Benzo-Fused Bicyclic Imides

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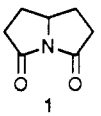
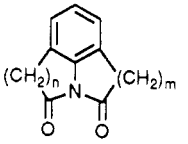
The benzo-fused bicyclic imides, **2** and **3**, were synthesized via acetic anhydride promoted ring closure of lactam acids **10** and **15**. Attempts to carry out the analogous reaction with lactam acid **21** failed to afford the desired 5,5-benzo-fused bicyclic imide **4**. Possible reasons for the failure of this reaction are discussed.

Rolziracetam (**1**, CI-911) is a cognition activator of the nootropic class that has advanced to clinical trials.[1] In a search for improved derivatives of **1**, we undertook the synthesis of several related benzo-fused bicyclic imides (**2**–**4**).[2] Herein we describe the successful preparation of 6,6- and 5,6-fused bicyclic imides and unsuccessful attempts to prepare the corresponding 5,5-system.



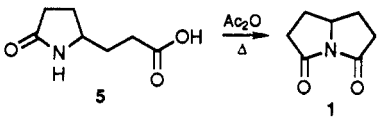
1
Rolziracetam, CI-911



2: $n = 2$; $m = 2$
3: $n = 1$; $m = 2$
4: $n = 1$; $m = 1$

Chemical Synthesis

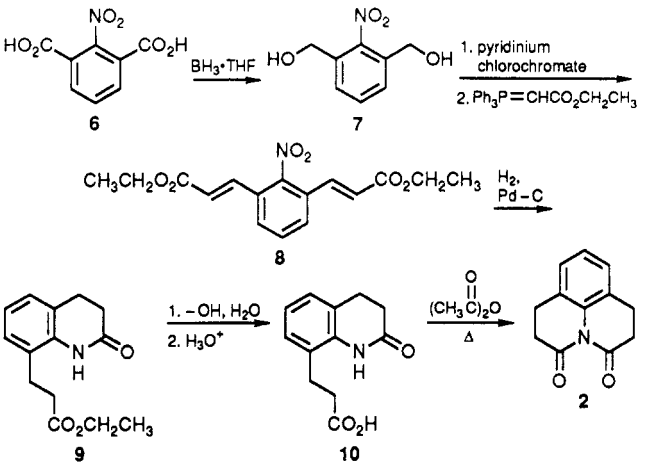
The synthesis of **1** and a number of its analogues utilized an acetic anhydride promoted closure of a lactam acid to a bicyclic imide as the final step (eq 1).[1] We planned to use this same general approach to prepare the corresponding benzo-fused bicyclic imides.



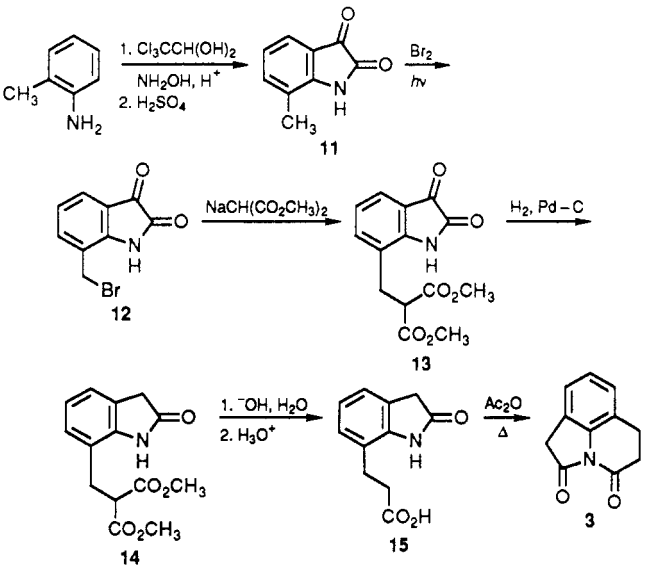
(1)

Preparation of the 6,6-compound, **2** (Scheme I), began with 2-nitro-1,3-benzenedicarboxylic acid, **6**, which was readily obtained by $KMnO_4$ oxidation of 2,6-dimethyl-1-nitrobenzene.[3] Two-carbon homologation was accomplished by oxidation of the diol **7** with PCC to afford the desired dialdehyde, which was not isolated but immediately treated with carbethoxymethylene triphenylphosphorane to afford **8** in 52% overall yield. Treatment of **8** with hydrogen in the presence of Pd-C resulted in saturation of the olefin and conversion of the nitro group to the amine. This intermediate underwent immediate cyclization to the desired amide **9** as expected. Ester hydrolysis was followed by treatment with Dowex 50×8 to generate the crude acid **10**, which was treated with acetic anhydride to effect cyclization to the benzo-fused bicyclic imide **2** in 74% combined yield for hydrolysis and cyclization.

