Synthesis of 7,7-Dimethylnorbornadiene

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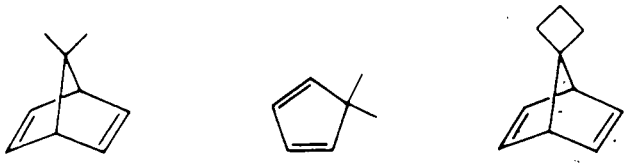
Received June 13, 1978

Two short syntheses of 7,7-dimethylnorbornadiene starting from 4,4-dimethylcyclopent-2-enone are described. The latter in its dienol form reacts with maleic anhydride to give the [4 + 2] adduct. Successive hydrolysis and oxidative decarboxylation gives 7,7-dimethylnorborn-2-en-5-one. The corresponding tosylhydrazone on treatment with lithium diisopropylamide gives 7,7-dimethylnorbornadiene. Alternatively, the cyclopentenone is reduced to the allylic alcohol, and then dehydrated to 5,5-dimethylcyclopentadiene. The [4 + 2] adduct of the latter and α-chloroacrylonitrile, on hydrolysis, affords the norbornenone, which is converted as before to 7,7-dimethylnorbornadiene.

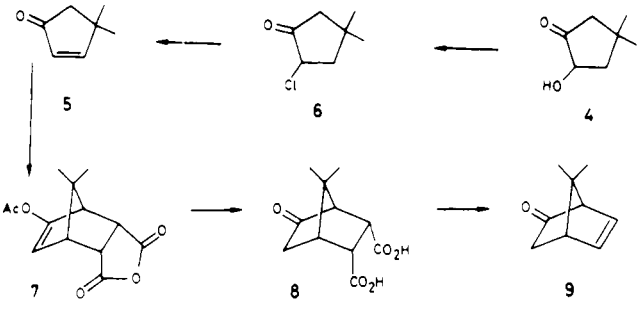
Norbornene and norbornadiene are standard molecules commonly exploited for the study of reaction mechanisms.[1] Derivatives geminally substituted at C-7 would be useful models on account of the hindrance introduced on the exo face of the molecule, thereby permitting a distinction between mechanisms having different steric requirements.[2] Unfortunately, such derivatives are more difficult to prepare than the parent structures.[3] We describe here a short synthesis of the hitherto unknown 7,7-dimethylnorbornadiene (1).



1 2 3

The obvious approach to 1 is to construct the bicyclo[2.2.1]heptadiene skeleton by a [4 + 2] cycloaddition of 5,5-dimethylcyclopentadiene (2) and a ketene equivalent[4] in a sequence of reactions similar to those used for preparing the spirocyclic norbornadiene 3.[5] As the diene partner, 2 is suitable since it is stable to 200 °C.[6] Moreover, it undergoes the Diels–Alder reaction with maleic anhydride.[7]

The original preparation of 2 entails difficulties,[7-9] but the Rühlmann modification[10] allows the conversion of 3,3-dimethylglutaric acid into 4,4-dimethyl-2-hydroxycyclopentan-1-one (4) in improved yields.[11,12] Unfortunately, acid-catalyzed dehydration of 4 to the corresponding cyclopentenone (5) is normally accompanied by some rearrangement



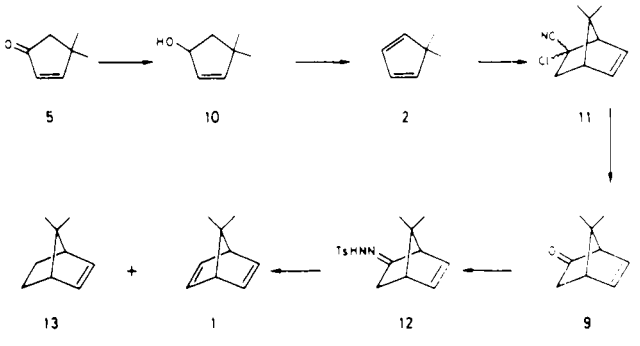
5 6 4 7 8 9

to 2,3-cyclopent-2-enone.[9] Nonetheless, this difficulty can be circumvented by using basic conditions. Accordingly, the acyloin 4 was first converted to its chloro derivative 6 by making the tosylate derivative and then treating it with lithium chloride in acetone. The resulting α-chloro ketone 6 on dehydrochlorination with lithium carbonate and lithium bromide in dimethylformamide furnished 5. This modification avoids chromatography and gave an overall yield of 32% of 5 starting from 3,3-dimethylglutaric acid.[13]

Having 4,4-dimethyl-2-cyclopentenone (5) readily available as our starting point, we describe two synthetic routes to 7,7-dimethylnorbornenone (9), which subsequently affords 7,7-dimethylnorbornadiene in good yields.

