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SYNTHESIS OF 2-METHYLENETRICYCLO[4.3.2.0^{1,5}]UNDECAN-3-ONES INVOLVING A SPIRO CYCLOPROPANE RING

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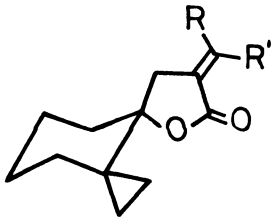
Biologically active 2-methylenetricyclo[4.3.2.0^{1,5}]undecan-3-ones involving *a spiro cyclopropane ring* related to quadrone have been synthesized.

As part of study on the unique transformations of [m.n.2]propellanes, we have already reported the synthesis of various 7-alkylidene-5-oxadispiro[2.0.4.4]-dodecan-6-ones (1) containing *a spiro cyclopropane ring* by using the skeletal rearrangement of [4.4.2]propella-δ-lactone (2) and their interesting biological activities.[1] Furthermore, we have recently synthesized biologically active



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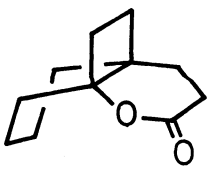

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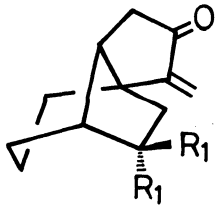
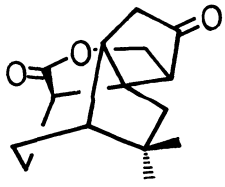


3 R_1=CH_3
4 R_1=H



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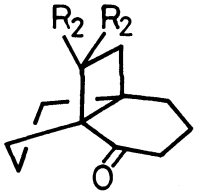
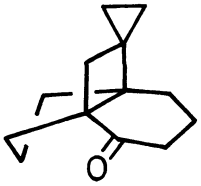


6 R_2=H
7 R_2=$-(CH_2)_2-$



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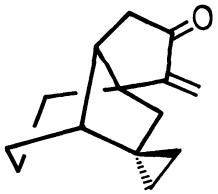

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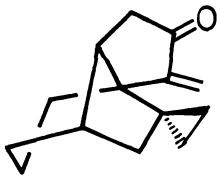
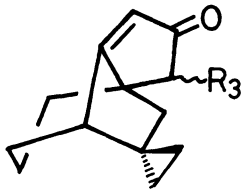


10

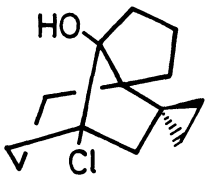
descarboxyquadrone (3)[2,3] and its binor derivative 4[2] related to quadrone (5)[4] by utilizing the novel acid-catalyzed rearrangement[5] of [4.3.2]propellanone (6) to the quadrone framework. From the viewpoint of exploitation of a new type of biologically active substances, we wish to describe here the synthesis of 2-methylenetricyclo[4.3.2.$0^{1,5}$]undecan-3-ones (9 and 10) having *a spiro cyclopropane ring* by application of the rearrangement to [4.3.2]propellanone derivatives 7 and 8, and their biological activities.

At first, we prepared the key intermediate 11 from 7[6] for the synthesis of 9 as described before.[2] Condensation of the enolate of 11 [1.1 equiv. LDA, THF, -78 °C] with gaseous formaldehyde at -20 °C followed by hydrogenation of 12[7] [Pd/C, AcOEt, rt] and acid-catalyzed dehydration [*p*-toluenesulfonic acid, C_6H_6, 40-50 °C] gave 9[7] in 54% overall yield.

