, dried over sodium sulfate, and concentrated to give the product as a yellow solid (1.55 g, 95% overall). The analytical sample was prepared from methylene chloride/petroleum ether: mp 110.5–112 °C; IR (KBr) 3226, 1680 cm^{-1}; UV (CH_3OH) 205, 217 nm; mass spectrum, m/e 167 (M^+); ^1H NMR (Me_2SO-d_6) δ 9.95 (br s, 1 H, NH), 7.56 (br s, 1 H), 7.24 (br s, 1 H, both furan H), 1.58 (s, 6 H, CH_3). Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.48; N, 8.38. Found: C, 57.46; H, 5.50; N, 8.20.

4,4-Dimethyl-1-methyl-4*H*-furo[3,4-*d*][1,3]oxazin-2-(1*H*)-one (14b). The sodium salt from above (0.38 g, 0.002 mol) was dissolved in dimethylformamide (dry, 5 mL) and treated with methyl iodide (1.42 g, 0.6 mL, 0.01 mol) for 1 h. The mixture was poured into water (25 mL) and the aqueous layer was extracted with methylene chloride (3 × 25 mL). The combined organic layers were concentrated, the residue was triturated with petroleum ether, and the residue was distilled to give the product as a waxy solid (0.27 g, 75%): bp 100 °C (0.05 mmHg); IR (mull) 1705 cm^{-1}; UV (CH_3OH) 203, 216 nm; mass spectrum, m/e 181 (M^+); ^1H NMR ($CDCl_3$) δ 7.15 (d, 1 H), 7.04 (d, 1 H, both furan H), 3.24 (s, 3 H, CH_3N), 1.66 (s, 6 H, CH_3C). Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.28; H, 6.12; N, 7.52.

4,4-Diethyl-4*H*-furo[3,4-*d*][1,3]oxazin-2(1*H*)-one (14c). A mixture of 4-(1-ethyl-1-hydroxypropyl)-3-furancarbamic acid ethyl ester (**12b**; 6.72 g, 0.028 mol) and sodium hydride (0.70 g, 0.029 mol) was refluxed in dry toluene (150 mL) as above. The sodium salt (5.96 g, 98.5%) was collected and dried. A sample of the salt (1.25 g, 0.006 mol) was suspended between methylene chloride (50 mL) and 1 N hydrochloric acid (25 mL) for 1 h and worked up as above to give the product as cream crystals (0.85 g, 95%): mp 146–147 °C; IR (KBr) 3280, 1725 cm^{-1}; UV (CH_3OH) 202, 212 nm; mass spectrum, m/e 195 (M^+); ^1H NMR ($CDCl_3$) δ 9.20 (br s, 1 H, NH), 7.16 (br s, 1 H), 7.10 (br s, 1 H, both furan H), 1.88 (q, 4 H, CH_2), 0.96 (t, 6 H, CH_3). Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.36; H, 6.77; N, 7.08.

4,4-Diethyl-1-methyl-4*H*-furo[3,4-*d*][1,3]oxazin-2(1*H*)-one (14d). The sodium salt from above (0.435 g, 0.002 mol) in dry dimethylformamide (5 mL) was treated with methyl iodide (2 mL) and worked up as above to give the product (0.319 g, 76%) which was recrystallized from petroleum ether at −78 °C to give the analytical sample: mp 31–33 °C; IR (KBr) 1709 cm^{-1}; UV (CH_3OH) 203, 216, 270 nm; mass spectrum, m/e 209 (M^+); ^1H NMR ($CDCl_3$) δ 7.08 (m, 2 H, furan H), 3.26 (s, 3 H, NCH_3), 1.86 (q, 4 H, CH_2), 0.94 (t, 6 H, CH_3CH_2). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 61.81; H, 7.31; N, 6.55. Found: C, 61.60; H, 7.11; N, 6.51.

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Registry No. **2**, 78329-55-2; **3**, 34501-80-9; **4**, 78329-56-3; **5**, 78329-57-4; **6a**, 78329-58-5; **6b**, 78329-59-6; **6c**, 78329-60-9; **6d**, 78329-61-0; **6e**, 78329-62-1; **8a**, 78329-63-2; **8b**, 78329-64-3; **10**, 78329-65-4; **11**, 78329-66-5; **12a**, 78329-67-6; **12b**, 78329-68-7; **14a**, 78329-69-8; **14a**·Na, 78329-70-1; **14b**, 78329-71-2; **14c**, 78329-72-3; **14c**·Na, 78329-73-4; **14d**, 78342-36-6; furan-3,4-dicarboxylic acid diethyl ester, 30614-77-8; methylamine, 74-89-5; aniline, 62-53-3; diethylamine·HCl, 660-68-4; phenethylamine, 64-04-0; 4-carboxy-3-furancarbamic acid, 78329-74-5.

Synthesis of Carbazole Alkaloids Hyellazole and 6-Chlorohyellazole[1]

Shinzo Kano,* Eiichi Sugino, Shiroshi Shibuya, and Satoshi Hibino

Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

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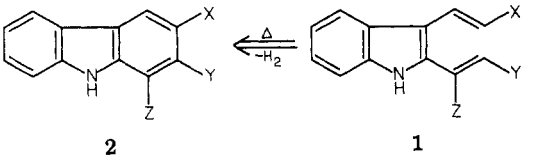
2-(1-Cyclohexenyl)-3-(β-methoxyvinyl)indole was heated in decalin in the presence of 5% Pd–C to give 1,2,3,4-tetrahydro-5-methoxy-11*H*-benzo[*a*]carbazole and 5-methoxy-11*H*-benzo[*a*]carbazole. 3-(β-Methoxyvinyl)-2-(1-phenyl-1-propenyl)indole and 5-chloro-3-(β-methoxyvinyl)-2-(1-phenyl-1-propenyl)indole were also heated in decalin in the presence of 5% Pd–C at 210 °C, yielding the carbazole alkaloids hyellazole and 6-chlorohyellazole, respectively.

We have investigated a new synthetic route to carbazoles by way of thermal cyclization of the triene system (**1**) in the presence of 5% Pd–C, based on the electrocyclic reaction of 1,3,5-trienes providing the cyclohexa-1,3-dienes by either thermal condition or photolysis.[2] Although there

Scheme I



2 **1**

are a number of preparative routes to carbazoles,[3-10] our proposed synthetic method would be useful for preparation

(1) A part of this work was reported in *J. Chem. Soc., Chem. Commun.*, **1980**, 1241, as a preliminary communication.
(2) R. Hoffmann and R. B. Woodward, *Chem. Unserer Zeit*, 6, 167 (1972).

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