Scheme I



Scheme II



Preparation of 5,6-benzo-fused bicyclic imide **3** (Scheme II) required that the groups ortho to the aromatic nitrogen be differentially functionalized, precluding the synthesis used for **2**. Reaction of *o*-toluidine with chloral hydrate under standard isatin-forming conditions[4] afforded 7-methylisatin,[5] **11**, which had the requisite five-membered ring and a methyl group we hoped could be further elaborated. Bromination of **11** afforded bromomethyl derivative **12**, which upon reaction with sodium dimethyl

(1) (a) Butler, D. E.; Leonard, J. D.; Caprathe, B. W.; L'Italien, Y. J.; Pavia, M. R.; Hershenson, F. M.; Poschel, P. H.; Marriott, J. G. *J. Med. Chem.* **1987**, *30*, 498. (b) Compounds of this class may have potential in treating disorders of learning and memory, for example, Alzheimer's disease (AD), age-associated memory impairment (AAMI), and other forms of senile cognitive decline (SCD). For more background information, refer to: Moos, W. H.; Davis, R. E.; Schwarz, R. D.; Gamzu, E. R. *Med. Res. Rev.* **1988**, *8*, 353.

(2) Butler, D. E.; Pavia, M. R.; Hershenson, F. M. U.S. patent 4,677,112, 1987.

(3) Notting, E.; Gachot, C. *Chem. Ber.* **1906**, *39*, 73.

(4) General isatin synthesis: Marvel, C. S.; Hiers, G. S. *Organic Syntheses*; Wiley: New York, 1941, Collect. Vol. I, p 327.

(5) Colombara, H. U.S. Patent 1,856,210, 1932; *Chem. Abstr.* **1932**, *26*, P3523[1].

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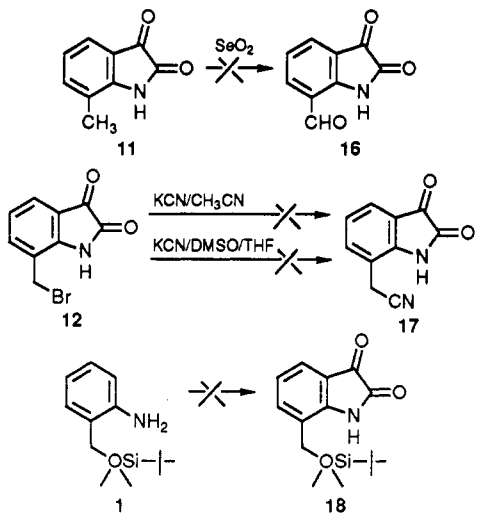
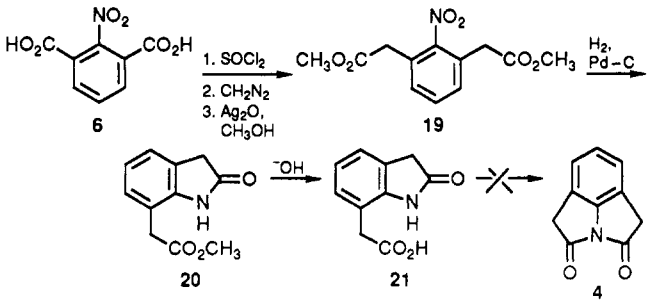
Scheme III



Scheme IV



malonate gave compound **13** in 38% yield for the two steps. While the yield for this sequence is modest, alternatives were unsuccessful. Among the reactions attempted were oxidation of compound **11** to corresponding aldehyde **16** with selenium dioxide and reaction of bromomethyl derivative **12** with KCN to afford **17** (Scheme III). In addition, attempts to prepare an isatin where the 7-substituent contains an oxygen functionality, as in **18**, were unsuccessful.

Isatin **13** was converted into the corresponding oxindole upon catalytic hydrogenation. On occasion, incomplete reduction of the carbonyl function resulted in the 3-hydroxyoxindole. This material could be converted into compound **14** by treatment with acetic anhydride to form the acetate and further hydrogenolysis of the acetate. The diester of **14** was then selectively hydrolyzed and decarboxylated to afford **15**, which was semipurified by column chromatography. This material was cyclized to benzo-fused bicyclic imide **3** in acetic anhydride at 90 °C for 1 h. The yield of this reaction was 41% after purification by chromatography and sublimation.

