80 °C for 1 h (or refluxed when MeOH was used) and poured onto 200 ml of ice–water, and the solid product(s) was filtered. It was subsequently determined that the use of 0.045 mol (1.1 equiv) of thiol gave comparable results.

General Literature[1] Thiolation Method. The thiol (0.05 mol) was added to a cold (ca. 0 °C), stirred solution of 2.8 g (0.05 mol) of KOH in 50 ml of MeOH (or 50 ml of DMF), followed by dropwise addition (ca. 15 min) of 0.04 mol of **1** in 30 ml of MeOH (or 30 ml of DMF), maintaining the temperature at ca. 0 °C. The mixture was refluxed (or heated at 80 °C when DMF was used) for 40 min and poured onto 200 ml of ice-cold 10% HCl, and the solid product(s) was filtered.

Separation of 2b and 3b–d. A portion of the crude solid (7.1 g) obtained from the reaction of CH_3SNa with **1b** was chromatographed on 350 g of silica gel (J. T. Baker Chemical Co., no. 5-3405) in a 5-cm column. After elution of **3b** with CH_2Cl_2–hexane (1:9), the solvent ratio was changed to 3:20 and the remaining compounds were eluted in the order **3c, 2b, 3d.** Azoxybenzenes **3b–d** were recrystallized from ethanol and **2b** was recrystallized from hexane: UV[11] λ_{max} (log ϵ), **3b** 230 (4.07), 268 (4.01), 330 (4.35); **3c** 240 (4.01), 364 (4.38); **3d** 247 (4.09), 380 (4.52); **2b,** 225 (3.84), 334 (4.18). Anal. **3b.** Calcd: C, 41.71; H, 1.50; N, 6.95, Cl, 17.59. Found: C, 41.73; H, 1.75; N, 6.69; Cl, 17.50. **3c.** Calcd: C, 43.43; H, 2.19; N, 6.55; Cl, 8.55; S, 7.73. Found: C, 43.36, H, 2.38; N, 6.66; Cl, 8.71; S, 7.97. **3d.** Calcd: C, 45.06; H, 2.84; N, 6.57; S, 15.04. Found: C, 44.70; H, 3.00; N, 6.45; S, 15.50. **2b.** Calcd: C, 40.50; H, 2.55; N, 5.91; S, 13.52. Found: C, 40.73; H, 2.68; N, 5.87; S, 13.51.

References and Notes

(1) H. H. Hodgson and F. W. Handley, *J. Soc. Chem. Ind., London,* **46,** 435T (1927).
(2) For example, in ref 1, the addition of *p*-chloronitrobenzene (**1a**) to a methanolic solution of sodium methanethiolate affords mainly 4,4-dichloroazoxybenzene (**3a**) and only a "very small amount" of the desired thioanisole (**2a,** R = CH_3).
(3) This is in contrast to the analogous substitution of **1a** by methoxide, which proceeds readily in good yield: R. Filler and H. Novar, *J. Org. Chem.,* **26,** 2707 (1961).
(4) It was expected that the buffering effect of the excess thiol would slow the rate of reduction, presumably by lowering the effective reduction potential of the system.
(5) The success with DMF obviated studies with other potentially useful solvents [e.g., Me_2SO, see R. L. Jacobs, *J. Org. Chem.,* **36,** 242 (1971)].
(6) For example, the addition of solvent (see Table I, entries 4, 9, 11).
(7) W. R. Waldron and E. E. Reid, *J. Am. Chem. Soc.,* **45,** 2399 (1923).
(8) R. H. Baker, R. M. Dodson, and B. Riegel, *J. Am. Chem. Soc.,* **68,** 2636 (1946).
(9) J. Miller and A. J. Parker, *J. Am. Chem. Soc.,* **83,** 117 (1961).
(10) Table I, entries 4–8.
(11) UV spectra were taken in ethanol on a Cary 14 instrument.