Firstly, we had good reason to believe that the dienol derived from 5 would undergo the crucial [4 + 2] cycloaddition, as it dimerizes easily.[8] In fact, reaction of 5 with maleic anhydride in isopropenyl acetate containing *p*-toluenesulfonic acid[15] gave high yields (85–95%) of the *endo*-anhydride 7. Hydrolysis gave the keto diacid 8 (76% yield). Oxidative decarboxylation with lead tetraacetate in pyridine gave 7,7-dimethylnorbornenone (9) as a colorless waxy solid in yields of 18–22%. The poor yields are difficult to explain, but seem to be characteristic of the sterically encumbered molecule,[16] as structurally simpler acids give better yields.

The second route begins with the selective reduction of cyclopentenone (5) to the allylic alcohol 10, which was accomplished conveniently in high yield (90–93%) with sodium



5 10 2 11 13 1 12 9

borohydride and cerium chloride in methanol.[17] Direct dehydration of 10 was effected in excellent yield (90%) under mild conditions by using methyltriphenoxyphosphonium iodide in hexamethylphosphoric triamide[18] to give dimethylcyclopentadiene (2) in high purity. Finally, α-chloroacrylonitrile was used as the ketene equivalent on account of its easy addition to hindered dienes.[19] The resulting adduct 11 was hydrolyzed without purification to give 7,7-dimethylnorbornenone (9) in 65% yield after distillation.

On comparing these two routes to 9, we see that the second is the simpler as the alcohol 10 and the diene 2 are obtained directly in high purity. Furthermore, the yield (53%) is some four times better than that of the first route. Moreover, the three steps can be performed on a larger scale and at lower cost.

Lastly, 7,7-dimethylnorbornenone (9) was converted to the *N*-tosylhydrazone (12) in 84% yield by refluxing with *N*-tosylhydrazine in ethanol for 10 h.[20] The final step, treatment of 12 with lithium diisopropylamide in tetrahydrofuran,[21,22] gave 7,7-dimethylnorbornadiene (1) in 43% yield accompanied by 7,7-dimethylnorbornene (13) in a ratio of 7:3. Separation was effected by gas–liquid chromatography, giving 1 as a waxy solid (27%).

0022-3263/79/1944-0689$01.00/0

Experimental Section

General. All melting points and boiling points are uncorrected. The infrared spectra (IR) were recorded on a Perkin-Elmer 257 spectrophotometer. ^1H NMR spectra were obtained in the specified solvent on Varian T60-A and XL-100 instruments. Chemical shifts are reported in δ units downfield from tetramethylsilane. Coupling constants (J) are expressed in hertz; signal multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet higher than first order. The ^{13}C NMR spectra were determined on a Varian XL-100 spectrometer. Mass spectra were obtained on a Varian SM-1 instrument; the most abundant fragments are reported with relative intensities as a percentage of the base peak intensity. We are grateful to A. Buchs and F. Klöti for the careful execution of these measurements. Microanalyses were performed by E. Eder (Geneva). Gas–liquid chromatography (GLC) analyses were carried out on a Carlo Erba (flame ionization detector) and separations on a Perkin-Elmer F21 (thermal conductivity detector) instrument, using the columns designated in the Experimental Section.

All solvents for anhydrous reactions were distilled as follows: tetrahydrofuran (THF) was freshly distilled from potassium benzophenone, diethyl ether from sodium benzophenone, and hexamethylphosphoric triamide (HMPA) and diisopropylamine from calcium hydride.