The next target molecule was the 5,5-benzo-fused bicyclic amide **4** (Scheme IV). Since this is once again a symmetrical molecule, both groups adjacent to the nitrogen on the aromatic ring can be elaborated simultaneously. The starting material was 2-nitro-1,3-benzenedicarboxylic acid. A double one-carbon homologation was accomplished by application of the Arndt-Eistert sequence[6a,b] (conversion to the diazoketone followed by silver-catalyzed rearrangement in the presence of methanol) to afford bis-(methyl ester) **19**. Catalytic hydrogenation (Pd–C) reduced the nitro group to the corresponding aniline, with concomitant cyclization to oxindole **20**. The methyl ester could be hydrolyzed as previously described to yield carboxylic acid **21**, which is the cyclization substrate. The reaction of **21** with acetic anhydride as described for compounds **1–3** was unsuccessful, affording either starting material or unidentifiable products, depending on reaction conditions, but never the desired **4**. Among the conditions tried were slow warming of an acetic anhydride solution of **21**, addition of **21** to refluxing acetic anhydride, and carrying out the reaction in toluene with 1.2 equiv of acetic anhydride present. We also examined the reaction of **21** with dicyclohexylcarbodiimide and DMAP under varying dilutions and temperatures, or alternatively with oxalyl chloride, but none of the desired product was identified in any case.

Theoretical Calculations

The lack of success in forming **4** was initially surprising since this *exo-trig* ring closure is favored according to Baldwin's rules.[7,8] However, as initially formulated, these empirical rules pertain to ring closures wherein the chain is composed of sp^3-hybridized carbon atoms. Any change that alters chain geometry/conformation will influence ring closure. In the present case, sp^2 carbons are involved, thus the ring closure might be predicted to be more difficult. It is clear that the general closure is not precluded, as evidenced by the synthesis of compound **3**. In the case of compound **4**, though, the combination of ring closure conformation and nucleophile orientation may be prohibitive. Unfortunately, other reasons for the failed ring closure are not obvious from the experimental data, and evaluation of the effect of aromatic substituents on ring closure is beyond the scope of the present study.

In the hope of elucidating possible reasons for the singular difficulty in preparing compound **4**, a series of semiempirical molecular orbital (MO) calculations was undertaken. Molecular models were built using SYBYL[9] (Tripos Assoc., Releases 3.4–5.1 operating on a Digital Equipment Corp. VAX Cluster containing a VAX 11/785, a micro VAX-II, and a micro VAX 3600). Compound **1** was constructed first from the FRAGMENT pyrrolidine, and analogues were constructed from **1**. Initial optimization of **1** began with all non-hydrogen atoms coplanar. The process utilized SKETCH or BUILD to construct and complete the crude models, and the simplex and molecular mechanics methods MINIM, MAXIMIN,[10] or MAXIMIN2 for initial geometry optimization, all within SYBYL. In each case the calculations were run to convergence. (Allinger's molecular mechanics programs (e.g., MM2[11]) were not used because they are not fully parameterized for the molecules under study.) Final geometries were optimized and heats of formation (H_f) were calculated using semiempirical molecular orbital methods. For this purpose, the AMPAC[12] option, AM1[13,14] (within SYBYL),

(6) (a) Arndt, F.; Eistert, B. *Chem. Ber.* **1935**, *68*, 200. (b) Bachmann, W. E.; Struve, W. S. *Org. React.* **1942**, 38.

(7) Baldwin, J. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(8) See also the discussion of Baldwin's rules, and references cited in: March J. *Advanced Organic Chemistry; Reactions, Mechanisms, and Structure*, 3rd ed.; John Wiley and Sons: New York, 1985; p 187.

(9) *SYBYL Molecular Modeling System; VAX-Evans & Sutherland Manual*; Tripos Associates, Inc.: St. Louis, MO; Release 3.4, October 1986, through Release 5.1, April 1988.

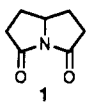
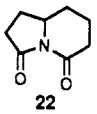
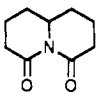
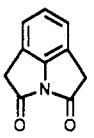
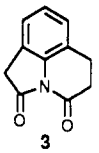
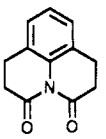
(10) Labanowski, J.; Motoc, I.; Naylor, C. B.; Mayer, D.; Dammkoehler, R. A. *Quant. Struct.-Act. Relat.* **1986**, *5*, 138.

