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245. *Condensation of Substituted Benzaldehydes with Creatinine: Influence of Substituents.*

By Venancio Deulofeu and Manuel Fondovila.

Usually, condensation of substituted benzaldehydes with creatinine by heating at 140° gives derivatives of 5-benzylidenecreatinine (I) and at 190° derivatives of benzylidene-*NN'*-bis-(5-benzylidenecreatinine) (II) are obtained. The fact that *m*-chlorobenzaldehyde gave even at 140° the compound of type (II) while *o*-chlorobenzaldehyde behaved normally, led us to study the influence of substituents. It has been found that *p*-chloro-, *m*-bromo-, *m*-iodo, and *m*-nitro-benzaldehydes condense normally, whereas *p*-nitrobenzaldehyde gives even at 140° a mixture of both types of compound (I) and (II).

The condensation of creatinine with aromatic aldehydes by fusion was carried out first by Richardson, Welch, and Calvert (*J. Amer. Chem. Soc.*, 1929, **51**, 3075); later, Cornthwaite and Jordan (*ibid.*, 1934, **56**, 2733) effected condensation by heating the two reactants at 130—140°, and Cornthwaite, Lazarus, Snelling, and Denoon (*ibid.*, 1936, **58**, 628) described the condensation of a series of substituted benzaldehydes by heating them with creatinine from 150° to 180° until the reaction ceased. They found that some aldehydes produced two series

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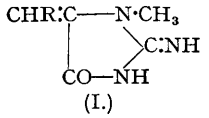
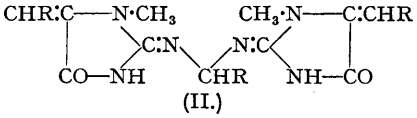
of compounds : the usual 5-benzylidenecreatinine derivatives (I) and also a compound formed by condensation of 3 mols. of aldehyde with 2 mols. of creatinine to which the general formula (II) was assigned.



(I.)



(II.)

The constitution of the latter compounds was confirmed by Cattaneo, Deulofeu, and Guerrero (*Ber.*, **1939**, **72**, 1461) in the case of benzylidene-*NN'*-bis-(5-benzylidenecreatinine), for hydrolysis with aqueous baryta gave ammonia, benzaldehyde, and 5-benzylidene-1-methylhydantoin, all explicable on the basis of formula (II). They also noted that when the substituted benzaldehydes were heated with creatinine at 140°, only compounds of type (I) could be isolated, whereas heating at 190° afforded compounds of type (II). An exception was *m*-chlorobenzaldehyde, which even at 140° gave only the compound of type (II), the *o*-chlorobenzaldehyde behaving normally. It was therefore considered of interest to study the behaviour of other halogenated benzaldehydes and of the nitrobenzaldehydes, the nitro-group being in some aspects of the opposite type to the halogens.

The halogenated aldehydes employed were *p*-chloro-, *m*-bromo-, and *m*-iodo-benzaldehyde. At 140° all gave only the substituted 5-benzylidenecreatinine (I). The structure of these compounds was ascertained by acetylation to their 2-*acetyl* derivatives, identical with those obtained by direct condensation of the aldehydes with creatinine under the influence of acetic anhydride. As a further confirmation, the original 2-acetyl-5-benzylidenecreatinines were deacetylated with hydrochloric acid and found to be identical with the compounds obtained by fusion.

When the halogenated aldehydes were heated with creatinine at 190°, compounds of formula (II) were practically the only ones that could be isolated.

Of the three isomeric nitrobenzaldehydes, no definite compounds could be isolated from the condensation of *o*-nitrobenzaldehyde with creatinine at 140° or at 190°. *m*-Nitrobenzaldehyde gave at 140° the product of type (I), and at 190° that of type (II), but *p*-nitrobenzaldehyde yielded at 140° a mixture of the two types of compound, type (I) predominating, thus being similar in reactivity, at low temperature, to *m*-chlorobenzaldehyde.

It is difficult to explain the difference of reactivity of the aldehydes in terms of the inductive or tautomeric effects of the substituents until more data are available.

Experimental.

M. p.s are not corrected. Although not specifically stated, mixed m. p.s were determined with all pairs of identical compounds obtained by different methods. Acetylation was always carried out on the substituted 5-benzylidenecreatinines obtained by fusion at 140°. The time of heating creatinine with the aldehydes at 140° or 190° was 30 minutes.

