Acknowledgment. This work was supported by U. S.–Spain Collaborative Grant INT-8412811 (Conjunto Hispano-Norteamericano Grant 84020061), by C.A.C.Y.T. Grant 0352-84, and by NSF Grant NSF CHE-8314169. We are grateful to Professor Derek J. Hodgson and Dr. Y. Yokomori for help with the unexpectedly difficult X-ray structure determination and to Dr. Ernesto Brunet Romero for determining the conformational energy of the SMe_2^+ group in the cyclohexyl system and for helpful discussions.

Registry No. (±)-1, 109392-49-6; (±)-2, 109392-50-9; (±)-3, 109392-51-0; (±)-4, 109392-52-1; (±)-5, 109392-54-3; (±)-*cis*-7, 109392-57-6; (±)-*trans*-7, 109392-58-7; (±)-8, 109392-60-1; (±)-9, 109392-61-2; (±)-*cis*-10, 109392-59-8; (±)-*trans*-10, 109392-68-9; (±)-*cis*-11, 109392-63-4; (±)-*trans*-11, 109392-70-3; (±)-12, 109392-64-5; (±)-13, 109392-65-6; (±)-14, 109392-66-7; (±)-15, 109392-67-8; (±)-2-methyl-3,4-dihydro-2*H*-pyran, 75795-70-9; (±)-*cis*-thioacetyl-2-methyltetrahydropyran, 109392-55-4; (±)-*trans*-thioacetyl-2-methyltetrahydropyran, 109392-56-5.

Supplementary Material Available: Tables 1a, 3a, and 4a (expanded versions of Tables 1, 3, and 4), Tables S1 (bond lengths), S2 (bond angles), S3 (torsion angles), and S4 (anisotropic thermal parameters), infrared data for compounds **2–5**, *cis*- and *trans*-**7**, **8**, **9**, *cis*- and *trans*-**10**, *cis*- and *trans*-**11**, and **13–15**, and mass spectral data for compounds **2–4**, *cis*- and *trans*-**7**, **8**, **9** (14 pages); Table S5 (observed and calculated structure amplitudes) (7 pages). Ordering information is given on any current masthead page.

Notes

New Routes to 1,2-Diazetidin-3-ones

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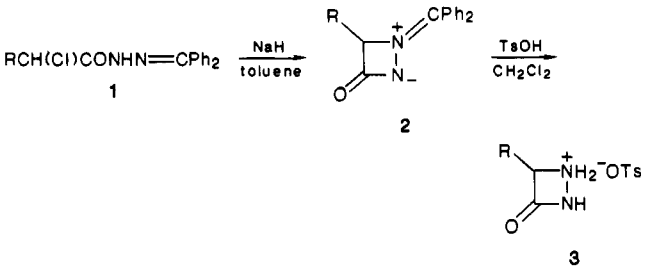
Received February 12, 1987

In a series of recent papers we have described the preparation and properties of both monocyclic and bicyclic 1,2-diazetidin-3-ones, which were prepared as highly strained bridgehead aza analogues of the carbapenem and carbacephem β-lactam antibiotics.[1-9] Our preferred route to the parent 1,2-diazetidin-3-one system has involved intramolecular dehydrohalogenation of α-chloroacyl hydrazones of diaryl ketones to generate ylides of type **2**, which were then hydrolyzed to the *p*-toluenesulfonate salts of 1,2-diazetidin-3-ones (Scheme I).[7-9] Methods for the subsequent conversion of these key intermediates to target aza β-lactams have been described.[1-3,6] A number of alternate routes to 1,2-diazetidin-3-ones are also known;[4] they range from the cycloaddition of ketenes with azines[10] (which is only of historical interest, since its applicability is severely limited by lack of regioselectivity, low yields and inaccessibility of reaction partners with appropriate functionality) to a recently described and potentially versatile carbene coupling of (α-azoacyl)hydrazines.[11]