2-Chloro-4,4-dimethylcyclopentanone (6).[23] Tosyl chloride (53.4 g, 0.28 mol) was added to a chilled solution (−5 to −10 °C) of 4,4-dimethyl-2-hydroxycyclopentanone (**4**;[12] 17.94 g, 0.14 mol) in dry pyridine (200 mL) and then stirred at 0 °C for 84 h. The mixture was poured onto ice (900 g), diluted with water (800 mL), and extracted with ether (5 × 200 mL). The ether solution was successively washed with water (4 × 200 mL), 1 N HCl (200 mL), water (200 mL), and saturated aqueous NaCl (200 mL) and finally dried over Na_2SO_4. The solution was evaporated. To ensure complete chlorination, acetone (300 mL) and LiCl (10 g, 0.24 mol) were added to the resultant oil and the mixture was heated under reflux for 10 h. The solution was evaporated, diluted with hexane, filtered through Celite, and reevaporated. The yellow oil on distillation, bp 83–85 °C at 12 torr, gave **6** (10.7 g, 73 mmol, 52% yield): NMR ($CDCl_3$, 100 MHz) δ 1.12 (s, 3 H), 1.23 (s, 3 H), 1.7–2.7 (m, 4 H), 4.3 (dd, J = 8 Hz, 1 H); IR (neat) 1760 s cm^{-1}; MS m/e 146–148 (M, 8 and 25), 133–131 (3 and 10), 83 (100), 69 (43), 56 (57).

4,4-Dimethylcyclopent-2-enone (5). Chloro ketone **6** (25.2 g, 0.17 mol), LiBr (54.0 g, 0.62 mol), anhydrous Li_2CO_3 (38.2 g, 0.52 mol), and DMF (400 mL) were stirred and heated to 140 °C for 2 h. The mixture was then shaken with water (1.5 L) and extracted with hexane (3 × 300 mL). The hexane solution was washed with water (2 × 150 mL) and dried over Na_2SO_4. The combined aqueous phases were diluted with water (400 mL), extracted with $CHCl_3$ (3 × 150 mL), washed with water (2 × 100 mL), and dried (Na_2SO_4). The presence of DMF was monitored by GLC (FFAP, 120 °C); if present, the $CHCl_3$ was evaporated and the residue was dissolved in hexane (500 mL) and washed with water (2 × 250 mL). The organic solutions were evaporated, and the resulting oil was distilled, bp 45–49 °C at 10–12 torr (lit.[14] bp 47–49 °C at 15 torr), to give **5** (16.06 g, 145 mmol, 85% yield): NMR (CCl_4, 60 MHz) δ 1.21 (s, 6 H), 2.15 (s, 2 H), 5.90 (d, J = 5.5 Hz, 1 H), 7.28 (d, J = 5.5 Hz, 1 H); IR (neat) 1720, 1598 cm^{-1}.

7,7-Dimethylnorbornan-5-one-2,3-dicarboxylic Acid (8). The cyclopentenone (**5**; 16.36 g, 149 mmol), resublimed maleic anhydride (18.5 g, 189 mmol), p-toluenesulfonic acid (250 mg), and isopropenyl acetate (200 mL) were stirred at 95 °C for 20 h. The solution was evaporated in vacuo, and the resulting oil was dissolved in ethyl acetate (400 mL) and filtered over neutral alumina (100 g). Evaporating and drying in vacuo gave the crystalline anhydride adduct **7** (35.5 g, 142 mmol, 95% yield): NMR ($CDCl_3$, 100 MHz) δ 1.0 (s, 3 H), 1.2 (s, 3 H), 2.1 (s, 3 H), 3.0 (m, 2 H), 3.8 (m, 2 H), 5.7 (m, 1 H); IR (Nujol) 1855 vs, 1780–1755 vs, 1630 m, 1320 m, 1295 m, 1200 b, 1100 s, 930 s, 800 m, 705 m cm^{-1}; MS m/e 250 (7), 208 (36), 190 (11), 180 (22), 136 (7), 135 (13), 121 (7), 110 (31), 43 (100).

For hydrolysis, **7** (40.45 g, 162 mmol) and water (350 mL) were heated at 90 °C for 6 h and cooled and acetone was added (250 mL). Evaporation in vacuo (3.5 h) gave a product which on trituration with ether/acetone and recrystallization from a 6:1 mixture of acetone/hexane gave **8** as colorless crystals: 27.7 g, 122 mmol; mp 168–171 °C; NMR (acetone-d_6, 100 MHz) δ 1.8 (s, 6 H), 2.0–2.6 (m, 4 H), 3.5 (s, 2 H), 8.6 (s, 2 H); IR (Nujol) 3400 b, 3140 b, 1760 b, 1700 s, 1315 m, 1305 m, 1285 m, 1255 m, 1225 m, 1210 m, 1195 m, 1070 m, 1015 m, 970 m, 930 m, 890 m, 870 m, 835 m cm^{-1}; MS m/e 226 (24), 208 (69), 180 (20), 152 (50), 137 (27), 113 (20), 107 (29), 94 (100), 93 (35), 79 (35).

Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.49; H, 6.45.

7,7-Dimethylnorborn-2-en-5-one (9). The acid **8** (dry, 21.24 g, 94 mmol) and dry lead tetraacetate (66.5 g, 150 mmol) were added to oxygenated pyridine (200 mL, freshly distilled from BaO) at room temperature. The stirred mixture was placed in an oil bath at 67 ± 2 °C. After 5 min carbon dioxide evolved briskly, and 5 min later the flask was cooled and its contents were poured into stirred nitric acid (3 N, 1 L). The solution was extracted with ether (4 × 150 mL). The ether solution was washed with aqueous $NaHCO_3$ (2 × 100 mL) and NaCl (2 × 100 mL) and then dried over Na_2SO_4. Ether was removed at 1 atm pressure, and the residue was dissolved in hexane (200 mL) and washed with hydrochloric acid (2 N, 30 mL) and water (2 × 40 mL). The solution was dried (Na_2SO_4) and evaporated at normal pressure. Brief drying in vacuo (water pump pressure) gave **9** as a pale yellow oil (2.8 g, 21 mmol, 22% yield). Purification was effected by vacuum distillation to afford **9** as a waxy solid, mp 73–77 °C. Its spectral data were identical with those of the sample obtained by cycloaddition (vide infra).

4,4-Dimethyl-1-hydroxy-2-cyclopentene (10). Cyclopentenone **5** (2 g, 18.18 mmol) was dissolved in 45.5 mL of a 0.4 M $CeCl_3$ solution in methanol. Sodium borohydride (0.7 g, 18 mmol) was added slowly with stirring. The mixture was allowed to stand for 5 min, followed by hydrolysis and extraction with ether. The ethereal phase was washed with brine, dried over $MgSO_4$, and concentrated (10 °C/100 torr) to give alcohol **10** (1.89 g, 93%), pure according to GLC (FFAP 15%/Chromosorb W, 3 m × 3 mm, 80 °C) and spectroscopic analysis: NMR (CCl_4, 100 MHz) δ 1.03 (s, 3 H), 1.13 (s, 3 H), 1.50 and 2.0 (ABX centered at δ 1.74, J_{AB} = 14 Hz, J_{AX} = 5 Hz, J_{BX} = 7 Hz, 2 H), 3.59 (s, 1 H, OH), 4.79 (m, 1 H), 5.63 (m, 2 H); IR (neat) 3320 s, 3040 m, 1622 w, 1050 s, 780 m cm^{-1}; MS m/e 112 (M, 20), 97 (100), 69 (28), 57 (21), 55 (34), 43 (65), 41 (59), 39 (23).

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 75.32; H, 10.93.

5,5-Dimethylcyclopentadiene (2). 4,4-Dimethyl-2-cyclopentenol (**10**) (5.6 g, 0.05 mol) was added dropwise to a mixture of methyltriphenoxyphosphonium iodide (41.5 g, 0.09 mol) in freshly dried hexamethylphosphoric triamide (100 mL). The resulting mixture rapidly darkened on warming at 50 °C and stirring during 2 h. The mixture was then distilled overnight under water pump pressure (15 torr) from a bath at 50 °C. The product was trapped in a −78 °C bath to give pure 5,5-dimethylcyclopentadiene (**2**; 4.23 g, 90%): NMR (CCl_4, 60 MHz) δ 1.15 (s, 6 H), 6.16 (s, 4 H); MS m/e 94 (M, 30), 93 (16), 91 (15), 79 (100), 77 (46); IR (CCl_4) 3120 m, 3100 m, 3060 m, 1655 m, 1476 s, 1460 m, 1400 m, 1377 s, 1370 s, 1320 w, 678 w cm^{-1}.

Anal. Calcd for C_7H_{10}: C, 89.29; H, 10.71. Found: C, 89.13; H, 10.90.

