Antitumor Imide Derivatives of 7-Oxabicyclo[2.2.1]heptane-2,3-dimethyl-2,3-dicarboxylic Acid

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Abstract □ The imide and methylimide derivatives of 7-oxobicyclo-[2.2.1]heptane-2,3-dimethyl-2,3-dicarboxylic acid were synthesized and shown to have antitumor inhibitory activity (growth inhibition) against the KB cell line. The compounds were prepared according to standard procedures. Interest in the respective imide derivatives stemmed from their structural relationship to antitumor-active derivatives of 7-oxobicyclo[2.2.1]heptane-2,3-dicarboxylic acid which lacked 2,3-dimethyl substituents or which were derivatives of isoindolines and lacked the carbonyl groups.

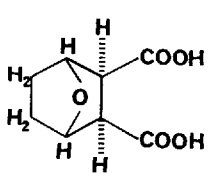
Various anhydride and imide derivatives of 7-oxobicyclo-[2.2.1]heptane-2,3-dicarboxylic acid (**1**) have been reported and shown to exhibit a wide spectrum of biological activities including antitumor properties. These include *n*-fluoroarylimide derivatives[1] (**2**) which showed central nervous system depressant properties, alkyl, aryl, and halogenated aryl derivatives[2] (**2**) which showed anticonvulsant properties, and bicyclic imides[3,4] (**3**) and isoindolines[3,4] (**4**) which showed antitumor properties. The preparation of two new derivatives which showed antitumor activity relative to this group of compounds is described in this report: the imide (**5a**) and the methylimide (**5b**) of 7-oxobicyclo[2.2.1]heptane-2,3-dimethyl-2,3-dicarboxylic acid (**5**) which, by having methyl groups in the 2,3-positions, differ from prior noted compounds.

Results and Discussion

As reported in Table I, antitumor properties were observed in both **5a** and **5b** when screened for growth inhibition against the KB cell line in tissue culture.[5] Satisfactory analytical data (±0.4% for C, H, N) are also reported for the new compounds listed in Table I.

NMR spectra obtained on a Varian EM-390 spectrometer were in agreement with assigned structures in signals. The anhydride of **5**, cantharidin (**6**), was used as a reference standard. (Ruiting et al.[6] reported antitumor inhibitory activity for **6** on reticulocell sarcoma and on ascites hepatoma in mice.) The NMR spectra for **5b** consisted of a singlet at π = 8.74 assigned to the methyl protons of the 2,3-dimethyl groups, a doublet at π = 8.21 assigned to adjacent pairs of protons on the cyclohexane ring, a singlet at π = 7.10 assigned to the methyl protons attached to imide nitrogen, and a broad, low-field absorption centered at π = 5.25 assigned to tertiary protons at the oxide bridge positions.

In conclusion, the newly synthesized imide and methylimide derivatives of 7-oxobicyclo[2.2.1]heptane-2,3-dimethyl-2,3-dicarboxylic acid were shown to have antitumor activity, like the structurally related derivatives of 7-oxobicyclo-[2.2.1]heptane-2,3-dicarboxylic acid.



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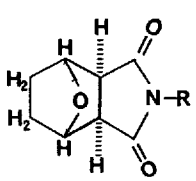

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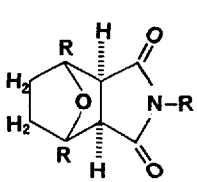

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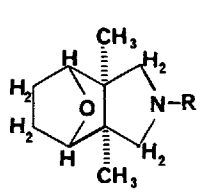

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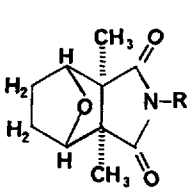
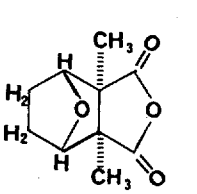


5a R= - H
5b R= - CH_3



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Experimental Section

Compounds reported herein were prepared according to published procedures by heating the desired primary amine with 7-oxobicyclo-[2.2.1]heptane-2,3-dimethyl-2,3-dicarboxylic acid anhydride. Melting points were determined in capillary tubes in a Fisher-Johns apparatus and are uncorrected. The NMR spectra were run on a Varian EM-390 spectrometer in $CDCl_3$, using trimethylsilane (TMS) as the internal reference standard. Elemental analysis for C, H, and N was performed by Atlantic Microlabs, Atlanta, GA.

Imide (5a)—A mixture of 7-oxabicyclo[2.2.1]heptane-2,3-dimethyl-2,3-dicarboxylic anhydride (10.1 g, 51 mmol) in 50 mL of ammonium hydroxide solution (28–30%) was heated to 220 °C and refluxed for 2 h. The solvent was refluxed off and the residue further heated at 200 °C for another 1 h. After cooling, the solid mass was recrystallized from ethanol to give 6.7 g (66% yield) of product, mp 205–206 °C.

Anal.—Calc. for $C_{10}H_{13}NO_3$: C, 61; H, 6.71; N, 7.17. Found: C, 61.34; H, 6.73; N, 7.14.

Methylimide (5b)—The methylimide of 7-oxabicyclo[2.2.1]heptane-2,3-dimethyl-2,3-dicarboxylic acid was prepared in the same fashion as **5a**, except for using 50 mL of a 40% aqueous solution of methylamine. The solution was refluxed 2 h at 220 °C, after which the solvent was refluxed off and the dried mass was refluxed for an additional 2 h. After cooling, the dried mass was recrystallized from

Table I—Antitumor Screening Data

Compound	R	Formula	ED_{50}, μg/mL[a]	NCI ED_{50}, μg/mL[b]	TSC[c]
5a	−H	$C_{10}H_{13}NO_3$	0.72	≦10	20C
5b	$-CH_3$	$C_{11}H_{15}NO_3$	0.88	≦10	15

[a] Screening was conducted by National Cancer Institute (NCI); values represent dose that inhibit growth of 50% of control growth using a KB (Eagle) cell culture, which is a cell line derived from a human carcinoma of the nasopharynx. [b] NCI criteria for KB Activity (ref 8). [c] Test status code: 15 indicates passed stage 2 of sequential screening; 20 indicates confirmation testing; C indicates activity confirmed in vitro only.

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ethanol. Using 10.3 g (52 mmol) of anhydride, the reaction gave 9.6 g (93% yield) of product, mp 221–222 °C.

Anal.—Calc. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.23; H, 7.30; N, 6.63.

References

1. Dominianni, S. J.; Young, R. L. *J. Med. Chem.* **1971**, *14*, 175.
2. Bocksthler, E. R.; Weaver, L. C.; Wright, D. L. *J. Med. Chem.* **1968**, *11*, 603–606.
3. Grogan, C. H.; Rice, L. M. *J. Med. Chem.* **1963**, *6*, 802–805.
4. Rice, L. M.; Grogan, C. H.; Reid, E. E. *J. Org. Chem.* **1953**, *75*, 4911–4915.
5. Geran, P. I.; Greenberg, N. H.; MacDonald, M. N.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep.* **1972**, *Pt. 3*, 1–103.
6. Ruiting, C.; Ze, H.; Jinlong, Y.; Jiaxian, H.; Suyin, Z.; Feili, L.; Bin, X. *Chinese Med. J.* **1980**, *93*, 183–187.
7. Hargreaves, M. K.; Pritchard, J. G.; Dave, H. R. *Chem. Rev.* **1970**, *70*, 439–443.
8. Instruction 14, Screening Data Summary Interpretation and Outline of Current Screen; Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute, Silver Spring, MD, 1980.

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