were significantly deformed and nonplanar. Nevertheless, in the presence of water, the formation of colorful molecular complexes of **2** with certain electron donors such as TTF, anthracene, and thianthrene was observed. These complexes have a nonfixed stoichiometry containing H_2O and exhibit high resisitivities. Furthermore, they are not stable and readily dissociate into individual components either on heating or by dissolution in solvent.

Experimental Section

All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Beckmann IR-4250 spectrophotometer with polystyrene as the calibration standard and UV–vis spectra on a Hewlett Packard UV/vis spectrophotometer. ^1H NMR spectra were recorded in $CDCl_3$ on a Bruker WP-80 spectrometer with tetramethylsilane as an internal standard. Low-resolution mass spectra were obtained on a Finnigan 4000 quadrupole instrument. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

General Procedure for the Condensation of Anthraquinones with Malononitrile. The following is an illustrative procedure for the condensation reaction.

To a well-stirred mixture of 20 mmol of anthraquinone and 3.5 g (55 mmol) of malononitrile in 125 mL of methylene chloride at an ice-bath temperature were added dropwise 11.5 mL of TiC_4 over a period of 20 min and 35 mL of pyridine over a period of 30 min. After the addition, the ice bath was removed to allow the reaction to continue at room temperature for another 5 h. The reaction mixture was evaporated and the residue was treated with 100 mL of 10% aqueous HCl solution with vigorous stirring. The solid product was filtered and washed several times with water and dried. Purification of the product was accomplished either by recrystallization from an appropriate solvent or by column chromatography.

(a) 11,11,12,12,-Tetracyanoanthraquinodimethane (2): recrystallized from acetic acid in 87% yield: mp >350 °C dec; ^1H NMR ($CDCl_3$) 7.8–8.6 (AA'BB'); IR (KBr pellet) 2235 cm^{-1} (CN); UV–vis (CH_2Cl_2) λ_{max} (ϵ) 285 (30 500), 305 (16 300), 350 nm (26 000): MS, *m/e* (relative intensity): 304 (100), 277 (30), 250 (20), 223 (8), 212 (5), 198 (6), 152 (7), 138 (9), 125 (19), 111 (14). Anal. Calcd for $C_{20}H_8N_4$: C, 78.94; H, 2.65; N, 18.41. Found: C, 78.94; H, 2.83; N, 18.29.

(b) 11,11,12,12-Tetracyano-2-*tert*-butylanthraquinodimethane (4): purified by column chromatography on silica gel (ethyl acetate: hexane, 1:4) in 59% yield: mp 313–14 °C: ^1H NMR ($CDCl_3$) δ 1.4 (s, 9 H), 7.6-8.4 (m, 7 H); IR (KBr pellet) 2235 (CN) cm^{-1}. Anal. Calcd for $C_{24}H_{16}N_4$: C, 79.98; H, 4.47; N, 15.54. Found: C, 80.09; H, 4.40; N, 15.51.

(c) 1,3-Dimethyl-10-(dicyanomethylene)anthrone (5): recrystallized from acetic acid in 72% yield: mp 215–16 °C; ^1H NMR ($CDCl_3$) δ 2.45 (s, 3 H), 2.75 (s, 3 H), 7.3–8.3 (m, 6 H); IR (KBr pellet) 2230 (CN), 1680 (C=O) cm^{-1}. Anal. Calcd for $C_{19}H_{12}N_2O$: C, 80.26; H, 4.25; N, 9.85; O, 5.63. Found: C, 80.35; H, 4.23; N, 9.81; O, 5.67.

Molecular Complexes of 11,11,12,12-Tetracyanoanthraquinodimethane (2). The following preparation of the complex of **2** with anthracene is illustrative of the procedure. A mixture of 0.304 g (1 mmol) of **2** and 0.178 g (1 mmol) of anthracene was dissolved in 80 mL of acetonitrile by heating. The solution was poured into 240 mL of water with stirring, resulting in the formation of a purplish solid. The product was filtered and dried in vacuo at 50 °C for 24 h; the yield was 0.44 g. The product, when finely dispersed as particulates on a transparent substrate, displayed a charge-transfer band at 505 nm. When heated to ~300 °C, it turned into a purplish melt, but changed to a pale yellow solid on cooling. It also lost its color when dissolved in solvents (e.g., methylene chloride), indicating its dissociation into individual components.

The complex of **2** with tetrathiafulvalene is dark green in color while that with thianthrene is brownish in color. Attempts to record their charge-transfer absorptions were not successful because of the difficulty in dispersing them. Conductivity measurements on these complexes in the form of pressed pellets showed that they had very high resistivities.

