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

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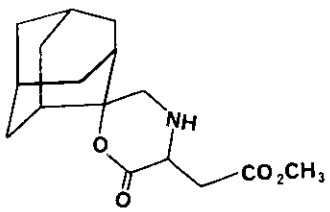
Abstract - The synthesis of a series of novel (2-oxo-3-morpholinylidene)acetic acid methyl esters is described.

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.



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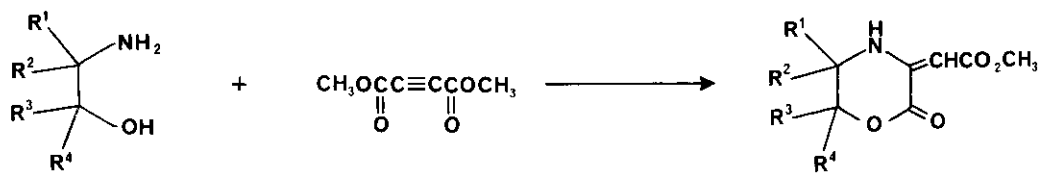
As an extension of our previous work [1,2], we now wish to report the preparation of a series of novel (2-oxo-3-morpholinylidene)acetic acid methyl esters (4-13) (Table). Thus, condensation of an appropriate aminoalcohol precursor (2) with dimethyl acetylenedicarboxylate (3) furnished the desired methyl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



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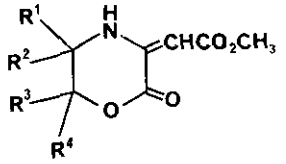
When tested in the disc diffusion assay at 500 µg per disc derivatives 4, 5 and 6 showed moderate to marked activity against Neisseria gonorrhoeae.

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
4	CH_3	CH_3	H	H	94-97	ethanol	$C_9H_{13}NO_4$	C,H,N
5	H	H	CH_3	H	98-101	ethanol	$C_8H_{11}NO_4$	C,H,N
6	H	H	H	H	76-79	ethanol	$C_7H_9NO_4$	C,H,N
7	H	H	CH_2OH	H	112-114	ethanol	$C_8H_{11}NO_5$	C,H,N
8	CH_3	H	C_6H_5	H	117	ether	$C_{14}H_{15}NO_4$	C,H,N
9	H	H	C_6H_5	H	125-126	ethanol	$C_{13}H_{13}NO_4$	C,H,N
10	CH_2OH	CH_3	H	H	62-63	hexane	$C_9H_{13}NO_5$	C,H,N
11	$CH_2C_6H_5$	H	H	H	82-83	hexane	$C_{14}H_{15}NO_4$	C,H,N
12	C_2H_5	H	H	H	68-70	hexane-ethyl acetate	$C_9H_{13}NO_4$	C,H,N
13	$(CH_3)_2CH$	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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