The Wolff Rearrangement Approach to the Tricyclo[3.2.0.0^{2,6}]heptane System

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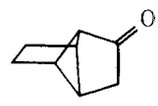
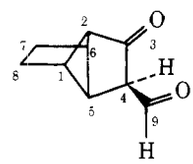
N,N-Dimethyltricyclo[3.2.0.0^{2,6}]heptane-7-carboxamide (IX) is obtained in low yield from the irradiation of 4-diazotricyclo[3.3.0.0^{2,6}]octan-3-one (III) in the presence of dimethylamine. Diazo ketone III was prepared using Rebek's polymeric tosyl azide from tricyclo[3.3.0.0^{2,6}]octan-3-one (I) via its previously unreported formyl derivative, II. Other products from the irradiation are described, and the ^{13}C NMR spectra of IX and its precursors are tabulated.

A long-standing interest in the chemistry of tricyclo[3.3.0.0^{2,6}]octane derivatives and other strained ring systems[2] led us to investigate the use of such precursors in a ring-contractive entry into the rather more strained tricyclo[3.2.0.0^{2,6}]heptane system, of which we are aware of only one previous example.[3] The earlier derivative was formed by photochemical ring closure of a bicyclic phenyl ketone, a method which appears amenable only to rather limited alteration of functionality; the extensive (if sometimes rather variable) success of the photochemical Wolff rearrangement of α-diazo ketones[4] encouraged us to try this approach. In the course of this project, the ^{13}C NMR spectra of a number of tricyclooctane derivatives were measured, and these we wish to report as well.

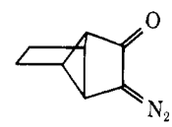
As our starting material, we chose the ketone I, which is readily if not rapidly preparable by a well-established route.[2a,e]



I



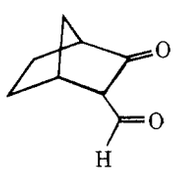
II



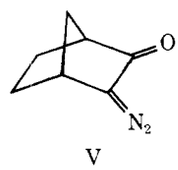
III

While conventional formylation procedures were unsuccessful, generation of the enolate anion of I with excess lithium tetramethylpiperidide in THF, followed by quenching in ethyl formate, all at −78 °C under nitrogen,[4c] led to a 32% yield of the pure formyl ketone (II). The NMR and IR spectra of II ($CDCl_3$) both show that II is exclusively in the unenolized dicarbonyl form; this is not unexpected in such a strained system.[4c]

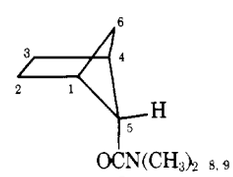
Reaction of II with tosyl azide in methylene chloride[5] gave a material whose IR and NMR spectra indicated the formation of the desired diazo ketone (III), but this product could not be purified without decomposition, either by distillation or other means. The desirability of obtaining III in a less crude state prompted us to prepare some of Rebek's "polymeric tosyl azide" reagent,[6] whose microanalytical and chemical properties (tested on acetylacetone and benzoylacetone in both ethanol and, more conveniently, in methylene chloride) equalled those reported. This reagent was also tested on 3-formylbicyclo[2.2.1]heptan-2-one[4a,7] (IV), and gave a 51% yield of the corresponding diazo ketone[4a,7] (V), whose IR and NMR spectra were satisfactory. Irradiation of the model diazo ketone V under the same sets of conditions as later used with III consistently gave 30–40% of the purified (TLC, silica gel, ether; or by GC) bicyclic amide[8] (VI). After gaining this experience with model compounds, we treated II with the polymeric azide to get up to 50% yield of crude, orange, oily III, which was characterized by its IR and NMR spectra, stored in solution at −20 °C, and used soon after its preparation. We are unable to explain the poor material balance in these latter diazo ketone preparations, except (trivially) to state that the lost material must have become irreversibly bound to the resin.