Acknowledgment. We extend our gratitude to our colleague Dr. R. O. Loutfy for electrochemical characterization.

Registry No. **2**, 70359-39-6; **2**–anthracene complex, 92720-72-4; **2**–tetrathiafulvalene complex, 92720-73-5; **2**–thianthrene complex, 92720-74-6; **4**, 92720-70-2; **5**, 92720-71-3; $NCCH_2CN$, 109-77-3; $TiCl_4$, 7550-45-0; anthraquinone, 84-65-1; 2-*tert*-butylanthraquinone, 84-47-9; 1,3-dimethylanthraquinone, 3285-97-0; anthracene, 120-12-7; tetrathiafulvene, 31366-25-3; thianthrene, 92-85-3.

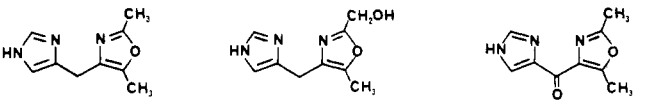
Oxygenated Analogues of 4-[(1*H*-Imidazol-4-yl)methyl]-2,5-dimethyloxazole

Michael J. Kukla* and James M. Fortunato

Department of Chemistry, McNeil Pharmaceutical, Spring House, Pennsylvania 19477

Received May 29, 1984

In a program to discover histidine decarboxylase inhibitors, histidine derivative **1**[1] was found to have analgesic properties in a number of our animal models. Subsequently, we synthesized the oxygenated analogues **2** and **3**. The syntheses of these compounds, reported here, led



1 2 3

to some approaches that may offer wider applicability for imidazolyloxazoles and related compounds with these substitution patterns.

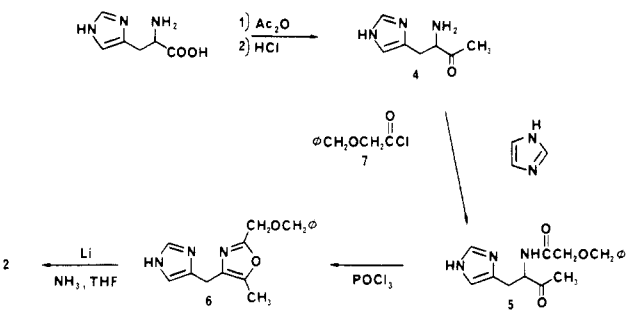
The synthesis of **2** (Scheme I) was based on the classic Dakin–West reaction,[2,3] yielding keto amine **4** followed by specific acylation to keto amide **5**. 2-(Phenylmethoxy)-acetyl chloride (**7**), a key intermediate, was reported[4] in 35% yield by a three-step synthesis beginning with the alkoxide obtained from benzyl alcohol and sodium metal. We found a much improved yield (85–90%) of **7** if alkoxide was generated with sodium hydride. Subsequent acylation of the imidazole derivative **4** with **7** required initial acylimidazole formation through addition of 1 equiv of imidazole to acid chloride **7** prior to addition of **4**. This obviated the problem of simultaneous acylation of the imidazole ring of **4**. Cyclodehydration to the oxazole **6** was accomplished in refluxing phosphorus oxychloride in 83% yield after column chromatography. Several catalytic hydrogenolysis and chemical methods to remove the benzyl protecting group were employed unsuccessfully. However, lithium in a mixture of THF–liquid ammonia at −78 °C cleanly removed the protecting group to give the desired alcohol **2**.

The synthesis of **3** (Scheme II) began with the protected imidazole **8** reported by Breslow.[5] Unlike that group, we were not able to efficiently form the requisite anion of **8** using lithium disopropylamide under a number of reaction conditions and turned to *n*-butyllithium for the conversion. Subsequent reaction with aldehyde **9**[6] gave alcohol **10** in