Thermolysis of 4,4,10β-Trimethyl-*trans*-decal-3β-ol Azidoformate

Michael R. Czarny, Barrett W. Benson,[1] and Thomas A. Spencer*

Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755

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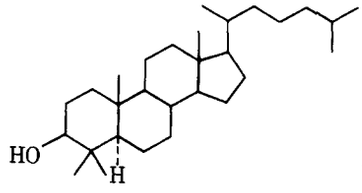
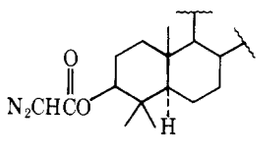
A recent report[2,23] of thermolysis of the azidoformate derived from lanostanol prompts us to describe the results of an analogous experiment in the decalin series.[3] Our aim, like that of Jones, Alewood, Benn, and Wong,[2] was to see if functionalization of one or both of the C-4 methyl groups of a compound like 4,4-dimethylcholestan-3β-ol (**1**) could be achieved by intramolecular insertion of the nitrene formed from an azidoformate derivative of the C-3 β-hydroxyl group. Although such insertion would lead to a six-membered ring carbamate, rather than the usually predominant[4,5] five-membered ring carbamate which would result from nitrene attack at C-2, molecular models indicate that insertion into either C-4 methyl group is relatively favorable geometrically. Because we had previously succeeded in functionalizing the C-4 β-methyl group via photolysis of a doxyl derivative of 4,4-dimethylcholestan-3-one,[6] our hope was that insertion would occur at the equatorial, 4α-methyl group. As indicated below, this hope was realized in the conversion of **5** to **8,** although in lower yield than in the comparable conversion in the lanostanol series.[2]

Initially, we explored decomposition of diazoacetate **2,** derived from **1** by the method of House,[7] to see if carbenoid insertion at a C-4 methyl group would occur. However, the products from thermolysis or photolysis of **2** were very complex mixtures, which contained predominantly material which afforded **1** upon treatment with $LiAlH_4$. Since these facts indicated that a useful amount of intramolecular insertion had not occurred, we turned to azidoformate decomposition.

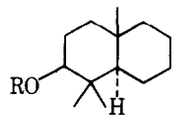
The azidoformate selected for thermolysis was **5,** derived from 4,4,10β-trimethyl-*trans*-decal-3β-ol (**3**).[8,9] Preparation



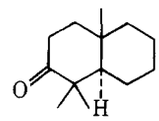
1



2



3, R = H
4, R = COCl
5, R = CON_3



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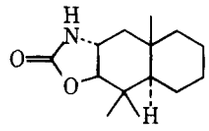

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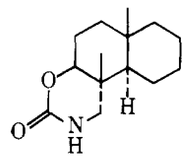


8

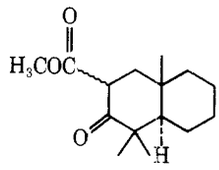
of **5,** mp 55–57 °C, was accomplished in excellent yield by treatment of **3** with phosgene to afford **4,** which was readily converted to **5** with sodium azide. When a vacuum degassed CCl_4 solution of **5** was heated at 180 °C for 3 h, a much simpler product mixture was formed than from **2,** and the three principal products were easily separated by chromatography. One was readily identified, by comparison with an authentic sample,[10] as 4,4,10β-trimethyl-*trans*-decal-3-one (**6,** 14%), a type of product, like the other two described below, which has previously been obtained from azidoformate decompositions.[2,5]

The other two products both had molecular formula $C_{14}H_{23}NO_2$, consistent with their being intramolecular nitrene insertion products. The major product, mp 185–186 °C (51%), had ν_{max} 1740 cm^{-1} and three methyl peaks in its NMR spectrum suggesting that it was an oxazolidinone formed by insertion at C-2. The third product, mp 164–166 °C (14%), had ν_{max} 1715 cm^{-1} and only two methyl peaks plus a new two-proton signal at ~3 ppm in its ^1H NMR spectrum, suggesting that it was the desired type of product resulting from insertion at a C-4 methyl group. These inferences were confirmed by identification of the two substances as **7** and **8,** respectively, by comparison with authentic samples of **7** and **8** synthesized by the alternate pathways delineated below.

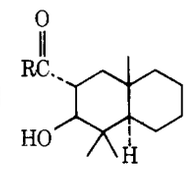
These results are very similar to those obtained in the thermolysis of lanostanyl azidoformate,[2] which afforded ca. 15% of lanostanone, ca. 30% of an oxazolidinone of unassigned stereochemistry at C-2, and ca. 35% of the product analogous to **8.** Assignment of structure to the latter two insertion

products was based on analysis of their ^{13}C NMR spectra,[2] as opposed to the chemical means utilized in this study. The only apparent difference between the two sets of results is the greater proportion of insertion at the C-4 α-methyl in the steroidal case. The reason for this difference is not obvious from examination of molecular models.