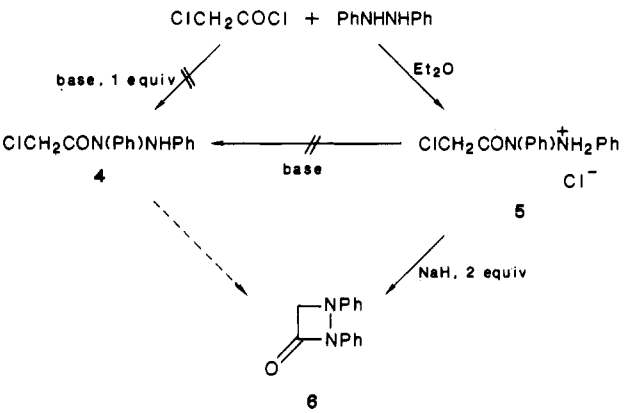
We describe in this paper several additional synthetic routes to 1,2-diazetidin-3-ones. We were motivated in this investigation by considerable difficulties which we have encountered in directly introducing appropriate substituents at N-1, N-2, and/or C-4 on preformed 1,2-diazetidin-3-ones, as well as difficulties experienced in further modifying substituents on this fragile ring system. It would obviously be attractive to have in hand a synthetic procedure which would make it possible to introduce desired substituents at a stage prior to formation of the diazetidinone ring.

The first route explored is outlined in Scheme II and involves intramolecular alkylation of an (α-haloacyl)-hydrazine precursor. The feasibility of this concept for direct diazetidinone synthesis was explored with (α-chloroacetyl)-1,2-diphenylhydrazine. Stirring 1,2-diphenylhydrazine with chloroacetyl chloride in ether at 0

Scheme I



Scheme II

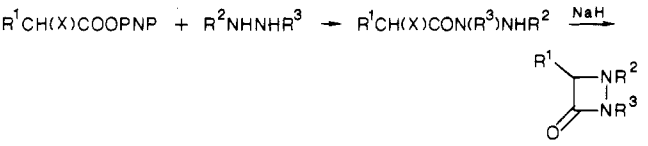


†Ortho Pharmaceutical Corporation, Raritan, NJ 08869-0602.

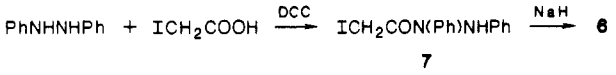
(1) Taylor, E. C.; Davies, H. M. L. *J. Org. Chem.* **1986**, *51*, 1537.
(2) Taylor, E. C.; Davies, H. M. L.; Hinkle, J. S. *J. Org. Chem.* **1986**, *51*, 1530.
(3) Taylor, E. C.; Davies, H. M. L. *J. Org. Chem.* **1984**, *49*, 4415.
(4) Taylor, E. C.; Davies, H. M. L.; Lavell, W. T.; Jones, N. D. *J. Org. Chem.* **1984**, *49*, 2204.
(5) Taylor, E. C.; Davies, H. M. L. *J. Org. Chem.* **1984**, *49*, 113.
(6) Taylor, E. C.; Clemens, R. J.; Davies, H. M. L. *J. Org. Chem.* **1983**, *48*, 4567.
(7) Taylor, E. C.; Haley, N. F.; Clemens, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 7743.
(8) Taylor, E. C.; Davies, H. M. L.; Clemens, R. J.; Yanagisawa, H.; Haley, N. F. *J. Am. Chem. Soc.* **1981**, *103*, 7660.
(9) Taylor, E. C.; Clemens, R. J.; Davies, H. M. L.; Haley, N. F. *J. Am. Chem. Soc.* **1981**, *103*, 7659.
(10) Staudinger, H. *Die Ketene*; F. Enke: Stuttgart, 1912; p 91.

0022-3263/87/1952-4107$01.50/0

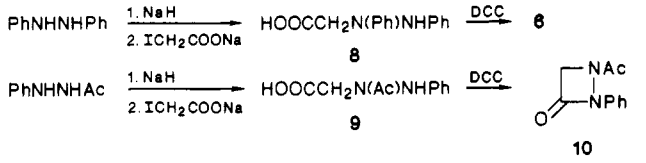
Scheme III



Scheme IV



Scheme V



°C in the absence of base gave the hydrochloride salt **5**. Although the free base **4** could not be generated from the salt without oligomerization, addition of 2 equiv of sodium hydride to the salt resulted in intramolecular alkylation to generate the desired diazetidinone **6**. Bromoacetyl bromide provided **6** in slightly better overall yield. The conversion of **5** to **6** represents a new and direct synthesis of the diazetidinone ring system. Attempts to extend this reaction to include a variety of α-halo acid halides and hydrazines gave evidence of diazetidinone formation, but yields were low, and this strategy was not explored further because of the developments described below.

