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MECHANISM OF FORMATION OF p-SUBSTITUTED PRODUCTS IN DISPLACEMENT REACTIONS ON ∝-CHLORODIPHENYLACETAMIDES*

K. Nagarajan and C.L. Kulkarni

CIBA Research Centre, Goregaon, Bombay 63, India.

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We reported previously[1] on the formation of novel products in the displacement reactions on ∝-chlorodiphenylacetamides such as I with bulky secondary, especially cyclic secondary amines, e.g. N-methylpiperazine. For the formation of the p-substituted product III in addition to the normal ∝-substituted product II, we considered the possibility of the intervention of an ∝-lactam intermediate X. We wish to communicate now results of our recent experiments which show that an ∝-lactam may not be involved in the formation of III and provide additional information on the course of this reaction.

Interaction of N-t-butyl-∝-chlordiphenylacetamide (IV), m.p. 91-93°[2] with 3 molar equivalents of N-methyl piperazine alone at 130° for 3 hrs. or in boiling toluene for 6 hours led to the formation of basic products in 80-85% yield, which consisted essentially of a mixture (TLC - silica plate) of the ∝-substituted product V (maleate, m.p. 171-172°) and the p-substituted product VI, m.p. 177-178°, in equal proportions (NMR analysis). The composition of the basic mixture was practically unchanged by the addition of 1 molar equivalent each of KCl and t-BuOH. Treatment of amide IV with 1.2 molar equivalents of t-BuOK in toluene at -10 to -20° for 45 min. led to its conversion in over 95% yield to the ∝-lactam XI (IR band at 1850 cm^{-1}). Treatment of this solution with 3 molar equivalents of N-methyl-piperazine or a mixture of 2.5 molar equivalents of N-methylpiperazine and 0.5 molar equivalent of its dihydrochloride gave only

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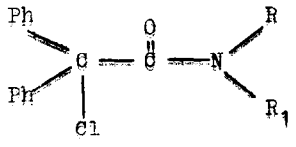
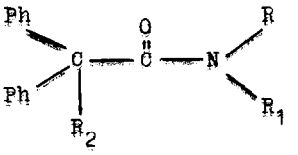
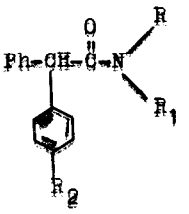
amide V as the sole identifiable product in 90% yield. Thus the possibility of the α-lactam XI being involved in the formation of VI is ruled out.[3,4,5]

Treatment of liquid N,N-diethyl-α-chlorodiphenylacetamide (VII) with 3 molar equivalents of N-methylpiperazine at 120° for 3 hrs afforded in 85% yield a basic mixture in which the p-substituted product IX, m.p. 67-69°, was present to the extent of 75% (NMR). Spectral evidence for the presence of VIII in the







I R=H; R_1=PhCH$_2$CH$_2$-

II R=H; R_1=PhCH$_2$CH$_2$-

III R=H; R_1=Ph-CH$_2$-CH$_2$

IV R=H; R_1=t-Bu-

V R=H; R_1=t-Bu-

VI R=H; R_1=t-Bu

VII R=R_1=Et

VIII R=R_1=Et

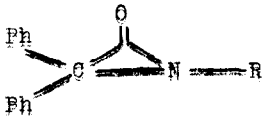
IX R=R_1=Et

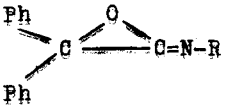
XVI R=H; R_1=Ph

XIV -N(R)(R_1) = N'-methyl piperazino

XV -N(R)(R_1) = N'-methyl-piperazino

(R_2 = N'-methylpiperazino in all structures)