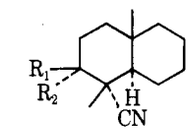
The decision to synthesize **7** rather than its C-2 epimer was based on the report by Edwards and Paryzek[5] that the trans-fused oxazolidinone formed by insertion at the 6α position is the predominant product from thermolysis of 3β-acetoxy-11-oxolanostan-7β-yl azidoformate. Work of Pavia, Winternitz, and Wylde[11] suggested the pathway we used to prepare **7**, through the sequence **6** → **9** → **10** → **11** → **7**. The



9



10, R = OCH_3
11, R = $NHNH_2$



12, R_1, R_2 = O
13, R_1 = OH, R_2 = H

conversion of ketone **6** to β-keto ester **9** was accomplished in 92% yield using methylmagnesium carbonate.[12] This method for introducing the carbomethoxyl function at C-2 was impressively superior to several others, including the recent procedure employing NaH–KH and dimethyl carbonate in tetrahydrofuran,[13] all of which gave only very low yields of the largely enolic **9**.

The next step, reduction of **9** to **10**, proved to be the most troublesome conversion in the sequence. A wide variety of reducing agents gave only low yields of what was eventually identified as the desired 3β-hydroxy 2α-carbomethoxy compound. A good yield (67%) of **10** was finally obtained using $NaBH_4$ as reductant in isopropyl alcohol–water at −50 °C. The stereochemistry of **10** was determined from its ^1H NMR spectrum, which showed (in the presence of D_2O to eliminate coupling to the hydroxyl proton) a doublet at 3.42 ppm with J = 11 Hz for the C-3 H, and a triplet of doublets at 2.65 ppm with J = 11, 11, and 4 Hz for the C-2 H, a pattern consistent only with both protons being axially disposed.[14,15]

Conversion of **10** to hydrazide **11** with hydrazine in methanol was essentially quantiative, and diazotization of **11**, inducing migration of C-2 to nitrogen with retention of configuration,[16] afforded **7** in 91% yield. This product was identical in all respects with the oxazolidinone obtained by thermolysis of **5**.

Synthesis of **8** was accomplished using the known 4α-cyano-4β-methyldecal-3-one **12**, which was prepared from the readily accessible 4,10-dimethyl-$\Delta^{4,5}$-octal-3-one[18] in a somewhat better yield (44%) by a modification of the venturesome reductive cyanation procedure of Kuehne and Nelson.[17] Reduction of **12** with $NaBH_4$ afforded **13** in essentially quantitative yield. Hydrogenation of the nitrile function of **13** proved more effective than $LiAlH_4$ reduction for generation of the presumed 4α-aminomethyl-3β-hydroxy intermediate, which, without purification, was converted by treatment with phosgene to **8** in excellent overall yield from **13**. The **8** thus prepared was identical with the third product from thermolysis of **5**, establishing conclusively that functionalization of the 4α-methyl group had been achieved, albeit in low yield.

Experimental Section

Melting points were determined in open capillaries using a Thomas-Hoover apparatus and are uncorrected. Unless otherwise specified, IR spectra of solids were obtained as KBr pellets and of liquids as neat films on a Perkin-Elmer 137 spectrophotometer. Unless otherwise specified, NMR spectra were determined in $CDCl_3$ on a Perkin-Elmer R-24 spectrometer with Me_4Si as an internal standard. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Mass spectra were determined by Dr. Catherine Costello at the MIT Mass Spectrometry Facility, sponsored by the USPHS Division of Research Resources through Grant RR00317. Preparative TLC was performed on 20 × 20 cm plates coated with 1.45-mm thick layers of silica gel $PF_{254+366}$ (Brinkmann Instruments, Inc., Westbury, N.Y.) which had been mixed with 0.002% Rhodamine 6G dye (Eastman Kodak Co., Rochester, N.Y.). UV light was used to visualize TLC plates. Brine refers to saturated aqueous sodium chloride solution.

