REACTIONS OF ALIPHATIC DIAZO COMPOUNDS

XXVI. SYNTHESIS AND PHYSIOLOGICAL ACTIVITY OF ESTERS AND AMIDES OF N-CARBOXYMETHYLSYDNONE

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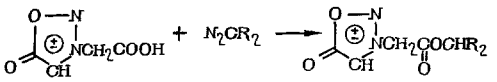
UDC 615.213:547.875

Many sydnone derivatives possess high physiological activity [1]. Continuing our researches into sydnone and sydnonimines [2], we have prepared a number of novel esters and amides of N-carboxymethylsydnone (I-XIV) which may be of interest as potential biologically active compounds or intermediates for the synthesis of such compounds.

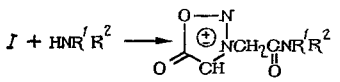
The known method of preparing sydnone-4-carboxylic acid esters is based on the reaction of the corresponding acid chlorides with alcohols in the presence of pyridine [3]. However, the widespread use of this method is limited owing to the difficulties involved in the synthesis of sydnone-4-carbonyl chlorides.

We have studied the reaction of N-carboxymethylsydnone with some aliphatic diazo compounds. For this purpose we used diazomethane, phenyldiazomethane, diphenyldiazomethane, diazofluorene, ethyl diazoacetate, and a series of α-diazo ketones with different substituents, viz. alkyl, adamantyl, and aryl. In all cases, we succeeded in isolating the corresponding N-carboxymethylsydnone esters.



I-XI

The reaction of N-carboxymethylsydnone with diazomethane, its aryl derivatives and ethyl diazoacetate proceeds smoothly under mild conditions. The α-hydroxy ketone esters are more difficult to prepare: The reagents have to be heated in a solvent for 10-24 h to complete the reaction. In some cases, the reaction proceeds only when the α-diazo ketone is fused with the N-carboxymethylsydnone.



XII-XIV

$NR'R^2 = NH_2$, $NHCH_3$, $N(CH_3)_2$

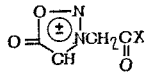
The synthesized N-carboxymethylsydnone esters and amides are compounds which crystallize readily, are insoluble in water, but are soluble in alcohol and acetone. Their characteristics are given in Table 1.

The IR spectra of the N-carboxymethylsydnone esters have intense absorption bands in the 1760-1740 and 3170-3115 cm^{-1} regions, which are characteristic of the carbonyl and CH groups of the sydnone ring [4]. The band in the 1730-1690 cm^{-1} region corresponds to the carbonyl vibrations of the ester group. The absorption of the amides in the 1650-1630 cm^{-1} region is due to the stretching vibrations of the amide carbonyl group, and the absorption in the 1620-1600 cm^{-1} region is due to the bending vibrations of the NH group (amide II band) [5].

Compound VIII shows high spasmolytic activity in the maximum electric shock test (MEST) [6]; its ED_{50} is 495 mg/kg, while its LD_{50} is 900 mg/kg. Compound IX has a depressant action on the central ner-

Perm State Pharmaceutical Institute. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 10, No. 2, pp. 53-56, February, 1976. Original article submitted December 26, 1974.

TABLE 1. Esters and Amides of N-carboxymethylsydnone (I-XIV)