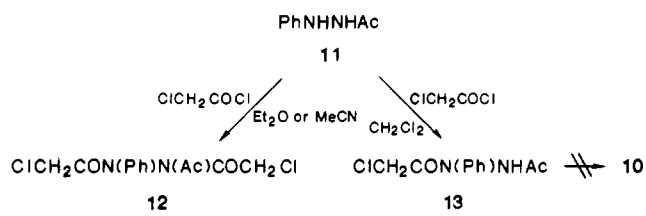
In view of the above difficulties encountered during attempted isolation of the intermediate (α-haloacyl)-hydrazines, precursors to the intramolecular alkylation reaction, several modifications were explored. The first involved the use of an active ester instead of an acid halide for the condensation. Thus, α-halo *p*-nitrophenyl esters were condensed with a variety of hydrazines, and the resulting hydrazides were then cyclized with sodium hydride to give a series of 1,2-diazetidin-3-ones (Scheme III).[12] A second modification to obtain these requisite (α-haloacyl)hydrazides is outlined in Scheme IV and involves DCC coupling of 1,2-diphenylhydrazine with iodoacetic acid. It is noteworthy that the subsequent intramolecular alkylation step proceeded in considerably better yield with this iodo intermediate (**7**) than with the corresponding bromo or chloro compounds, a result clearly consistent with the generally greater reactivity of iodo vs. bromo and chloro compounds as alkylating agents.

1,2-Diphenyl-1,2-diazetidin-3-one (**6**) can also be prepared by the reverse sequence of reactions (see Scheme V) involving initial alkylation of 1,2-diphenylhydrazine with iodoacetic acid, followed by DCC dehydrative cyclization. This alternate strategy was also successful for the preparation of 1-acetyl-2-phenyl-1,2-diazetidin-3-one (**10**), which was obtained by N-1 alkylation of 1-acetyl-2-phenylhydrazine with iodoacetic acid, again followed by intramolecular dehydrative cyclization with DCC. This contrasts with our failure to prepare **10** via the chloroacetyl chloride route outlined in Scheme VI. Compound **10** represents one of the few known examples of a 1-acyl-1,2-diazetidin-3-one[11a] (several 1,2-diacyl-1,2-diazetidin-3-ones are known).[4]

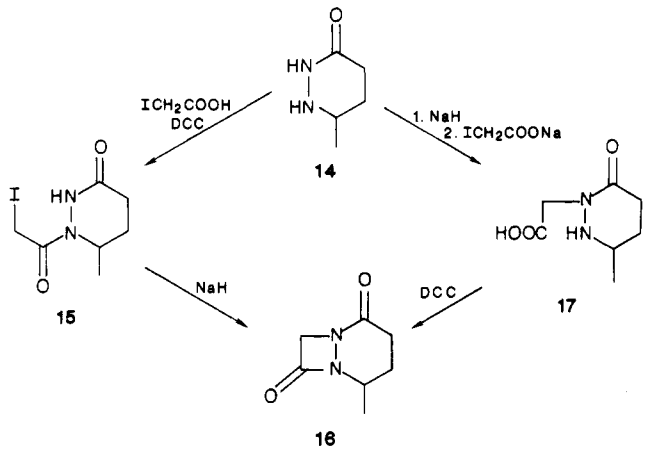
(11) Lawton, G; Moody, C. J.; Pearson, C. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 899.

(12) Compounds prepared by this procedure are reported in: Taylor, E. C.; Greenhill, J. V., manuscript in preparation.

Scheme VI



Scheme VII



Both of these latter strategies were successfully applied to the preparation of the bicyclic diazetidinone **16** from 6-methyltetrahydropyridazin-3-one (**14**). Thus, acetylation of **14** with iodoacetic acid using DCC as the coupling reagent gave the 1-iodoacetyl derivative **15**, which underwent smooth intramolecular alkylation with sodium hydride to generate the target bicyclic diazetidinone **16** in 24% yield. Alternatively, **16** could be formed by reversing the above order of reactions, namely, by initial alkylation at N-2 with iodoacetic acid to provide **17**, followed by DCC intramolecular dehydrative cyclization (Scheme VII).

Applications of these new strategies to the preparation of more complex mono and bicyclic 1,2-diazetidin-3-ones are under further investigation.