(11) See the discussion of molecular mechanics in: Clark, T. *A Handbook of Computational Chemistry; A Practical Guide to Chemical Structure and Energy Calculations*; John Wiley and Sons: New York, 1985, pp 12ff.

(12) QCPE No. 506, Quantum Chemistry Program Exchange, Department of Chemistry, Indiana Univ., Bloomington, IN.

(13) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

Table I

compound	H_f,[a] kcal/mol	dipole moment, D	energy, eV HOMO[b]	energy, eV LUMO
 1	-68.86	6.39	-10.41	0.61
 22	-79.80	6.50	-10.25	0.76
 23	-84.66	6.45	-10.12	0.89
 4	-3.56	5.62	-9.28	-0.22
 3	-33.15	5.73	-9.19	-0.16
 2	-47.31	5.44	-9.08	-0.09

[a] Because calculated heats of formation depend somewhat on starting geometries, even with full geometry optimization in AM1, the values listed are approximate. [b] Ionization potential = -(HOMO energy).

was chosen. Molecular mechanics and semiempirical methods predicted similar geometries and energy differentials. (Standard SYBYL techniques were used in all procedures; default options were chosen wherever possible.)

For comparison purposes, addition of a methylene group often lowers the heat of formation by approximately 10 kcal/mol. Thus, based on MAXIMIN geometries and AM1 energies, butane is 6 kcal/mol lower in energy than propane, cyclohexane is 9 kcal/mol lower in energy than cyclopentane, and 2-piperidone is 13 kcal/mol lower in energy than 2-pyrrolidone (and the carbocyclic equivalents of compounds **1** and **23** differ by about 15–30 kcal/mol). Fusing of cyclic systems to existing ones may be expected to alter energies differently.

The heats of formation listed in Table I show compound **4** to be significantly higher in energy than **1**, **3**, and other relatives that were readily synthesized. The non-hydrogen atoms in compound **4** would be essentially coplanar, thereby creating considerable bond angle strain.

The higher heat of formation of compound **4** relative to **3** is greater than would be expected based simply on a difference of one methylene group. Thus, difficulties encountered in the attempted preparation of compound **4** may be explained on the basis of bond angle strain energy inherent to the benzo-fused bicyclic imide structure. While the results do not preclude the possible existence of **4**, they certainly help to explain why closely related analogues were synthesized with little difficulty while the synthesis of this analogue failed.

(14) For a comparison of AMPAC methods vs experiment, see: Stewart, J. J. P. *QCPE Bull.* **1983**, *3*, 54.

The present analysis has not been exhaustive, and other factors may also be operational. For example, as alluded to earlier, reaction trajectories leading to the formation and decomposition of the tetrahedral intermediate may play a role in the ease of synthesis.

Biological Activity

Compounds **2** and **3** were compared to CI-911 in an in vivo model of amnesia reversal.[1] Compound **3** possessed a similar activity profile to that seen with **1** while compound **2** was nearly devoid of amnesia reversing activity.

Experimental Section

All melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded with a Varian EM-390 spectrometer using Me_4Si as the internal standard and deuteriochloroform or Me_2SO-d_6 as solvent. NMR values are reported in ppm. Purity was determined by microanalysis and by TLC with 0.25 mm thick plates coated with silica gel G as the stationary phase. IR spectra were recorded with a Nicolet XS-20 FT-IR spectrometer using KBr pellets. All compounds possessed microanalytical and spectral data consistent with the proposed structures.

2-Nitro-1,3-benzenedimethanol (7). A solution of 2-nitro-1,3-benzenedicarboxylic acid[3] (12.7 g, 0.06 mol) in tetrahydrofuran (60 mL) was cooled to 0 °C, and 1 N borane–tetrahydrofuran (300 mL, 0.3 mol) was added dropwise over 1 h. The mixture was allowed to warm slowly to 25 °C and stirred for 36 h. Methanol (50 mL) was added slowly, and the mixture was filtered and evaporated. The residue was dissolved in ethyl acetate (100 mL) and washed with water (25 mL), dried ($MgSO_4$), filtered, and evaporated to a yellow solid, which was further purified by flash chromatography over silica (elution with 1:1 hexane–ethyl acetate) to afford after concentration pure 2-nitro-1,3-benzenedimethanol

(8.0 g, 73% yield): mp 100–101 °C; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) 7.48 (3 H, s, aromatic), 4.63 (6 H, s, CH_2OH); IR ($CHCl_3$) 3690, 3610, 1600, 1528, 1390, 1357 cm^{-1}. Anal. Calcd for $C_8H_9NO_4$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.64; H, 5.03; N, 7.48.