IV



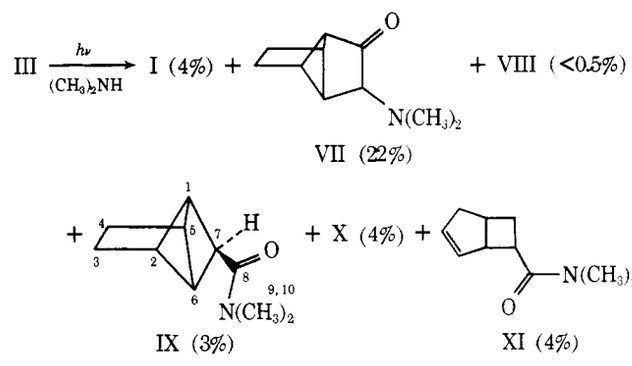
V



VI

Irradiation of III was carried out using dimethylamine to trap the ketene intermediate, in the hope of suppressing the acid-catalyzed processes that can occur even in methanol.[4b] The reaction was first tried at low temperature (with dry ice cooling of acetone circulating through the immersion well, the outlet temperature was found to hover within a few degrees of −45 °C) in dimethylamine, then at 10 °C in ca. 4:1 ether/dimethylamine (use of methylene chloride as cosolvent gave appreciable amounts of dimethylamine hydrochloride). The product mixtures were very similar in both cases. After workup and preparative GC, several products were characterized, as summarized in Scheme I (in which the products are listed in order of GC retention times).

Scheme I



The separation is described in the Experimental Section, but it will be noted here that because compounds IX and X could not be separated from each other on a preparative scale on any of the GC columns used (SE-30, Carbowax 20M, or FFAP), X was selectively and efficiently destroyed by brief bromine treatment[9] to allow isolation of IX. However, X could be partially characterized by its mass spectrum and by comparing the NMR and IR spectra of the two in the mixture with those of IX alone, and seems likely to be structurally related to XI.

Tricyclooctanone I was identified by GC retention time, IR, and NMR spectra. Compound VII, at intermediate retention time, was readily separated from the others. Its IR spectrum showed the presence of a carbonyl group; its NMR spectrum

Table I. ^{13}C NMR Spectrum of IX[a]

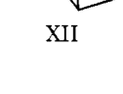
Position	Shift, ppm from Me_4Si	Multiplicity	J_{C-H}, Hz
C-1, C-6	41.3	d	163
C-2	52.0	dtr	142, 3.4
C-3	26.1	tr	130
C-4	27.6	tr	138
C-5	57.7	ddd	152, 12.8, 6.7
C-7	59.8	dtr	155, 13.4
C-8	172.4	s	
C-9, C-10	36.0	(broadened coalesced peak)	

[a] The sample was run in $CDCl_3$ using a JEOL PS-100 instrument, both with and without broad-band proton decoupling.

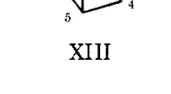
suggested that the tricyclooctane skeleton was intact and showed a six-proton singlet at δ 2.35, indicating amine *N*-methyl protons. Its mass spectrum confirmed the molecular formula and appeared otherwise consistent with the assigned structure. Products analogous to VII have been observed previously.[4c] Compounds VIII–XI appeared to be a series of dimethylamides. Product VIII was present in such small amount that it was not characterized beyond its mass spectrum.

Compound IX, the goal of our work, showed itself to be an amide on the basis of its IR spectrum (1640 cm^{-1}) and mass spectrum [base peak *m/e* 72, $(CH_3)_2NCO^+$], but its structure was most strikingly demonstrated by its NMR spectrum. This showed a slightly broadened singlet at δ 1.68 (4 H, assigned to the two methylene groups), "W-coupled" doublets at δ 2.63 and 3.22 (J = 6 Hz, H at C-2 and C-5), singlets at 2.50 (H at C-1 and C-6) and 2.92 (H at C-7), and six *N*-methyl protons at 2.96. This is in good qualitative agreement with the analogous spectrum described by Padwa and Eisenberg,[3] with the difference that the carboxamide substitution at C-7 in IX appears to "unbalance" the molecular environment rather less than the hydroxyl/phenyl substitution in their derivative. The ^{13}C NMR spectrum of IX, which also supports the given structure, is summarized in Table I.

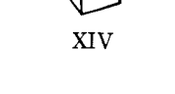
Compound X appears to be an unsaturated amide, judging from the NMR spectrum of the IX/X mixture; its mass spectrum is also consistent with this view. The IR spectrum of the mixture is very similar to that of IX alone, except for the inclusion of bands at 3060 and 695 cm^{-1}. Compound XI was assigned the structure shown on the basis of its IR spectrum (amide), a mass spectrum indicating a very facile loss of C_5H_5 (very weak M^+, and a base peak at *m/e* 100 far stronger than any other in the spectrum), and finally on the basis of an NMR shift reagent experiment. Increments of "Resolve-Al EuFOD" (Aldrich) were added until the XI:reagent molar ratio reached ca. 1:1. A single proton (multiplet) moved most rapidly downfield; the olefinic "singlet" gradually became two multiplets, but moved very little; a nonidentical (presumed geminal) pair of protons also moved very little, and the other peaks moved at intermediate rates. Whether the carboxamide group is endo or exo is uncertain, but exo seems plausible because IX has the longest retention time on polar GC columns. The position of the double bond could not be assigned with complete certainty, but mechanistic speculation makes its $\Delta^{2,3}$ position appear likely. Precedents support the general plausibility of such a structure.[3,4c]



XII



XIII



XIV

The ^{13}C NMR spectra of I and II, and their precursors XII, XIII, and XIV,[2a] as well as that of VI, are summarized in Table II.