Experimental Section

Commercial reagents were utilized (Aldrich, Fluka) without further purification unless otherwise noted. Methylene chloride and DMF were dried over 4-Å molecular sieves, and THF was freshly distilled over sodium benzophenone ketyl. Melting points were determined in open capillaries with a Thomas-Hoover apparatus and are uncorrected. Infrared data were obtained from a Perkin-Elmer 467 or 1320 spectrophotometer. NMR data were obtained on a JEOL FX-90Q spectrometer operating at 90 MHz for ^{1}H NMR and at 22.5 MHz for ^{13}C NMR (heteronuclear decoupling was used unless multiplicities are indicated). Mass spectral data were obtained by Dr. Dorothy Little on an AEI MS-902 instrument at 70 eV (unless otherwise noted).

The R_f values reported are for TLC data obtained on 2.5 × 7.5 cm silica gel plates (Bakerflex IB2-F), and products were detected by UV and/or iodine staining. The silica used in column chromatographic separations was Merck #60 (230–400 mesh ASTM-cat. #9385).

Elemental analyses were determined by Eli Lilly and Co., Indianapolis, IN, and by Hoffmann LaRoche, Inc., Nutley, NJ.

1-(2-Chloroacetyl)-1,2-diphenylhydrazinium Chloride (5). Chloroacetyl chloride (0.40 mL, 5 mmol) was dripped into a stirred solution of 1,2-diphenylhydrazine (0.95 g, 5 mmol) in dry ether (25 mL) at −5 °C, and the resulting mixture was stirred for 1 h at 0 °C. The precipitate was collected by filtration and washed with ether to provide 1.01 g (68%) of pale pink crystals. The crystals discolored and gradually decomposed upon standing in air or light (the amine could not be freed from its salt): mp

160–166 °C (turns orange), 250–260 °C dec, gas evolution; IR (KBr) 2800 (br), 1670, 1600, 1500 cm^{-1}.

Anal. Calcd for $C_{14}H_{14}Cl_2N_2O$: C, 56.58; H, 4.75; N, 9.43; Cl, 23.86. Found: C, 56.25; H, 4.99; N, 9.09; Cl, 23.94.

1,2-Diphenyl-1,2-diazetidin-3-one (6). Procedure A. Sodium hydride (0.2 g of a 60% dispersion in mineral oil, 2 equiv) was added in two portions to a solution of 1-(2-chloroacetyl)-1,2-diphenylhydrazinium chloride (0.31 g, 1 mmol) in methylene chloride (25 mL) at 0 °C. After being stirred for 30 min at 0 °C and 30 min at room temperature, the solution was washed with saturated ammonium chloride, dried ($MgSO_4$), and evaporated under reduced pressure to provide an oil. Column chromatography on silica with 50/50 ether/petroleum ether provided 0.06 g (25%) of the product as a white, crystalline solid (R_f 0.7).

Procedure B. The use of 1,2-diphenyl-1-(2-iodoacetyl)-hydrazine (7) as per procedure A gave the product in 35% yield.

Procedure C. DCC (1.1 g) was added to a solution of 1-(carboxymethyl)-1,2-diphenylhydrazine (8) (1.21 g, 5 mmol—prepared by adding the sodium salt of 1,2-diphenylhydrazine to the sodium salt of iodoacetic acid at 0 °C) in methylene chloride (40 mL) at 0 °C. After being stirred for 1 h at room temperature, the mixture was filtered, and the filtrate was evaporated under reduced pressure. Column chromatography (as in procedure A) gave 0.47 g (42%) of the product: mp 117–118 °C; IR ($CHBr_3$ film) 1780, 1598, 1492 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.4–6.9 (m, 10 H), 4.7 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 150.9, 129.2, 129.1, 124.4, 117.5, 115.8, 70.9; LRMS (70 eV), m/z (relative intensity) 224 (M^+, 5) 195 (5), 169 (8), 167 (7), 119 (100), 105 (70), 104 (55), 91 (70); HRMS calcd for $C_{14}H_{12}N_2O$ m/z 224.0949, found m/z 224.0944 ± 0.002.