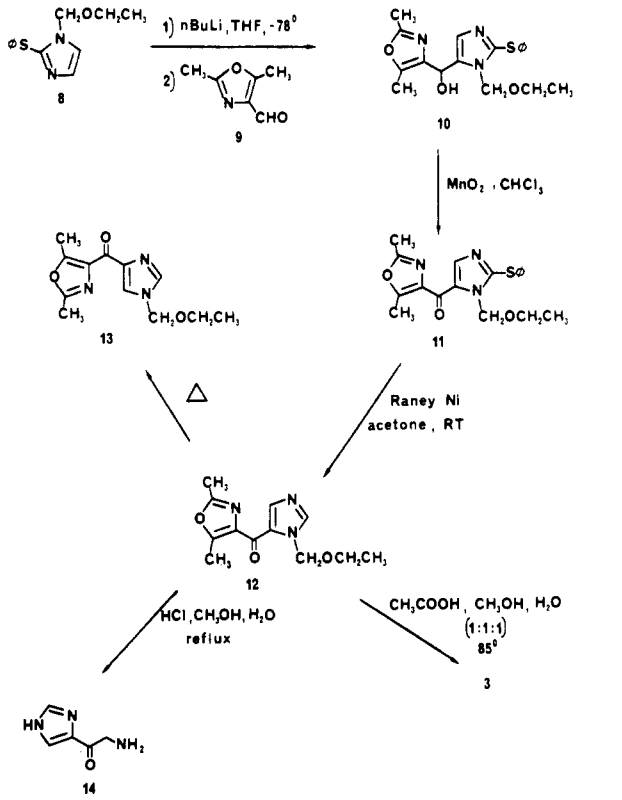
(1) Wrede, F.; Keil, W. *Z. Phys. Chem.* **1931**, *203*, 279. This compound was synthesized in the laboratories of the late Dr. Edward Smissman, University of Kansas, and tested at McNeil in a collaborative research program.
(2) Dakin, H. D.; West, R. *J. Biol. Chem.* **1928**, *78*, 91, 745, 757.
(3) Iwakura, Y.; Toda, F.; Suzuki, H. *J. Org. Chem.* **1967**, *32*, 440.
(4) Bennington, F.; Morin, R. D. *J. Org. Chem.* **1961**, *26*, 194. Wenner, W.; Plati, J. T. *Ibid.* **1946**, *11*, 751.
(5) Tang, C. C.; Davalian, D.; Huang, P.; Breslow, R. *J. Am. Chem. Soc.* **1978**, *100*, 3918.

0022-3263/84/1949-5003$01.50/0

Scheme I



Scheme II



nearly quantitative crude yield, and oxidation to ketone **11** was accomplished with activated manganese dioxide. The protecting groups were removed sequentially. The desulfurization reaction of **11** to **12** was accomplished with Raney nickel and required a 10:1 ratio by weight of metal to substrate to carry out the reaction at room temperature. However, if heated to reflux in ethanol a single product was obtained in which the carbonyl was reduced to a methylene in addition to removal of thiophenol. Interestingly, the intermediate **12** was found to undergo a seemingly facile thermal rearrangement to the positional isomer **13**. However, a crude kinetic study by NMR to verify that fact indicated that this conversion was actually bimolecular ($t_{1/2} \sim 10$ h, 110 °C, $C_6H_5NO_2$-d_5). When hydrochloric acid in refluxing methanol was used to hydrolyze the *N*-ethoxymethylimidazole **12**, none of the desired **3** was obtained. Rather, the oxazole ring was also hydrolyzed and a single product identified as **14** resulted. Hydrolysis with a mixture of acetic acid–water–methanol gave **3** in nearly quantitative yield.

Unfortunately, analogues **2** and **3** showed no advantages over the initial lead compound **1** and were not developed further as analgesic agents.

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on either a Varian EM360 or Perkin-Elmer R32 spectrometer and, ^{13}C NMR spectra were recorded on a Varian FX60Q instrument with $(CH_3)_4Si$ as an internal standard in all cases. Mass spectra were recorded on a Vg 7035 or a Finnigan 3300 instrument with methane as the reagent gas for chemical ionization (CI) spectra. Elemental analyses were carried out by Atlantic Microlab, Inc., Atlanta, GA, or Scandinavian Labs, Herlev, Denmark.

2-(Phenylmethoxy)acetyl Chloride (7). Sodium hydride (29.06 g, 1.2 mol; Alfa 99%) was added portionwise over 1.25 h to stirred cold (0–10 °C) benzenemethanol (500 mL, 4.8 mol) under argon. The temperature was maintained at 0–10 °C for another 2 h, and then the thick heterogeneous mixture was heated at 55–65 °C for 3 h. The resultant clear solution was cooled with an ice bath, and ethyl chloroacetate (66.4 mL, 0.6 mmol) was added dropwise over 45 min. The solution was stirred at ambient temperature for 2 h and at 60 °C for 30 min before it was quenched with the addition of 200 mL of CH_3OH, 130 mL of H_2O, and potassium hydroxide pellets (43.85 g, 0.66 mol). After 3 h at 60 °C the mixture was allowed to cool to room temperature and stored over a weekend before it was concentrated on a rotary evaporator. The residue was diluted with water and extracted with ethyl ether 3 times. The aqueous layer was then acidified with concentrated hydrochloric acid (100 mL) and extracted twice with ethyl ether. These extracts were combined, washed with brine, dried with $MgSO_4$, and concentrated to yield 92.82 g (92.5%) of crude 2-(phenylmethoxy)acetic acid. To a portion of this acid (71.77 g, 0.43 mol) was added thionyl chloride (48 mL, 1.5 equiv) dropwise at 0–10 °C over 45 min. The resultant mixture was heated at 65 °C for 30 min and recooled to ambient temperature, and the excess thionyl chloride was distilled off at aspirator pressure to yield a pot residue of crude **7** (75.3 g, 94%). This could be Kugelrohr distilled (84–87 °C (0.3–0.5 mm)) to give an 83% yield of material whose NMR spectrum is consistent with the desired product:[4] ^{1}H NMR ($CDCl_3$) δ 7.35 (s, 5 H, Ph), 4.62 (s, 2 H, $PhCH_2$), 4.38 (s, 2 H, $CH_2C{=}O$).