7,7-Dimethylnorborn-5-en-2-one (9). (a) 2-Chloro-2-cyano-7,7-dimethylnorborn-5-ene (11).[25] A solution of 5,5-dimethylcyclopentadiene (**2**; 9.17 g, 97 mmol) and freshly distilled α-chloroacrylonitrile (17.25 g, 200 mmol) in toluene (100 mL) was warmed during 3 days at 100 °C under nitrogen. After cooling, the solvent was distilled off (30 °C/10 torr), leaving crude adduct (13.84 g) which was used without purification for the next step. A pure sample (as judged by analytical gas–liquid chromatography and its spectral analysis) was obtained by vacuum distillation in a bubble tube (130 °C/9 torr): NMR (CCl_4, 100 MHz) δ 1.14 (s, 3 H), 1.3 (s, 3 H), 1.80 (d, J = 14 Hz, 1 H), 2.59 (m, 1 H), 3.00 (dd, J = 14 and 4 Hz, 1 H), 6.26 (m, 2 H), 3.00 (masked m, 1 H); IR (neat) 3100 w, 2250 w, 1465 m, 1480 m, 1400 m, 1380 m, 1330 m, 1290 m, 1150 m, 738 s, 728 s cm^{-1}.

(b) 7,7-Dimethylnorborn-5-en-2-one (9). A warm solution of potassium hydroxide (14 g, 0.21 mol, 85%) in water (4.3 mL) was added to a solution of **11** (13.84 g, 76 mmol) in dimethyl sulfoxide (70 mL) in a 500-mL flask. The reaction mixture was stirred for 36 h and then steam distilled. The distillate was extracted three times with ether, and the ethereal phase was dried over $MgSO_4$ and evaporated (100 torr). Distillation of the resulting oil gave pure norbornenone **9** as a colorless waxy solid: mp 73–77 °C (8.57 g, 65% from **2**); bp 100 °C/47 torr; NMR ($CDCl_3$, 100 MHz) δ 1.10 (s, 3 H), 1.15 (s, 3 H), 1.8 (d, J = 18 Hz), 2.2 (dd, J = 18 and 3 Hz, 1 H), 2.6 (m, 2 H), 6.28 (m, 1 H), 6.51 (dd, 1 H, J = 5.5 and 3 Hz); IR (CCl_4) 3070 m, 2880 m, 1750 s, 1640 w, 1483 m, 1380 m, 1330 m, 1300 m cm^{-1}; MS m/e 136 (M, 15), 93 (80), 78 (100).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.32; H, 9.00.

7,7-Dimethylnorborn-5-en-2-one *N*-Tosylhydrazone (12). 7,7-Dimethylnorbornenone (**9**; 1.6 g, 11.76 mmol), N-tosylhydrazine (2.51 g, 13.48 mmol), and absolute ethanol (2.8 mL) were stirred and heated under reflux and nitrogen overnight. The hydrazone **12** crystallized out (2.99 g, 9.83 mmol, 83.9% yield): mp 154–157 °C dec; NMR ($CDCl_3$, 100 MHz) δ 0.75 (s, 3 H), 0.96 (s, 3 H), 1.73 (d, 1 H, J = 15 Hz), 2.25 (dd, 1 H, J = 15 and 4 Hz), 2.4 (s, 3 H), 2.43 (masked, 1 H), 2.8

(m, 1 H), 5.8 (dd, 1 H, J = 5 and 3 Hz), 6.16 (dd, 1 H, J = 5 and 3 Hz), 7.23 (d, 2 H, J = 9 Hz), 7.76 (d, 2 H, J = 9 Hz), 7.7 (masked, 1 H); MS m/e 305 (8), 303 (20), 151 (100), 149 (100), 107 (52), 105 (30), 91 (40), 79 (42).

Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20; S, 10.53. Found: C, 63.28; H, 6.68; N, 9.16; S, 10.60.