4,4-Dimethyl-3β-diazoacetoxycholestane (2). 4,4-Dimethylcholestan-3β-ol (**1**) was prepared in 74% yield with mp 155–156 °C by $LiAlH_4$ reduction of 4,4-dimethylcholestan-3-one.[19] The tosylhydrazone of glyoxylic acid and its acid chloride were prepared according to the procedure of House.[20] To a stirred solution of 3.00 g (7.19 mmol) of **1** in 40 ml of distilled CH_2Cl_2 was added 1.90 g (7.28 mmol) of the acid chloride at room temperature. Triethylamine, 0.74 g (7.32 mmol), which had been purified by successive distillations from phthalic anhydride and potassium hydroxide, was added dropwise with stirring over 10 min, while the solution was maintained at 25–30 °C. Over the next hour additional half equivalents of acid chloride and triethylamine were sequentially added to the solution, followed by dropwise addition of a further 1.15 g of triethylamine. After a further 1.5 h at room temperature, TLC analysis of a sample of the yellow-orange solution showed almost no **1**. The reaction mixture was evaporated to a solid residue which was partitioned between ether and brine. The aqueous layer was extracted with two 50-ml portions of ether. The combined ether extracts were washed with dilute $NaHCO_3$ solution and water, dried over Na_2SO_4, and evaporated to afford 3.9 g of yellow solid which was recrystallized in two crops from benzene–methanol to yield 2.03 g (58%) of **2**, which TLC analysis showed to contain a small amount of unidentified impurity. Preparative TLC (1:9 ether–hexane), followed by recrystallization from benzene–methanol, gave pure **2**: mp 156–157 °C dec (sealed tube); IR 2100 and 1700 cm^{-1}; UV λ_{max} (hexane) 245 nm (ϵ 12 500); NMR (C_6D_6) δ 4.1 (s, 1, HC=N) and 4.5–4.8 ppm (m, 1, HCO–).

Anal. Calcd for $C_{31}H_{52}N_2O_2$: C, 76.81; H, 10.81; N, 5.78. Found: C, 76.89; H, 10.82; N, 5.71.

4,4,10β-Trimethyl-*trans*-decal-3β-ol Chloroformate (4). Through a solution of 1.00 g (5.10 mmol) of 4,4,10β-trimethyl-*trans*-decal-3β-ol (**3**)[9] and 0.67 ml (4.9 mmol) of triethylamine in 100 ml of anhydrous benzene was bubbled a gentle stream of phosgene (Matheson) for 10 min, causing formation of a white precipitate. The mixture was stirred for 1 h at room temperature, treated with phosgene for an additional 10 min, stirred for another 1 h at room temperature, washed with two 50-ml portions of brine, dried ($MgSO_4$), and evaporated to afford 1.258 g (96%) of **4** as an oil which was homogeneous by TLC (hexane, twice): IR 1760 cm^{-1}; NMR δ 0.89 (s, 3), 0.97 (s, 6) and 4.55 ppm (dd, 1, J = 5 and 9 Hz, 3α H): M^+ m/e 258.1413 (calcd for $C_{14}H_{23}O_2Cl$, 258.1387).

4,4,10β-Trimethyl-*trans*-decal-3β-ol Azidoformate (5). A solution of 1.160 g (4.49 mmol) of **4** in 50 ml of dry dimethylformamide was added to a flask containing 1.20 g (18.5 mmol) of sodium azide. The resulting suspension was stirred for 1 h at room temperature, after which 150 ml of ether and 50 ml of water were added. The aqueous layer was separated and extracted with 50 ml of ether, and the combined organic layers were washed with two 50-ml portions of brine, dried ($MgSO_4$), and evaporated to afford 1.179 g of a colorless oil, which was chromatographed on 30 g of silica gel. Elution with hexane afforded 1.019 g (92%) of **5**. Elution with 1:9 ether–hexane gave 0.030 g of **3**. The oily **5** was purified by sublimation at 60 °C (0.05 mm) to afford 0.902 g (77%) of pure **5**: mp 55–57 °C: IR 2190, 2120, and 1730 cm^{-1}; NMR δ 0.83 (s, 3), 0.90 (s, 3), 0.94 (s, 3) and 4.49 ppm (dd, 1, J = 5 and 9 Hz, 3α H).

Anal. Calcd for $C_{14}H_{23}N_3O_2$: C, 63.37; H, 8.74; N, 15.84. Found: C, 63.48; H, 8.67; N, 15.85.

Thermolysis of 5. A vacuum degassed solution of 0.200 g (0.754 mmol) of **5** in 10 ml of CCl_4 was heated at 180 °C in a sealed tube for 3 h. The resulting light yellow solution was evaporated to afford 0.196 g of oil, which was separated by preparative TLC using ether into three principal fractions. The band with the highest R_f value afforded 0.021 g (14%) of 4,4,10β-trimethyl-*trans*-decal-3-one (**6**), identified by comparison of its IR and NMR spectra and TLC mobility with those of an authentic sample.[10] The second band afforded 0.090 g (51%) of **7** as a white, oily solid, which was recrystallized from 1:1 methylene chloride–hexane to give 0.063 g (36%) of **7**: mp 185–186 °C; IR 3400 and 1740 cm^{-1}; NMR δ 0.95 (s, 3, 10β H_3C–), 1.05 (s, 3), 1.09 (s, 3), 3.5–4.0 (bm, 2, 2β H and 3α H), and 6.2 ppm (bs, 1, HN); M^+ m/e 237.1729 (calcd for $C_{14}H_{23}NO_2$, 237.1729).