Diethyl 3,3′-(2-Nitro-1,3-phenylene)bis(2-propenoate) (8). A solution of **7** (5.0 g, 0.027 mol) in dichloromethane (90 mL) was mixed with anhydrous sodium acetate (10 g). The mixture was cooled to 0 °C, and pyridinium chlorochromate (4.0 equiv, 21.4 g, 0.1 mol) was added portionwise over 10 min. The reaction was allowed to warm to room temperature over 6 h. The mixture was poured into diethyl ether (1 L) and filtered through Florisil. The colorless solution was concentrated at reduced pressure and azeotroped with heptane to remove pyridine. The resulting crude 2-nitro-1,3-benzenedialdehyde (3.4 g, 0.019 mol) was dissolved in toluene (60 mL), and carbethoxymethylene triphenylphosphorane (19.2 g, 0.06 mol) was added. The mixture was heated at 60 °C for 8 h, cooled, and concentrated at reduced pressure. Diethyl ether (100 mL) was added, and the mixture was filtered. The filtrate was concentrated and purified by flash chromatography over silica (elution with 4:1 hexane–ethyl acetate) to afford, after concentration, pure **8** (4.6 g, 52% yield): mp 114–115 °C; ^{1}H NMR ($CDCl_3$) 7.72–7.36 (3 H, m, aromatic), 7.52 (2 H, d, J = 16.8 Hz, CH=CH), 6.40 (2 H, d, J = 16.8 Hz, CH=CH), 4.22 (4 H, q, J = 6.8 Hz, $CO_2CH_2CH_3$), 1.32 (6 H, t, J = 6.8 Hz, CH_2CH_3); IR (KBr) 1695, 1632, 1520, 1473, 1366, 1280, 1272, 1228 cm^{-1}. Anal. Calcd for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; H, 4.39. Found: C, 60.36; H, 5.31; N, 4.35.

1,2,3,4-Tetrahydro-2-oxo-8-quinolinepropanoic Acid, Ethyl Ester (9). A solution of **8** (3.5 g, 0.011 mol) in absolute ethanol (100 mL) was treated with hydrogen at 1 atm of pressure for 12 h in the presence of 20% Pd/C. The mixture was filtered and concentrated at reduced pressure to yield 1,2,3,4-tetrahydro-2-oxo-8-quinolinepropanoic acid ethyl ester (2.5 g, 92% yield): mp 102–103 °C; ^{1}H NMR ($CDCl_3$) 8.38 (1 H, br s, NH), 6.96 (3 H, m, aromatic), 4.17 (2 H, q, J = 6.9 Hz, CH_2CH_3), 3.05–2.48 (8 H, m, CH_2CH_2CO and $CH_2CH_2CO_2$), 1.24 (3 H, t, J = 6.9 Hz, CH_2CH_3); IR (KBr) 3235, 1722, 1681, 1600, 1470, 1386 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.07; H, 6.86; N, 5.56.

1,2,6,7-Tetrahydro-3*H*,5*H*-*benzo*[*ij*]quinolizine-3,5-dione (2). A solution of **9** (2.5 g, 0.01 mol) in methanol (50 mL) was treated with a 0.5 N sodium hydroxide solution (19.5 mL, 0.00975 mol), and the mixture was heated at 50 °C for 2 h. The mixture was concentrated at reduced pressure to yield the sodium salt of 1,2,3,4-tetrahydro-2-oxo-8-quinolinepropanoic acid as a solid. This salt was dissolved in 2:1 water–methanol (5 mL), and the solution was passed over a Dowex 50×8 ion exchange column. The solution was concentrated at reduced pressure to yield a near quantitative yield of crude 1,2,3,4-tetrahydro-2-oxo-8-quinolinepropanoic acid, which was used without further purification. The material (2.1 g, 0.0096 mol) was dissolved in acetic anhydride (10 mL), and the solution heated to 100 °C for 1 h. Excess acetic anhydride was removed at reduced pressure, and the residual anhydride was removed by addition of toluene and repeated concentration. The solid was recrystallized from ethyl acetate to yield pure 1,2,6,7-tetrahydro-3*H*,5*H*-benzo[*ij*]quinolizine-3,5-dione (1.49 g, 74%): mp 136–140 °C; ^{1}H NMR ($CDCl_3$) 7.11 (3 H, s, aromatic), 3.08–2.67 (8 H, m, CH_2CH_2); IR (KBr) 1760, 1687, 1602, 1465, 1342, 1224 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.54; H, 5.49; N, 6.73.