2-*Acetyl*-5-p-*chlorobenzylidenecreatinine*.—(*a*) 1 G. of creatinine, 0·5 g. of *p*-chlorobenzaldehyde, 1 g. of fused sodium acetate, and 4 c.c. of acetic anhydride were heated in an oil-bath at 140°. Water was then added, and the precipitated solid filtered off, well washed with water, and recrystallised from ethanol; yellow plates, m. p. 199—201°. (*b*) 0·1 G. of 5-*p*-chlorobenzylidenecreatinine, m. p. 261—263°, was acetylated with acetic anhydride–fused sodium acetate in the usual way, affording yellow plates, m. p. 199—201°, after purification (Found : N, 15·45. $C_{13}H_{12}O_2N_3Cl$ requires N, 15·1%).

5-p-*Chlorobenzylidenecreatinine*.—(*a*) 0·2 G. of the foregoing *acetyl* compound was heated for 5 minutes with 5 c.c. of 2N-hydrochloric acid. The solution was cooled, and a small excess of ammonia added. The precipitate was filtered off, washed with water, and recrystallised from ethanol; yellow needles, m. p. 262—263°. (*b*) 1 G. of creatinine (2 mols.) and 1·68 g. of aldehyde (3 mols.) were heated at 140°. The *product*, washed with cold ethanol and warm water, had m. p. 253°; on recrystallisation from ethanol, yellow needles, m. p. 261—263°, were obtained (Found : N, 17·6. $C_{11}H_{10}ON_3Cl$ requires N, 17·8%).

p-*Chlorobenzylidene*-NN'-*bis*-(5-p-*chlorobenzylidenecreatinine*).—1 G. of creatinine and 1·68 g. of *p*-chlorobenzaldehyde were heated at 190°. The solid *product* was washed with warm water and warm ethanol, and the residue recrystallised from acetic acid or nitrobenzene. In both cases yellow-orange needles, m. p. 315—316° (Found : N, 14·5. $C_{29}H_{23}O_2N_6Cl_3$ requires N, 14·2%), were obtained.

2-*Acetyl*-5-m-*bromobenzylidenecreatinine*.—The *m*-bromobenzaldehyde was prepared from *m*-aminobenzaldehyde (Buck and Ide, *Org. Synth.*, Coll. Vol. II, p. 132) with the necessary precautions to avoid production of *m*-chlorobenzaldehyde. (*a*) 0·5 G. of creatinine and 1·2 g. of *m*-bromobenzaldehyde were condensed in the usual way with acetic anhydride–fused sodium acetate. Recrystallisation from ethanol gave yellow needles, m. p. 160—161°. (*b*) Acetylation of 5-*m*-bromobenzylidenecreatinine gave the same compound, m. p. 161° (Found : N, 12·45. $C_{13}H_{12}O_2N_3Br$ requires N, 12·4%).

5-m-*Bromobenzylidenecreatinine*.—(a) By deacetylation of the above *acetyl* compound with 2N-hydrochloric acid, slight yellow plates, m. p. 251—252°, were obtained from ethanol. (*b*) 0·5 G. (2 mols.) of creatinine and 1·1 g. (3 mols.) of aldehyde were heated at 140°. The *product*, washed with cold ethanol, warm water, and warm ethanol, had m. p. 249°, and recrystallised from ethanol, m. p. 249—250° (Found : N, 14·7. $C_{11}H_{10}ON_3Br$ requires N, 15·0%).

m-*Bromobenzylidene*-NN'-*bis*-(5-m-*bromobenzylidenecreatinine*).—0·5 G. of creatinine and 1·1 g. of aldehyde were heated at 190°. The *product* was washed with ethanol, water, and again ethanol, and crystallised twice from aniline and twice from nitrobenzene; yellow needles, m. p. 296—298° (Found : N, 11·4. $C_{29}H_{23}O_2N_6Br_3$ requires N, 11·6%).

2-*Acetyl*-5-m-*iodobenzylidenecreatinine*.—The *m*-iodobenzaldehyde was prepared according to Patterson (*J.*, 1896, **69**, 1002); m. p. 57°. (*a*) 0·5 G. of creatinine and 0·5 g. of *m*-iodobenzaldehyde were condensed in the usual way; yellow plates, m. p. 192°, were obtained from ethanol. (*b*) Acetylation of 5-*m*-iodobenzylidenecreatinine gave the same *compound*, m. p. 190—192° (Found : N, 11·4. $C_{13}H_{12}O_2N_3I$ requires N, 11·4%).

5-m-*Iodobenzylidenecreatinine*.—(*a*) By deacetylation of the foregoing compound with 6N-hydrochloric acid, slight

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yellow needles, m. p. 241—242° (from alcohol), were obtained. (*b*) By heating 0·5 g. (2 mols.) of creatinine and 1·4 g. (3 mols.) of aldehyde to 140°, and washing the product with warm water and warm ethanol, this *compound* was obtained, m. p. 233—235°. After recrystallisation from ethanol, it had m. p. 241—243° (Found : N, 12·2. $C_{11}H_{10}ON_3I$ requires N, 12·8%).

m-*Iodobenzylidene*-NN′-*bis*-(5-m-*iodobenzylidenecreatinine*).—0·5 G. of creatinine and 1·4 g. of aldehyde were heated to 190°. The crude *product* was washed with warm ethanol and warm acetic acid. Recrystallised from nitrobenzene, it formed bright yellow needles, m. p. 317—319° (Found : N, 10·5. $C_{29}H_{23}O_2N_6I_3$ requires N, 11·2%).

