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A NOVEL DISPLACEMENT REACTION ON α-CHLORODIPHENYLACETAMIDES*

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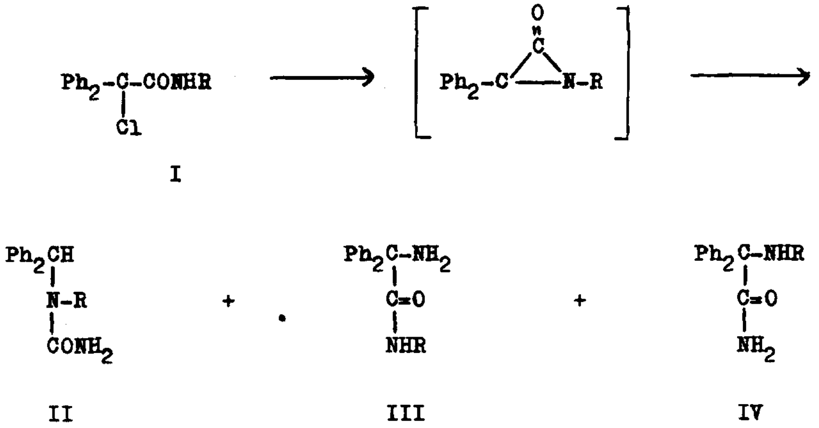
The reaction of bases with α-haloamides is being increasingly recognized in recent years to be a complicated one, very often, due to the participation of α-lactam or equivalent intermediates. Thus the action of sodamide in liquid ammonia on α-halodiphenylacetamides (I) leads to three different products II, III and IV, presumably <u>via</u> an α-lactam[1]. Such α-lactams have been actually isolated from the reaction of N-t-butyl-α-chlorophenylacetamide[2],



N-t-butyl-1-bromocyclohexane carboxamide[3] and N-t-butyl-α-bromo-α,α-dimethylacetamide[4] with potassium t-butoxide. Treatment of α-chlorodiphenylacetanilide with sodium hydride[5] or α-chlorodiphenylacetyl chloride with N,N-dimethylhydrazine[6] leads to oxindole derivatives. N,N-Dimethyl-α-chlorodiphenylacetylhydrazine is presumed to be initially formed in the latter

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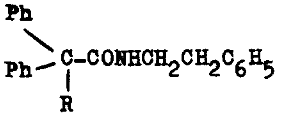
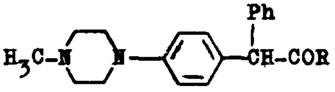
reaction. α-Lactam intermediates have been invoked in both cases to explain the products. We wish to record here a unique displacement reaction on α-chlorodiphenylacetamides wherein the attacking base enters the <u>para</u> position to the side chain from which the halogen is leaving. To our knowledge, the reaction has few parallels in the literature.[7]

Treatment of N-β-phenethyl-α-chlorodiphenylacetamide[8](V) m.p. 88-89° with three molar equivalents of N-methylpiperazine at 120° for 3 hrs. afforded, on conventional work-up, three products, N-β-phenethylbenzilamide (VI)(5%), m.p. 139-141°, N-β-phenethyl-α-N(N'-methylpiperazino)diphenylacetamide (VII) (40%), m.p. 128-29° and N-β-phenethyl-p-N-(N'-methylpiperazino) diphenylacetamide (VIII)(30%), m.p. 159-160°. The benzilamide VI was identified with a specimen resulting from the saponification of V. Structure proof for VII was obtained by treatment with hot 6N HCl, when a quantitative yield of VI was obtained. Similar acid hydrolysis of VIII resulted in the formation of p-N-(N'-methylpiperazino) diphenylacetic acid (IX), m.p. 215-19° (d). A few other secondary, mainly cyclic, bases, on reaction with chloramide V likewise afforded both <u>alpha</u> and <u>para</u> displacement products.

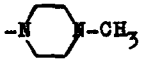


$Ph_2C(R)\text{-}CONHCH_2CH_2C_6H_5$



V R = Cl

VI R = OH

VII R = 

VIII R = $-NHCH_2CH_2Ph$

IX R = OH

Consistent with the structure of VIII, its U.V. spectrum in alcohol (λ_{max} 253 mμ, log ε 4.19, λ inflex 288 mμ, log ε 3.26) was strongly similar to that of N-methyl-N'-p-tolylpiperazine[9] (λ_{max} 246 mμ, log ε 4.05, λ inflex 288 mμ, log ε 3.12) and became benzenoid in 2N HCl; it also gave an evanescent red colouration with ceric sulphate, a reaction characteristic of anilines. The amide VII on the other hand gave a negative 'ceric reaction' and its

U.V. spectrum was benzenoid in character. The IR spectrum (as mulls) of VII and VIII as expected showed bonds for the NH and CO groups (VII - 3375, 1660; VIII - 3240, 1625 cm^{-1}). As compared to VII, the 60 MC NMR spectrum of VIII in $CDCl_3$ showed that one of the phenyl rings had acquired a substituent at the <u>para</u> position to the side chain (A_2B_2 multiplet at 6.80 and 7.13 ppm)[10]. Further, a one proton singlet at 4.8 ppm was characteristic of the benzhydryl hydrogen[11]. Other features of the NMR spectrum of VIII were in full agreement with the structure. Unambiguous synthetic proof for one such '<u>para</u>-substituted' product has been obtained.

Experiments designed to gain insight into the mechanism of this reaction gave the following results. Treatment of α-chlorodiphenylacetonitrile[12] with N-methylpiperazine was slow but complex, and gave no characterizable products. N-(α-Chlorodiphenylacetyl)-N'-methylpiperazine[13] and β-phenethylamine did not give rise to VII or VIII. The amides VII and VIII were not interconvertible by the action of heat. α-Chlorodiphenylacetyl derivatives of arylamines on treatment with secondary bases yielded again both <u>alpha</u> and <u>para</u> substituted products, whereas only straight-forward displacement reaction occurred in the cases of benzhydryl bromide, trityl bromide and α-chlorophenylacetamides. Neither hydroxide ion nor alcohol effected a '<u>para</u>-displacement' on V.

These data are highly suggestive of an α-lactam intermediate being implicated in the reaction of V with secondary amines. Perhaps due to steric reasons, the nucleophile seeks the <u>alpha</u> and <u>para</u> positions for attack, rather than the carbonyl group of the lactam. Preliminary attempts at obtaining at least IR spectral evidence for this intermediate by the action of potassium t-butoxide or tertiary bases on amides of the type V have not been so far successful. This does not however preclude the α-lactam being involved as a short lived, highly reactive intermediate. Full details of this work will be published elsewhere.

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7. The reaction reported by J.D. Loudon and D.M. Smith (kindly brought to our attention by Dr. E.F. Jenny of CIBA, Basel to whom we are thankful) in Proc. Chem. Soc., 1963, 182, has some analogy to our finding.
8. Correct elemental analyses have been obtained for all new compounds reported here.
9. K. Nagarajan and A. Venkateswarlu, Tetrahedron Letters, 293 (1967).
10. Chemical shifts are in ppm relative to TMS as internal standard.

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