O-Carbamoyl Oximes as Potential Analgesics

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Preparation of oxadiazinones **2**, from α-anilinoacetophenone oximes and *O*-carbamoyl-2,3-dihydro-4-quinolinone oximes **3**, from quinolinones are described.

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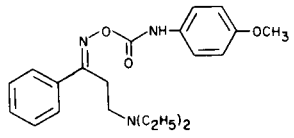
In our continuing search for novel analgesic agents, two types of compounds, **2** and **3**, were prepared having the *O*-carbamoyl oxime structure characteristic of anidoxime (E-142) **1** (1).



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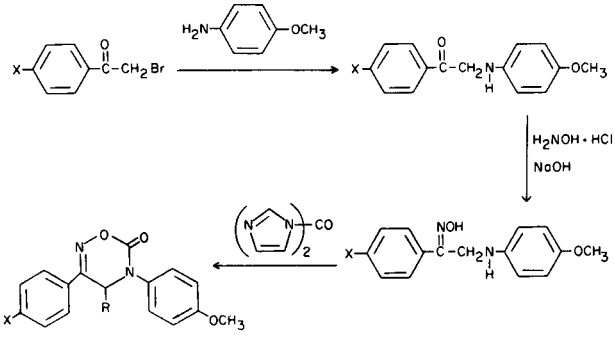
Oxadiazinones, **2** (R = H) were made by a modification of the method of Gnichtel and Thiele (2) from α-anilinoacetophenone oximes (Scheme I).

Scheme I



2a (X = H, R = H)
2b (X = NO_2, R = H)

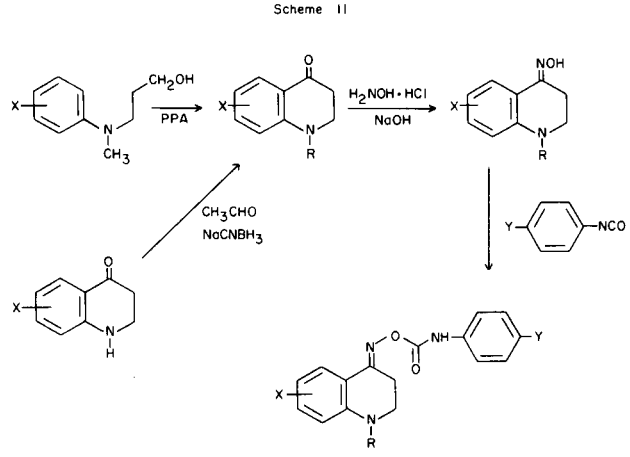
Attempts to place an aminomethyl function (R = $CH_2NR'_2$) at the 4-position failed either by the Mannich reaction on **2** or by introducing it at an earlier stage.

A series of *O*-carbamoyl-2,3-dihydro-4-quinolinone oximes, **3**, were prepared as shown in Scheme II.

The intermediate quinolinones leading to **3** were made by modifications of the method of Atwal, *et al* (3) from β-anilinopropionic acids and reductive alkylations of the unsubstituted quinolinones using acetaldehyde and sodium cyanoborohydride. The data for the *O*-carbamoyl-2,3-dihydro-4-quinolinones are listed in Table I.

All the novel compounds were tested for analgesia in mice but were inactive. However, screening in a battery of tests for central nervous system activity showed weak to moderate body temperature lowering in mice. This may be indicative of CNS depressant activity.

Scheme II



3

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus. Calibration against standard compounds showed no correction was necessary.

Dihydro-5-(4-methoxyphenyl)-3-phenyl-6*H*-1,2,5-oxadiazin-6-one (**2a**).

A solution of 2-[(4-methoxyphenyl)amino]acetophenone oxime (12.8 g., 50.0 mmoles), prepared by the method of Julian, *et al* (4), in tetrahydrofuran (75 ml.) was treated with 1,1'-carbonyldiimidazole (9.7 g., 60.0 mmoles) and stirred at ambient temperature under nitrogen for 2.5 hours. The mixture was concentrated *in vacuo* and the residue dissolved in methylene chloride, washed with water, dried (sodium sulfate), and concentrated *in vacuo*. The oil was crystallized from ethyl acetate-hexane to give 3.95 g., m.p. 99-101.5°. The filtrate was chromatographed on silica gel eluting with chloroform to give 2.32 g., m.p. 98.5-100° of a white solid (overall yield 45%); ir (Nujol): 1734 (C=O), 1610, 1585, 1515, 1500 (C=C/C=N), 1245, 1140, 925 cm^{-1} (C-O/C-N/N-O); nmr, (deuteriochloroform): δ 3.8 (s, 3H), 4.7 (s, 2H), 6.9 (d, 2H), 7.3 (d, 2H), 7.7 (m, 5H).

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 67.89; H, 4.93; N, 9.67.

