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A NOVEL REACTION OF GUANIDINE WITH BENZALDEHYDES[1]

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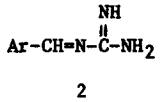
We have obtained an unexpected oxidation-reduction product from the reaction of guanidine and benzaldehydes in the presence of strong base. For example, p-chlorobenzaldehyde, guanidine carbonate and sodium methoxide (3:1:2) in abs. ethanol (room temp., 4 hrs.) gave, after acidification with conc. HCl, 42% of 1-(p-chlorobenzoyl)-3-(p-chlorobenzyl)guanidine HCl (1·HCl, Ar = p-Cl-C_6H_4). From the mother liquors smaller amounts of the Cannizzaro reaction products, p-chlorobenzoic acid and p-chlorobenzyl alcohol, could be isolated (equation 1).

$$ArCHO + (NH_2)_2C{=}NH\cdot 1/2\ H_2CO_3 \xrightarrow[2)\ HCl]{1)\ NaOCH_3,\ EtOH} Ar\text{-}C(=O)\text{-}NH\text{-}C(=NH\cdot HCl)\text{-}NH\text{-}CH_2\text{-}Ar + ArCO_2H + ArCH_2OH \quad (1)$$

1·HCl

This reaction was discovered when benzaldehyde was heated at reflux with ethanolic alkaline guanidine and there was obtained, after acidification, 11% of 1·HCl (Ar = C_6H_5[3]), identical to authentic material which had been prepared from benzoyl cyanamide and benzylamine[4], together with benzoic acid and benzyl alcohol. The expected product from this reaction, benzylideneguanidine (2, Ar = C_6H_5), could not be isolated. We had previously attempted to prepare 2 by a literature procedure (guanidine carbonate refluxed in excess benzaldehyde[5]), only to obtain a complex mixture of products from which benzoguanamine (3, Ar = C_6H_5, identical with authentic material prepared by an Organic Syntheses procedure[6]), could be isolated in 30% yield.



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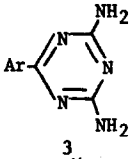

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There are at least three distinct mechanisms for formation of the rearranged product, all proceeding by way of a presumed benzylideneguanidine (2) intermediate. Mechanism I features an intramolecular hydride shift in the adduct 4 (eq. 2). Mechanism II is an intermolecular variant, possibly with benzoic acid and benzyl alcohol being formed concomitantly with rearranged product (1) by multiple hydride shifts. Mechanism III involves initial formation of a cycloadduct (5), followed by

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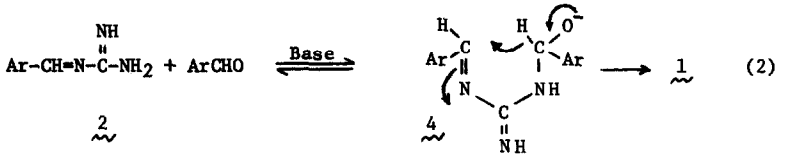
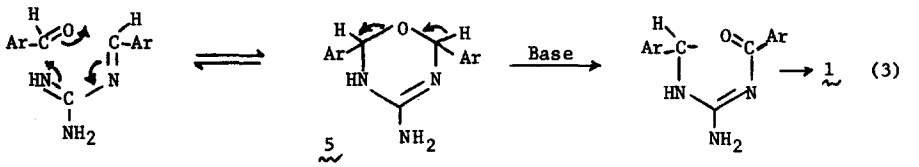
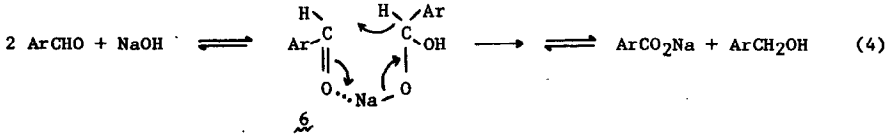


deprotonation and ring opening to a carbanionic intermediate (eq. 3).



While co-formation of Cannizzaro reaction products during the rearrangement suggested parallel mechanisms, a labelling experiment was undertaken to test that assumption. When 1-deuterio p-chlorobenzaldehyde, conveniently prepared by the method of Seebach[7], was subjected to the reaction conditions, there was obtained a poor yield of rearranged product containing two deuterium atoms, according to its nmr (fig. 1) and ir spectra, besides the normal Cannizzaro reaction products and unreacted aldehyde. The benzyl protons (labelled g in fig. 1a), which form an upfield doublet in the unlabelled material (due to coupling to the adjacent N-H proton in the DMSO-d_6 solvent system, since they collapse to a singlet upon addition of a drop of D_2O (fig. 1a')), are completely missing from the spectrum of the labelled material (fig. 1b), and the adjacent N-H proton absorption (labelled b) is sharper for the latter. Since mechanism III would have resulted in abstraction of a proton from EtOH solvent, it is excluded. A similar experiment has been reported for the Cannizzaro reaction[8].

