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2-p-CHLOROPHENYLOXAZOLIN-5-ONES IN THE MANNICH REACTION

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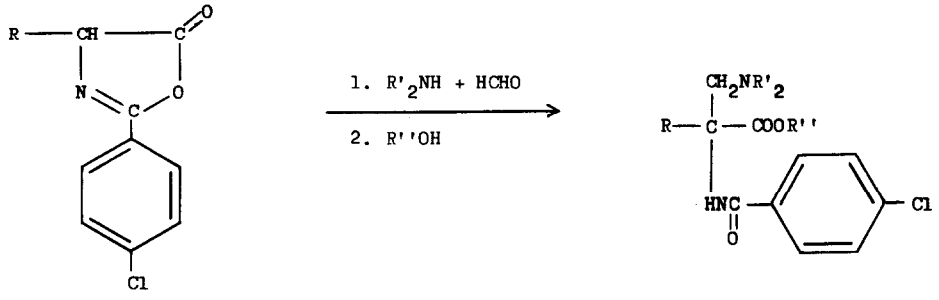
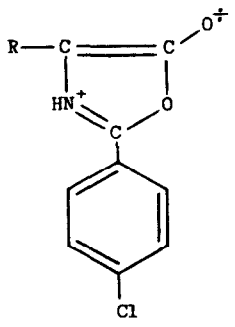
In the search for 2-substituted analogues of 2-p-chlorobenzamido-3-dialkylaminopropionic acids which possessed analgetic activity (1) it was disclosed that 2-p-chlorophenyloxazolin-5-ones I, as active 4H-compounds, enter into an aminoalkylation reaction with secondary amines and formaldehyde, prior to ring cleavage in a hydroxylic solvent. The initial step in this concerted conversion of I into II is believed to be the first reported example of a Mannich reaction involving the 4-position of I, although other reactions are known to occur at this position (2).

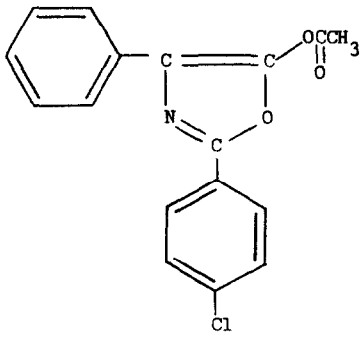


I II

A number of relatively stable 2-p-chlorophenyloxazolin-5-ones was prepared in good yield by brief heating of the respective α-p-chlorobenzamido acids in acetic anhydride at 90-125°C. The compounds could be recrystallized from anhydrous ethanol. Their I.R. spectra (KBr) showed characteristic absorptions at 1815-25 cm^{-1} (C=O) and 1645-65 cm^{-1} (C=N). Exceptions were found with R=COOEt (Ia) and R=C_6H_5 (Ib), displaying broad absorption at 2300-2900 cm^{-1} and at 1625-1725 (Ia) and 1645-65 cm^{-1} (Ib). This, in addition to the very poor solubility in organic media, points to the assignment of the isomeric structure III as the more appropriate one for (Ia-b). Recently similar structural arguments for 2-p-nitrophenyl-4-phenyloxazolin-5-one have been presented (3). (Ia) gave an intensely blue colour with ethanolic ferric chloride, as reported for 2-phenyl-4-carbethoxyoxazolin-5-one (4).



III (Ia-b)



IV

On prolonged heating in acetic anhydride the formation of the strongly yellow Ib was accompanied by the appearance of fair amounts of a new product, mp. 132.5-33°C. Elemental analysis, I.R. and N.M.R. spectra as well as reactions established the structure IV, $C_{17}H_{12}ClNO_3$. I.R. (KBr): 1795 and 1645 cm^{-1}. N.M.R. (10%, CCl_4): 9 aromatic protons (δ 7.60, m) and 3 methyl protons (δ 2.37, s). U.V.: $\lambda_{max}^{EtOH}(\varepsilon)$: 240 mμ (20.500), 299 mμ (18.900). With traces of alkali in ethanol IV was quickly converted into Ib. Triethylamine-catalyzed reaction with aniline in ether gave Ib and acetanilide. The formation of the 2-p-nitrophenyl analogue of IV under like conditions and a more general synthesis of enol esters of this type have been described (3, 5).

Addition of I to a small excess of secondary amine and aqueous formaldehyde in methanol or ethanol at 0-20°C and reaction for 1-20 hours gave the respective esters II in 65-90% yield. Some esters were hydrolyzed to the free acid (R''=H) with alkali. Starting from L-α-p-chlorobenzamido acids optically inactive products were obtained. The I.R. spectra (KBr) of the esters had absorptions at 3400-3440 (NH), 1730-40 (ester C=O) and 1650-70 (amide C=O) cm^{-1}. No reaction was observed in ethanol, when ethyl α-p-chlorobenzamido-α-phenylacetate was used in place of Ib (6).

In a single attempt of reaction in aqueous solution the glycine azlactone (I, R=H) with dimethylamine and formaldehyde gave a 10% yield of the amino acid II (R=R''=H, R'=CH_3) which was identical with the compound obtained by addition of dimethylamine to α-p-chlorobenzamidoacrylic acid (7).