7-Methyl-1*H*-indole-2,3-dione (11). To a solution of chloral hydrate (90 g, 0.54 mol) in water (1200 mL) was added sodium sulfate decahydrate (1300 g, 10.9 mol) followed by a solution of *o*-methylaniline (54 g, 0.5 mol) in water (300 mL) containing concentrated hydrochloric acid (43 mL, 0.5 mol). A solution of hydroxylamine hydrochloride (110 g, 1.58 mol) in water (50 mL) was then added. The reaction mixture was heated to reflux over a 90-min period and refluxed for 30 min. The reaction was cooled in ice, and the resulting crystalline *o*-isonitrosoacetotoluidide was isolated by filtration and air-dried. The *o*-isonitrosoacetotoluidide was dissolved in portions in concentrated sulfuric acid (325 mL) that was preheated to 50 °C with vigorous stirring. The reaction temperature was maintained under 75 °C. When the addition was complete, the mixture was heated at 80 °C for 30 min, cooled, and poured onto ice (3 kg). 7-Methyl-1*H*-indole-2,3-dione was isolated by filtration and purified by dissolution in dilute sodium hydroxide; the basic solution was treated with 4 N hydrochloric acid until a slight amount of precipitation was evident. The mixture was filtered and the filtrate acidified. Pure **11** (33 g, 38% yield) was recovered by filtration and dried in vacuo at 80 °C and 0.1 mm of pressure, mp 270–273 °C (lit. mp 267 °C).

7-(Bromomethyl)-1*H*-indole-2,3-dione (12). 7-Methyl-1*H*-indole-2,3-dione (16.1 g, 0.1 mol) was suspended in dichloroethane (2000 mL) and heated and irradiated with a high-intensity light source to the reflux point. Bromine (24.3 g, 0.15 mol) was added dropwise over a 1-h period. The solution was filtered hot and concentrated at reduced pressure to yield the product as an orange solid after washing with anhydrous diethyl ether. The product was purified using flash chromatography on silica (elution with 24:1 dichloromethane–diethyl ether) to afford **12** (17.8 g, 72% yield) after drying (60 °C at 0.1 mm): mp 199–200 °C dec; ^{1}H NMR (DMSO-d_6) 11.38 (1 H, br s, NH), 7.62 (1 H, dd, J = 5.2, 1.0 Hz, aromatic), 7.47 (1 H, d, J = 5.2 Hz, aromatic), 7.03 (1 H, dd, J = 5.2 Hz, aromatic), 4.68 (2 H, s, CH_2Br); IR (KBr) 3460, 3180, 3114, 1740, 1620, 1601, 1487, 1438, 1325 cm^{-1}. Anal. Calcd for $C_9H_6NO_2Br$: C, 45.03; H, 2.52; N, 5.83. Found: C, 45.41; H, 2.59; H, 5.82.

2-[(2,3-Dihydro-2,3-dioxo-1*H*-indol-7-yl)methyl]-propanedioic Acid, Bis(methyl ester) (13). A solution of dimethyl malonate (15.7 mL, 0.138 mol) in tetrahydrofuran (150 mL) was cooled to 0 °C, and sodium hydride (50% in mineral oil, 6.5 g, 0.138 mol) was added portionwise over 15 min. The reaction was stirred at 0 °C for 30 min, and a suspension of **12** (15.0 g, 0.0625 mol) in tetrahydrofuran (50 mL) was added in one portion. The resulting deep purple solution was stirred at room temperature for 30 min. Hydrochloric acid (1.2 N) was added until the mixture turned clear yellow, and the solution was then concentrated at reduced pressure to 20% of the original volume. The concentrate was extracted with dichloromethane (2 × 300 mL); the combined extracts were dried ($MgSO_4$), filtered, and concentrated to yield a yellow solid that was purified by flash chromatography on silica (elution with 9:1 dichloromethane–diethyl ether) to afford, after concentration, **13** (9.6 g, 53% yield): mp 137–140 °C; ^{1}H NMR ($CDCl_3$) 8.95 (1 H, br s, NH), 7.31–6.68 (24, m, aromatic), 7.04 (1 H, dd, J = 5.0 Hz, aromatic), 3.72 (6 H, s, CH_3), 3.62 (1 H, d, J = 4.5 Hz, CH), 3.12 (2 H, dd, J = 4.5, 1.4 Hz, CH_2); IR (KBr) 3272, 1738, 1608, 1489, 1463, 1437, 1288 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NO_6$: C, 57.73; H, 4.50; N, 4.80. Found: C, 57.81; H, 4.80; N, 4.50.