1,2-Diphenyl-1-(2-iodoacetyl)hydrazine (7). DCC (1.14 g, 1.1 equiv) was added in a solution of iodoacetic acid (0.92 g, 5 mmol) in methylene chloride (30 mL), and the mixture was cooled to 0 °C. Diphenylhydrazine (0.92 g, 5 mmol) was added, and the solution was stirred for 2 h at 0 °C and then for 48 h at room temperature. Methylene chloride (20 mL) was added, and the mixture was filtered (to remove the DCU). The filtrate was evaporated under reduced pressure to provide an orange oil. Column chromatography on silica with 30/70 ether/petroleum ether gave 0.81 g (46%) of the product as a yellow, crystalline solid (unstable in methylene chloride or Me_2SO solution): mp 144.5–145 °C; IR (KBr) 3385, 1651, 1599, 1590 (sh) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.96 (s, 1 H), 7.51–6.99 (m, 7 H), 6.75–6.57 (m, 3 H), 3.94 (s, 2 H); HRMS calcd for $C_{14}H_{13}IN_2O$ m/z 352.0074, found m/z 352.0063 ± 0.0036.

1-(Carboxymethyl)-1-acetyl-2-phenylhydrazine (9). A solution of sodium iodoacetate [prepared by dissolving iodoacetic acid (0.97 g, 5 mmol) in THF (15 mL) and adding sodium hydride (0.2 g of a 60% dispersion in mineral oil, 5 mmol)] was added to a solution of the sodium salt of 2-acetylphenylhydrazine in THF [prepared by dissolving 2-acetylphenylhydrazine (0.75 g, 5 mmol) in THF (15 mL) and adding sodium hydride (0.2 g of a 60% dispersion in mineral oil)]. After the mixture was stirred for several hours, the precipitate was removed by filtration and the filtrate evaporated under reduced pressure to provide a brown oil. Trituration with ether gave 0.61 g (59%) of the product as a yellow solid: mp >250 °C; IR (neat) 1720 (br), 1640 (br), 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.2 (br s, 1 H), 7.9–7.7 and 7.4–7.2 (m, total 5 H), 4.1 (s, 2 H), 2.5 (s, 3 H).

Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.37; H, 6.02; N, 13.21.

1-Acetyl-2-phenyl-1,2-diazetidin-3-one (10). 1-(Carboxymethyl)-1-acetyl-2-phenylhydrazine (0.61 g, 2.9 mmol) was dissolved in methylene chloride (15 mL). DCC (1.10 g, 5.5 mmol) was added, and the mixture was stirred overnight. The mixture was then filtered (to remove DCU) and the filtrate evaporated under reduced pressure. Column chromatography on silica with 20/80 ether/petroleum ether (R_f 0.5) gave 0.10 g (18%) of the product as a bright orange oil (decomposes on silica): IR (neat) 2905, 1795, 1693, 1594, 1493 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–6.85 (m, 5 H), 4.06 (s, 2 H), 2.17 (s, 3 H); LRMS (70 eV), m/z (relative intensity) 190 (M^+, 5), 162 (5), 147 (8), 77 (100); HRMS calcd for $C_{10}H_{10}N_2O_2$ m/z 190.0742, found m/z 190.0759 ± 0.0019.

2-Acetylphenylhydrazine (11). A solution of acetic anhydride (3.77 mL, 40 mmol) in ether (25 mL) was slowly dripped into a stirred mixture of phenylhydrazine (97%, 1.77 mL, 18 mmol) and ether (2.5 mL) at 0 °C over the course of 10–15 min. The mixture was then stirred for 10 min. The resulting white precipitate was collected by filtration and washed with cold ether to provide 2.70 g (100%) of a white crystalline solid: mp 130–131 °C (lit.[13] mp 128–131 °C); IR (KBr) 3280, 3235, 1665 (sh), 1641, 1598, 1544, 1494 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.19 (br s, 1 H), 8.21 (br d, J = 2.5 Hz, 1 H), 7.82–7.63 and 7.36–7.20 (m, total 5 H), 2.49 (s, 3 H); LRMS (70 eV), m/z (relative intensity) 150 (M^+, 82), 108 (100), 93 (30), 77 (35).