***N*-[1-(1*H*-Imidazol-4-ylmethyl)-2-oxopropyl]-2-(phenylmethoxy)acetamide (5).** A solution of 2-(phenylmethoxy)acetyl chloride (**7**, 8.16 g, 44.2 mmol) in 75 mL of CH_2Cl_2 was added over 8 min to a cold (ice bath) stirred solution of imidazole (3.01 g, 44.2 mmol) in 160 mL of CH_2Cl_2 under nitrogen. After 2 min a mixture of **4**[2,8] (10.0 g, 44.2 mmol) and imidazole (3.01 g, 44.2 mmol) was added in one portion and the ice bath was removed. The mixture was heated to reflux and maintained for 16 h before it was allowed to cool to room temperature and diluted with 30 mL of 95% EtOH. The solution was poured directly onto a column of silica gel (CC-7, 450 g) slurry packed with petroleum ether. It was then eluted with progressively more polar solvents from petroleum ether to 10% EtOH–CH_2Cl_2. Concentration of the appropriate fractions yielded 16.12 g of product which was pure by NMR but was estimated to contain ca. 3 g of EtOH. Recrystallization from EtOH–CH_2Cl_2–hexane gave 3.86 g (29%) of analytically pure material: mp 162.5–163.5 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.25 (d, 1 H, NH), 7.5 (s, 1 H, imidazole), 7.35 (s, 5 H, Ph), 6.85 (s, 1 H, imidazole), 4.53 (s, 3 H, $OCH_2C{=}O$ and buried CH), 3.95 (s, 2 H, OCH_2Ph), 3.0 (d, 2 H, CH_2-imidazole), 2.1 (s, 3 H, CH_3).

Anal. Calcd for $C_{16}H_{19}N_3O_2$: C, 63.77; H, 6.36; N, 13.94. Found: C, 63.86; H, 6.58; N, 13.78.

4-(1*H*-Imidazol-4-ylmethyl)-5-methyl-2-[(phenylmethoxy)methyl]oxazole (6). A mixture of **5** (5.51 g, 18.3 mmol) and phosphorus oxychloride (25 mL) was heated at 100–110 °C for 0.5 h. The $POCl_3$ was removed under reduced pressure and the residue was redissolved in toluene and reconcentrated. The brown

(6) This aldehyde was synthesized in a two-step sequence of reduction ($LiBH_4$) followed by oxidation ($MnO_2/CHCl_3$) of the previously reported[7] ethyl 2,5-dimethyloxazole-4-carboxylate. Thanks are extended to Dr. Brian Reynolds and Ms. Marge Nemia for the details of those procedures which are given in the Experimental Section.

(7) Saito, N.; Tanaka, C. *J. Pharm. Soc. Jpn.* **1956**, *76*, 305; *Chem. Abstr.* **1956**, *50*, 13874a.

(8) U.S. Patent 3646208.

residue was cooled with an ice bath and treated with K_2CO_3 (41 g), 40 mL of 95% EtOH, and 4 mL of H_2O. The resulting slurry was chromatographed on alumina to yield 4.77 g (83%) of **6** which was pure by NMR. A crystalline derivative was obtained and purified as the oxalate salt for analysis: mp 137.5–139.5 °C; ^{1}H NMR (Me_2SO-d_6) δ 13.3 (s, 2 H, oxalic acid), 8.4 (s, 1 H, imidazole), 7.3 (s, 5 H, Ph), 7.12 (s, 1 H, imidazole), 4.53 (s, 2 H), 4.48 (s, 2 H), 3.80 (s, 2 H), 2.25 (s, 3 H, CH_3).

Anal. Calcd for $C_{16}H_{17}N_3O_2 \cdot {}^{13}/_{16}C_2H_2O_4$: C, 59.38; H, 5.27; N, 11.79. Found: C, 59.68; H, 5.39; N, 12.18.