In a similar fashion, the key intermediate of 16[7] for the synthesis of 10 was easily derived from 8[6,7]: i) acid-catalyzed rearrangement of 8 [concd HCl, Et_2O, reflux] followed by dehydration of the crude 13 [$SOCl_2$, Py, CH_2Cl_2, rt, 79% overall yield]; ii) reduction of 14[7] with tributyltin hydride [2,2'-azobis-isobutyronitrile, cyclohexane, reflux, 93%]; iii) allylic oxidation of 15[7] with Collins reagent [CrO_3-Py_2, CH_2Cl_2, rt, 74%]. At the final stage, hydroxymethylation of 16 and subsequent hydrogenation of 17[7] as described for 11 followed by dehydration [i) $MeSO_2Cl$, Py, rt; ii) 1,8-Diazabicyclo[5.4.0]undec-7-ene, C_6H_6, rt] afforded 10[7] in 50% overall yield.



11 R_3=H
12 R_3=CH_2OH



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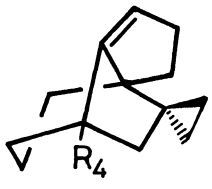
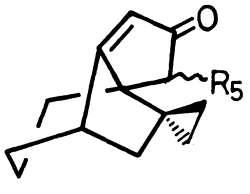


14 R_4=Cl
15 R_4=H



16 R_5=H
17 R_5=CH_2OH

The bioassay of 9 and 10 was undertaken against tumor cells of mice in vitro and the results are summarized in Table 1 together with those of quadrone (5). As shown in Table 1, the cytotoxicity of 9 and 10 has been observed at almost the

same level as the antibiotic 5. Interestingly, 9 has exhibited antimicrobial activity against *Stphylococcus aureus*, *Candida albicans*, and *Trichoyhyton foetus* (minimum inhibitory concentration: MIC, 2.5-5 μg/ml) and the activity of 10 was somewhat lower than that of 9 (MIC, 20 μg/ml or above), while quadrone (5) has not been found to have antibacterial or antifungal activity at levels of 100 μg/ml or below.[8] These datails of the assay will be reported shortly.

Table 1. Antitumor Activity of Quadrone (5) and Related Compounds 9 and 10

Test cell	IC_{50} (ng/ml)		
	5	9	10
P388	190	173	416
L1210	650	106	487
3LL	390	80	357
LY	>1000	263	>1000

We would like to thank Dr. N. Ida and Mr. H. Koike of Basic Laboratories, Toray Industries, Inc. for the screening.

References

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6) The propellanones 7 and 8 were prepared by photocycloaddition of allene to bicyclo[4.3.0]undec-1(6)-en-2-one [CH_2Cl_2, -78 °C] followed by cyclopropanation [i) LAH, Et_2O, rt; ii) Me_3SiCl, Et_3N, THF, rt; iii) Et_2Zn, CH_2I_2, hexane, rt; iv) 5% HCl, MeOH, rt; v) CrO_3-Py_2, CH_2Cl_2, rt] in 26% and 53% overall yields. The stereochemistry of the two allene photoadducts were elucidated on the basis of LIS ^1H NMR study.

7) All new compounds gave satisfactory spectral and analytical data. Selected data are as follows:

9: ^1H NMR (CCl_4) δ 0.4-0.8 (m, 4H), 1.2-2.1 (m, 10H), 2.2-2.5 (m, 2H), 4.91 (s, 1H), 5.71 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 207.4 (s), 153.2 (s), 112.3 (t), 53.4 (s), 52.4 (d), 47.1 (d), 45.7 (t), 39.8 (t), 34.3 (t), 31.3 (t), 23.1 (s), 20.0 (t), 17.9 (t), 6.8 (t).

10: ^1H NMR (CCl_4) δ 0.2-0.8 (m, 4H), 1.2-2.4 (m, 12H), 4.64 (s, 1H), 5.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 207.8 (s), 150.8 (s), 112.8 (t), 53.2 (d), 53.1 (s), 39.8 (t), 39.7 (t), 37.5 (d), 33.2 (t), 32.9 (t), 24.9 (s), 19.1 (t), 16.1 (t), 7.2 (t).

8) G. J. Calton, R. L. Ranieri, and M. A. Espensade, J. Antibiot., 31, 38 (1978).

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