2-Acetyl-1,2-bis(chloroacetyl)phenylhydrazine (12). A solution of chloroacetyl chloride (0.16 mL, 2 mmol) in acetonitrile (10 mL) was added dropwise to a stirred solution of 2-acetylphenylhydrazine (0.21 g, 2 mmol) and triethylamine (0.28 mL, 2 mmol) in acetonitrile (5 mL) at 0 °C. After 30 min, the mixture was filtered through Celite and the filtrate evaporated under reduced pressure to an oil. Column chromatography on silica with 50/50 ether/petroleum ether (R_f 0.8) gave 0.21 g (35%) of the product as an oil: IR (neat) 3300, 3015, 2960, 1725 (br), 1596, 1491 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52 (s, 5 H), 4.74 (s, 2 H), 4.15 (s, 2 H), 2.48 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.1, 167.0, 165.9, 139.1, 130.0, 129.7, 129.4, 126.0, 45.5, 40.6, 23.9; LRMS (70 eV), m/z (relative intensity) 304 (M^+, 5), 302 (7), 262 (17), 260 (22), 186 (100); HRMS calcd for $C_{12}H_{12}Cl_2N_2O_3$ m/z 302.0227, found m/z 302.0232 ± 0.003.

2-Acetyl-1-(2-chloroacetyl)phenylhydrazine (13). Chloroacetyl chloride (0.18 mL, 2.2 mmol) was added to a solution of 2-acetylphenylhydrazine (0.35 g, 2.2 mmol) in methylene chloride (10 mL). A white precipitate was formed after 5–10 min, which disappeared after 20 min. The solution was evaporated under reduced pressure to provide 0.50 g (100%) of an oil which crystallized upon standing: mp 98–100 °C; IR (KBr) 3380, 1704, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (s, 5 H), 4.0 (br s, 2 H), 3.5 (var) (br s, 1 H), 1.99 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 169.4, 140.6, 129.5, 128.8, 127.1, 126.4, 41.9, 20.7; LRMS (70 eV), m/z (relative intensity) 228 (M^+, 2), 226 (5), 186 (4), 184 (10), 150 (75), 108 (65), 107 (60), 77 (100); HRMS calcd for $C_{10}H_{11}ClN_2O_2$ m/z 226.0510, found m/z 226.0498 ± 0.0022.

6-Methyl-1,4,5,6-tetrahydro-3(2*H*)-pyridazinone (14). Successive portions of 2 N hydrochloric acid in methanol followed by sodium cyanoborohydride (10 mL, 1 g; 4 mL, 1 g; and 3 mL, 1 g, respectively) were added to a solution of 4,5-dihydro-6-methyl-3(2*H*)-pyridazinone (2.24 g, 20 mmol) in methanol (100 mL) at 0 °C in 30-min intervals (after reaction from previous addition subsided). The mixture was stirred and gradually warmed to room temperature over 4 h and then made slightly basic to litmus with 2 N potassium hydroxide in methanol (2–3 mL) and sodium bicarbonate (1–2 g). The solution was evaporated under reduced pressure and the oily residue continuously extracted from an aqueous sodium bicarbonate solution (100 mL) with methylene chloride for 36 h. The methylene chloride layer was dried ($MgSO_4$) and evaporated under reduced pressure to give 2.2 g (96%) of the product as a yellow solid: mp 68–74 °C (lit.[14] mp 68–69 °C); IR (KBr) 1650 (br), 1395, 1231, 891 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.6–7.1 (br s, 1 H), 3.9–3.0 (2 br s, total 2 H), 2.6–1.3 (m, 4 H, superimposed dd, J = 6, 9 Hz centered at δ 2.52), 1.18 (d, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.0, 50.0, 30.5, 28.5, 18.7.

1-(Iodoacetyl)-6-methyl-1,4,5,6-tetrahydro-3(2*H*)-pyridazinone (15). DCC (0.96 g) was added to a solution of iodoacetic acid (0.82 g, 4.2 mmol) in methylene chloride (30 mL) at 0 °C. A solution of 6-methyl-1,4,5,6-tetrahydro-3(2*H*)-pyridazinone (0.48 g, 4.2 mmol) in THF (5 mL) was then added and the mixture stirred for 24 h. The reaction mixture was evaporated under reduced pressure, and the residue washed with ether to provide 1.02 g (86%) of the product as an oil: IR (neat) 3200 (br), 2959, 2909, 1700 (sh), 1660 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.8–3.2 (m, 4 H), 2.5–2.1 (m, 4 H), 1.14 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.3, 167.4, 48.9, 47.7, 29.8, 29.3, 18.8; LRMS (70 eV), m/z (relative intensity) 282 (M^+, 54), 253 (8), 183 (26), 169 (17), 156 (10), 141 (17), 128 (18), 127 (18), 114 (100), 99 (70), 59 (62), 55 (63); HRMS calcd for $C_7H_{11}IN_2O_2$ m/z 281.9867, found m/z 281.9861 ± 0.0028.