4-(1*H*-Imidazol-4-ylmethyl)-5-methyl-2-oxazolemethanol (2). A solution of **6** (7.15 g, 25.2 mmol) in dry THF (80 mL) was cooled to −70 °C and ammonia (400–500 mL) was condensed into the flask. Lithium wire (0.81 g, 113.6 mmol) was added over 40 min to the stirred mixture under argon. It was stirred an additional 25 min before 3 mL of 95% EtOH was added. The ammonia was then allowed to evaporate under a slow stream of nitrogen overnight. The residue was dissolved in 100 mL of 1:1 EtOH–CH_2Cl_2, filtered and concentrated to give a yellow semisolid. This was dissolved in 95% EtOH, treated with ethereal HCl, and concentrated to give a crude salt. Recrystallization from 95% EtOH–Et_2O gave 2.86 g (42%); mp 170–171 °C dec. An analytical sample was recrystalyzed from *i*-PrOH–H_2O–Et_2O: mp 184–188 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 9.3 (d, 1 H, imidazole), 8.68 (bs, 2 H, exchangeables with D_2O), 7.39 (d, 1 H, imidazole), 4.41 (s, 2 H, CH_2OH), 3.90 (s, 2 H), 2.3 (s, 3 H, CH_3).

Anal. Calcd for $C_9H_{11}N_3O_2 \cdot 2HCl \cdot {}^1/_8H_2O$: C, 40.28; H, 4.98; N, 15.66; Cl, 26.42; H_2O, 1.00. Found: C, 40.38, H, 4.94; N, 15.78; Cl, 26.61; H_2O, 1.00.

2,5-Dimethyl-4-oxazolemethanol. Sodium borohydride (5.04 g, 0.132 mol) was dissolved in dry diglyme (140 mL) and lithium chloride (5.64 g, 0.132 mol) added. The mixture was stirred at room temperature for 1 h, and ethyl 2,5-dimethyloxazole-4-carboxylate[7] (33.8 g, 0.2 mol) was added. The mixture was heated at 90–100 °C for 6 h. The cooled mixture was carefully poured onto 240 g of ice and 24 mL of concentrated hydrochloric acid and extracted with ether. The ether extracts were discarded. The aqueous layer was made basic and continuously extracted with $CHCl_3$ for 7 h. The organics were dried over sodium sulfate and evaporated to give 2,5-dimethyl-4-oxazolemethanol as an off-white solid. Recrystallization from methylcyclohexane afforded 14.3 g (56%) of white solid: mp 82–84 °C; ^{1}H NMR ($CDCl_3$) δ 4.9 (bt, 1 H, OH), 4.45 (bd, 2 H, CH_2O), 2.35 (s, 3 H, CH_3), 2.25 (s, 3 H, CH_3).

Anal. Calcd for $C_6H_9NO_2$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.42; H, 7.03; N, 10.86.

2,5-Dimethyl-4-oxazolecarboxaldehyde (9). 2,5-Dimethyl-4-oxazolemethanol (30 g) was added to activated manganese dioxide (300 g) in 1.5 L of $CHCl_3$, and the mixture was stirred at room temperature for 21 h. Its was filtered and the filtrate concentrated to yield 25.8 g (87.5% yield) of amber liquid. Vacuum distillation (38–40 °C (0.2 mm)) afforded 18.5 g of clear colorless oil: ^{1}H NMR ($CDCl_3$) δ 9.88 (s, 1 H, CHO), 2.58 (s, 3 H, CH_3), 2.44 (s, 3 H, CH_3).

Anal. Calcd for $C_6H_7NO_2$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.66; H, 5.71; 11.24.

α-[1-(Ethoxymethyl)-2-(phenylthio)-1*H*-imidazol-5-yl]-2,5-dimethyl-4-oxazolemethanol (10). *n*-Butyllithium in hexane (232 mL of 1.62 M, 0.38 mol) was added to a stirred, cold (−78 °C bath) solution of **8**[5] (90 g, 0.36 mol) in THF (500 mL) under nitrogen over a period of 30 min. The resultant orange solution was stirred at −78 °C for 2 h before aldehyde **9** (47 g, 0.38 mol) in 100 mL of THF was added over 12 min. The mixture was stirred at −78 °C for 2 h and then at room temperature for 3 h before it was quenched with the addition of 500 mL of water. After the mixture had set overnight it was diluted with water and ether. The organic phase was separated, washed with water twice and then brine, dried with $MgSO_4$, and concentrated to yield 122 g of yellow oil. ^{1}H NMR indicated 25% unreacted **8** plus **10** (i.e., >98% yield based on unreacted **8**): ^{1}H NMR of **10** ($CDCl_3$) δ 7.25 (s, 5 H, Ph), 7.05 (s, 1 H, imidazole), 5.87 (bs, 1 H, C*H*OH), 5.70 (d, 1 H, CH_2O, J = 11 Hz), 5.42 (d, 1 H, CH_2O, J = 11 Hz), 4.55 (bs, 1 H, OH), 3.35 (q, 2 H, OCH_2CH$_3$, J = 7 Hz), 2.35 (s, 3 H, CH_3), 2.2 (s, 3 H, CH_3), 1.05 (t, 3 H, OCH$_2$CH_3, J = 7 Hz).