2-*Acetyl*-5-o-*nitrobenzylidenecreatinine*.—2 G. of creatinine and 1 g. of *o*-nitrobenzaldehyde were condensed as usual with acetic anhydride. The crude *product*, recrystallised from ethanol or acetic acid, gave long yellow needles, m. p. 228—230° (Found : N, 19·3. $C_{13}H_{12}O_4N_4$ requires N, 19·4%). By deacetylation with 2N-hydrochloric acid, 5-o-*nitrobenzylidenecreatinine*, yellow needles, m. p. 250—252°, was obtained from ethanol or acetic acid (Found : N, 23·3. $C_{11}H_{10}O_3N_4$ requires N, 22·8%). By acetylation, the original substance, m. p. 228—230°, was produced.

2-*Acetyl*-5-m-*nitrobenzylidenecreatinine*.—(*a*) 1 G. of creatinine and 0·5 g. of aldehyde were condensed with acetic anhydride. The *acetyl* compound, washed with warm water and ethanol, and recrystallised from nitrobenzene, afforded yellow needles, m. p. 263—264°. (*b*) Acetylation of 5-*m*-nitrobenzylidenecreatinine (below) gave the same product, m. p. 261° (Found : N, 19·9%).

5-m-*Nitrobenzylidenecreatinine*.—(*a*) By deacetylation of the above acetyl compound with 6N-hydrochloric acid, and recrystallisation of the crude product from acetic acid, yellow crystals, m. p. 315° (darkening from 285°) were obtained. (*b*) 0·5 G. (2 mols.) of creatinine and 0·9 g. (3 mols.) of the aldehyde were heated to 140°. The crude product, washed with water and ethanol, had m. p. 285—288°. Recrystallisation from acetic acid afforded yellow needles, m. p. 315° (darkening from 285—288°) (Found : N, 22·5. Calc. for $C_{11}H_{10}O_3N_4$: N, 22·8%). Richardson *et al.* (*loc. cit.*) give m. p. 288°.

m-*Nitrobenzylidene*-NN′-*bis*-(5-m-*nitrobenzylidenecreatinine*).—1 G. of creatinine (2 mols.) and 2 g. of aldehyde (3·6 mols.) were heated to 190°. The crude *product*, washed with warm water and ethanol and recrystallised from nitrobenzene, formed long yellow needles, m. p. 342—344° (Found : N, 20·4. $C_{29}H_{23}O_8N_9$ requires N, 20·15%).

2-*Acetyl*-5-p-*nitrobenzylidenecreatinine*.—(*a*) 1 G. of creatinine and 0·5 g. of the aldehyde were condensed. The crude *product*, after recrystallisation from acetic acid, was obtained as long yellow needles, m. p. 243—244°. (*b*) Acetylation of 5-*p*-nitrobenzylidenecreatinine gave the same substance, m. p. 240° (Found : N, 20·04%).

5-p-*Nitrobenzylidenecreatinine*.—(*a*) By deacetylation of the acetyl derivative with 6N-hydrochloric acid, and recrystallisation from acetic acid, this *nitro*-compound was obtained as yellow prisms, m. p. 284°. (*b*) 1 G. of creatinine and 1·8 g. of the aldehyde were heated at 140°. The crude product, washed with ethanol, warm water and warm ethanol, afforded 0·97 g., m. p. 265°. By boiling with acetic acid soluble and an insoluble fraction (0·16 g.) were separated. By cooling and partial evaporation, the acetic acid solution yielded 0·6 g. of yellow prisms, m. p. 272—275°, raised by recrystallisation from the same solvent to 282—284° (Found : N, 22·0%). The insoluble fraction after recrystallisation from nitrobenzene yielded the *compound* of type (II), m. p. 338—340° (see below).

p-*Nitrobenzylidene*-NN′-*bis*-(5-p-*nitrobenzylidenecreatinine*).—1 G. of creatinine and 1·8 g. of the aldehyde were heated to 190°. The crude product was washed with the usual solvents and extracted with boiling acetic acid but no 5-*p*-nitrobenzylidenecreatinine could be isolated. Recrystallisation from nitrobenzene afforded red needles, m. p. 338—340° (Found : N, 21·0%).

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