The third band afforded 0.024 g (14%) of **8** as a white solid which

was recrystallized from 1:1 methylene chloride–hexane to afford 0.014 g (8%) of pure **8**: mp 164–166 °C; IR 3350, 3150, and 1715 cm^{-1}; NMR δ 0.97 (s, 3, 10β H_3C–), 1.01 (s, 3, 4β H_3C–), 2.85–3.1 (m, 2, H_2CNH), 3.85 (bt, 1, J = 6 Hz, 3α H), and 6.5 ppm (bs, 1-HN); M^+ *m/e* 237.1742 (calcd for $C_{14}H_{23}NO_2$, 237.1729).

2-Carbomethoxy-4,4,10-trimethyl-*trans*-decal-3-one (9). A solution of 2.30 g (11.85 mmol) of **6**[10] in 10 ml of dimethylformamide was added to 60 ml of a freshly prepared solution of methylmagnesium carbonate[12] in dimethylformamide (~2 mmol/ml). The resulting solution was heated at 110–115 °C for 15 h under a slow stream of CO_2. The solution was cooled to 5 °C and brought to pH ~2 with 175 ml of 10% H_2SO_4. The solution was extracted with 300- and 100-ml portions of ether, and the combined ether layers were washed with 3 × 100 ml of water and then dripped into an ethereal solution of diazomethane, freshly prepared from EXR-101.[21] After 1 h the mixture was evaporated to afford 2.953 g of colorless oil, which TLC (7:1 hexane–ether) indicated to be **9** containing a small amount of **6.** The latter was removed by chromatography on 30 g of Florisil. Elution with hexane gave 2.756 g (92%) of pure **9** as a clear, colorless oil: IR 1760, 1715, 1660, and 1610 cm^{-1}; NMR δ 0.91 (s, 3), 1.07 (s, 3), 1.16 (s, 3), 3.73 (s, H_3COOC–), and 12.67 (s, 1, HOC=); M^+ *m/e* 252.1732 (calcd for $C_{15}H_{24}O_3$, 252.1725).

2α-Carbomethoxy-4,4,10β-trimethyl-*trans*-decal-3β-ol (10). To a solution of 1.862 g (7.38 mmol) of **9** in 75 ml of isopropyl alcohol, cooled to −50 °C, was added 8 ml of an aqueous $NaBH_4$ solution (0.5 mmol/ml). The resulting slurry was stirred for 1 h at −50 °C, then an additional 3 ml of the $NaBH_4$ solution was added and the viscous reaction mixture was allowed to warm to room temperature and stirred for 6 h. After being stored at −10 °C for 12 h, the reaction mixture was evaporated to a white solid residue. This was dissolved in a mixture of 50 ml of ether and 30 ml of 10% H_2SO_4, which was then added to 200 ml of ether and 100 ml of H_2O. The aqueous layer was extracted with 100 ml of ether and the combined ether layers were washed with 2 × 100 ml of H_2O, dried ($MgSO_4$), and evaporated to give 1.86 g of oily solid. Preparative TLC (3:2 hexane–ether, twice) afforded five fractions. The first was 0.015 g of **9.** The second was 0.102 g of a hydroxy ester (2α-carbomethoxy-4,4,10β-trimethyl-*trans*-decal-3α-ol?[14]): NMR δ 0.86 (s, 3), 0.88 (s, 3), 1.01 (s, 3), 2.8–3.1 (m, 1), 3.71 (s, 3, H_3COOC–), and 4.11 ppm (d, 1, J = 10 Hz). The third was 0.177 g, tentatively identified as another hydroxy ester of unknown stereochemistry: NMR δ 0.84 (s, 3), 1.0 (s, 6), 2.7–3.1 (complex m), and 3.75 ppm (s, 3, H_3COOC–). The fourth fraction was 1.254 g (67%) of **10,** which was purified by sublimation at 85–90 °C (0.25 mm) to afford 1.081 g (58%) of pure, white flakes of **10:** mp 71–73 °C; IR 3600 and 1715 cm^{-1}; NMR δ 0.75 (s, 3), 0.94 (s, 3), 0.96 (s, 3), 2.5–2.8 (complex m, 2), 3.42 (dd, J = 11 and 5 Hz, 1, 3α H), and 3.70 ppm (s, 3, H_3COOC–). Upon addition of a drop of D_2O the following changes in the spectrum were observed: δ 2.65 (dt, 1, J = 11, 11, and 4 Hz, 2β H) and 3.42 ppm (d, 1, J = 11 Hz, 3α H). M^+ *m/e* 254.1908 (calcd for $C_{15}H_{26}O_3$, 254.1882).