Compound	X	Yield (%)	Melting point (deg)	Found (%)			Empirical formula	Calculated (%)		
				C	H	N		C	H	N
I	CH_3O	80	118—9	37,78	3,87	17,69	$C_5H_6N_2O_4$	37,97	3,90	17,72
II	CH_3COCH_2O	77	109—10	42,22	3,99	14,05	$C_7H_8N_2O_5$	42,00	4,00	14,00
III	$C_2H_5COOCH_2O$	91	113—5	41,94	4,44	12,19	$C_8H_{10}N_2O_6$	41,74	4,35	12,17
IV	$AdCOCH_2O$*	76	123—4	55,74	6,34	8,78	$C_{15}H_{20}N_2O_5$	56,25	6,25	8,75
V	$C_6H_5CH_2O$	81	100—1	57,15	4,38	12,14	$C_{11}H_{10}N_2O_4$	57,39	4,35	12,17
VI	$C_6F_5COCH_2O$	73	143—4	51,07	1,51	8,68	$C_{12}H_5F_5N_2O_5$	40,99	1,42	7,95
VII	$C_6H_5CH_2COCH_2O$	83	99—100	56,37	4,41	10,19	$C_{13}H_{12}N_2O_5$	56,50	4,34	10,15
VIII	$(C_6H_5)_2CHO$	78	105—7	65,77	4,49	9,07	$C_{17}H_{14}N_2O_4$	65,86	4,52	9,03
IX	$(C_6H_5)_2CHCOCH_2O$	76	119—21	65,01	4,61	7,99	$C_{19}H_{16}N_2O_5$	64,77	4,55	7,95
X	$p\text{-}(CH_3)_3CC_6H_4COCH_2O$	79	151—2	60,03	5,58	8,85	$C_{16}H_{18}N_2O_5$	60,00	5,62	8,81
XI	$(C_6H_4)_2CHO$	78	171—2	65,70	3,79	9,61	$C_{16}H_{12}N_2O_4$	65,53	4,10	9,55
XII	NH_2	72	169—71	33,32	3,41	29,31	$C_4H_5N_3O_3$	33,56	3,49	29,37
XIII	$NHCH_3$	55	106—9	37,98	4,53	21,37	$C_5H_7N_3O_3$	38,21	4,46	26,75
XIV	$N(CH_3)_2$	65	128—9	41,91	5,12	24,62	$C_6H_9N_3O_3$	42,11	5,26	24,56

* Ad = adamantyl.

vous system at high doses, and also protects half the mice against the extensor phase of the MEST paroxysms at a dose of 700 mg/kg, its LD_{50} being 800 mg/kg.

The results of microbiological investigations show that the majority of the compounds synthesized have slight antibacterial activity, inhibiting the growth of Gram-positive and Gram-negative bacteria. Sydnone X inhibits the growth of Staphylococcus aureus at a dilution of 1:4000 and of E. coli at a dilution of 1:2000. Compounds V, VII, and XI inhibit the growth of the above microbes at dilutions of 1:2000. N-carboxymethylsydnone and its dimethylamide are even less active. Sydnones III and VIII are inactive.

EXPERIMENTAL METHOD

Methyl Ester of N-carboxymethylsydnone (I). A solution of 4 g of N-carboxymethylsydnone in 15 ml of methanol was added to an ether solution of diazomethane prepared from 7.5 g of nitrosomethylurea at 5°. After 30 min, the mixture was evaporated in air, and the residue washed with ether and recrystallized from ethanol. Yield 3.2 g.

Benzyl Ester of N-carboxymethylsydnone (V). This was prepared analogously.

Biphenylmethyl Ester of N-carboxylmethylsydnone (XI). A solution of 1 g of diazofluorene in 10 ml of benzene was treated portionwise with 0.8 g of N-carboxymethylsydnone and the mixture kept at 50-60° for 24 h. The product was isolated, washed with ether, and recrystallized from ethanol. Yield 0.6 g.

Benzhydryl Ester of N-carboxymethylsydnone (VIII). This was prepared analogously in chloroform at 15-20°.

p-t-Butylbenzoylmethyl Ester of N-carboxymethylsydnone (X). A solution of 0.7 g of p-t-butylbenzoyldiazomethane in 5 ml of methylene chloride was treated portionwise with 0.5 g of N-carboxymethylsydnone and the mixture kept at 20-25° for 24 h. The precipitate was isolated, washed with ether, and recrystallized from ethanol. Yield 0.4 g.

Adamantanoylmethyl Ester of N-carboxymethylsydnone (IV). A melt of 1 g of adamantanoyl-diazomethane was treated portionwise with 1.5 g of N-carboxymethylsydnone. When nitrogen evolution ceased, the reaction mixture was cooled, washed with ether, and recrystallized from ethanol. Yield 1.1 g.

Compounds II, VI, VII, and IX. These were prepared analogously.

Amide of N-carboxymethylsydnone (XII). A portion (0.5 g) of the methyl ester of N-carboxymethylsydnone was added to 10 ml of 25% ammonia at room temperature. The mixture was left for 3 days, evaporated to dryness in air, and the residue recrystallized from ethanol. Yield 0.36 g.

Amides XIII and XIV. These were prepared analogously.

The substituted α-diazo ketones used for the preparation of II, IV, VII, IX, and X were synthesized by the methods described in [7-11] respectively.

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