2-[(2,3-Dihydro-2-oxo-1*H*-indol-7yl)methyl]propanedioic Acid, Bis(methyl ester) (14). Compound **13** (1.4 g, 0.0048 mol) was dissolved in acetic acid (100 mL) and treated with hydrogen gas in the presence of 20% Pd/C at 50 psi. The solution was filtered and concentrated to yield a solid that was purified by flash chromatography on silica (elution with 7:3 hexane–ethyl acetate) to give after concentration pure **14** (1.23 g, 93% yield): ^{1}H NMR ($CDCl_3$) 8.39 (1 H, br s, NH), 7.13–6.91 (3 H, m, aromatic), 3.74 (6 H, s, CH_3), 3.66 (1 H, t, J = 7.3 Hz, CH), 3.53 (2 H, s, $PhCH_2CO$), 3.16 (2 H, d, J = 7.3 Hz, $PhCH_2CH$); IR (KBr) 3180, 2940, 1752, 1738, 1698, 1627, 1460, 1436, 1300, 1157 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.57; H, 5.22; N, 4.98.

5,6-Dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-2,4(1*H*)-dione (3). A solution of **14** (4.6 g, 0.0166 mol) was dissolved in methanol (50 mL), and 1 N sodium hydroxide (33.2 mL, 0.0332 mol) was added. The mixture was stirred at 50 °C for 90 min and concentrated at reduced pressure. The residue was dissolved in water (75 mL) and methanol (50 mL). The solution was made acidic with excess Dowex 50×8 acidic ion exchange resin and heated with stirring at 70 °C for 24 h. The solution was cooled, filtered, and concentrated to dryness to yield crude **15**, which was partially purified by flash chromatography on silica (elution with 9:1 dichloromethane–methanol). A solution of crude **15** (2.0 g, 0.0098 mol) in acetic anhydride (8 mL) was heated to 90 °C with stirring for 1 h, and then excess acetic anhydride was removed at reduced pressure. The red crystalline material was purified by flash chromatography over silica (elution with 23:2 dichloromethane–diethyl ether). Final purification by fractional sublimation (0.1 mm, 150 °C) gave **3** (0.77 g, 41% yield): mp 194–197 °C; ^{1}H NMR ($CDCl_3$) 7.15 (3 H, m, aromatic), 3.68 (2 H, s, CH_2, lactam), 3.07 (2 H, dd, J = 7.4 Hz, $COCH_2$, δ-lactam), 2.85, 2.84 (2 H, 2 t, J = 7.4 Hz, $PhCH_2$, δ-lactam); IR (KBr) 1766, 1696, 1631, 1604, 1472,

1352 cm^{-1}. Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.50. Found: C, 70.32; H, 4.76; N, 7.24.

2-Nitro-1,3-benzenediacetic Acid, Bis(methyl ester) (19). A suspension of 2-nitro-1,3-benzenedicarboxylic acid[3] (25 g, 0.118 mol) in 1,1,2,2-tetrachloroethane (100 mL) was treated with thionyl chloride (30 mL), and the mixture was refluxed for 7 h. The mixture was concentrated at reduced pressure, and after crystallization from *n*-heptane yielded pure 2-nitro-1,3-benzenedicarbonyl chloride (mp 129-131.5 °C), which was used immediately. A solution of diazomethane (4.2 g, 0.1 mol) in diethyl ether (500 mL) was cooled to 0 °C, and 2-nitro-1,3-benzenedicarbonyl chloride (2.93 g, 0.0118 mol) was added in portions. The mixture was stirred for 17 h and concentrated at reduced pressure to yield 2-nitro-1,3-diazoacetylbenzene as a tan solid. This compound was dissolved in methanol (250 mL), and the solution was added to freshly prepared silver oxide (synthesized by the reaction of 5 mL of a 10% silver nitrate solution with sodium hydroxide). The mixture was stirred at 0 °C for 1 h and at 55-60 °C for 2 h. The solution was filtered and concentrated to yield crude **20**. Recrystallization from *n*-heptane afforded pure **19** (1.83 g, 58% yield): mp 144-145 °C; ^{1}H NMR (DMSO-d_6) 7.46 (3 H, m, aromatic), 3.81 (4 H, s, CH_2), 3.56 (6 H, s, CH_3); IR (KBr) 2950, 1740, 1612, 1528, 1436, 1347 cm^{-1}. Anal. Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.81; H, 4.68; N, 5.01.