(2,5-Dimethyl-4-oxazolyl)[1-(ethoxymethyl)-2-(phenylthio)-1*H*-imidazol-5-yl]methanone (11). Powdered activated manganese dioxide (1.2 kg from California Aromatics and Flavors) was added to a stirred solution of crude alcohol **10** (122 g but estimated by NMR to contain only 100 g; 0.28 mol) in chloroform (1 gal). The mixture was stirred at room temperature overnight. It was then briefly heated to reflux and the $CHCl_3$ was decanted from the dark solid. A second portion of $CHCl_3$ was added, heated to reflux, and filtered through Dicalite. This was repeated with a third portion of $CHCl_3$, and all the washes were combined and concentrated to yield 70.5 g of yellow oil (70%). This oil was dissolved in 100 mL of hot 95% ethanol and seeded. The pale yellow fine crystals were isolated on a filter, washed with 95% EtOH, and allowed to air dry to yield 39.4 g (40%): mp 79–80 °C; ^{1}H NMR ($CDCl_3$) δ 8.65 (s, 1 H, imidazole), 7.2–7.6 (m, 5 H, Ph), 5.97 (s, 2 H, OCH_2N), 3.57 (q, 2 H, OCH_2CH_3, J = 7 Hz), 2.65 (s, 3 H, CH_3), 2.45 (s, 3 H, CH_3), 1.13 (t, 3 H, OCH_2CH_3).

Anal. Calcd for $C_{13}H_{19}N_3O_3S$: C, 60.49; H, 5.36; N, 11.76; S, 8.97. Found: C, 60.01 (Δ 0.48); H, 5.52; N, 11.52; S, 8.82.

(2,5-Dimethyl-4-oxazolyl)[1-(ethoxymethyl)-1*H*-imidazol-5-yl]methanone (12). Raney nickel (~400 g wet weight) from W. R. Grace was rinsed with 95% EtOH 3 times and with absolute EtOH 3 times, in each case the solvent was decanted from the black solid. The catalyst was then rinsed into a solution of **11** (39.4 g, 0.11 mol) in acetone (1.3 L total) and the mixture was stirred. After 18 h the supernatant solution was decanted off the catalyst which was resuspended in a mixture of EtOH–acetone, stirred, and then decanted. After three washings all the solutions were combined, swirled with $MgSO_4$, filtered through Dicalite, and concentrated to yield 22.1 g of pale green oil which was used in the next step without further purification. The spent nickel was suspended in 25 mL of concentrated ammonium hydroxide and allowed to sit over the weekend before it was continuously extracted with acetone in a Soxelet extractor. The extracts were concentrated, dissolved in ether, washed with water and then brine, dried with $MgSO_4$, and concentrated to yield 4.4 g of yellow oil which crystallized on standing (total crude yield 96%). A portion of this crude solid was recrystallized from cyclohexane and then sublimed (70–90 °C (0.15 mm) to yield white solid: mp 66.5–67.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.70 (s, 1 H, imidazole), 7.94 (s, 1 H, imidazole), 5.84 (s, 2 H, OCH_2N), 3.60 (q, 2 H, OCH_2CH$_3$), 2.69 (s, 3 H, CH_3), 2.50 (s, 3 H, CH_3), 1.20 (t, 3 H, OCH$_2$CH_3).

Anal. Calcd for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.82; H, 6.07; N, 16.85.

The residue from the sublimation was examined by ^{1}H NMR and found to be almost pure isomeric **13** as verified by MS (m/e 249). A sample was crystallized from methyl ethyl ketone to yield pale pink crystals, mp 140.5–142 °C. ^{1}H NMR of **13** was identical with that of **12** except for the shift of one of the imidazole protons from δ 7.94 to 7.80 and a shift in the methylene singlet to δ 5.42.

