smaller than the value of 107.1° reported for norbornane,[19] reflecting increased strain. The flap angle C(5)–O(1)–C(5′) is also small (97.3°) but not quite as low as the corresponding angle in norbornane (95.3°)[19] or the dimer (95.1°).[18] The presence of this tight angle pinching C(5) and C(5′) causes an elongation of the C(1)–C(4) bond to 1.576 Å; the other bond lengths are more or less normal. The same reflex effect is present in norbornane (1.578 Å)[19] and the dimer (1.568 Å)[18] and appears to be a general phenomenon in bicyclo[2.2.1] systems.

As **1** and **2** cannot interconvert under our conditions,[15] it is not possible to write a plausible mechanism from **2** to **3** or from **1** to **7**. Nonetheless, a second piece of corroborating evidence was desired. Consequently, the reaction of **4** with malondialdehyde was investigated, since it was expected that if 2,6-bis(methoxycarbonyl)-5-hydroxycyclohex-2-en-1-one (the six-membered-ring analogue of **1**) were to form at low pH, it would aromatize to 2,6-bis(methoxycarbonyl)phenol (**9**, Scheme III). In fact, no **9** could be isolated at pH 7–9, which is in itself remarkable considering the high yields of phenols obtained from **4** and many 2-substituted malondialdehydes.[20] The product in this pH range was 2,4,6,8-tetrakis(methoxycarbonyl)bicyclo[3.3.1]nonane-3,7-dione (**10**, 60% yield).[21] In complete confirmation of our prediction, **9** was produced in 41% yield at pH 5, where the yield of **10** was 35%.[22] Treatment of **9** with **4** at pH 8 does not produce any **10**. Although phenol formation is generally more rapid at basic pH's, higher yields have been obtained at pH 5 when the starting material decomposed at higher pH.[23] This is not the case in our system. The striking similarity in the behavior of malondialdehyde to that proposed for glyoxal provides strong support for the intermediacy of **1** at low pH.

Attempts to isolate **1** have thus far failed, which is not surprising in light of the fact that 2-(methoxycarbonyl)-cyclopent-2-en-1-one is stable in dilute solution at −10 °C but polymerizes upon attempted purification.[14] Compound **1** is presumably even more reactive. A 1:1 adduct has been observed spectroscopically upon admixture of **4** and phenylglyoxal, but it was too labile to be isolated.[4] Now that the pH dependence of the condensations of dimethyl 3-oxoglutarate with glyoxal and malondialdehyde is understood, it will be possible to use these previously recondite reactions in a more rational manner for the quick construction of complex natural products and man-made molecules of theoretical interest.

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Registry No. **1**, 77589-52-7; **4**, 1830-54-2; **5b**, 68703-09-3; **7b**, 58648-30-9; **8**, 77589-53-8; **10**, 77589-54-9; glyoxal, 107-22-2.

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(21) Satisfactory analytical and spectral data have been obtained for this new compound.
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Supplementary Material Available: Crystal and refinement data, atomic coordinates, and bond and torsion angles (4 pages). Ordering information is given on any current masthead page.

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Aporphines. 35. Synthesis of (*R*)-(−)- and (*S*)-(+)-Apomorphine from Thebaine and (+)-Bulbocapnine

Summary: A practical method for the synthesis of (−)-apomorphine and (−)-*N*-*n*-propylnoramorphine from the opioid thebaine is presented. The method is also applicable to the transformation of (+)-bulbocapnine to (+)-apomorphine.

Sir: Apomorphine (APO, **8a**) was first prepared in 1869 by the acid treatment of morphine.[1] The structure of APO was elucidated in 1902,[2] and its absolute configuration was determined to be *R* in 1955.[3] In 1970 the total synthesis of (±)-APO was carried out by a multistep process from isoquinoline and vanillin.[4] (±)-APO was resolved into (−) and (+) enantiomers in 1973,[5] and it was established that dopaminergic activity resides principally in the 6a*R* (levorotatory) isomer. In the century following its first preparation, APO was used in a variety of clincal disorders.[6] With the demonstration in the mid and late 1960's that APO is a dopamine (DA) receptor agonist and evidence that a derangement of DA function may play a role in various neurological, psychiatric, and other disorders, there has been a renewed interest in clinical and pharmacological research with this compound and its more potent *N*-propyl homologue **8b** (NPA).

The actions of (−)-APO at DA-sensitive cells have received further support in studies of the iontophoretic application of APO to striatal neurons,[7] the stimulation of DA-sensitive adenylate cyclase by APO[8,9] and the use of radioactive ligands including ^3H-APO[10] and ^3H-NPA[11] to