Dihydro-5-(4-methoxyphenyl)-3-(4-nitrophenyl)-6*H*-1,2,5-oxadiazin-6-one (**2b**).

A solution of *p*-nitrophenacyl-*p*-anisidine oxime (0.3 g., 1.0 mole), prepared by the manner of Julian, *et al* (4), in tetrahydrofuran (10 ml.) was treated with 1,1'-carbonyldiimidazole (0.24 g., 1.5 mmoles) and stirred at ambient temperature under nitrogen for 2.5 hours. The solution was concentrated *in vacuo* and the residue dissolved in methylene chloride, washed with water, dried (sodium sulfate), and concentrated *in vacuo*. The product was recrystallized from methylene chloride-methanol-ethyl acetate to give a white solid, m.p. 154-156°, 0.2 g. (61%); ir (Nujol): 1730 (C=O), 1605, 1530, 1515 (C=C/C=N/NO_2), 1345 (NO_2), 1250, 1145, 1035, 935 cm^{-1} (C-O/C-N/N-O); nmr (deuteriochloroform): δ 3.83 (s, 3H), 4.8 (s, 2H), 6.95 (d, 2H), 7.35 (d, 2H), 7.9 (d, 2H), 8.3 (d, 2H).

Anal. Calcd. for $C_{16}H_{13}N_3O_5$: C, 58.72; H, 4.00; N, 12.84. Found: C, 58.96; H, 4.12; N, 12.78.

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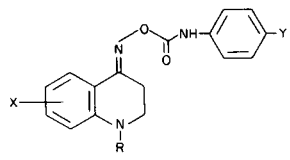
Table I

O-Carbamoyl-2,3-dihydro-4-quinolinone Oximes



Compound No.	X	R	Y	M.p. °C	% Yield	Formula	Analysis Calcd. C	H	N	S/Cl	Found C	H	N	S/Cl
3a	H	CH_3	4-OCH_3	133-137	41	$C_{25}H_{21}N_3O_6S$ (a)	60.35	5.47	8.45	6.44	60.45	5.40	8.40	6.53
3b	H	CH_3	4-Cl	119-124	84	$C_{17}H_{16}ClN_3O_2$	61.91	4.89	12.74	10.75	61.86	4.92	12.78	10.79
3c	H	C_2H_5	H	159-162	88	$C_{18}H_{19}N_3O_2$	69.88	6.19	13.58		69.71	5.82	13.38	
3d	H	C_2H_5	4-OCH_3	94-96.5	65	$C_{19}H_{21}N_3O_3$	67.24	6.24	12.38		67.21	6.34	12.50	
3e	H	C_2H_5	4-Cl	165-168	84	$C_{18}H_{18}ClN_3O_2$	62.88	5.28	12.22	10.31	67.76	5.45	12.21	10.26
3f	H	C_2H_5	2,5-DiCl	161-164	93	$C_{18}H_{17}Cl_2N_3O_2$	57.15	4.53	11.11	18.75	57.29	4.62	11.21	18.80
3g	H	C_2H_5	4-NO_2	175-177 (b)	80	$C_{18}H_{18}N_4O_4$	61.01	5.12	15.81		60.62	5.44	15.94	
3h	6-OCH_3	C_2H_5	4-OCH_3	139-144	37	$C_{20}H_{23}N_3O_4$	65.03	6.28	11.38		64.87	6.34	11.44	
3i	6-OCH_3	C_2H_5	4-Cl	131-135	66	$C_{19}H_{20}ClN_3O_3$	61.04	5.39	11.24	9.48	60.95	5.43	11.23	9.61
3j	6-OCH_3	C_2H_5	2,5-DiCl	162-163.5	60	$C_{19}H_{19}Cl_2N_3O_3$	55.89	4.69	10.29	17.37	56.14	4.64	10.45	17.52
3k	6-OCH_3	C_2H_5	4-NO_2	122-125	63	$C_{19}H_{20}N_4O_5$	59.37	5.24	14.58		59.33	5.28	14.58	

(a) Obtained as 4-methylbenzenesulfonate salt. (b) Had distinct softenings at 124°, 144° and 164°.

General Procedure for *O*-Carbamoyl-2,3-dihydro-4-quinolinone Oximes (**3**).

A solution of the appropriately substituted 2,3-dihydro-4-(4*H*)quinolinone oximes were dissolved in benzene and treated with an equivalent amount of the substituted phenylisocyanate. The mixtures were stirred at ambient temperature under nitrogen for 1 hour. The mixtures were concentrated *in vacuo* and the residues dissolved in methylene chloride, washed with water, dried (sodium sulfate), and concentrated *in vacuo*. The residues were crystallized from ethyl acetate-hexane to give the products listed in Table I.

Acknowledgement.

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REFERENCES AND NOTES

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