(2,5-Dimethyl-4-oxazolyl)(1*H*-imidazol-4-yl)methanone (3). Crude **12** (22.1 g, 0.09 mol) was suspended in 450 mL of CH_3O-H–H_2O–HOAc (1:1:1), and the stirred mixture was heated to 85 °C. After 45 h the mixture was concentrated on a rotary evaporator to yield 16.5 g of tan solid (97% crude yield). A sample was recrystallized from *i*-PrOH to yield fine off-white crystals: mp 195.5–197 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.45 (s, 1 H), 8.0 (s, 1 H), 2.6 (s, 3 H), 2.45 (s, 3 H). A sample was dissolved in hot CH_3OH, and 1 equiv of solid fumaric acid was added. The mixture was boiled for a short time and allowed to cool. The crystals were collected and recrystallized from EtOH to yield an off-white solid which was dried at 100 °C, mp 232–233 °C dec.

Anal. Calcd for $C_9H_9N_3O_2 \cdot {}^1/_2C_4H_4O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 53.05; H, 4.46; N, 16.85.

2-Amino-1-(1*H*-imidazol-4-yl)-1-ethanone (14). Imidazole **12** (1.0 g) was dissolved in 10 mL of CH_3OH, and 10 mL of 3 N HCl were added. The solution was heated under reflux for 16 h and then concentrated on a rotary evaporator to yield 0.7 g of tan solid. Mass spectrum (CI) indicated a molecular ion of 125: ^{1}H NMR (D_2O) δ 9.18 (s, 1 H, imidazole), 8.6 (s, 1 H, imidazole), 4.75 (s, 2 H, CH_2); ^{13}C NMR (D_2O) δ 183.291 (C=O), 138.302 (CH, imidazole), 129.404 (-C-, imidazole), 126.485 (CH, imidazole), 45.841 (CH_2).

Registry No. **2**, 92901-83-2; **3**, 92901-84-3; **4**, 24579-23-5; **5**, 92901-85-4; **6**, 92901-86-5; **6** oxalate/salt, 92901-87-6; **7**, 19810-31-2; **8**, 67319-06-6; **9**, 92901-88-7; **10**, 92901-89-8; **11**, 92901-90-1; **12**,

92901-91-2; 13, 92901-92-3; 14, 92901-93-4; $PhCH_2OH$, 100-51-6; $ClCH_2C(O)OEt$, 105-39-5; $PhCH_2OCH_2C(O)OEt$, 32122-09-1; $PhCH_2OCH_2CO_2H$, 30379-55-6; 2,5-dimethyloxazole-4-methanol, 92901-94-5; ethyl 2,5-dimethyloxazole-4-carboxylate, 23000-15-9.

A New Route to the Pyridine Nucleus Fused to Some Heterocycles

Satoshi Hibino*

Faculty of Pharmacy and Pharmaceutical Sciences, Fukuyama University, 985 Higashimura, Fukuyama, Hiroshima 729-02, Japan

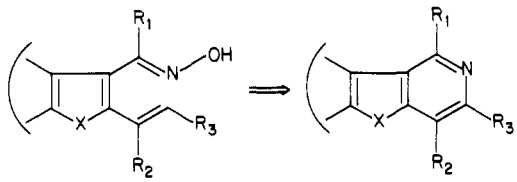
Shinzo Kano, Naoki Mochizuki, and Eiichi Sugino

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

Received April 18, 1984

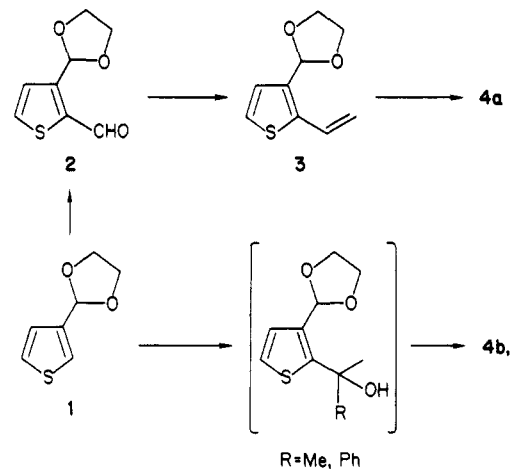
In a previous paper,[1] we reported a synthesis of 9-aza-6-thiaellipticine in connection with studies of the antitumor 6*H*-pyrido[4,3-*b*]carbazole ellipticine isostere. As a starting material we required the unsubstituted thieno[3,2-*c*]-pyridine. Although Barger and Easson[2] failed to produce thieno[3,2-*c*]pyridine by the Bischler–Napieralski reaction, this compound was prepared by Gronowitz and Sandberg[3] using the Pictet–Spengler reaction, which requires a difficult final oxidation step. Thieno[3,2-*c*]pyridines and 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridines prepared in a similar way have also been reported as the isoquinoline isosteres and have attracted much attention because of their biological activity.[4]

In seeking a more direct route to fused pyridine ring systems, we have found that 1-aza-1,3,5-hexatrienes based on the five-membered ring of thiophene or indole undergo a facile intramolecular thermal cyclization with loss of water to yield fused pyridine rings.[5] We here report on the use of this cyclization to prepare some thieno[3,2-*c*]-pyridines and some 5*H*-pyrido[4,3-*b*]indoles.