(13) Hearn, M. J.; Grimwade, J. E. *Org. Prep. Proc. Int.* **1980**, *12*, 249.
(14) Ege, S. N.; Carter, M. L. C.; Ortwine, D. F.; Chou, S. P. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1252. Spectral data also compare.

8-Methyl-1,4-diazabicyclo[4.2.0]octane-2,5-dione (16). Procedure A. Sodium hydride (0.2 g of a 60% dispersion in mineral oil, 2 equiv) was added to a solution of 1-(iodoacetyl)-6-methyl-1,4,5,6-tetrahydro-3(2*H*)-pyridazinone (**15**, 0.71 g, 2.5 mmol) in methylene chloride (40 mL), and the mixture was stirred for 1 h. The mixture was evaporated under reduced pressure and the residue purified by column chromatography on silica with 30/70 ether/petroleum ether to give 0.09 g (24%) of the product as an orange oil.

Procedure B. DCC (0.80 g, 1.1 equiv) was added to a solution of 2-(carboxymethyl)-6-methyl-1,4,5,6-tetrahydro-3(2*H*)-pyridazinone (**17**, 0.60 g, 3.5 mmol) in methylene chloride (45 mL), and the mixture was stirred for 2 h. The mixture was then filtered, and the filtrate was evaporated under reduced pressure. Column chromatography of the residue (as in procedure A) gave 0.22 g (40%) of the product: IR (neat) 1798, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.1 (s, 2 H), 3.5–2.5 (m, 5 H), 1.2 (d, J = 7.5 Hz, 3 H). LRMS (70 eV), m/z (relative intensity) 154 (M^+, 5), 141 (90), 139 (90), 127 (100), 101 (100); HRMS calcd for $C_7H_{10}N_2O_2$ m/z 154.0742, found m/z 154.0740 ± 0.0015.

2-(Carboxymethyl)-6-methyl-1,4,5,6-tetrahydro-3(2*H*)-pyridazinone (17). Sodium hydride (0.16 g, 1.1 equiv) was added to a solution of 6-methyl-1,4,5,6-tetrahydro-3(2*H*)-pyridazinone (0.45 g, 3.9 mmol) in THF (10 mL) at 0 °C. A solution of sodium iodoacetate [prepared from sodium hydride (0.16 g) and iodoacetic acid (0.75 g, 3.9 mmol) in THF (10 mL)] was added, and the mixture was stirred for 2 h at 0 °C. The mixture was warmed to room temperature and filtered, the filtrate evaporated under reduced pressure, and the residue taken up in methylene chloride. This material was used directly in subsequent reactions, since it decomposed upon attempted purification. The product was identified by spectral data and chemical conversion to **16**: IR (neat) 1720 (br), 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.0 (s, 2 H), 3.4–2.4 (m, 7 H), 1.1 (d, J = 7.5 Hz, 3 H).

Registry No. **5**, 108511-40-6; **6**, 14790-51-3; **7**, 108511-41-7; **8**, 108511-42-8; **9**, 108511-43-9; **10**, 108511-44-0; **11**, 114-83-0; **12**, 108511-45-1; **13**, 108511-46-2; **14**, 33018-73-4; **15**, 108511-47-3; **16**, 108511-48-4; **17**, 108511-49-5; DCC, 538-75-0; $ClCH_2C(O)Cl$, 79-04-9; PhNHNHPh, 122-66-7; ICH_2CO_2H, 64-69-7; PhNHNHAc·Na, 108511-50-8; ICH_2CO_2Na, 305-53-3; PhNHNHPh·2Na, 23458-78-8; sodium cyanoborohydride, 25895-60-7; 4,5-dihydro-6-methyl-3(2*H*)-pyridazinone, 5157-08-4.