Experimental Section

General Remarks. Boiling points are uncorrected. NMR spectra were run in $CDCl_3$ with added Me_4Si on a Varian A-60A instrument, and are reported in δ units. IR spectra were run on a Perkin-Elmer Model 257 instrument, and are reported in cm^{-1}. Low-resolution mass spectra were obtained on a Finnigan 3300 gas chromatograph/mass spectrometer; high-resolution mass spectra were from an AEI MS-902 instrument. Microanalysis was done by Galbraith Laboratories, Inc. "Nitrogen" refers to commercial "prepurified" grade. Analytical GC work was performed with a Varian 2100 instrument, preparative GC using a Varian 200 instrument; glass columns were used throughout.

4-Formyltricyclo[3.3.0.0^{2,6}]octan-3-one (II). Into a solution of 21 ml (125 mmol) of 2,2,6,6-tetramethylpiperidine in 200 ml of dry THF at 0 °C in a nitrogen-filled three-necked (nitrogen inlet, rubber septum, and 125-ml pressure-equalizing addition funnel topped with a straight-bore stopcock) 500-ml flask with magnetic stirring bar was dropped 45 ml of *n*-butyllithium in hexane (Ventron, 2.5 M, 113 mmol) over 15 min. After a further 1.25 h, the ice bath was replaced with a dry ice/ethanol bath, and 90 ml of additional dry THF was injected. Over the next 30 min was added 6.2 g (51 mmol) of I in 70 ml of THF, via the addition funnel, and the resulting solution was stirred for an additional 1.5 h before use. Another dry, nitrogen-filled flask (1000 ml) with magnetic stirrer and 500-ml jacketed addition funnel (capped with a rubber septum) was charged with 17 ml (210 mmol) of dry ethyl formate and 150 ml of dry THF. Both flask and funnel were then chilled with dry ice/ethanol. The ketone enolate solution was transferred (large-bore double-tipped flexible needle) to the cold addition funnel and added dropwise to the ethyl formate solution over the next 1.25 h. After a further 3 h, 100 ml of 10% aqueous HCl was added (froze to a slurry in the flask) and stirring continued without the dry ice bath. After reaching room temperature (ca. 45 min), the layers were separated, and the acidic aqueous layer extracted with 3 × 25 ml of ether. The combined organic phase was washed with 2 × 20 ml of saturated aqueous sodium chloride and evaporated down to a small volume of yellow liquid. This was dissolved in 100 ml of ether and extracted with 7 × 35 ml of 8% aqueous sodium hydroxide; the extracts were poured into 250 ml of cold 10% aqueous hydrochloric acid under 100 ml of ether. After separation, the acid layer was extracted with 3 × 100 ml of ether. After a final wash (saturated sodium chloride solution) the ethereal phase was dried over anhydrous sodium sulfate at −20 °C overnight. Filtration and evaporation followed by vacuum distillation gave 2.47 g (32%) of II: bp 60–65 °C (0.1 Torr); IR ($CDCl_3$) 2980 s, 2930 w, 2890 m, 2840 w, 2740 w, 1757 vs, 1710 vs, 1650 cm^{-1} w; NMR δ 1.95 (slightly broadened s, 4 H), a series of seven peaks at 2.25–3.10 (4 H), 3.52 (sl br s, 1 H), and 9.80 (d, J = 1.5 Hz, 1 H); mass spectrum (EI) *m/e* (rel intensity) 150 (2), 123 (3), 122 (36), 121 (20), 107 (23), 106 (22), 104 (19), 103 (22), 95 (12), 94 (74), 93 (84), 92 (11), 91 (86), 81 (54), 80 (36), 79 (80), 78 (73), 77 (100), 68 (41), 67 (26), 66 (54), 65 (38), 63 (14), 55 (33), 53 (31), 51 (25), 41 (12). Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.92; H, 6.87.