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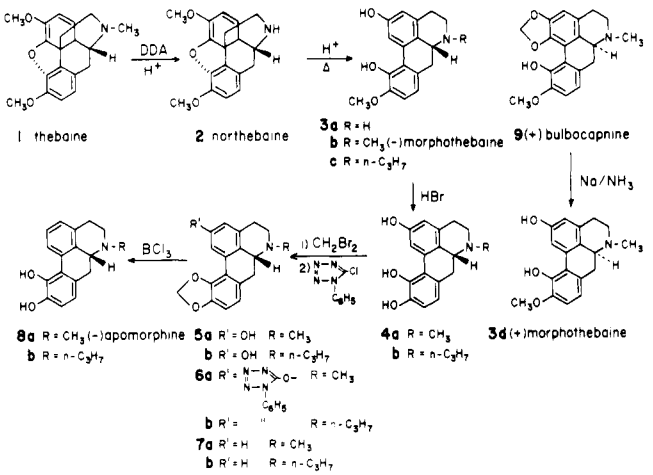
Scheme I. Transformation of Thebaine, (*R*)-Apomorphine, and (*S*)-Bulbocapnine to (*S*)-Apomorphine



evaluate binding of DA-agonists[12] to their presumed receptors in forebrain tissue preparations.

This communication describes a procedure for the transformation of the opioid thebaine (1) to the aporphines (-)-apomorphine (**8a**) and (-)-*N*-*n*-propylnorapomorphine (**8b**) as well as the preparation of (+)-apomorphine from the naturally occurring aporphine alkaloid (*S*)-(+)-bulbocapnine (Scheme I).

Northebaine (**2**)[13] was treated with concentrated HCl in a pressure bottle as described for the thebaine (**1**) → morphothebaine (**3b**)[14] conversion to give normorphothebaine (**3a**). *N*-*n*-Propylnormorphothebaine was prepared from **3a** with propyl iodide in acetonitrile. O-Demethylation of **3b** and **3c** was achieved by heating with 48% HBr to give **4a** and **4b** in quantitative yields.[15] The catechol-protected derivatives **5a** and **5b** were secured by treatment of triphenols **4a** and **4b** with methylene dibromide in alkaline aqueous Me_2SO[16] [for **5a**·HCl: mp 245–246 °C; mass spectrum, *m/e* 295; NMR (Me_2SO-d_6) δ 7.45 (d, 1 H, C_1 H), 6.85 (m, 2 H, C_8 H), 6.65 (d, 1 H, C_3 H), 6.05 and 6.2 (d, 2 H, CH_2), 2.8–3.23 (m, 7 H), 2.5 (s, 3 H, NCH_3)].[17] Removal of the phenolic hydroxyl group at the 2-position of the aporphine ring in **5a** and **5b** was achieved in two steps by formation of the phenyl tetrazolyl ethers **6a**·HCl (mp 224–27 °C; mass spectrum, *m/e* 439) and **6b**·HCl (mp 167–175 °C; mass spectrum, *m/e* 467) followed by hydrogenolysis over 5% Pd/C in acetic acid at 40 °C for 48 h to give **7a** and **7b** in greater than 90% yields[18] [**7a**·HCl, mp 270–273 °C (lit.[16] 273–279 °C); **7b**·HCl, mp 238–244 °C; mass spectrum, *m/e* 307]. Comparison samples of **7a** and **7b** were prepared from the disodium salt of the aporphines **8a** and **8b** with methylene dibromide in Me_2SO–H_2O. The products thus obtained were identical with respect to their mass spectra, R_f values, and melting points.

The removal of the methylenedioxy group in **7a** and **7b** was carried out in quantitative yields with boron trichloride in CH_2Cl_2 by methods recently described.[19] The mass spectrum as well as the optical rotation of **8a** and **8b** was in agreement with authentic samples obtained by the rearrangement of the corresponding morphine derivatives.[4,20]

The aporphine alkaloid (*S*)-bulbocapnine, isolated from the roots of *Corydalis cava*, has been converted to (+)-morphothebaine (**3d**).[21,22] By a sequence of reactions described for the transformation of (-)-morphothebaine (**3b**) to (-)-apomorphine (**8a**) described above, a facile route to (+)-apomorphine has thus been effected.

This approach to the synthesis of the enantiomers of apomorphine from readily available natural products containing the desired chirality appears to be superior to the procedure involving an involved multistep process followed by separation of the racemic mixture[5] and thus provides an alternative process for the preparation of apomorphine and *N*-propylnorapomorphine for biochemical and clinical use.

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Registry No. **1**, 115-37-7; **2**, 2579-67-1; **3a**, 61774-59-2; **3b**, 478-53-5; **3c**, 77629-99-3; **3d**, 77630-00-3; **4a**, 77630-01-4; **4b**, 77630-02-5; **5a**·HCl, 77630-03-6; **5b**, 77630-04-7; **6a**·HCl, 77630-05-8; **6b**·HCl, 77630-06-9; **7a**·HCl, 40609-94-7; **7b**·HCl, 77630-07-0; **8a**·2Na, 77630-08-1; **8b**·2Na, 77630-09-2; **9**, 298-45-3.

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Asymmetric Induction in Additions to Epoxides. Addition of α-Anions of N,N-Disubstituted Carboxamides

Summary: The addition of α-anions of monosubstituted *N,N*-dialkylacetamides to monosubstituted epoxides has been shown to give significant 1,3 asymmetric induction at the carbanionic center when the alkyl substituents are large.

Sir: Asymmetric induction during carbon–carbon bond formation has been[1] and continues to be[2-4] a topic of great

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