IV with 2 moles of aqueous dimethylamine and 1 mole of formaldehyde in methanol gave II, (R=C_6H_5, R'=R''=CH_3) in 80% yield, presumably via intermediate formation of Ib. Under similar conditions in 2-trifluoroethanol IV afforded the free acid II (R=C_6H_5, R'=CH_3, R''=H), apparently as a result of a concomitant smooth hydrolysis of the 2-trifluoroethyl ester in the weakly

II, $R-C(CH_2NR'_2)(NHCOC_6H_4\text{-}Cl\text{-}p)-COOR''$

R	I mp. °C	R'_2	R''	mp. °C	Formula	Calcd.% C	H	N	Found % C	H	N
H	126-28	$(CH_3)_2$	H	172-73	$C_{12}H_{15}ClN_2O_3$	53.24	5.59	10.35	53.33	5.69	10.13
CH_3	104-05	$(CH_3)_2$	H[a]	140-43	$C_{13}H_{20}Cl_2N_2O_4$	46.06	5.95	8.26	46.21	6.12	8.10
CH_3	104-05	$(CH_3)_2$	CH_3	83-83.5	$C_{14}H_{19}ClN_2O_3$	56.27	6.41	9.37	55.95	6.41	9.15
CH_3	104-05	$(CH_3)_2$	C_2H_5	73-74	$C_{15}H_{21}ClN_2O_3$	57.56	6.76	8.95	57.64	6.70	8.84[f]
$CH_3S(CH_2)_2$	not isol.	$(CH_3)_2$	CH_3	78-79.5	$C_{16}H_{23}ClN_2O_3S$	53.55	6.46	7.80	53.60	6.50	7.73[g]
$C_6H_5CH_2$	137-38	$(CH_3)_2$	H[b]	170-70.5	$C_{19}H_{23}ClN_2O_4$	60.21	6.12	7.39	60.09	6.13	7.14
C_9H_8N[c]	163-65	$(CH_3)_2$	CH_3	150-52	$C_{22}H_{24}ClN_3O_3$	63.84	5.84	10.16	63.56	5.90	9.96
C_9H_8N	163-65	C_4H_8O[d]	CH_3	124-26	$C_{24}H_{26}ClN_3O_4$	63.22	5.75	9.22	63.13	5.93	9.24
C_9H_8N	163-65	C_4H_8O	C_2H_5	176.5-77.5	$C_{25}H_{28}ClN_3O_4$	63.89	6.01	8.94	63.84	6.13	8.82
C_9H_8N	163-65	$C_5H_{11}N$[e]	C_2H_5	161-64	$C_{26}H_{31}ClN_4O_3$	64.65	6.47	11.60	64.70	6.53	11.55
C_6H_5	163-63.5	$(CH_3)_2$	H	150	$C_{18}H_{19}ClN_2O_3$	62.30	5.52	8.07	62.21	5.70	7.96
C_6H_5	163-63.5	$(CH_3)_2$	CH_3	122.5-24	$C_{19}H_{21}ClN_2O_3$	63.24	5.86	7.76	63.22	5.86	7.62[h]

a): hydrochloride, hydrate; picrate: mp. 205-206.5°C: b): hydrate: c): 3-Indolylmethyl:

d): NR'_2=morfolino; e): NR'_2=N-methylpiperazino.

f): Cl calcd.: 11.33: found 11.36%

g): S calcd.: 8.93; found 9.12%

h): Cl calcd.: 9.83: found 9.80%

alkaline medium.

The N.M.R. data of some 3-dimethylaminopropionic acid derivatives are compiled in the following table.

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$CH_2N(CH_3)_2$ | R-C-COOR'' | $NHCOC_6H_4Cl$-p	N.M.R. data (Varian A60A. δ ppm from T.M.S., (J) cps).					
	R	R''	$N^{CH_3}_{CH_3}$	$-CH_2N<$		Solvent
R=CH_3 R''=CH_3	1.68 s	3.77 s	2.27 s	2.80 d (14) 3.00 d	7.43 d (8) 7.77 d	$CDCl_3$
R=CH_3 R''=CH_3CH_2-	1.68 s	$-CH_2CH_3$ 4.26 q (7) $-CH_2CH_3$ 1.28 t	2.27 s	2.82 d (14) 3.03 d	7.43 d (8) 7.77 d	$CDCl_3$
R=$CH_3SCH_2CH_2$- R''=CH_3	S-CH_2CH_2 2.50 m_a CH_3S- 2.04 s	3.83 s	2.23 s	2.75 d (14) 3.40 d	7.45 d (8) 7.80 d	$CDCl_3$
R=C_6H_5 R''=CH_3	7.37 m	3.75 s	2.25 s	3.47 d (13) 3.70 d	7.45 d (9) 7.82 d	$CDCl_3$
R=3-indolyl-CH_2- R''=CH_3	indol 7.15 m_a $-CH_2-$ 3.37 d (15) 3.91 d	3.73 s	2.23 s	2.95 d (14) 3.63 d	7.49 m_a	$CDCl_3$
R=CH_3 R''=H	1.92 s		3.13 s 3.30 s	3.85 d (15) 4.07 d	7.58 d (9) 7.90 d	CF_3COOD
R=$C_6H_5CH_2$- R''=H	C_6H_5 7.50 m_a $-CH_2-$ 4.05 s or 3.55 m		3.13 s 3.22 s	3.55 m or 4.05 s	7.50 m_a	CF_3COOD
R=3-indolyl-CH_2- R''=H	indol 7.10 m_a $-CH_2-$ 3.10 m_a or 3.70 m_a		2.18 s	3.10 m_a 3.70 m_a or	7.10 m_a	NaOD + D_2O

m_a: complex overlapping pattern.

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