4-Diazotricyclo[3.3.0.0^{2,6}]octan-3-one (III). Mixed together and allowed to stir for 13 h at room temperature were 1.59 g (10.6 mmol) of II, 8.0 g (ca. 25 mequiv of azide) of polymeric tosyl azide,[6] 40 ml of methylene chloride (AR, distilled from calcium hydride), and 12 ml of purified triethylamine. The mixture was then filtered and the solid reagent washed with several small portions of ether. The combined solution was evaporated, taken up again in ether. The combined solution was evaporated, taken up again in ether (leaving insoluble material behind), dried over anhydrous sodium sulfate, refiltered, and reevaporated to give 0.79 g (50%) of crude orange oil which slowly evolved gas bubbles when completely free of solvent. This material was stored in a few milliliters of ether at −20 °C before use: IR ($CDCl_3$) 3070 vw, 2980 m, 2890 w, 2090 vs, 1745 m, 1695 s, 1650 s, 1400 m, 1330 m, 1155 cm^{-1} m; NMR δ 1.80–2.0 (narrow m, ca. 4 H), 2.15 (d, J = 9 Hz, ca. 1 H), 2.90 (d, J = 9 Hz, ca. 1 H), and 3.2 (sl br s, ca. 2 H), significant contamination was indicated by a series of small absorptions in the ranges 0.9–1.7, 2.5–3.4, and 5.6–5.8.

Irradiation of III. Apparatus for the experiment consisted of a quartz immersion well in a 200-ml reaction vessel with two joints and a magnetic stirring bar. One joint was covered with a rubber septum pierced by a nitrogen inlet tube, and the other was vented to the hood by a bubbler type connection. The assembled apparatus was thoroughly flushed with nitrogen, then the vessel was cooled in dry ice and ca. 50 ml of dimethylamine (Matheson) was condensed in via a tube

Table II[a]

Registry no.	Compd	C-2	C-3	C-4	C-5	C-6	C-1	C-7	C-8	C-9
60803-19-2	II	64.9 (d, 160)	206.3 (s)	62.4 (dd, 135, 20)	47.6 (d, 150)	(53.0 (d, 155	53.3) d, 155)	(24.5 (tr, 130	25.6) tr, 128)	197.7 (dd, 180, 10)
15774-41-1	I	66.1 (d, 155)	213.2 (s)	38.3 (tr, 135)	46.3 (d, 160)	55.2 (d, 150)		25.6 (tr, 135)		
15774-44-4	XIV	56.8 (d, 140)	71.6 (d, 150)	36.3 (tr, 130)	(47.3 (d, 150	48.7 d, 145	51.2) d, 150)	(24.3) (tr, 135)		
15774-47-7	XIII	58.6 (d, 140)	60.0 (d, 155)	38.0 (tr, 130)	(49.5 (d, 150		52.0) d, 145)	(24.3 (tr, 130	25.1) tr, 130)	
250-21-5	XII	50.9 (d, 145)	25.5 (tr, 130)							
60803-20-5	VI	23.8		42.1	49.3	36.0		171.3	(34.7	36.5)

[a] Spectra were run in $CDCl_3$ using a Bruker HX-90 instrument in the FT mode. With the exception of VI, all were run both with and without broad-band proton decoupling; chemical shift reference was the center of the $CDCl_3$ triplet (taken as δ 76.9 from Me_4Si). In parentheses below each value is its multiplicity and C–H coupling constant (in Hz, ±5 Hz); sets in parentheses indicate uncertainty of individual assignments within the sets. Assignments were based on shifts, multiplicities, and coupling constants; where isochrony occurred, intensities were also taken into account, but isochronous signals were not duplicated in the tabulation.