General Approach to the Synthesis of Polyquinanes. Preparation of *trans,trans*-4,8-Diacetoxytetracyclo[9.3.0.0^{1,5}.0^{7,11}]-tetradecan-6-one[1]

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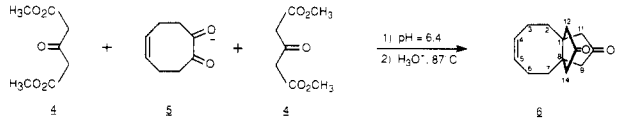
Received March 24, 1987

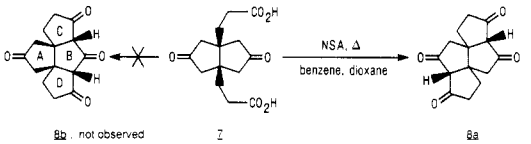
In 1971 Nozoe et al. reported the structure of a novel polyquinane 1,[2] the parent ring system of which is composed of four fused five-membered rings. This diketone **1** arose through cyclization of a transformation product of the sesterterpene ophioboline D.[2] Since we have been interested for some time in a general approach to polyquinanes via the reaction of 1,2-dicarbonyl compounds with dimethyl 3-oxoglutarate,[3] the unusual system of four fused five-membered rings attracted our attention. Outlined below is the synthesis of *trans,trans*-4,8-diacetoxytetracyclo[9.3.0.0^{1,5}.0^{7,11}]tetradecan-6-one (**2**), the first synthetic compound to contain four five-membered rings joined as in **1**. The importance of diacetate **2** goes far beyond the preparation of a new polyquinane ring system. Two of the five-membered rings in **2** are held in a disposition such that elimination of the two acetate groups (**2** → **3a**) would provide a diene in which through-space interactions of the olefinic π electrons can be anticipated. Furthermore, the p orbital of the carbonyl group of **3a** is orthogonal to those of the diene but would project into the diene system. Comparison of the photoelectron spectrum of **3a** with that of **3b** would, therefore, be interesting in regard to interaction of the electrons in these π orbitals.[4] This possibility provided additional stimulus for the synthesis of a molecule such as **2**.

Scheme I

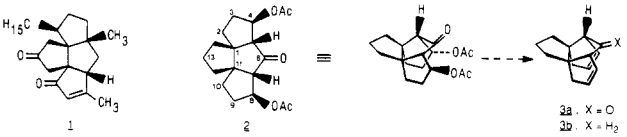


4 5 4 6

Scheme II



8b, not observed 7 8a



1 2

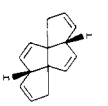
The condensation of 1,2-dicarbonyl compounds with dimethyl 3-oxoglutarate (Scheme I) has been shown to be a facile and general method for the preparation of polyquinanes.[3] The reaction in aqueous buffer of dimethyl 3-oxoglutarate (**4**) with the 1,2-dione **5**, prepared by the method of Yates,[5] results in an excellent yield of the [6.3.3]propellene, tetramethyl 10,13-dioxotricyclo-[6.3.3.0^{1,8}]tetradec-4-ene-9,11,12,14-tetracarboxylate.[3] Hydrolysis of the ester functions followed by decarboxylation gave tricyclo[6.3.3.0^{1,8}]tetradec-4-ene-10,13-dione **6** in 87% yield.[3] The [6.3.3]propellene **6** could be converted into the diacid **7**; however, the generation of four five-membered rings fused as in **2** would be expected to

(1) This work was presented in preliminary form: Venkatachalam, M.; Wehrli, S.; Kubiak, G.; Weiss, U.; Cook, J. M. *Tetrahedron Lett.* **1986**, *27*, 4111–4114.

(2) Nozoe, S.; Itai, A.; Iitaka, Y. *J. Chem. Soc. D* **1971**, 872–873.

(3) Mitschka, R.; Oehldrich, J.; Takahashi, K.; Weiss, U.; Silverton, J. V.; Cook, J. M. *Tetrahedron* **1981**, *37*, 4521–4542.

(4) (a) McMurry, J. E.; Haley, G. J.; Matz, J. R.; Clardy, J. C.; Duyne, G. V.; Gleiter, R.; Schäfer, W.; White, D. H. *J. Am. Chem. Soc.* **1984**, *106*, 5018–5019. (b) Gleiter, R.; Cook, J., M.; unpublished results. The photoelectron spectrum of polyquinene **28** does not show any evidence for interaction of the π bonds via homoconjugation. The peak at 9.0 eV is due to the ionization from all four π MO's. It is not split at all; it is therefore difficult to prove that the signal is composed of four bands. The disposition of the double bonds in **3a**, however, is much different from that in **28**.



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(5) Yates, P.; Lewars, E. G.; McCabe, P. H. *Can. J. Chem.* **1972**, *50*, 1548–1556.

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