Analogy for mechanism I may be found in the Cannizzaro reaction[9], which was initially formulated as an intramolecular process. A major controversy ensued, leading ultimately to acceptance of an intermolecular mechanism[10,11]. Recently, however, new evidence for intramolecularity, based upon formation of a Meerwein complex (6) before hydride transfer, has been advanced[12,13]. The parallelism between this modern formulation of the Cannizzaro reaction mechanism (eq. 4) and our mechanism I



(eq. 2) is obvious. Several other cyclic hydride transfer mechanisms, such as in the Tishchenko reaction[12,14], and in Grignard reductions and Oppenauer oxidations[15], are well established.

While mechanism II is not excluded, formation of 1 by consecutive hydride shifts, with or without simultaneous generation of the Cannizzaro products, is more complex and requires at least one other intermediate. Although such intermolecular hydride shifts were invoked to explain the ring contraction product from 1,2-cyclohexanedione and alkaline guanidine[16], in our case the more straightforward intramolecular mechanism I is preferred.

Other evidence supporting a hydride transfer mechanism includes preliminary observations on reaction rates with various benzaldehydes. Qualitatively the relative rate order (p-Cl>H>p-CH_3) is similar to that observed in the Cannizzaro reaction[17]; the relative rates of aldehyde and deuterio isomer (p-Cl-C_6H_4-CHO>p-Cl-C_6H_4-CDO) also correspond to those observed for the Cannizzaro reaction[18], suggesting that C-H bond breaking occurs in the transition state. Interestingly, guanidine in dilute aq. NaOH gives some rearrangement product (ca. 3% of 1, Ar = p-Cl-C_6H_4, in 3 days at room temp.), but the rearrangement does not occur in the absence of alkali, despite guanidine's high base strength (pK_a 13.7). Thus, when guanidine free base was prepared from its carbonate salt by the action of barium hydroxide in ethanol[19] and heated with p-chlorobenzaldehyde (27 hrs. reflux), there was obtained 18% of 2,4-diamino-6-(p-chlorophenyl)-s-triazine (3, Ar = p-Cl-C_6H_4, identical to authentic material[20]), unreacted starting material, and no appreciable yield of 1.

Further attempts to isolate the elusive intermediate (2) are planned, in order to continue to explore the scope and mechanism of this interesting rearrangement.

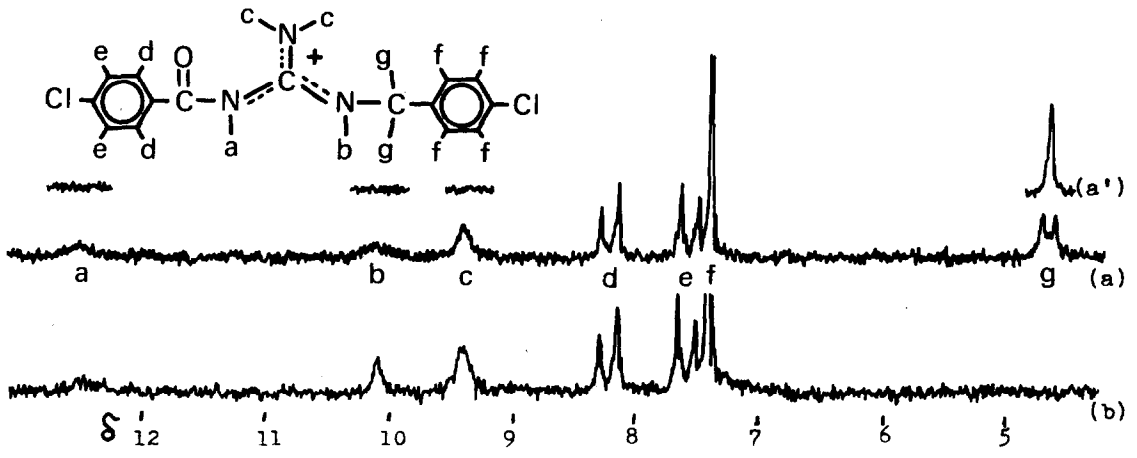


Figure 1. Nmr spectra (60 mHz, DMSO-d_6). (a) 1-(p-chlorobenzoyl)-3-(p-chlorobenzyl)guanidine hydrochloride; (a') same, after adding deuterium oxide; (b) analogous product derived from p-chlorobenzaldehyde-1-d.

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