561. *Some Derivatives of* N-*Phenacylaniline.*

By D. L. Pain and R. Slack.

The action of formaldehyde on *N*-acyl derivatives of some *N*-*p*-nitrophenacylanilines has been examined. *N*-Chloroacetyl-*N*-phenacylanilines react with bases to give intramolecular dehydrohalogenated products, probably by way of an intermediate enol. *N*-*p*-Nitrophenacylaniline reacts readily with ethyl chloroformate and with nitrous fumes.

Long and Troutman (*J. Amer. Chem. Soc.*, 1949, **71**, 2473) have described the hydroxymethylation of α-acetamido-*p*-nitroacetophenone to give (±)-2-acetamido-1-*p*-nitrophenylpropane-1 : 3-diol, an intermediate of value in the synthesis of chloramphenicol [(+)-*threo*-2-dichloroacetamido-1-*p*-nitrophenylpropane-1 : 3-diol]. It seemed possible that aryl analogues (*e.g.*, I; R = CO·$CHCl_2$, R′ = aryl) of the antibiotic might be obtained by application of a

(I.) *p*-NO_2·C_6H_4·CH(OH)·CH(NRR′)·CH_2·OH *p*-NO_2·C_6H_4·CO·CH_2·NRR′ (II.)

similar sequence of reactions to *N*-phenacylanilines (II; R = acyl, R′ = aryl). Moreover, dearylation of this type of compound (*e.g.*, I; R = H, R′ = *p*-NO·C_6H_4) by alkaline hydrolysis would give the intermediate 2-amino-1-*p*-nitrophenylpropane-1 : 3-diol useful in the synthesis of chloramphenicol.

However, a study of the reactivity towards formaldehyde of the methylene group in compounds of type (II; R = acyl, R′ = aryl) suggested that hydroxymethylation might well be uncontrollable. Using potassium carbonate as catalyst, Long and Troutman (*ibid.*, p. 2469) found that α-benzamidoacetophenone and formaldehyde gave 2 : 4-dibenzamido-1 : 5-diphenylpentane-1 : 5-dione but that α-acetamido-*p*-nitroacetophenone (*ibid.*, p. 2463) (II; R = H, R′ = Ac), formaldehyde, and sodium hydrogen carbonate gave the required hydroxymethyl compound (I; R = H, R′ = Ac). We believed that the single alteration from R = H to R = Ph in (II) would increase the electron mobility—and hence the reactivity—about the methylene group to such an extent that substituted methanes, rather than hydroxymethyl compounds, would invariably be formed. Experiment has shown that this is so and, although a wide variety of conditions have been examined, we have been quite unable to stop these reactions at the hydroxymethyl stage.

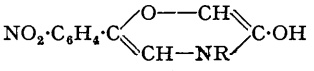
p-Nitrophenacyl bromide reacted readily with anilines and substituted anilines, except those bearing a bulky electro-negative substituent in the *ortho*-position. Thus *N*-*p*-nitro-

phenacyl derivatives of aniline and *o*- and *m*-chloroaniline were easily prepared, but anthranilic acid reacted sluggishly. Reaction with *o*-nitroaniline was too slow to be of practical value.

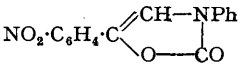
N-*p*-Nitrophenacylaniline, with the appropriate acid chlorides or anhydrides, gave acetyl, chloroacetyl, dichloroacetyl, and benzoyl derivatives; *o*- and *m*-chloro-*N*-*p*-nitrophenacylaniline gave the corresponding acetyl compounds.

Attempts to effect monohydroxymethylation of these amides are described in the Experimental section. From reactions with aqueous formaldehyde or paraformaldehyde and a basic catalyst 2 : 4-bisacetarylamido-1 : 5-di-*p*-nitrophenylpentane-1 : 5-diones, $CH_2[CH(NAcAr)\cdot CO\cdot C_6H_4\cdot NO_2]_2$, were obtained in which Ar was phenyl, *o*- or *m*-chlorophenyl.

Attempted hydroxymethylations of chloroacetylated aniline derivatives provided anomalous results of interest. No reaction occurred with formaldehyde in the presence of organic bases, sodium hydrogen carbonate, or potassium carbonate. With sodium hydroxide, however, the elements of hydrogen chloride were readily eliminated and *N*-*p*-nitrophenacyl-*N*-chloroacet-anilide and -*m*-chloroanilide gave, respectively, crystalline products which are



(III.)