X R = PhCH$_2$CH$_2$-

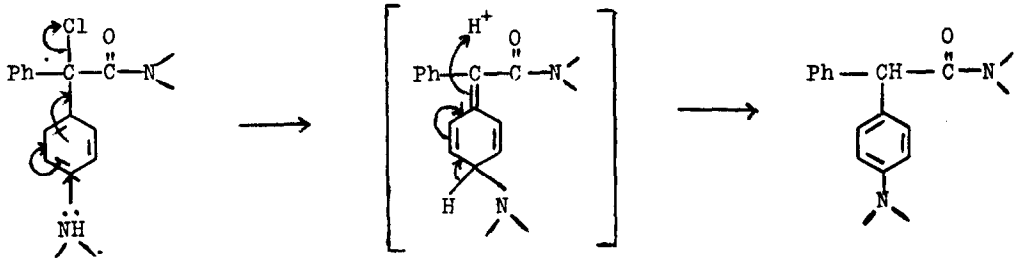
XI R = t-Bu

XII

XIII

mixture was available, but its isolation in a pure form was not achieved. These results indicate that neither α-lactams of the type X and XI nor oxiranes of the type XII are obligatory intermediates in the formation of p-substituted products. Another possible intermediate XIII can be ruled out as this should also yield at least detectable amounts of amides XIV and XV in these reactions, unless there is an overwhelming propensity for N-methyl-piperazine to be ejected from XIII in preference to phenethylamine, t-butylamine, etc.

From past[1,3] and present data, the formation of the abnormal products appears to be best explained by a S_N2'' type displacement, necessitated by the crowded arrangement around the halogen-containing center. As the steric inaccessibility would be significantly attenuated in the α-lactam, product VI was not obtained in the reaction of XI with N-methylpiperazine. The role of steric factors is highlighted by the fact that in the reaction of the series of amides I, XVI, IV



and VII with N-methylpiperazine, the proportion of the p-products increases with increasing bulk of the amide group. Further, an α-substituted product is exclusively formed in the reaction of N-methylpiperazine with 9-chlorofluorene-9-carboxanilide wherein the phenyl groups have been 'tied together'. The contribution of the size of the nucleophile has been discussed previously[3].

An alternative mechanism for the formation of the p-products would be one in which a preliminary ionisation occurs, followed by attack of the nucleophile at the doubly vinylogous p-position and proton shift. This is considered unlikely since the reaction of trityl bromide with such bases does not show evidence for the formation of p-substituted products.[1] However, for the formation of the 'normal' products, it is possible that one or more of the following pathways may operate : i) a distinct α-lactam intermediate, ii) ionisation, unassisted or assisted by the amide function, followed by base capture, iii) S_N2 displacement.

The role of solvent in the displacement reactions of amide IV was studied. Reaction was carried out with 3 molar equivalents of N-methylpiperazine at 70°C for 6 hrs separately in toluene, acetone and alcohol solutions. In all the three cases, the basic product was shown to be essentially a mixture of the p- and α-products, which were analyzed by NMR. The results are tabulated below :

Solvent	% total basic product	% recovery IV	Ratio of p- to ∝-product
Toluene	15	83	1:1
Acetone	55	30	4:3
Alcohol	16	70[6]	5:3

The course of the reaction of amide IV with excess t-BuOK in t-BuOH illustrates another aspect of the problem, viz. that p-substitution requires the satisfaction of other criteria in addition to the bulk of the nucleophiles. The crude product mixture (60% of the weight of the starting material) showed no evidence of p-substitution, but contained as a major component (65%) N-benzhydryl-t-butylamine, m.p. 54-55°, identical with a synthetic sample. Its formation can be envisaged to have occurred via lactam XI, by opening with the nucleophile to give a urethane and subsequent loss of the carboalkoxy function.[7]

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1. K. Nagarajan, C.L. Kulkarni and A. Venkateswarlu, Tetrahedron Letters, 1387(1967).
2. Structures of all new compounds reported here are supported by analytical and spectral (IR, UV, NMR) data.
3. Part of this work was presented by K. Nagarajan, C.L. Kulkarni and A. Venkateswarlu at the 154th meeting of the American Chemical Society, Chicago, Sept. 10-15, 1967.
4. J.C. Sheehan and J.H. Beeson, J. Am. Chem. Soc., 89, 366 (1967), have reported the formation of lactam XI in solution.
5. H.E. Baumgarten et al have reported recently [Tetrahedron Letters, 5033 (1967)] the isolation and characterization of lactam XI.
6. The neutral product in this case was ∝-ethoxy-N-t-butyldiphenylacetamide (NMR). Because of the large excess of ethanol used as a solvent, attack has occurred preponderantly by solvent rather than by N-methylpiperazine.
7. The formation of this product has been reported independently by H.E. Baumgarten et al (Ref. 5)