

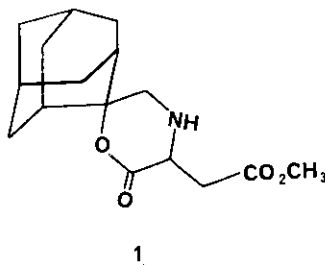
SYNTHESIS OF NOVEL METHYL (2-OXO-3-MORPHOLINYLIDENE)ACETATES

George B. Mullen, Vassil St. Georgiev*, and Christopher G. Acker

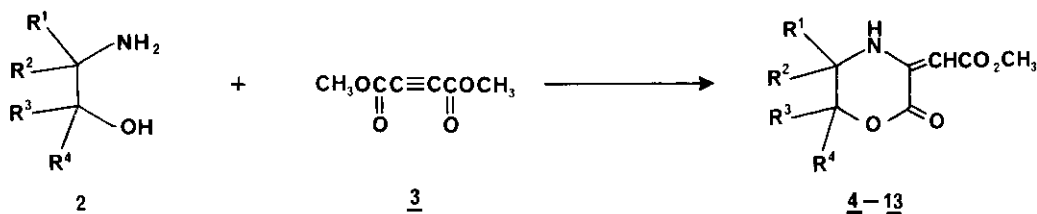
Department of Organic Chemistry, Pennwalt Corporation,
Pharmaceutical Division, Rochester, New York 14623, U.S.A.

Abstract - The synthesis of a series of novel (2-oxo-3-morpholinylidene)acetic acid methyl esters is described.

Previously, we have described the synthesis of spiro[3,4,5,6-tetrahydro-2,4-oxazin-2-one-6,2'-tricyclo[3.3.1.1^{3,7}]decane] (1), a novel adamantane-spiro-heterocyclic system ^{1,2}. When tested for anti-inflammatory activity, compound 1 at an oral dose of 50 mg/kg exerted a 27.9% ($p < 0.05$) inhibition of the carrageenin-induced rat paw edema.

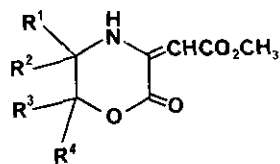


As an extension of our previous work ^{1,2}, we now wish to report the preparation of a series of novel (2-oxo-3-morpholinylidene)acetic acid methyl esters (4-13) (Table). Thus, condensation of an appropriate aminoalcohol precursor (2) with dimethyl acetylenedicarboxylate (3) furnished the desired methyl (2-oxo-3-morpholinylidene)acetate analog (4-13):



When tested in the disc diffusion assay at 500 µg per disc derivatives 4, 5 and 6 showed moderate to marked activity against Neisseria gonorrhoeae.

Table. Substituted Methyl (2-Oxo-3-morpholinylidene)acetates



4-13

Compound	R ¹	R ²	R ³	R ⁴	Mp °C	recrystn solvent	formula	analysis
<u>4</u>	CH ₃	CH ₃	H	H	94-97	ethanol	C ₉ H ₁₃ NO ₄	C, H, N
<u>5</u>	H	H	CH ₃	H	98-101	ethanol	C ₈ H ₁₁ NO ₄	C, H, N
<u>6</u>	H	H	H	H	76-79	ethanol	C ₇ H ₉ NO ₄	C, H, N
<u>7</u>	H	H	CH ₂ OH	H	112-114	ethanol	C ₈ H ₁₁ NO ₅	C, H, N
<u>8</u>	CH ₃	H	C ₆ H ₅	H	117	ether	C ₁₄ H ₁₅ NO ₄	C, H, N
<u>9</u>	H	H	C ₆ H ₅	H	125-126	ethanol	C ₁₃ H ₁₃ NO ₄	C, H, N
<u>10</u>	CH ₂ OH	CH ₃	H	H	62-63	hexane	C ₉ H ₁₃ NO ₅	C, H, N
<u>11</u>	CH ₂ C ₆ H ₅	H	H	H	82-83	hexane	C ₁₄ H ₁₅ NO ₄	C, H, N
<u>12</u>	C ₂ H ₅	H	H	H	68-70	hexane-ethyl acetate	C ₉ H ₁₃ NO ₄	C, H, N
<u>13</u>	(CH ₃) ₂ CH	H	H	H	oil		C ₁₀ H ₁₅ NO ₄	

REFERENCES

1. V. St. Georgiev and G. B. Mullen, U.S. Patent 4,549,014 (1985).
2. V. St. Georgiev, G. B. Mullen, and C. G. Acker, *Heterocycles*, 1986, 24(3), in press.

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