The fifth fraction was 0.183 g of a mixture of two compounds which showed no H_3COOC– peak in its NMR spectrum.

Hydrazide 11. A mixture of 0.500 g (1.96 mmol) of **10,** 5 ml of 98% hydrazine, and 20 ml of methanol was stirred at room temperature for 18 h, concentrated in vacuo, and partitioned between CH_2Cl_2 and H_2O. Evaporation of the organic layer yielded 0.500 g (100%) of white, solid **11.** Recrystallization from ether–dimethoxyethane afforded 0.385 g (77%) of pure **11:** mp 200–202 °C; IR 3350 and 1600 cm^{-1}; NMR δ 0.76 (s, 3), 0.97 (bs, 6), 2.7–3.25 (bm), and 3.5 ppm (d, 1, J = 12 Hz, 3α H); M^+ *m/e* 254.2006 (calcd for $C_{14}H_{26}N_2O_2$, 254.1994).

Conversion of 11 to 7. To a stirred suspension of 0.100 g (0.39 mmol) of **11** in 4 ml of 0.5 N HCl, cooled to 10 °C, was added a solution of 0.050 g (0.72 mmol) of $NaNO_2$ in 2 ml of H_2O. The resulting gummy suspension was stirred for 1 h at 10 °C and extracted with ether, which was evaporated to afford 0.104 g of gum. This was dissolved in 5 ml of ethanol, which was heated at reflux for 90 min and then evaporated to give 0.091 g (98%) of crude, gummy **7.** Preparative TLC (ether) afforded 0.083 g (91%) of **7** as a colorless solid, which was recrystallized from CH_2Cl_2–hexane to give 0.064 g (69%) of **7:** mp 186–187 °C; IR 3400 and 1740 cm^{-1}; NMR δ 0.95 (s, 3), 1.05 (s, 3), 1.09 (s, 3), 3.5–4.0 (bm, 2, 2β H and 3α H), and 6.17 ppm (bs, 1, HN); mmp with **7** from **5** 185–186 °C; M^+ *m/e* 237.1752 (calcd for $C_{14}H_{23}NO_2$, 237.1729).

4α-Cyano-4β,10β-dimethyl-*trans*-decal-3-one (12). The following modification of the procedure of Kuehne and Nelson[17] was employed for reductive cyanation of 4,10-dimethyl-$\Delta^{4,5}$-octal-3-one.[18] Liquid ammonia (150 ml) was placed into an oven-dried apparatus consisting of a 500-ml three-necked round-bottomed flask, a Dewar condenser, and a mechanical stirrer equipped with a glass paddle. Lithium wire (250 mg, 35.7 mmol), freshly cleaned by wiping with a hexane-soaked cloth, was added to the liquid ammonia and the resulting blue solution was stirred for 30 min. A solution of 2.287 g (12.84 mmol) of enone in 20 ml of dry tetrahydrofuran was added as rapidly as possible. The resulting mixture was stirred for 20 min, and then an additional 20 ml of tetrahydrofuran containing 1 ml of isoprene was added to destroy excess lithium. A heating mantle was placed under the flask and the tetrahydrofuran suspension was refluxed until all the ammonia had evaporated and for 45 min further. The suspension was cooled to 0 °C and a solution of 4.5 g (73 mmol) of cyanogen chloride, prepared by the method of Coleman, Leeper, and Schulze,[22] and freshly distilled, in 20 ml of tetrahydrofuran was added. The solution was stirred overnight, and then was concentrated in vacuo to a brown oil. This oil was partitioned between 200 ml of ether and 100 ml of 10% H_2SO_4. The aqueous layer was extracted with an additional 200 ml of ether, and the combined organic layers were washed with 100 ml of water, dried ($MgSO_4$), and evaporated to afford 2.583 g of brown oil. This was chromatographed on 60 g of Florisil, and 1.4 g (51%) of crude cyano ketone **12,** contaminated with starting material, was eluted with 4:1 ether–hexane. Preparative TLC of this oily solid (1:1 ether–hexane, twice) afforded 1.158 g (44%) of crystalline **12.** Two recrystallizations from hexane afforded 0.766 g (29%) of pure **12** as white prisms: mp 84–86 °C (lit.[17] mp 82–83 °C); IR 2250 and 1715 cm^{-1}; NMR δ 1.16 (s, 3) and 1.46 ppm (s, 3).