7,7-Dimethylnorbornadiene (1). A solution of tosylhydrazone **12** (1.2 g, 3.94 mmol) in 10 mL of dry THF was added slowly at −78 °C over a period of 10 min to a stirred solution of lithium diisopropylamide (prepared from diisopropylamine (1.62 g, 16 mmol) and 5.4 mL of a 1.85 M solution of n-BuLi in hexane) in 15 mL of dry THF. Stirring was maintained for 10 min at −78 °C, and the temperature was allowed to rise to room temperature overnight. The brown mixture was diluted with 150 mL of pentane and washed with brine (4 × 50 mL), then with a 1 M solution of NaH_2PO_4 (2 × 30 mL), and finally with brine again (2 × 30 mL). Drying over Na_2SO_4 followed by distillation of most of the solvent (40–70 °C) gave a concentrated solution which was shown by GLC (10% SE 30/Chromosorb W, 56 °C, N_2 1.4 kg/cm², 3 m × 3 mm, Carlo Erba chromatograph) to be a clean mixture of 7,7-dimethylnorbornadiene (**1**) (70%, retention time 5.7 min) and 7,7-dimethylnorbornene (**13**) (30%, retention time 6.7 min). Purification and isolation was achieved by preparative GLC (15% SE 30/Chromosorb W, 124 °C, N_2 100 mL/min, 3 m × 8 mm, Perkin-Elmer 990 chromatograph) to give **1** as a colorless waxy solid (127 mg, 27%) and **13** (40 mg, 8%).[3c] The yield of **1** before GLC separation was estimated to be 43% by GLC calibration. Samples not stored in ampules volatilized rapidly even at 0 °C.

7,7-Dimethylnorbornadiene (1): ^{1}H NMR ($CDCl_3$, 100 MHz)[24] δ 1.12 (s, 6 H), 3.05 (m, 2 H), 6.58 (t, J = 2 Hz, 4 H); ^{13}C NMR ($CDCl_3$)[24] (δ from Me_4Si) 24.26 (s, C-8,9), 59.99 (s, C-1,4), 84.83 (s, C-7), 142.44 (s, C-2,3,5,6); mass spectrum, m/e 120 (10), 105 (100). Exact mass: calcd 120.09389; found 120.09270.

7,7-Dimethylnorbornene:[3c] ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3 H), 0.95 (s, 3 H), 1.5–2.2 (m, 4 H), 2.25 (m, 2 H), 5.95 (t, J = 2 Hz, 2 H).

Registry No.—**1**, 68757-94-8; **2**, 4125-18-2; **4**, 54639-78-0; **5**, 22748-16-9; **6**, 68757-95-9; **7**, 68757-96-0; **8**, 68757-97-1; **9**, 68757-98-2; **10**, 68757-99-3; **11**, 68758-00-9; **12**, 68758-01-0; **13**, 6541-60-2; maleic anhydride, 108-31-6; α-chloroacrylonitrile, 920-37-6.

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(24) ^{1}H and ^{13}C NMR data are in good correlation with those of norbornadiene itself [^{1}H NMR ($CDCl_3$) δ 2.00 (t, 2 H), 3.58 (m, 2 H), 6.75 (t, 4 H); ^{13}C NMR ($CDCl_3$) δ 50.9 (C-1,4), 75.4 (C-7), 143.4 (C-2,3,5,6)] or 1,7,7-trimethyl-2,5-norbornadiene [^{1}H NMR ($CDCl_3$) δ 1.02 (s, 6 H), 1.19 (s, 3 H), 3.03 (m, 1 H), 6.5 (m, 4 H)].
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On a New Azatetracycline Ring System

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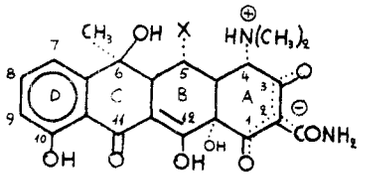
Received May 19, 1978

The structures of some substances having a novel azatetracycline ring system were determined. The azatetracycline ring system was produced by a rearrangement of the tetracycline ring system.

During a study of the transformations of some substances of the tetracycline group, we have found an unusual reaction which, via a molecular rearrangement, leads to a novel azatetracycline ring system.[1] Thus, when 11a-chloro-5-hydroxytetracycline 6,12-hemiketal (**2a**),[2] which is a derivative of 5-oxytetracycline (**1b**), was suspended in its amphoteric form in pyridine and warmed gently, it was observed that shortly after dissolution a crystalline yellow substance precipitated. We call this substance cyclazoxytetracycline (COT). Determination of its structure as **7** is detailed herein.



1a X = H
1b X = OH

Although other ring systems are derived from the tetracycline one, in order to facilitate the understanding of the transformations we will in general identify throughout the article the different functional groups or rings by the usual nomenclature in this field, i.e., by the number or letter of the position occupied on the original tetracycline ring system (**1**).

The analysis of cyclazoxytetracycline indicated that its elemental composition was the same as that of the starting

0022-3263/79/1944-0691$01.00/0