2,3-Dihydro-2-oxo-1*H*-indole-7-acetic Acid, Methyl Ester (20). A solution of **19** (5.98 g, 02.022 mol) in tetrahydrofuran and methanol (2:1, 100 mL) was treated with hydrogen gas in the presence of 20% Pd/C for 18 h. The mixture was filtered and concentrated at reduced pressure to yield 2,3-dihydro-2-oxo-1*H*-indole-7-acetic acid methyl ester. Final purification was accomplished using flash chromatography on silica (elution with 1:19 methanol-dichloromethane) and resulted in pure **20** (4.01 g, 89% yield): mp 156-157 °C; ^{1}H NMR ($CDCl_3$) 9.15 (1 H, br s, NH), 7.15-6.85 (3 H, m, aromatic), 3.68 (3 H, s, CH_3), 3.60 (2 H, s, CH_2CO), 3.05 (2 H, s, CH_2CO); IR (KBr) 3180, 3050, 1722, 1703, 1619, 1600, 1458 cm^{-1}. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.44; H, 5.39; N, 6.73.

2,3-Dihydro-2-oxo-1*H*-indole-7-acetic Acid (21). A solution of **20** (2.05 g, 0.01 mol) in methanol (50 mL) was treated with 1 N sodium hydroxide (10 mL, 0.01 mol), and the mixture was heated at 60 °C for 1 h. The reaction was concentrated at reduced pressure to yield the sodium salt of 2,3-dihydro-2-oxo-1*H*-indole-7-acetic acid. The sodium salt was dissolved in 2:1 water-methanol, and the solution was passed over a Dowex 50X-8 ion exchange resin. The eluant was concentrated at reduced pressure to yield pure **21** (1.60 g, 84% over Dowex 50×8 234-236 °C; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) 9.95 (1 H, br s, NH), 7.10-6.75 (3 H, m, aromatic), 3.55 (2 H, s, CH_2CO), 3.40 (2 H, s, CH_2CO); IR (film) 3290, 3072, 2960, 1749, 1690, 1545, 1458, 1440 cm^{-1}. Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.55; H, 5.00; N, 7.21.

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Asymmetric Halogenation and Hydrohalogenation of *trans*-2-Butenoic Acid in a Crystalline α-Cyclodextrin Complex

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trans-2-Butenoic acid was asymmetrically hydrohalogenated and halogenated in a crystalline α-cyclodextrin complex. Exposure to gaseous hydrogen bromide at 20 °C and to hydrogen chloride at 0 °C gave (*S*)-(+)-3-bromobutanoic acid in 58% and (*S*)-(-)-3-chlorobutanoic acid in 64% enantiomeric excesses, respectively. At 45-50 °C, the guest in the cavity of the cyclodextrin reacted with gaseous bromine or chlorine to produce erythro-dihalides with extremely low optical activities; no products were obtained on treatment with bromine for 50 h at the lower temperature of 20 °C. The crystal structure of the complex was determined to be: $C_{36}H_{60}O_{30}\cdot C_4H_6O_2\cdot 5H_2O$; FW = 1149.0; orthorhombic; space group, $P2_12_12_1$; Z = 4; a = 14.406 (5), b = 38.174 (12), and c = 9.430 (3) Å; V = 5185.9 Å^3; D_X = 1.472, D_m = 1.475 g/cm^2. A mechanism for the observed chiral induction in the present gas-solid reaction is discussed in terms of the crystal structure of the complex.

Introduction

The inclusion phenomenon in cyclodextrin enables guest molecules to exhibit different and sometimes new properties relative to those of the free molecules. Some of these properties, including physical, chemical, and biological phenomena, have been studied over the recent years.[1] Asymmetric reactions catalyzed by cyclodextrin are of particular interest, as a quick and easy method for the synthesis of chiral compounds from achiral materials would thus be made available. In this regard, some asymmetric reactions have been attempted in solution in the presence of cyclodextrin, but all of these reactions have afforded the products in low optical yields.[1]

Recently, we achieved high enantioselectivity in the chlorination of methacrylic acid in crystalline cyclodextrin complexes.[2] Moreover, we have observed asymmetric additions of gaseous halogens and hydrogen halides to *trans*-cinnamic acid, ethyl *trans*-cinnamate, and styrene included in crystalline cyclodextrins.[3-5] This paper describes the asymmetric halogenation and hydro-

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