through the septum. Anhydrous ether (150 ml) was syringed in, and the vessel allowed to come to room temperature as excess dimethylamine bubbled out (final volume was ca. 190 ml). Diazo ketone III (0.79 g, 5.3 mmol) in a few milliliters of ether was injected. With stirring, a slow nitrogen stream, and water cooling of the well condenser jacket (outlet temperature 10 °C), the solution was irradiated through Corex using a 450-W Hanovia lamp until small aliquots (withdrawn by syringe) no longer showed the diazo band at 2090 cm^{-1} (about 2 h). Evaporation to an orange, viscous oil was followed by preparative GC (6% SE-30 column) to give I (30 mg, ca. 3%), VII (194 mg, 22%; this also showed a single peak on a 6% Carbowax 20M column), and a mixture of VIII–XI (149 mg). This last fraction was separated further by a 3% FFAP column, giving pure VIII (trace), a mixture of IX and X (72 mg), and pure XI (37 mg, 4%). To get pure IX, the mixture of IX and X in ca. 2 ml of ether was treated with 4% bromine in carbon tetrachloride until the red-orange color persisted, then the mixture was quenched with excess saturated aqueous sodium bisulfite (the whole of this took only 20–30 s). Preparative GC then gave IX (30 mg, ca. 3%). Compound VII: IR (neat) 2970 m, 2930 vw, 2890 w, 2830 w, 2780 w, 1750 s, 1640 vw, 1160 m, 890 cm^{-1} w; NMR δ 1.88 (sl br s, 4 H), 2.30 (s, 2 H), 2.35 (s, 6 H), and 2.43, 2.66, 2.90, 3.03 (totaling 3 H); mass spectrum (EI) *m/e* (rel intensity) 166 (5), 165 (46), 137 (41), 136 (100), 122 (56), 94 (57), 93 (47), 92 (28), 91 (55), 82 (50), 79 (24), 77 (26), 71 (32), 70 (29), 68 (12), 67 (18), 66 (9), 65 (13), 58 (23), 57 (13), 56 (11), 55 (14), 53 (13), 46 (11), 45 (6), 44 (24), 42 (61), 41 (18). High-resolution mass spectrum: Calcd for $C_{10}H_{15}NO$ (M^+): 165.1152. Found: 165.1145. Calcd for $C_9H_{14}N^+$: 136.1125. Found: 136.1109. Compound VIII: mass spectrum (EI) *m/e* (rel intensity) 126 (2), 124 (1), 101 (6), 100 (100), 72 (18), 67 (15), 55 (22), 46 (10). This compound was unaffected by the conditions of bromination used to destroy X. Compound IX: IR (neat) 2960 m, 2880 w, 1640 s, 1495 w, 1455 w, 1410 m, 1400 m, 1160 cm^{-1} m; NMR described in the discussion; mass spectrum (EI) *m/e* (rel intensity) 166 (0.5), 165 (4), 164 (4), 150 (3), 137 (2), 121 (15), 120 (38), 119 (9), 103 (16), 98 (12), 93 (36), 92 (17), 91 (69), 87 (14), 80 (5), 79 (15), 78 (10), 77 (58), 73 (6), 72 (100), 68 (4), 67 (8), 66 (7), 65 (22), 55 (45), 45 (15), 44 (19). High-resolution mass spectrum: Calcd for $C_{10}H_{15}NO$ (M^+): 165.1152. Found: 165.1144. Calcd for $C_3H_6NO^+$: 72.0449. Found: 72.0453. Compound X (from NMR of mixture with IX): δ 5.8 (s, olefinic) and 2.9 and 3.0 (*N*-methyl); mass spectrum (EI) *m/e* (rel intensity) 166 (2), 165 (18), 150 (1), 101 (4), 100 (62), 99 (7), 98 (21), 93 (12), 72 (51), 66 (100), 55 (27), 46 (16), 45 (13), 44 (14). Compound XI: IR (neat) 3060 w, 2960 m, 2860 w, 1650 s, 1500 w, 1450 w, 1400 m, 1155 m, 1050 w, 720 cm^{-1} mw; NMR δ 2.13–2.50 (m, 4 H), 2.88 (s, 3 H), 2.95 (s, 3 H), 3.1–3.5 (m, 3 H), 5.73 (sl br s, 2 H); mass spectrum (EI) *m/e* (rel intensity) 165 (1), 101 (6), 100 (100), 99 (2), 94 (1), 93 (3), 92 (2), 91 (12), 79 (2), 78 (2), 77 (8), 72 (18), 66 (15), 55 (21), 46 (12); (CI, methane) *m/e* 194 (7) ($M + 29^+$), 167 (12), 166 (100), 165 (2), 164 (7), 121 (2), 101 (5), 100 (84), 93 (2), 72 (16), 66 (1). High-resolution mass spectrum: Calcd for $C_{10}H_{15}NO(M^+)$: 165.1152. Found: 165.1149. Calcd for $C_5H_{10}NO^+$: 100.0761. Found: 100.0757. Calcd for $C_3H_6NO^+$: 72.0449. Found: 72.0469.

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Registry No.—III, 60803-21-6; VII, 60803-22-7; IX, 60803-23-8; XI, 60803-24-9; ethyl formate, 123-38-6; tosyl azide, 938-10-3.

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