(IV.)

considered to be probably the 1 : 4-oxazines (III; R = Ph and *m*-Cl·C_6H_4 respectively). Intervention of the enol–hydroxy-group of phenacylanilines in ring formation has been observed by McCombie and Parkes (*J.*, 1912, 1991). McCombie and Scarborough (*J.*, 1913, 56) were unable to condense *N*-phenacylaniline itself with ethyl chloroformate but obtained 3 : 5-diphenyloxazol-2-one by the direct action of carbonyl chloride. *N*-*p*-Nitrophenacylaniline, however, reacted with ethyl chloroformate in pyridine to give 5-*p*-nitrophenyl-3-phenyloxazol-2-one (IV). The possibility of ring-closure involving one or other of the benzene nuclei has been carefully considered in all these cases, but the experimental conditions employed seem to preclude this. The extreme reactivity in the enol forms naturally cast doubts on the structure of the compounds derived by reaction of the various phenacylanilides with formaldehyde. Spectral evidence, however, did not indicate *O*-alkylation in the condensation products.

N-*p*-Nitrophenacylaniline reacted quantitatively with nitrous fumes (cf. Möhlau *Ber.*, 1882, **15**, 2472) to give the corresponding *N*-nitroso-compound (II; R = NO) but attempts either to condense this with formaldehyde or to effect migration of the nitroso-group into the *para*-position led to the regeneration of *N*-*p*-nitrophenacylaniline. Although the loss of a *N*-nitroso-group is fairly common, extreme lability towards both acid and alkali, as was here the case, is less usual.

Experimental.

N-p-*Nitrophenacylaniline.*—*p*-Nitrophenacyl bromide (9 g.) in alcohol (75 c.c.) was shaken at room temperature with aniline (8·5 g.) for 3 hours. The N-p-*nitrophenacylaniline* was filtered off, washed with alcohol, and recrystallised from benzene in dark-red needles (7·8 g.), m. p. 146° (Found: C, 64·9; H, 4·5; N, 10·9. $C_{14}H_{12}O_3N_2$ requires C, 65·6; H, 4·7; N, 10·9%).

o-*Chloro*-N-p-*nitrophenacylaniline.*—*p*-Nitrophenacyl bromide (16 g.) in hot alcohol (130 c.c.) was treated with *o*-chloroaniline (17 g.) and refluxing continued for 15 minutes. o-*Chloro*-N-p-*nitrophenacylaniline* (6·5 g.) was collected and recrystallised from alcohol in orange needles, m. p. 166—168° (Found: N, 9·65; Cl, 11·9. $C_{14}H_{11}O_3N_2Cl$ requires N, 9·6; Cl, 12·2%). Further heating of the liquors gave a crop of less pure material (13 g.).

The m-*chloro*-isomer, prepared similarly, formed orange needles (8·5 g.), m. p. 163—164°, from methanol (Found: N, 9·6%).

N-p-*Nitrophenacylanthranilic Acid.*—This *acid*, obtained from the bromide (4·9 g.) and anthranilic acid (2·8 g.) in alcohol (20 c.c.), formed microcrystalline red prisms (from nitrobenzene), m. p. >300° (Found: N, 9·1. $C_{15}H_{12}O_5N_2$ requires N, 9·3%).

N-p-*Nitrophenacylacetanilide.*—*N*-*p*-Nitrophenacylaniline (1·0 g.) was heated at 100° for 10 minutes with acetic anhydride (5 c.c.), and the mixture then poured on ice. The *amide* (100% yield) crystallised from methanol, giving colourless plates, m. p. 117—118° (Found: C, 64·7; H, 4·9; N, 9·4. $C_{16}H_{14}O_4N_2$ requires C, 64·4; H, 4·7; N, 9·4%).

The o-*chloroanilide*, prepared similarly (1 hour), formed plates, m. p. 131°, from methanol (Found: N, 8·4. $C_{16}H_{13}O_4N_2Cl$ requires N, 8·4%). The p-*chloro*-isomer formed, from aqueous acetic acid, pale yellow prisms, m. p. 156—157° (Found: N, 8·35%).

N-p-*Nitrophenacylchloroacetanilide*, m. p. 155—156° (Found: N, 8·45; Cl, 10·0. $C_{16}H_{13}O_4N_2Cl$ requires N, 8·4; Cl, 10·7%), was prepared from *N-p*-nitrophenacylaniline (2·6 g.) and chloroacetyl chloride (6 g.) at 100° (5 minutes). Similarly was obtained N-p-*nitrophenacylchloroaceto*-m-*chloroanilide*, needles (from benzene–light petroleum), m. p. 156—157° (Found: N, 7·5; Cl, 19·6. $C_{16}H_{12}O_4N_2Cl_2$ requires N, 7·65; Cl, 19·35%).

N-p-*Nitrobenzoylphenacylaniline*, obtained from *N*-p-nitrophenacylaniline (2·6 g.) and benzoyl chloride