4α-Cyano-4β,10β-dimethyl-*trans*-decal-3β-ol (13). To a solution of 0.455 g (2.21 mmol) of **12** in 25 ml of methanol, cooled to 10 °C, was added 0.060 g (1.5 mmol) of $NaBH_4$. The resulting soltuion was stirred at room temperature for 3 h, and then concentrated in vacuo. The residual oil was partitioned between ether and 10% H_2SO_4. Standard ether extraction and workup afforded 0.470 g of oil. Preparative TLC (3:2 hexane–ether) gave 0.411 g (98%) of **13** as a colorless oil: IR 3450 and 2250 cm^{-1}; NMR δ 0.91 (s, 3), 1.22 (s, 3), and 3.89 ppm (bt, 1, 3α H); M^+ *m/e* 207.1615 (calcd for $C_{13}H_{21}NO$, 207.1623).

Conversion of 13 to 8. A solution of 0.264 g (1.27 mmol) of **13** in 25 ml of ethyl acetate containing 1 drop of acetic acid was hydrogenated over PtO_2 at atmospheric pressure for 4 h. The mixture was filtered and concentrated in vacuo to afford 0.280 g of oil which was dissolved in 10 ml of $CHCl_3$, washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated to yield 0.224 g (83%) of crude 4α-aminomethyl-4β,10β-methyl-*trans*-decal-3β-ol as a colorless oil: IR 3400 cm^{-1}; NMR δ 0.82 (s, 3), 0.93 (s, 3), and 2.8–3.7 ppm (bm). Without purification, this oil was dissolved in 30 ml of ether containing 1 drop of triethylamine. Through this solution was bubbled a slow stream of phosgene until cloudiness developed, and the resulting mixture was stirred at room temperature for 2 h. The mixture was washed with $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated to afford 0.245 g (98%) of **8,** which was purified by preparative TLC (ether, twice) to yield 0.205 g (81%) of pure **8,** which was recrystallized from CH_2Cl_2–hexane to afford 0.175 g (69%) of **8:** mp 165–166 °C; IR 3350, 3170, and 1715 cm^{-1}; NMR δ 0.97 (s, 3), 1.01 (s, 3), 2.85–3.1 (m, 2, H_2CN), 3.85 (bt, 1, J = 6 Hz, 3α H), and 6.1 ppm (bs, 1, HN); mmp with **8** from **5** 164–165 °C; M^+ *m/e* 237.1761 (calcd for $C_{14}H_{23}NO_2$, 237.1729).

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Registry No.—**1,** 2550-84-7; **2,** 60705-86-4; **3,** 60761-10-6; **4,** 60705-87-5; **5,** 60705-88-6; **6,** 775-54-2; **7,** 60705-89-7; **8,** 60705-90-0; **9,** 60705-91-1; **10,** 60705-92-2; **11,** 60705-93-3; **12,** 60761-11-7; **13,** 60705-94-4; phosgene, 75-44-5; sodium azide, 26628-22-8; methylmagnesium carbonate, 14171-36-9; hydazine, 302-01-2; 4,10-dimethyl-$\Delta^{4,5}$-octal-3-one, 878-55-7; 4α-aminomethyl-4β,10β-methyl-*trans*-decal-3β-ol, 60705-95-5.

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1,3-Dipolar Cycloaddition Reactions with Isatin-*N*-acetic Acids. Synthesis of Dimethyl 9-Oxo-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylates

Wayne K. Anderson* and Paul F. Corey

Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14214

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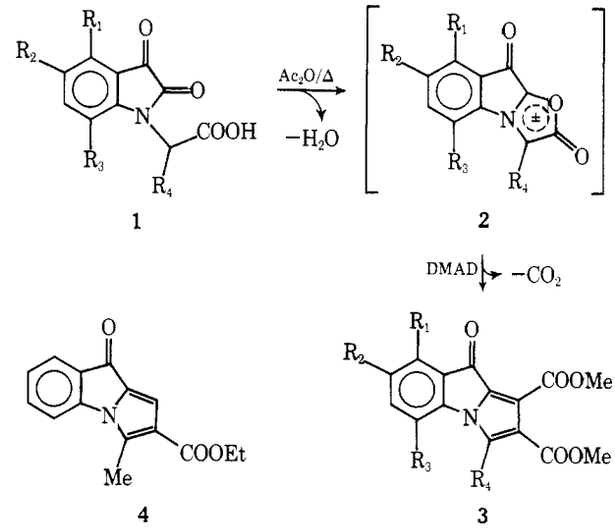
The 9*H*-pyrrolo[1,2-*a*]indole skeleton, first recognized in 1955,[1] has been encountered during the course of investigations directed toward the synthesis of the antitumor agent mitomycin.[2-5] More recently, derivatives of 9-oxo-9*H*-pyrrolo[1,2-*a*]indole have been shown to possess hypoglycemic[6] and anticancer[7] activities. The most commonly applied synthesis of 9-oxo-9*H*-pyrrolo[1,2-*a*]indoles involves an intramolecular Friedel–Crafts acylation of an appropriately substituted *N*-phenylpyrrole, generating the central ring through formation of a second bridge between the two aromatic moieties.[5,8,9]

Current work in our laboratory required a versatile synthesis of dimethyl 9-oxo-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylates (**3**) which would allow for the incorporation of a variety of substituents in the six-membered ring. We now wish to report a facile synthesis of **3** which involves a 1,3-dipolar cycloaddition of a mesoionic intermediate, **2**, derived from substituted isatin-*N*-acetic acids (**1**), with dimethyl acetylenedicarboxylate (DMAD). This approach affords some considerable versatility in that the starting isatins are available with a broad range of substituents.

The starting isatin was converted to the sodium salt by treatment with NaH in HMPA; the salt was alkylated, without isolation, with ethyl 2-bromopropionate and the resulting ester was saponified to give the corresponding isatin-*N*-(α-methyl) acetic acids (**1c–g**). The acids **1a** and **1b** were prepared according to previously described procedures.[10-12] The method we used to prepare **1** is both simple and mild, and makes possible N-alkylation of isatins labile to more vigorous conditions.

N-Acyl-α-amino acids, under dehydrating conditions, cyclize to mesoionic oxazolones which react as 1,3 dipoles with acetylenic compounds to give pyrroles.[13-16] Analogously, isatin-*N*-acetic acids (**1**) form mesoionic derivatives, **2**, that undergo 1,3-dipolar cycloaddition reactions in situ with DMAD to give **3**. This reaction (Scheme I) requires more

Scheme I



a, $R_1 = R_2 = R_3 = R_4 = H$
b, $R_1 = R_2 = R_3 = H$; $R_4 = Me$
c, $R_1 = R_3 = H$; $R_2 = Br$; $R_4 = Me$
d, $R_1 = R_3 = H$; $R_2 = R_4 = Me$
e, $R_1 = R_3 = Cl$; $R_2 = H$; $R_4 = Me$
f, $R_1 = H$; $R_2 = R_3 = Cl$; $R_4 = Me$
g, $R_1 = Cl$; $R_2 = H$; $R_3 = OMe$; $R_4 = Me$

vigorous conditions and gives lower yields than the comparable reaction of *N*-phenyl-*N*-acetylalanine with DMAD.[15] The lower reactivity may be due to decreased reactivity of the mesoionic intermediate, due to charge delocalization in **2** through the C-3 carbonyl of isatin, or it may be associated with an increased difficulty to form **2**. The increased strain introduced by the rigid isatin molecule or the development of a positively charged imminium group adjacent to an electron-withdrawing carbonyl could retard the formation of **2**.

The alkyl group α to the carboxylic acid moiety (i.e., R_4) of **1b–g** considerably increased reactivity over that observed for **1a**, where R_4 = H. Thus, **1b** reacts with acetic anhydride–DMAD to give **3b** in 62% yield whereas **1a** reacted to give only 20% yield of **3a**. Ethyl propiolate, a less reactive dipolarophile, gave **4** in 50% yield from **1b**; **1a** failed to react.

A cycloaddition reaction of this type involving an unsymmetrical dipolarophile is complicated by the possibility of two isomeric products, a problem recently discussed by Huisgen.[17] The reaction of **1b** with ethyl propiolate yielded only **4**, with no evidence of the other possible isomer. The direction of the cycloaddition was confirmed by x-ray crystallography.[18]

In summary, the 1,3-dipolar cycloaddition reaction affords a very simple approach to dimethyl 9-oxo-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylates. Each crystallized spontaneously from the cooling reaction mixture and, although no attempt was made to optimize conditions, the yields were good. Substituents R_1, R_2, and R_3 were chosen to illustrate the general applicability of this reaction to the large class of polysubstituted isatins.