The carbonyl intermediates **4a–c** needed for the thieno[3,2-*c*]pyridines were prepared as shown in Scheme I and converted into oximes **5a–c** by reaction with hydroxylamine. The oximes were cyclized by heating in Decalin at 200–210 °C for 4–6 h to give **6a**,[3] **6b**,[6] and **6c** in yields of 67–80% (Table I).

Scheme I



The carbonyl intermediates **11a–c** of 5*H*-pyrido[4,3-*b*]indoles[7] were prepared as shown in Scheme II. The corresponding oximes **12a–c** cyclized at a lower temperature (119 °C) than **5a–c**, presumably because of electron donation by the indole nitrogen, giving 5*H*-pyrido[4,3-*b*]indoles **13a–c** (Table II). In the preparation of **13a,b**, the intermediate oximes were not isolated; the methanol used in the oxime synthesis was replaced by toluene and the resulting solution refluxed to effect cyclization. Although the yields of **13a,b** obtained by this route were modest, the conversions based on recovered **11a,b** that had not been converted into oxime were 72–86%.

Thus the thermal cyclization of the 1-aza-1,3,5-hexatriene system offers a direct route to fused pyridine ring systems that avoids the necessity for oxidation of an intermediate tetrahydropyridine.[4,7]

Experimental Section

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on Varian T-60 and JEOL PMX-60Si instruments in $CDCl_3$ with Me_4Si as internal standard. Mass spectra were measured on Hitachi RMU-7L and Shimazu GC-MS 6020 spectrometers. Satisfactory elemental analyses for all purified compounds have been submitted to the editor.

2,3-Thiophenedicarbaldehyde 3-(Ethylene acetal) (2). To an ice-cooled solution of thiophene-3-aldehyde ethylene acetal (1, 31 g, 0.2 mol) in anhydrous THF (150 mL) was added dropwise a solution of *n*-BuLi (330 mL of 1.5 M solution in *n*-hexane, 0.2 mol) with stirring. After 0.5 h, dry dimethylformamide (17.5 g, 0.24 mol) in anhydrous THF (20 mL) was added. The ice bath was removed, and stirring was continued for 3 h at room temperature. The solution was quenched with water and extracted with benzene. The extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The oily residue was distilled to give **2** (35.6 g, 97%): bp 161-165 °C (2 torr); mass spectrum, *m/e* 184 (M^+); ^1H NMR δ 6.15 (1 H, s, CH), 9.95 (1 H, s, CHO).

2-Vinylthiophene-3-carbaldehyde Ethylene Acetal (3). A solution of **2** (28 g, 0.15 mol) in anhydrous THF (100 mL) was added dropwise to an ice-cooled solution of methyl triphenylphosphonium bromide (64 g, 0.18 mol) and *n*-BuLi (270 mL of 1.5 M solution in *n*-hexane, 0.18 mol) in anhydrous THF (120 mL). The mixture was stirred at room temperature overnight, quenched with brine, and extracted with benzene. The benzene was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to

(1) Kano S.; Mochizuki, N.; Hibino S.; Shibuya S. *J. Org. Chem.* **1982**, *47*, 3566.
(2) Barger G.; Easson A. P. T. *J. Chem. Soc.* **1938**, 2100.
(3) Gronowitz S.; Sandberg E. *Arkiv. Kemi* **1970**, *32*, 217.
(4) Barker J. H. In "Advances in Heterocyclic Chemistry"; Katritzky A. R., Boulton A. J., Ed.; Academic Press: New York, 1977; Vol. 21, pp 65–117.
(5) Recently, thermal electrocyclic reaction of 2-aza-1,3-butadiene derivatives at high temperature have been reported: Govindan C. K.; Taylor, G. *J. Org. Chem.* **1983**, *48*, 5348 and related references cited therein.
(6) Sandberg, E. *Chem. Scr.* **1972**, *2*, 241.
(7) Abramovitch R. A.; Spenser I. D. In "Advances in Heterocyclic Chemistry"; Katritzky A. R.; Ed; Academic Press, New York, 1964; Vol. 3, pp 79–202.
(8) Kano S.; Sugino E.; Shibuya S.; Hibino, S. *J. Org. Chem.* **1981**, *46*, 3856.

0022-3263/84/1949-5006$01.50/0